[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

$\Delta^{5,7}$-STEROIDS. VIII.[1,2] THE MALEIC ANHYDRIDE ADDUCT PRODUCTS OF $\Delta^{5,7}$-ANDROSTADIENE-3β-OL-17-ONE ACETATE AND $\Delta^{5,7}$-PREGNADIENE-3β-OL-20-ONE ACETATE

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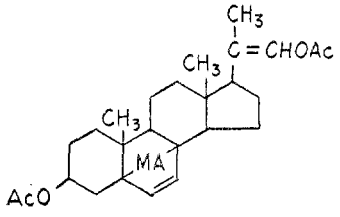
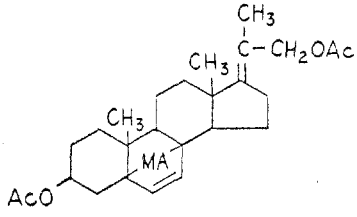
In 1948, Bergmann and Stevens (1) in a noteworthy publication reported on some of their investigations exploring the possibilities of utilizing ergosterol as a starting material for the synthesis of adrenal cortical hormones. Subsequently, Levin, Wesner, and Meinzer (2) announced results along similar lines. Due to the current interest in the synthesis of cortical hormones, we have considered further this sterol approach, and in this publication we wish to report on some of these results.

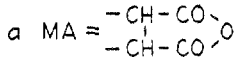
Bergmann and Stevens (1) developed a method of degrading ergosterol which gave the enol acetate of $\Delta^{5,7}$-bisnorcholadiene-3β-ol-22-al acetate maleic anhydride adduct to which the alternate structures I and II were assigned. Ozon-



I[a]



II

a MA = 

olysis gave a ketone to which the structure V was *tentatively* assigned on the basis of elemental analysis. Thus it was concluded that the intermediate enol acetate had the structure II.

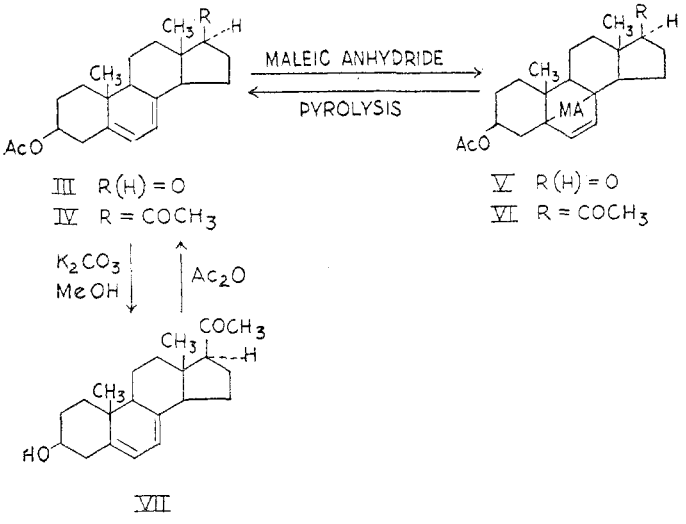
In Paper VI (3) of this series, there was reported the preparation of a number of $\Delta^{5,7}$-steroidal hormones by the NBS[3] method; among others, $\Delta^{5,7}$-androstadiene-3β-ol-17-one acetate (III) and $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate (IV). Thus, reaction of III with maleic anhydride should give an adduct product of the structure assigned by Bergmann and Stevens to their degradation product. The maleic anhydride adduct product (V) so obtained was not identical with the

[1] Paper VII. Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, 159 (1951).

[2] Presented in part before the Organic Group at the third annual meeting of the North Jersey Section, American Chemical Society, Newark, N. J., January 8, 1951.

[3] NBS = N-Bromosuccinimide.

Bergmann-Stevens compound.[4] The evidence included melting point, optical rotation, and infrared absorption analysis (Table I, Fig. I). A concurrent investigation of this problem by Bergmann and Schedl (4) indicated that the pre-



viously published analysis by Bergmann and Stevens (1) was in error, and that the corrected analysis indicated the compound to be the maleic anhydride adduct (VI) of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate. This analytical result was confirmed independently by us, and the structure of the compound was established unequivocally by synthesis from $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate (IV) (Table I, Fig. I). Accordingly, structure I has been assigned to the intermediate enol acetate.

TABLE I

PHYSICAL CONSTANTS OF MALEIC ANHYDRIDE ADDUCT PRODUCTS

COMPOUND	M.P., °C.	$[\alpha]^{25}_{D}$ ($CHCl_3$)	$[\alpha]^{25}_{Hg}$ ($CHCl_3$)
$\Delta^{5,7}$-Androstadiene-3β-ol-17-one acetate-maleic anhydride adduct	259–261	+28.1	+38.6
$\Delta^{5,7}$-Pregnadiene-3β-ol-20-one acetate-maleic anhydride adduct	288–289.5 291–293	+19.4	+28.6
Bergmann-Stevens compound	292–293	+20.5	+28.1

After the resolution of this structure problem, our attention was directed to a study of the pyrolysis of the adduct product (VI) for obtaining $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate (IV). After a preliminary study of this pyrolysis it was

[4] We wish to express our thanks to Dr. Werner Bergmann of Yale University for a generous amount of the maleic anhydride adduct product.

decided that probably the most advantageous procedure was for conducting the pyrolysis and evaporative distillation simultaneously at a pressure of 1–2 mm. and at a temperature of 260–300°. These conditions were selected for the dual

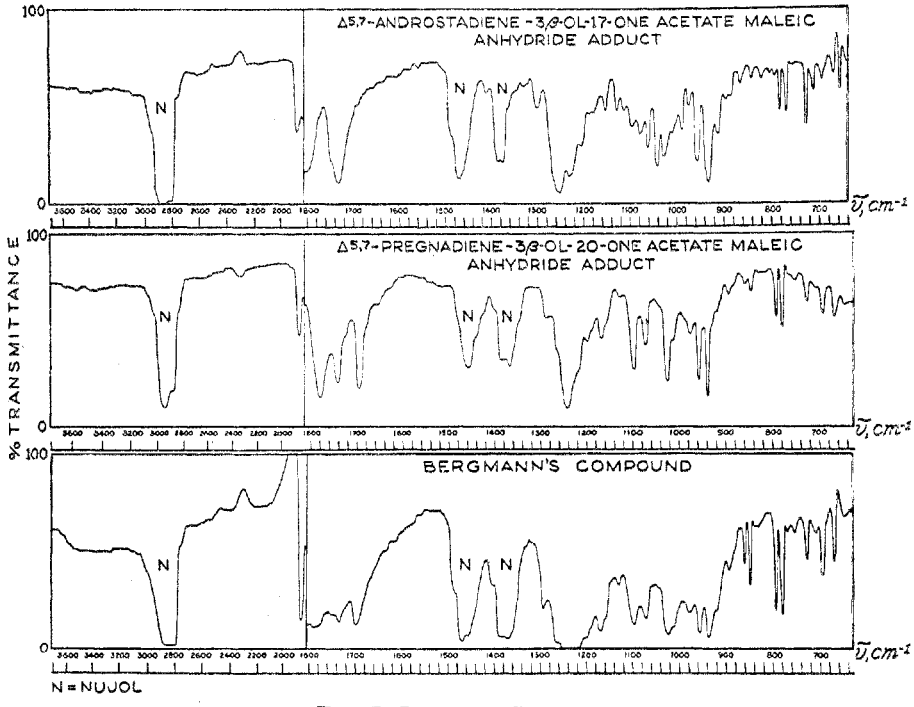


FIG. I. INFRARED SPECTRA

TABLE II

PHYSICAL CONSTANTS OF $\Delta^{5,7}$-PREGNADIENE-3β-OL-20-ONE ACETATE

SOURCE	M.P., °C.	$[\alpha]^{\circ}_{D}$ ($CHCl_3$)	$[\alpha]^{\circ}_{Hg}$ ($CHCl_3$)	U.V. ABSORPTION MAXIMA WITH MOLECULAR EXTINCTION COEFFICIENTS
NBS	166–168	−26.7	−35.1	$\epsilon_{271.5}$ 11,600, ϵ_{282} 12,200, $\epsilon_{293.5}$ 7,100
Pyrolysis of Lederle compound	167–169	−24.5	−33.1	$\epsilon_{271-271.5}$ 11,300, ϵ_{282} 12,000, $\epsilon_{293-294}$ 6,900
Pyrolysis of Bergmann-Stevens compound	166.5–169	−23.2	−31.7	$\epsilon_{271.5}$ 11,400, ϵ_{282} 12,300, ϵ_{294} 7,000

purpose of minimizing as much as possible the distillation of the adduct itself, and any thermal decomposition of the formed $\Delta^{5,7}$-steroid. The product so obtained appeared to be identical with an authentic sample of IV prepared by the

NBS method, except that its optical rotation differed by about 8°. Hydrolysis also gave a product of low rotation. However acetylation of the hydrolysis product gave the acetate (IV) which was now identical in all respects with an authentic sample (Table II, Fig. II).

Identical results were obtained in the pyrolysis of the Bergmann-Stevens adduct product (Table II).

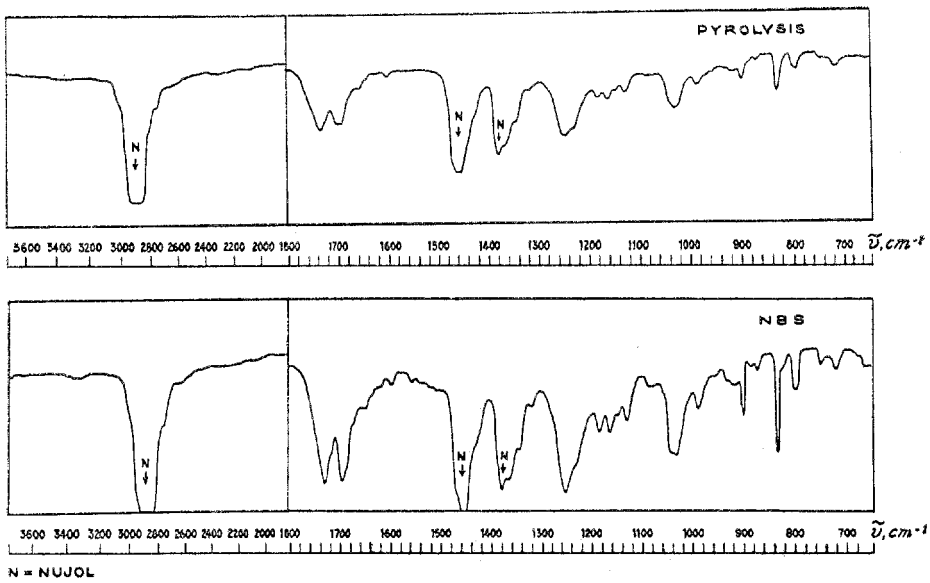


FIG. II. INFRARED SPECTRUM
$\Delta^{5,7}$-Pregnadiene-3β-ol-20-one Acetate

In conclusion, it may be stated that the preparation of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate (IV) from ergosterol establishes further the potentialities of this sterol as a starting material for the synthesis of adrenal cortical hormones.

EXPERIMENTAL

Melting points. All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers (total immersion).

Ultraviolet absorption spectra. All spectra were determined with a Beckman quartz spectrophotometer (Model DU, mfg'd by the National Technical Laboratories, So. Pasadena, California), and were determined, unless otherwise stated, in absolute alcohol spectrophotometrically free of benzene.

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

Infrared spectra. All spectra were determined by Dr. Robert C. Gore, Stamford Research Laboratories, American Cyanamid Company, with a Perkin-Elmer instrument converted to a double-beam spectrophotometer.

Maleic anhydride adduct (V) of $\Delta^{5,7}$-androstadiene-3β-ol-17-one acetate. A mixture of 1 g. of $\Delta^{5,7}$-androstadiene-3β-ol-17-one acetate (III), 0.4 g. of maleic anhydride, and 50 ml. of

xylene was refluxed for 18 hours. The xylene and excess maleic anhydride were removed *in vacuo*. The residue was dissolved in ether, and concentrated with the simultaneous addition of petroleum ether (b.p. 68°). This gave an oil which was separated by decantation. The decantate was similarly treated to give four oily fractions. The oils were combined and worked up in benzene. The dried benzene extract was evaporated *in vacuo*, and the residue was recrystallized from dilute acetic acid, wt. 80 mg., m.p. 259–261°; $[\alpha]_D^{29}$ +28.1°, $[\alpha]_{Hg}^{29}$ +38.6° (11.4 mg., α_D^{29} +0.16°, α_{Hg}^{29} +0.22°) $\alpha_{Hg}/\alpha_D = 1.38$ $[M]_D$ +120°.

Anal. Calc'd for $C_{25}H_{30}O_6$ (426.49): C, 70.40; H, 7.09.

Found: C, 70.56; H, 7.07.

Maleic anhydride adduct (VI) of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate. A. A mixture of 1.0 g. of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate (IV), 0.4 g. of maleic anhydride, and 50 ml. of xylene was refluxed for 19 hours. The xylene and excess maleic anhydride were removed *in vacuo*. The residue was worked with ether and filtered; wt. 0.83 g., m.p. 178–233° d. The ether treatment was repeated, wt. 0.71 g., m.p. 235–260° d. with considerable previous partial melt. Recrystallization to constant m.p. from glacial acetic acid gave 0.12 g. of VI, m.p. 288–289.5° d. above m.p. $\lambda_{max}^{1\%\ CA_5}$ none (235–340 mμ). $[\alpha]_D^{29}$ +19.4°, $[\alpha]_{Hg}^{29}$ +28.6° (21.7 mg., α_D^{29} +0.21°, α_{Hg}^{29} +0.31°) $\alpha_{Hg}/\alpha_D = 1.48$. $[M]_D$ +88°.

Anal. Calc'd for $C_{27}H_{34}O_6$ (454.54): C, 71.34; H, 7.54.

Found: C, 71.06; H, 7.54.

In another run with 10 g. of IV, 20 g. of maleic anhydride, and 150 ml. xylene there was obtained 3.14 g. of VI, m.p. 291–293° d., and 200 mg., m.p. 288–290° d.

B. Bergmann-Stevens compound. M.p. 292–293° d., $\lambda_{max}^{1\%\ CA}$ none. $[\alpha]_D^{30}$ +20.5°, $[\alpha]_{Hg}^{30}$ +28.1° (26.3 mg., α_D^{30} +0.27°, α_{Hg}^{30} +0.37°) $\alpha_{Hg}/\alpha_D = 1.37$° $[M]_D$ +93°.

Anal. Calc'd for $C_{25}H_{30}O_6$ (426.49): C, 70.40; H, 7.09.

$C_{27}H_{34}O_6$ (454.54): C, 71.34; H, 7.54.

Found: C, 71.03; H, 7.74.

Pyrolysis of the maleic anhydride adduct of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate. A. The adduct product (VI, 1.5 g.) was pyrolyzed and evaporatively distilled in the following manner. A pressure of 1.6 mm. was maintained throughout the experiment. The material was heated for 5 hours from room temperature to 298°. For the first 2 hours the temperature was raised from room temperature to 176°; third hour, 176° to 263°; fourth hour, 263° to 283°; and for the fifth and final hour, 283° to 298°. At about 231° a distillate was apparent. Between 264° and 282° a considerable amount of distillate, semi-solid and solid, had accumulated. The distillate was worked with ether, and a small amount of insoluble material (most probably starting material) was removed by filtration, wt. 70 mg., m.p. 280–285° d. The ether filtrate was evaporated with the simultaneous addition of methanol until all of the ether had been displaced. This gave 0.54 g. of crude product. Three recrystallizations from methanol gave 0.28 g. of IV, m.p. 165.5–169°, 167–171° (m.p. dependent on temperature of bath at time sample inserted), λ_{max} 263.5, 271, 282; 293.5 mμ, ε = 7,700, 10,900, 11,600, 6,700 resp., $[\alpha]_D^{29}$ −17.7°, $[\alpha]_{Hg}^{29}$ −23.9° (32.7 mg., α_D^{29} −0.29°, α_{Hg}^{29} −0.39°). From the mother liquors there was obtained an additional 130 mg. of product, m.p. 165–169°.

The $\Delta^{5,7}$-acetate (IV) (250 mg., main fraction obtained above by pyrolysis) in 20 ml. of methanol containing 0.15 g. of finely divided potassium carbonate was refluxed for 2 hours in a nitrogen atmosphere. The mixture was cooled, diluted with water, and the crystals were collected. Recrystallization from acetone and acetone-petroleum ether (b.p. 64–66°) gave 0.11 g., m.p. 230–233°, λ_{max} 271.5, 282, 293.5–294 mμ, ε = 10,900, 11,600, 6,800 resp., $[\alpha]_D^{29}$ −69.3°, $[\alpha]_{Hg}^{29}$ −92.7° (23.95 mg., α_D^{29} −0.83°, α_{Hg}^{29} −1.11°).

The free steroid (VII) (75 mg.) obtained above was refluxed for 20 minutes with 15 ml. of acetic anhydride. The excess acetic anhydride was evaporated *in vacuo* and the residue was crystallized from dilute methanol, wt. 71 mg., m.p. 162–168.5°. Two recrystallizations

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[5] 1% CA = 1% chloroform-absolute alcohol, *i.e.*, the weighed sample was dissolved in 1 ml. of reagent chloroform and this solution was rapidly diluted to 100 ml. with commercial absolute alcohol spectroscopically free of benzene.

from methanol gave pure IV, m.p. 167–169°, λ_{max} 271–271.5, 282, and 293–294 mμ, ϵ = 11,300, 12,000, 6,900 resp., $[\alpha]_D^{29}$ −24.5°, $[\alpha]_{Hg}^{29}$ −33.1° (27.8 mg., α_D^{29} −0.34°, α_{Hg}^{29} −0.46°) α_{Hg}/α_D = 1.35.

B. Pyrolysis of the Bergmann-Stevens compound (1.16 g.) in the manner described under (A) gave 263 mg. of IV, m.p. 166–169° λ_{max} 271.5, 282, and 293.5–294 mμ, ϵ = 11,300, 11,900, 6,900 resp. Hydrolysis of 0.2 g. of this material gave 94 mg., of VII, m.p. 227–230°, λ_{max} 271, 282, and 294 mμ, ϵ = 10,500, 11,100, 6,600 resp. Acetylation gave 70 mg. of IV, m.p. 166.5–169°, λ_{max} 271.5, 282, and 294 mμ, ϵ = 11,400, 12,300, 7,900 resp., $[\alpha]_D^{31}$ −23.2°, $[\alpha]_{Hg}^{31}$ −31.7° (35.3mg., α_D^{31} −0.41°, α_{Hg}^{31} −0.56°) α_{Hg}/α_D = 1.37.

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SUMMARY

1. The maleic anhydride adduct product of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate has been prepared, and was found to be identical with the product obtained by Bergmann and Stevens in their work on the degradation of ergosterol.

2. Pyrolysis of the adduct product gave $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate which was purified by hydrolysis and reacetylation.

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(4) Private communication.