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$\Delta^{5,7}$-STEROIDS. XIV.[1] ENOL ACETATES OF $\Delta^{4,7}$-3-KETOSTEROIDS

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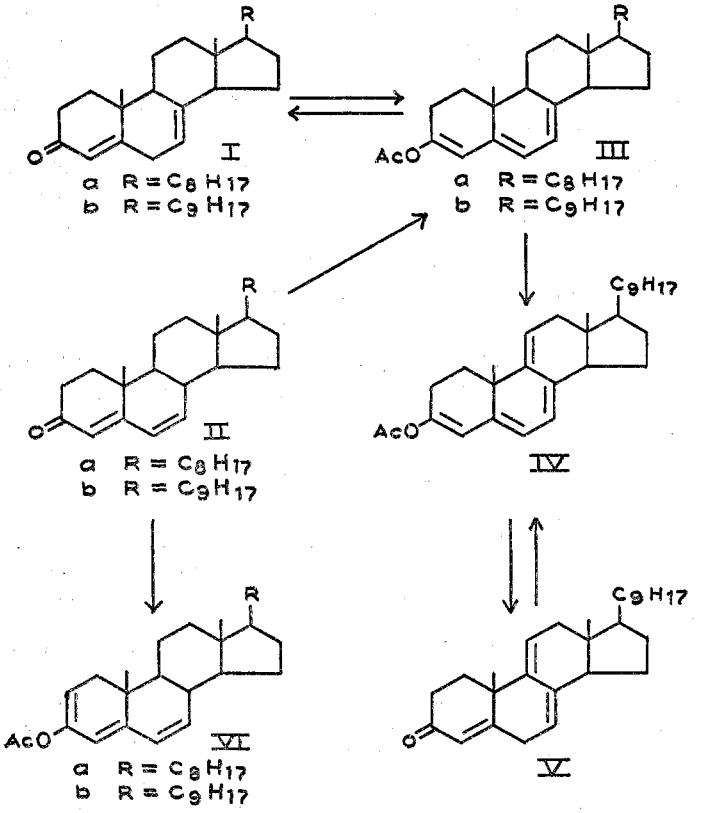
Recently, there was reported in a *Communication to the Editor* a method for the transformation of $\Delta^{4,6}$-cholestadiene-3-one (IIa) *via* $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (IIIa) to 7-dehydrocholesterol (1). This work was of interest to us since we have been investigating the preparation and transformation products of steroid enol acetates. We now wish to report on some observations pertinent to the formation of enol acetates, and to demonstrate their possible use as intermediates for the synthesis of cortical steroids.

Dauben and co-workers (1) reported the preparation of the $\Delta^{3,5,7}$-enol acetate (IIIa) from the $\Delta^{4,6}$-3-one (IIa) by the use of a mixture of acetyl chloride and acetic anhydride. Acetylation of IIa, however, with an acetic anhydride-pyridine mixture yielded the $\Delta^{2,4,6}$-enol acetate (VIa). No mention was made by these investigators of the possible formation of isomeric mixtures of enol acetates ($\Delta^{2,4,6}$- and $\Delta^{3,5,7}$-) in these preparations. We wish to point out, however, that Heilbron and co-workers (2) reported that a mixture of acetyl chloride and acetic anhydride converted $\Delta^{4,6,22}$-ergostatriene-3-one (isoergosterone) (IIb) into $\Delta^{2,4,6,22}$-ergostatetraene-3-ol acetate (VIb) in 64% yield. In order to clarify these contrasting results produced by acetyl chloride—acetic anhydride, although obtained on different, but nevertheless chemically related substances, it was desirable to prepare $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (IIIa) by another method. This was accomplished by treatment of $\Delta^{4,7}$-cholestadiene-3-one (7-dehydrocholestenone) (Ia) with acetic anhydride and pyridine to yield IIIa, the properties (m.p. 101.5–103°, $[\alpha]_D$ −147°, $\lambda_{max.}^{abs.\ alc.}$ 302.5–303, 315, and 330.5 mμ, ε 17,900; 22,600; and 16,200, respectively) of which did not agree favorably with those (m.p. 91–93°, $[\alpha]_D$ −69°, $\lambda_{max.}^{alc.}$ 305, 316, and 330 mμ, ϵ_{316} 20,000) reported for this compound by Dauben and co-workers (1). The structure assigned by us to IIIa was based on the analogous preparation of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate (IIIb) from $\Delta^{4,7,22}$-ergostatriene-3-one (Ib) by Heilbron and co-workers (2). The structure of IIIb, previously based on spectral data and method of synthesis (2), has been now further established by the following transformation. Mercuric acetate dehydrogenation (3) of IIIb afforded in 23% yield $\Delta^{3,5,7,9(11),22}$-ergostapentaene-3-ol acetate (IV), identical in all respects with IV prepared by Heilbron and co-workers (2) from $\Delta^{4,7,9(11),22}$-ergostatetraene-3-one (V) treated with acetic anhydride and pyridine. It is to be noted that the mercuric acetate dehydrogenation of a $\Delta^{3,5,7,22}$-3-ol acetate to a $\Delta^{3,5,7,9(11),22}$-3-ol acetate (IIIb→IV) is a hitherto unreported extension of this important dehydrogenation reaction.

It is our opinion that the reaction of $\Delta^{4,6}$-3-ketosteroids with acetyl chloride

[1] Paper XIII, Antonucci, Bernstein, Lenhard, Sax, and Williams, *J. Org. Chem.*, **17**, 1369 1952.

and acetic anhydride may lead to a mixture of isomeric enol acetates, namely $\Delta^{2,4,6}$- and $\Delta^{3,5,7}$-enol acetates. The successful isolation of $\Delta^{2,4,6,22}$-ergostatetraene-3-ol acetate (VIb) by Heilbron and co-workers (2) would indicate a ready separation of the two forms. (No mention was made of the presence of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate (IIIb) in the mother liquors.) Apparently, this does not pertain in the "cholesterol" series. The discrepancy in the physical properties of IIIa reported by Dauben, and by us may be explained by the assumption that the California investigators obtained a product which probably consisted of



mixed crystals. Dauben and co-workers (1) have offered as proof of structure of IIIa ultraviolet absorption spectrum, optical rotation, a positive Tortelli-Jaffé color test and the preparation of 7-dehydrocholesterol from IIIa. All of these conditions can be satisfied by assuming their product consisted of mixed crystals.

We have also concerned ourselves with the conversion of $\Delta^{3,5,7}$- and $\Delta^{3,5,7,9(11)}$-enol acetates to the respective $\Delta^{4,7}$- and $\Delta^{4,7,9(11)}$-3-one's. Previous hydrolysis studies (2, 4) of such enol acetates have led to completely conjugated systems. This may be attributed to the fact that under the conditions of hydrolysis any $\Delta^{4,7}$-3-one or $\Delta^{4,7,9(11)}$-3-one formed would rearrange into a $\Delta^{4,6}$-3-one or a $\Delta^{4,6,8}$-3-one respectively (2, 5). Therefore, it was reasoned that only mild hydrolysis

conditions would afford a $\Delta^{4,7}$-3-one and a $\Delta^{4,7,9(11)}$-3-one from the corresponding enol acetates. Ester exchange conditions with sodium methoxide in methanol-benzene served this purpose. Thus, treatment of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate (IIIb) gave $\Delta^{4,7,22}$-ergostatriene-3-one (Ib) (51% yield). Similar hydrolysis of $\Delta^{3,5,7,9(11),22}$-ergostapentaene-3-ol acetate (IV) yielded $\Delta^{4,7,9(11),22}$-ergostatetraene-3-one (V) (*ca.* 22% yield). Hydrolysis of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (IIIa) under these conditions produced only a syrup, but the presence of the $\Delta^{4,7}$-3-one moiety was demonstrated by the formation of the 2,4-dinitrophenylhydrazone, identical with an authentic sample prepared from $\Delta^{4,7}$-cholestadiene-3-one (Ia) ($\lambda_{max.}$ 255–256, 385–388 mμ). In this connection, the 2,4-dinitrophenylhydrazone of $\Delta^{4,7,22}$-ergostatriene-3-one was prepared and exhibited ultraviolet absorption maxima at 256–257 and 387 mμ. The ultraviolet absorption maxima of the 2,4-dinitrophenylhydrazones of $\Delta^{4,6}$-cholestadiene-3-one and $\Delta^{4,6,22}$-ergostatriene-3-one are at 309 and 402–404 mμ (6), and 308 and 400 mμ (7), respectively. Thus, it has been demonstrated that no isomerization of the Δ^{7}-double bond to the Δ^{6}-position occurred in the hydrolysis reaction or in the formation of the 2,4-dinitrophenylhydrazones.

These experiments establish a novel method for the preparation of $\Delta^{4,7,9(11)}$-3-one steroids (I→III→IV→V, or II$\xrightarrow{?}$III→etc.).

In deference to Dauben and co-workers, we have set aside an investigation on the sodium borohydride reduction of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (IIIa) to afford 7-dehydrocholesterol until a detailed report by them is forthcoming.

EXPERIMENTAL

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 in absolute alcohol, unless otherwise stated.

Melting points. All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

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.

$\Delta^{3,5,7}$-Cholestadiene-3-ol acetate (IIIa). A mixture of 1.4 g. of $\Delta^{4,7}$-cholestadiene-3-ol (Ia)[2] [m.p. 86–87°, $[\alpha]_D^{25}$ +32.9° (27.3 mg., α_D +0.45°), λ_{max} 238–239 mμ, ϵ 16,400], 10 ml. of acetic anhydride, and 10 ml. of pyridine was refluxed for 3 hours. The cooled reaction mixture was poured into ice-water, and the solid obtained was collected and washed with a copious amount of water. The crude product was recrystallized five times from acetone-methanol to constant m.p., optical rotation, and ultraviolet absorption spectrum, m.p. 101.5–103°, λ_{max} 302.5–303, 315, and 330.5 mμ, ϵ 17,900; 22,600; and 16,200, respectively, $[\alpha]_D^{25}$ −147° (11.7 mg., α_D −0.86°).

Anal. Calc'd for $C_{29}H_{44}O_2$ (424.64): C, 82.02; H, 10.44.

Found: C, 81.72; H, 10.43.

$\Delta^{3,5,7,22}$-Ergostatetraene-3-ol acetate (IIIb). This compound was prepared in the manner described by Heilbron and co-workers (2).[3] Two recrystallizations from alcohol-benzene gave colorless plates, m.p. 149–151°; λ_{max} 302, 315, and 331 mμ; ϵ 19,350; 23,950; and 16,950, respectively; $[\alpha]_D^{27}$ −144° (13.4 mg., α_D −0.97°).

$\Delta^{3,5,7,9(11),22}$-Ergostapentaene-3-ol acetate (IV).[4] To a solution of 1.35 g. of $\Delta^{3,5,7,22}$-

[2] (a) Windaus and Kaufmann, *Ann.*, **542**, 218 (1939); m.p. 88°, λ_{max}^{ether} 231 mμ (est.), $[\alpha]_D^{17}$ +34° (chloroform); (b) Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, 1453 (1951); m.p. 86–88°, $\lambda_{max}^{abs.alc.}$ 238 mμ, ϵ 15,500.

ergostatetraene-3-ol acetate (IIIb) in 75 ml. of alcohol was added 4.05 g. of mercuric acetate dissolved in 75 ml. of alcohol and 1.6 ml. of acetic acid. The resultant mixture was refluxed for 2 hours under nitrogen, filtered and the filtrate concentrated to a small volume *in vacuo*. Water and carbon tetrachloride were added, and the aqueous layer was extracted three times with carbon tetrachloride. The combined extracts were washed with dilute acetic acid, sodium bicarbonate, and water, dried over magnesium sulfate, treated with Norit and filtered. Removal of the solvent *in vacuo* resulted in a yellow oil, which was dissolved in acetone and treated with water to give a yellow solid. Successive recrystallizations from alcohol, acetone-alcohol, and ethyl acetate-methanol yielded 0.19 g., m.p. 160–161°, λ_{max} 339, 355, and 375 mμ; ϵ 12,700; 16,200; and 12,100, respectively, $[\alpha]_D^{27}$ −230° (11.3 mg., α_D −1.30°).

Anal. Calc'd for $C_{30}H_{42}O_2$ (434.64): C, 82.90; H, 9.74.
Found: C, 82.49; H, 9.80.

In another run using 2.5 g. of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate (IIIb) and 7.5 g. of mercuric acetate, a yield of 0.57 g. (23%) of IV, m.p. 158–159.5°, was obtained.

Hydrolysis of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate (IIIb). To a solution of 0.50 g. of the enol acetate (IIIb) in 15 ml. of methanol and 10 ml. of benzene placed under nitrogen was added 80 mg. of sodium methoxide in 10 ml. of methanol. After standing at room temperature for 20 minutes, the resultant dark red solution was acidified with a few drops of acetic acid, and the solvents were removed *in vacuo*. Water was added to the residue, and the yellow solid was filtered. Four recrystallizations from acetone yielded 0.23 g. (51% yield) of $\Delta^{4,7,22}$-ergostatriene-3-one (Ia),[5] m.p. 132–133°, λ_{max} 238–239 mμ, ϵ 15,100, $[\alpha]_D^{25}$ −11.8° (17.0 mg., α_D −0.10°).

Hydrolysis of $\Delta^{3,5,7,9(11),22}$-ergostapentaene-3-ol acetate (IV). A solution of 0.55 g. of the enol acetate (IV) in a mixture of 22 ml. of methanol and 15 ml. of benzene was placed in a nitrogen atmosphere, and 0.10 g. of sodium methoxide in 10 ml. of methanol was added. After standing at room temperature for 20 minutes, one ml. of acetic acid was added and the solvents were removed *in vacuo*. Water was added to the residue, and the oil was extracted three times with ether. The combined organic layers were washed with dilute sodium bicarbonate, treated with Norit, and dried over magnesium sulfate. Removal of the solvent gave a yellow solid which was recrystallized three times from acetone at the temperature of a Dry Ice-acetone bath yielding 56 mg. of V,[6] m.p. 136–138°, λ_{max} 235.5–236.5 (inflection), 242, and 249.5–250.5 (inflection) mμ; ϵ 26,600; 28,600; and 24,000, respectively; $[\alpha]_D^{25}$ +190° (9.8 mg., α_D +0.93°). Additional fractions of 15 mg., m.p. 135–136.5° and 40 mg., m.p. 133.5–135° were recovered from the mother liquors; *ca.* 22% yield.

Anal. Calc'd for $C_{28}H_{40}O$ (392.60): C, 85.65; H, 10.27.
Found: C, 85.84; H, 10.50.

Hydrolysis of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (IIIa). A solution of 180 mg. of IIIa in 5 ml. of methanol and 3 ml. of benzene was put under a nitrogen atmosphere, and 30 mg. of sodium methoxide in methanol was added. After standing at room temperature for 20 minutes, the solution was acidified with 3 drops of acetic acid, and the solvents were removed *in vacuo*. Acetone was added, and the solution was filtered. The filtrate was concentrated, but the resultant syrup could not be crystallized.

2,4-Dinitrophenylhydrazone of $\Delta^{4,7}$-cholestadiene-3-one. All 2,4-dinitrophenylhydrazones

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[3] Heilbron and co-workers (2); m.p. 146°; $\lambda_{max}^{alc.}$ 301, 316.5, and 331 mμ; $\epsilon_{316.5}$ 21,400; $[\alpha]_D^{20}$ −143.5° (chloroform).

[4] Heilbron and co-workers (2); m.p. 161°; $\lambda_{max}^{alc.}$ 339, 356, and 375 mμ; ϵ_{356} 17,400; $[\alpha]_D^{20}$ −232.5° (chloroform).

[5] (a) Heilbron and co-workers (2); m.p. 132°; $\lambda_{max}^{alc.}$ 230 and 320 mμ; ϵ 20,000 and 40, respectively, $[\alpha]_D^{25}$ −0.8° (chloroform); (b) Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, **16**, 1453 (1951); m.p. 133–135°; $\lambda_{max}^{abs.alc.}$ 239 mμ, ϵ 15,100.

[6] Heilbron and co-workers (2); m.p. 140–142°; $\lambda_{max}^{alc.}$ 242 mμ; ϵ 31,700; $[\alpha]_D^{20}$ +190° (chloroform).

were prepared by the method of Djerassi (8). *A*. A solution of 160 mg. of the above syrup in 1.5 ml. of acetic acid was warmed on a steam-bath and 92 mg. of 2,4-dinitrophenylhydrazine was added. After warming on the steam-bath for 10 minutes, the mixture was cooled, filtered, and the residue was washed with ethanol. Three recrystallizations from chloroform-alcohol gave 160 mg., m.p. 211°d, $\lambda_{max}^{1\%cs7}$ 255–256 and 383–389 mμ, ε 18,650 and 30,600, respectively.

B. A solution of $\Delta^{4,7}$-cholestadiene-3-one (Ia) in 2 ml. of acetic acid was warmed on a steam-bath, treated with 126 mg. of 2,4-dinitrophenylhydrazine, and then was heated an additional 10 minutes. After cooling, the crystals were filtered and washed with ethanol. Three recrystallizations from chloroform-ethanol gave 260 mg., m.p. 210–210.5°d, $\lambda_{max}^{1\%cs7}$ 255–256 and 385–387 mμ, ε 19,100 and 31,100, respectively.

Anal. Calc'd for $C_{33}H_{46}N_4O_4$ (562.73): C, 70.43; H, 8.24; N, 9.96.
Found: C, 70.64; H, 8.32; N, 9.84.

2,4-Dinitrophenylhydrazone of $\Delta^{4,7,22}$*-ergostatriene-3-one*. A solution of 800 mg. of Ib in 10 ml. of acetic acid was treated with 400 mg. of 2,4-dinitrophenylhydrazine in the usual manner. Three recrystallizations from chloroform-ethanol gave 0.55 of metallic orange plates, m.p. 230.5–232°, $\lambda_{max}^{1\%cs7}$ 256–257 and 387 mμ, ε 18,000 and 29,700, respectively, $[\alpha]_{6907}^{27}$ −58.8° (22.1 mg., α_{6907} −0.65°).

Anal. Calc'd for $C_{34}H_{46}N_4O_4$ (574.74): C, 71.05; H, 8.07; N, 9.75.
Found: C, 70.82; H, 8.12; N, 9.95.

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SUMMARY

1. $\Delta^{4,7}$-Cholestadiene-3-one when treated with acetic anhydride and pyridine yielded $\Delta^{3,5,7}$-cholestatriene-3-ol acetate, the properties of which did not agree with those reported for this compound by Dauben and co-workers.

2. Treatment of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate with mercuric acetate gave $\Delta^{3,5,7,9(11),22}$-ergostapentaene-3-ol acetate.

3. Hydrolysis of $\Delta^{3,5,7,22}$-ergostatetraene-3-ol acetate and $\Delta^{3,5,7,9(11),22}$-ergostapentaene-3-ol acetate with sodium methoxide in methanol-benzene gave $\Delta^{4,7,22}$-ergostatriene-3-one and $\Delta^{4,7,9(11),22}$-ergostatetraene-3-one, respectively.

4. Treatment of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate with sodium methoxide in methanol-benzene yielded a syrup which was identified as $\Delta^{4,7}$-cholestadiene-3-one by its 2,4-dinitrophenylhydrazone.

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[7] Solvent was 1% chloroform-absolute alcohol; the substance was dissolved in 1 ml. of chloroform and rapidly diluted to 100 ml. with absolute alcohol.