[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

# STEROIDS WITH AN AROMATIC B-RING[1]

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Within a program designed for the study of partial-synthetic approaches to certain natural products, it became desirable to prepare a variety of steroidal compounds containing an aromatic B-ring. Of representatives of this type, the literature[3] describes particularly those corresponding to ergosterol (2), 22-dihydroergosterol (3), their epimers (4), and cholesterol (5).

In our preparative work we used, with some modifications, the procedure introduced by Windaus and Borgeaud (2), namely the photooxidation of the appropriate $\Delta^{5,7}$-steroid and subsequent decomposition of the bis-$\Delta^{5,8(9)}$-diene (6). In the first reaction, the important factor, in regard to yield, was the selection of the proper solvent mixture. Thus, in the preparation of bisergostatrienol (III) from ergosterol (I), by using tetrahydrofuran instead of benzene as the second solvent, we could increase the yield by 15 to 20%. We found that the use of any one particular fluorescein sensitizer, or the use of a mixture of these sensitizers (7), had no effect on the final yield. By employing as the light source an arrangement of fluorescent lamps, we have devised a simple and convenient procedure for the photooxidation. In this manner we prepared: bisergostatrienol (III) from ergosterol (I), bis(methyl-3β-acetoxybisnorcholadienate) (IV) from methyl - 3β - acetoxy-$\Delta^{5,7}$ - bisnorcholadienate (II), bis(3β - acetoxy - 22 - isospirostadiene)[4] (X) from 3β-acetoxy-$\Delta^{5,7}$-22-isospirostadiene[4] (IX). Boiling, under reflux, the solutions of the bis-compounds in diethylene glycol monoethyl ether, readily produced the respective derivatives containing an aromatic B-ring: neoergosterol (V), methyl α - (3β - acetoxy - 5,7,9 - estratriene - 17 - yl) - propionate (VIIId), previously obtained by Jacobsen (9) by degradation of neoergosterol, and 3β-acetoxy-$\Delta^{5,7,9(10)}$-22-iso-19-norspirostatriene (XIb). The yields obtained varied from 75–95% of the theory.[5] The ultraviolet spectra of V, VIII, and XI showed maxima at 269–270 mμ, characteristic of the aromatic B-ring (10). The infrared spectra showed identical bands in the region of 810 cm$^{-1}$, which we found characteristic of the aromatic ring in these compounds.[6]

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[1] Taken in part from a thesis to be submitted by Irving Scheer to the Graduate School of Georgetown University in partial fulfillment of the requirements for the Ph.D. degree.

[2] National Institutes of Health Predoctoral Fellow 1950.

[3] For a recent bibliography see the article by J. L. Owades (1).

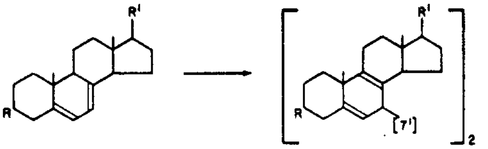
[4] Nomenclature follows, in principle, that proposed by Rosenkranz and Djerassi (8a). See also report by the 1950 conference held at the CIBA Foundation in London (8b).

[5] Based on the scheme (6) given for:

$$\underset{\text{bisergostatrienol}}{C_{56}H_{86}O_2} \rightarrow \underset{\text{neoergosterol}}{C_{27}H_{40}O} + CH_4 + \underset{\text{unknown}}{C_{28}H_{42}O}$$

[6] Compare Orr and Thompson (11) and Launer and McCaulay (12). A detailed account dealing with the infrared spectra of neoergosterol-type compounds, including their epimers, will be given in a later publication by Phyllis B. Humphries, *et al.*

In the course of various attempts to improve the yields of the ring-B aromatic steroids, and to study their by-products, we subjected the bis-compound III to Raney nickel hydrogenation under elevated pressure and temperature. The sole product we could isolate, in a yield of *ca.* 40%,[5] was dihydroepineoergosterol (VI). Attempts to oxidize the 3-hydroxyl group in neoergosterol according to the Oppenauer method (13) were unsuccessful in our hands and only very small amounts of epineoergosterol could be isolated. We obtained the desired ketone VII, in fair yields, by using Raney nickel as a catalyst for the oxidation, according to Kleiderer and Kornfeld (14). Epineoergosterol was formed as a by-product.

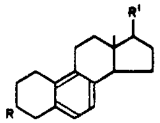


I $R = {<}^{H}_{OH}$, $R' = C_9H_{17}$

II $R = {<}^{H}_{OAc}$, $R' = CH(CH_3)CO_2CH_3$

III $R = {<}^{H}_{OH}$, $R' = C_9H_{17}$

IV $R = {<}^{H}_{OAc}$, $R' = CH(CH_3)CO_2CH_3$



V $R = {<}^{H}_{OH}$, $R' = C_9H_{17}$

VI $R = {<}^{OH}_{H}$, $R' = C_9H_{19}$

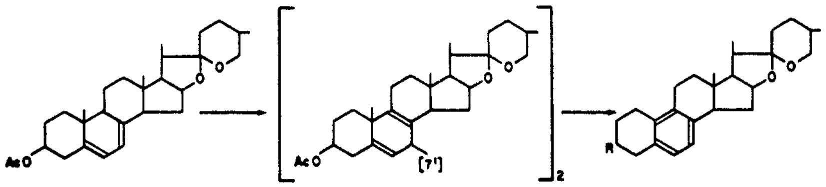
VII $R = O$, $R' = C_9H_{17}$

VIII a $R = {<}^{H}_{OH}$, $R' = CH(CH_3)CO_2H$

b $R = {<}^{H}_{OH}$, $R' = CH(CH_3)CO_2CH_3$

c $R = {<}^{H}_{OAc}$, $R' = CH(CH_3)CO_2H$

d $R = {<}^{H}_{OAc}$, $R' = CH(CH_3)CO_2CH_3$



IX

X

XI a $R = {<}^{H}_{OH}$

b $R = {<}^{H}_{OAc}$

*Acknowledgment:* We wish to express our thanks to Dr. G. Rosenkranz, of Syntex, S. A., for a generous gift of 3β-acetoxy-$\Delta^{5,7}$-22-isospirostadiene. The infrared spectra were taken by Mrs. Phyllis B. Humphries of this Laboratory. Microanalyses are by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford.

## EXPERIMENTAL[7]

*Photooxidations.* These reactions were carried out in a nitrogen atmosphere and with efficient stirring. The irradiation apparatus consisted of four horizontally fixed, 32-watt,

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[7] All melting points are corrected and were determined with a Hershberg melting point apparatus. Ultraviolet absorption spectra were determined in absolute alcohol and infrared spectra in carbon disulfide. Rotations were determined in a 2-dm. semi-micro tube. Unless otherwise noted, the sample was dissolved in chloroform to make an approximately 1% solution.

white, circular, fluorescent lamps,[8] with a minimum space between lamps, and enclosed with a reflecting shield made of highly polished aluminum.[9] The reaction vessel (usually a suitably sized Erlenmeyer flask fitted with a reflux condenser) was placed in the center of the circle of lamps.

*Bisergostatrienol* (III). A mixture of 60 g. of ergosterol (I) of m.p. 163–164° and 60 g. of eosin (free acid)[10] in 800 ml. of tetrahydrofuran and 1600 ml. of 95% ethanol was kept in the dark for 30 minutes to allow for complete replacement of air by nitrogen, and then irradiated for 48 hours.[11] The mixture was diluted with 5 l. of 95% ethanol. The fine silky needles were filtered, washed with ethanol and with ether, and dried *in vacuo* at 50–60°. Yield, 46.0 g. (77%); m.p. 201–203°d. [lit. (2) 202–203° d.]; $[\alpha]_D^{20}$ −172°. The yields of several reactions averaged 75–80%.

*Bis(methyl-3β-acetoxybisnorcholadienate)* (IV). A mixture of 20 g. of methyl-3β-acetoxy-$\Delta^{5,7}$-bisnorcholadienate (II) of m.p. 148–152° and 20 g. of eosin (free acid),[10] in 100 ml. of tetrahydrofuran and 700 ml. of 95% ethanol, was kept in the dark for 30 minutes and then irradiated for 90 hours.[11] The white, fluffy precipitate, formed during irradiation, was filtered, washed with ethanol, and dried *in vacuo* at 50–60°. Yield 12.8 g. (64%); m.p. 200–201°d. For analysis a sample was repeatedly recrystallized from tetrahydrofuran-ethanol and finally from chloroform-ethanol to give white silky needles, m.p. 206.5°d., $[\alpha]_D^{20}$ −162.5°, general absorption in the ultraviolet, $\nu CS_{2\max}$ 1736 $cm^{-1}$ (acetoxy and carbomethoxy) and 1238 $cm^{-1}$ (acetoxy).

*Anal.* Calc'd for $C_{50}H_{70}O_8$: C, 75.2; H, 8.8.
Found: C, 75.3; H, 8.8.

The mother liquor was concentrated *in vacuo* to near dryness, 400 ml. of water was added, and the red mixture made alkaline with 10% aqueous sodium hydroxide, and extracted with ether. An additional 1.8 g. of bis-compound melting at 192–194°d. was obtained.

*Bis(3β-acetoxy-22-isospirostadiene)* (X). A mixture of 20 g. of 3β-acetoxy-$\Delta^{5,7}$-22-isospirostadiene (IX) (15) of m.p. 201–209° and 20 g. of eosin (free acid),[10] in 200 ml. of tetrahydrofuran and 500 ml. of 95% ethanol, was irradiated for 168 hours[11] after first keeping the mixture in the dark for 30 minutes. The reaction mixture was poured into 1.5 l. of 95% ethanol, the crystalline precipitate filtered, washed with ethanol, and recrystallized once from benzene-ethanol to yield 14.0 g. (70%) of white needles, m.p. 212°d., $[\alpha]_D^{20}$ −171.6°, general absorption in the ultraviolet and $\nu CS_{2\max}$ 1736 $cm^{-1}$ and 1239 $cm^{-1}$ (acetoxy).

*Anal.* Calc'd for $C_{58}H_{82}O_8$: C, 76.8; H, 9.1.
Found: C, 76.5; H, 9.2.

*Decomposition of the bis-compounds.* A mixture (50 ml. of solvent for 1.0 g. of compound) of bis-compound and diethylene glycol monoethyl ether (Carbitol) was refluxed for five minutes in a nitrogen atmosphere. The solution was rapidly cooled to approximately 110° and cold water added (1 ml. per ml. of Carbitol), the precipitate filtered, washed with cold water and dissolved in hot methanol. The solution was treated with charcoal and concentrated to the desired volume, and finally the compound was recrystallized from a suitable solvent. In this manner we have decomposed quantities from 1 g. to 50 g.

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[8] The use of fluorescent lamps had several other practical advantages. Reaction temperatures of 40–45° were produced and maintained without the need for external cooling or heating. Light of the desired intensity was obtained with a 20-fold decrease in power consumption as compared to tungsten filament sources.

[9] When a reaction mixture (30°, $N_2$ atmosphere) was irradiated with two General Electric E-H1, 400 watt, mercury vapor lamps, complete decolorization occurred within one-half hour, but irrespective of the length of time of irradiation the yields did not surpass 30%.

[10] Eosin Yellow (Free Acid) C. I. #768, National Aniline Division, Allied Chemical & Dye Corporation, New York, N. Y.

[11] Regardless of time of irradiation, complete decolorization was never observed since in all experiments a slight excess of sensitizer was used. The reaction times given were experimentally determined to give the optimal yields.

*Neoergosterol* (V). From 50.0 g. of bisergostatrienol (III) there was obtained 18.6 g. (77%)[5] of crystalline material, m.p. 143–149°. One recrystallization from methanol yielded 16.3 g. of white needles, m.p. 152–154° [lit. (2) 151–152°], $\nu\mathrm{CS}_{2\mathrm{max}}$ at 3600 $\mathrm{cm}^{-1}$ (hydroxyl), 970 $\mathrm{cm}^{-1}$ (sidechain double bond), and 809 $\mathrm{cm}^{-1}$ (aromatic ring).

*Dihydroepineoergosterol* (VI). *a.* A mixture of 1.0 g. of III and 1.0 g. of Raney nickel in 100 ml. of ethanol was shaken in a hydrogen atmosphere at 150° and 2400 p.s.i. for three hours. The mixture was filtered and the solution concentrated to yield 0.21 g. (43%)[5] of VI, m.p. 162–166°. One recrystallization from ethanol gave 0.18 g. of material melting at 166–168°. It was shown (mixture melting point, rotation, and by direct comparison of the acetates) to be identical with dihydroepineoergosterol prepared by the procedure of Windaus and Deppe (4) from neoergosterol.

*b.* A mixture of 1.0 g. of V and 1.0 g. of Raney nickel in 60 ml. of ethanol was treated as in *a* to yield 0.62 g. (62%) of VI, m.p. 168–170°.

*Neoergosterone* (VII). ($\Delta^{5,7,9(10),22}$-19-norergostatetraen-3-one). A mixture of 2.0 g. of neoergosterol (V), 4.0 g. of Raney nickel, 20 ml. of dry cyclohexanone, and 60 ml. of dry toluene was refluxed, with vigorous stirring, for 48 hours. The mixture was cooled, filtered through a Celite mat, the filtrate evaporated *in vacuo* to dryness and the residue dissolved in benzene-petroleum ether (30–60°) and chromatographed on ethyl acetate-washed alumina. Elution with benzene yielded the ketone VII which was recrystallized from acetone-methanol to yield 0.53 g. (26.5%), m.p. 115–118°. Another recrystallization gave white needles, m.p. 116–118° [lit. (13) 121–122.5°], $[\alpha]^{20}_{\mathrm{D}}$ +23.3°, $\lambda_{\max}$ 269.5 mμ log ε 2.78. infrared showed no hydroxyl group, $\nu\mathrm{CS}_{2\mathrm{max}}$ 1724 $\mathrm{cm}^{-1}$ (carbonyl), 970 $\mathrm{cm}^{-1}$ (sidechain double bond), and 810 $\mathrm{cm}^{-1}$ (aromatic ring). VII in an alcohol solution gave a strong blue color when treated with a few drops of alcoholic sodium hydroxide solution. Acidification changed the blue to orange. This color test is characteristic of a β-tetralone not substituted in the 1-position (16).

*Anal.*[12] Calc'd for $C_{27}H_{38}O$: C, 85.7; H, 10.1.
Found: C, 86.3; H, 10.1.

The *semicarbazone*, prepared in the usual manner, decomposes at 200° but does not melt even at 300°.

*Anal.* Calc'd for $C_{28}H_{41}N_3O$: C, 77.1; H, 9.5; N, 9.3.
Found: C, 77.4; H, 9.8; N, 9.3.

Further elution of the alumina column with benzene-chloroform 3:1 yielded a small amount of crystalline material melting at 173–178° which did not show a melting point depression when mixed with epineoergosterol of m.p. 174–176°, prepared by the procedure of Windaus and Deppe (4).

*Methyl α-(3β-acetoxy-5,7,9-estratrien-17-yl)-propionate* (VIIId). The decomposition of 5.0 g. of bis (methyl-3β-acetoxybisnorcholadienate) (IV) gave 2.31 g. (96%)[5] of white plates (from methanol), m.p. 161–163° [lit. (9) 159.5–161.5°), $[\alpha]^{20}_{\mathrm{D}}$ +2.5°, $\lambda_{\max}$ 269 mμ, log ε 2.63 and $\nu\mathrm{CS}_{2\mathrm{max}}$1739 $\mathrm{cm}^{-1}$ (carbomethoxy and acetoxy), 1236 $\mathrm{cm}^{-1}$ (acetoxy), and 812 $\mathrm{cm}^{-1}$ (aromatic ring).

*Anal.* Calc'd for $C_{24}H_{32}O_4$: C, 75.0; H, 8.4.
Found: C, 74.7; H, 8.0.

*α-(3β-Hydroxy-5,7,9-estratrien-17-yl)-propionic acid* (VIIIa). Four grams of VIIId, in a mixture of 180 ml. of 95% ethanol and 24 ml. of a 20% aqueous sodium hydroxide solution, was refluxed for nine hours in a nitrogen atmosphere. Crystallization of the acid VIIIa from acetone gave 2.95 g. (86%) of colorless needles, m.p. 204–206°. Two recrystallizations from benzene raised the m.p. to 209–211° [lit. (9) 206.5–208.5°], $[\alpha]^{20}_{\mathrm{D}}$ −5.9° in EtOH, $\lambda_{\max}$ 269 mμ, log ε 2.75.

*Anal.* Calc'd for $C_{21}H_{28}O_3 \cdot H_2O$: C, 72.8; H, 8.7.
Found: C, 72.5; H, 8.6.
Calc'd for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6.

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[12] Although the analytical sample was chromatographed, sublimed and repeatedly recrystallized, the analysis could not be improved.

Found: C, 77.3; H, 8.5; after drying for 6 hours at 110° and 1 mm.; Wt. loss 5.5; Calc'd for 1 mole of $H_2O$, 5.2.

*α-(3β-Acetoxy-5,7,9-estratriene-17-yl)-propionic acid* (VIIIc). By boiling VIIIa in acetic anhydride for 40 minutes, in a nitrogen atmosphere, the 3-acetoxy acid (VIIIc) was obtained in a nearly quantitative yield of colorless needles, m.p. 211–215°. Two recrystallizations from benzene raised the m.p. to 215.5–217° [lit. (9) 206–211°], $[\alpha]_D^{20}$ −4.4°, $\lambda_{max}$ 269 mμ, log ε 2.60 and $\nu CS_{2max}$ 3400 $cm^{-1}$ (weak acid hydroxyl), 1754 $cm^{-1}$ (weak acid carbonyl), 1706 $cm^{-1}$ (weak carboxyl), 1739 $cm^{-1}$ and 1239 $cm^{-1}$ (acetoxy), and 810 $cm^{-1}$ (aromatic ring).

*Anal.* Calc'd for $C_{23}H_{30}O_4$: C, 74.6; H, 8.2.

Found: C, 74.3; H, 8.0.

*Methyl α-(3β-hydroxy-5,7,9,-estratriene-17-yl)-propionate* (VIIIb). Allowing a mixture of 1.0 g. of VIIId and 0.5% methanolic potassium hydroxide solution to stand at room temperature for 16 hours yielded 0.60 g. of VIIIb, m.p. 174.5–177° [lit. (9) 174–176.5°], $[\alpha]_D^{20}$-0.25°, $\lambda_{max}$ 269 mμ, log ε 2.64 and $\nu CS_{2max}$ 3600 $cm^{-1}$ (hydroxyl) 1739 $cm^{-1}$ and 1160 $cm^{-1}$ (carbomethoxy), and 810 $cm^{-1}$ (aromatic ring).

*Anal.* Calc'd for $C_{22}H_{30}O_3$: C, 77.2; H, 8.8.

Found: C, 77.1; H, 8.9.

*3β-Acetoxy-$\Delta^{5,7,9(10)}$-22-iso-19-norspirostatriene* (XIb). The decomposition of 2.5 g. of bis(3β-acetoxy-22-isospirostadiene) (X) gave 1.2 g. (99%)$^5$ of colorless needles, m.p. 138–141°. One recrystallization from ethanol yielded 1.1 g. of material, m.p. 141–143°, $[\alpha]_D^{20}$ −52°, $\lambda_{max}$ 270 mμ, log ε 2.61 and $\nu CS_{2max}$ 1736 $cm^{-1}$ and 1236 $cm^{-1}$ (acetoxy), and 811 $cm^{-1}$ (aromatic ring).

*Anal.* Calc'd for $C_{28}H_{38}O_4$: C, 76.7; H, 8.7.

Found: C, 76.7; H, 8.6.

*3β-Hydroxy-$\Delta^{5,7,9(10)}$-22-iso-19-norspirostatriene* (XIa). Alkaline hydrolysis of XIb gave the alcohol of m.p. 180–181°, $[\alpha]_D^{20}$ −55.8°, $\lambda_{max}$ 269.5, log ε 2.62, and $\nu CS_{2max}$ 3600 $cm^{-1}$ (hydroxyl) and 811 $cm^{-1}$ (aromatic ring).

*Anal.* Calc'd for $C_{26}H_{36}O_3$: C, 78.7; H, 9.1.

Found: C, 78.5; H, 8.9.

## SUMMARY

Bisergostatrienol, bis(methyl-3β-acetoxybisnorcholadienate) and bis(3β-acetoxy-22-isospirostadiene) were prepared by the photooxidation of ergosterol, methyl-3β-acetoxy-$\Delta^{5,7}$-bisnorcholadienate, and 3β-acetoxy-$\Delta^{5,7}$-22-isospirostadiene, respectively, using fluorescent lamps as the light source. The corresponding steroids containing an aromatic B-ring were obtained in excellent yields by heating the bis-compounds for a short time in diethylene glycol monoethyl ether.

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## REFERENCES

(1) OWADES, *Experientia*, **6,** 258 (1950).
(2) WINDAUS AND BORGEAUD, *Ann.*, **460,** 235 (1928).
(3) WINDAUS AND LANGER, *Ann.*, **508,** 105 (1933).
(4) WINDAUS AND DEPPE, *Ber.*, **70,** 76 (1937).
(5) SCHENK, BUCHHOLZ, AND WIESE, *Ber.*, **69,** 2696 (1936).
(6) INHOFFEN, *Naturwissenschaften*, **25,** 125 (1937); WINDAUS AND ROOSEN-RUNGE, *Ber* , **73,** 321 (1940).
(7) JACOBSEN AND NAWROCKI, *J. Am. Chem. Soc.*, **62,** 2612 (1940).
(8) (a) ROSENKRANZ AND DJERASSI, *Nature*, **166,** 104 (1950); (b) *Chemistry & Industry*, SN 2 (1951).

(9) JACOBSEN, *J. Am. Chem. Soc.*, **65**, 1789 (1943).
(10) DANNENBERG, *Abhandl. preuss. Akad. Wiss.*, **21**, 37 (1939).
(11) ORR AND THOMPSON, *J. Chem. Soc.*, 218 (1950).
(12) LAUNER AND McCAULAY, *Anal. Chem.*, **23**, 1875 (1951).
(13) MARKER, TURNER, OAKWOOD, ROHRMANN, AND ULSHAFAR, *J. Am. Chem. Soc.*, **64**, 720 (1942).
(14) KLEIDERER AND KORNFELD, *J. Org. Chem.*, **13**, 455 (1948).
(15) ROSENKRANZ, ROMO, AND BERLIN, *J. Org. Chem.*, **16**, 290 (1951).
(16) CORNFORTH AND ROBINSON, *J. Chem. Soc.*, 689 (1942).