Hydroxylation of $\Delta^5$-Steroids with N-Bromosuccinimide to 5$\alpha$,6$\beta$-Diols

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The reaction of N-bromosuccinimide with $\Delta^5$-steroids such as, diosgenin, cholesterol, stigmasterol and dehydroisoandrosterone were studied. It was found that NBS in a solvent mixture of acetone, water and acetic acid (8:1:0.1) oxidizes the olefinic bond of all the previous steroidal compounds to the corresponding transglycollic, 5$\alpha$,6$\beta$-di-hydroxylic products in about 60% yield at room temperature.

Since the Corpus luteum hormone, progesterone was first isolated during the 1930s, considerable interest has been attached to the synthesis of steroidal hormone analogs. Amongst the more interesting variations are those having the 6-methyl group and 6,7-unsaturation linkage for their high progestational activity [1].

Introduction of the 6-methyl substituent at the 6-position was affected by epoxidation of one of the early intermediates from diosgenin route, pregnenolone with alkaline hydrogen peroxide [2]. Petrow and his collaborators [3] have described several schemes that go back to diosgenin as the starting material. They reported a method for converting diosgenin into 3$\beta$-acetoxy-6-methyl-25D-spirost-5-ene via (i) the 5$\alpha$,6$\alpha$-epoxide (ii) the 6$\beta$-hydroxy-3,5-cyclo-25D-spirost-5-ene. Petrow also reported [4] the transformation of diosgenin to 6-methyl-25D-spirosta-3,6-diene-3-one employing the 3$\beta$-acetoxy-5$\alpha$-hydroxy-25D-spirostan-6-one as starting material. He obtained the 6-keto by first epoxidation of diosgenin followed by treatment of the epoxide by periodic acid in aqueous acetone and then oxidation of the triol.

In the present work we were seeking a more convenient method for preparation of the 5$\alpha$-hydroxy-6-ketone derivative of diosgenin (1c) which is important as a starting material for synthesis of the 6-methyl-6,7-dehydro progesterone [4]. Fieser et al. reported [5] that oxidation of cholesterol with N-bromosuccinimide and acetic acid in aqueous acetone afforded 5$\alpha$-cholestan-3$\beta$,5-diol-6-one (2e) in a moderate yield. We thought to extend this reaction to diosgenin hoping thereby to develop a convenient route for the preparation of the desired 5$\alpha$-hydroxy-6-keto derivative. When we used NBS for the oxidation of diosgenin under the same conditions reported by Fieser [5], we obtained a triol (1a), C$_{27}$H$_{44}$O$_5$, m. p. 281–283 °C. Its structure was established on the bases of spectral data (IR and MS) and by chemical conversion to 5$\alpha$-25D-spirosta-3$\beta$,5-diol-6-one (1c) with NBS in aqueous dioxane which is known to be specific for oxidation of 6$\beta$-hydroxy steroids [6]. Another proof for the triol structure (1a) was arrived at by its oxidation with Jone's reagent [7] to the diketo derivative, 5$\alpha$,25D-spirostane-5-ol-3,6-dione (1e). This accounts for the presence of the two secondary hydroxyl groups at C-3 and C-6 positions. The tertiary hydroxyl group attached to C-5 was eliminated in a dehydration process when the diketonic derivative (1e) was shaken in methanol containing 15% aqueous potassium hydroxide for 4 h at room temperature and 25D-spirost-4-ene-3,6-dione (1f) was obtained as shown from its UV spectrum. The previous transformation reactions are illustrated in the following Scheme:

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From the foregoing data, it is clear that diosgenin when treated with NBS in a solvent mixture of acetone, water and acetic acid (8:1:0.1), the 5:6-double bond is oxidised to a trans glycollic system, 5α,6β-diol.

The generality of the above mentioned method as a new way for trans hydroxylation of Δ5 bond in steroids was demonstrated by its application for the preparation of 5α-cholestane-3β,5,6β-triol (2a), 5α-stigmastane-3β,5,6β-triol (3a) and 5α-androstane-3β,5,6β-triol-17-one (4a) from cholesterol, stigmasterol and dehydroisoandrosterone, respectively. The structures of all the formed triols were proved by their transformation to the corresponding 4-en-3,6-dione products.

As a result of this work, two new compounds were prepared and reported here for the first time which are 5α,25D-spirostane-3β,5,6β-triol (1a) and 5α-stigmastane-3β,5-diol-6-one (3c).

Similar results were reported by Ueno [8] and Morita [9] who independently found that oxidation of cholesterol by N,N-dibromobenzene sulfonamide and isocyanor bromide gave 5α-cholestane-3β,5,6β-triol.

**Experimental**

Melting points were determined using a Büch 510 apparatus. IR spectra were recorded using Beckmann spectrophotometer 4220. Mass spectral data were obtained with mass spectrophotometer MAT 112. Ultraviolet spectra were recorded on CE 595 double beam digital ultraviolet spectrophotometer.

**5α,25D-Spirostane-3β,5,6β-triol (1a)**

A suspension of diosgenin (1), (5 g, 0.012 mole) in acetone (200 ml) and water (25 ml) was treated with NBS (2.68 g, 0.15 mole, 1.25 equiv) and acetic acid (2.5 ml) and was shaken occasionally at room temp. In the course of 45 min the mixture...
became yellow then orange and finally colorless where all the solid material disappeared in the solution. The reaction mixture was left overnight, diluted with water, extracted with ether and processed as usual to give an amorphous solid (5.6 g, 65% yield). Crystallisation from MeOH gave product 1a as shiny colorless plates, m.p. 282 to 284 °C. Reported [10] m.p. 281-283 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3400 (broad, OH), 1700, 970, 920, 890 and 865 (spirostane side-chain). MS: \( m/e(\%) \): 532 (15) (M\(^+\), C\(_{31}\)H\(_{48}\)O\(_7\)), 514 (5) (M\(^+\)-H\(_2\)O), 472 (20) (M\(^+\)-AcOH), 412 (40) (M\(^+\)-2AcOH).

5a,25D-Spirostan-3\(\beta\),5,6\(\beta\)-triol-3,6-diacetate (2b)

This derivative was obtained from product 2c by mild acetylation in 80% yield, m.p. 233-235 °C (from acetate), reported [5] m.p. 230 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3400 (OH) and 1710 (>C=O.). MS: \( m/e(\%) \): 448 (20) (M\(^+\), C\(_{27}\)H\(_{44}\)O\(_5\)), 430 (5) (M\(^+\)-H\(_2\)O), 394 (5) (M\(^+\)-3H\(_2\)O) and 139 (100) (due to ring F ions [11]).

5a,25D-Spirostan-3\(\beta\),5,6\(\beta\)-diol-3,6-dione (1e)

A solution of compound 1a (0.5 g, 0.001 mole) in pure acetone (100 ml) was cooled to 0 °C, treated with 2.3 ml of Jones’ reagent [7] and processed as usual to give the dione material (1e) in 96% yield (0.48 g). Crystallization from CHCl\(_3\)/MeOH gave colourless needles, m.p. 270-272 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3410 (broad, OH), 1700, 970, 920, 890 and 865 (spirostane side-chain). MS: \( m/e(\%) \): 446 (82) (M\(^+\), C\(_{27}\)H\(_{42}\)O\(_5\)), 428 (100) (M\(^+\)-H\(_2\)O) and 410 (70) (M\(^+\)-2H\(_2\)O). Analysis: C\(_{27}\)H\(_{40}\)O\(_5\), Found C 69.92 H 9.02, Calcd C 71.75 H 9.68.

5a-Cholestane-3\(\beta\),5,6\(\beta\)-triol (2a)

It was prepared in the same manner as with the triol (1a) in 80% yield, m.p. 235-237 °C (from acetone), reported [13] m.p. 237-239 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3395 (broad, OH). UV: \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.04), reported [10] \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.03). IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 1690, 1710, 970, 920, 890 and 865. MS: \( m/e(\%) \): 300 (M\(^+\), C\(_{32}\)H\(_{48}\)O\(_4\)).

5a-Cholestane-3\(\beta\),5,6\(\beta\)-triol-3,6-diacetate (2b)

This derivative was prepared from compound 2a in 90% yield, m.p. 160-163 °C (from acetone), reported [13] m.p. 167 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3395 (broad, OH) and 1730, 1250 (acetate groups). Analysis: C\(_{31}\)H\(_{52}\)O\(_5\), Found C 77.14 H 11.42, Calcd C 77.21 H 11.24.

5a-Cholestane-3\(\beta\),5,6\(\beta\)-triol-3,6-dione (1f)

To the dione product (1e) (0.5 g, 0.0011 mole) in MeOH (150 ml), was added KOH (7.5 ml from 15% aqueous solution) and the reaction mixture was left on a shaker for 4 h. After concentrating under vacuum (to 50 ml) water was added and the precipitated material was filtered, washed with acetone, dried to yield the monoacetate derivative (1d) as colorless needles, m.p. 198-200 °C. Reported [10] for 25D-spirostan-4-ene-3,6-dione, m.p. 194-195 °C. UV: \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.04), reported [10] \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.03). IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 1690, 1710, 970, 920, 890 and 865. MS: \( m/e(\%) \): 300 (M\(^+\), C\(_{32}\)H\(_{48}\)O\(_4\)).

5a-Cholestane-3\(\beta\),5,6\(\beta\)-triol-3,6-diacetate (2c)

This derivative was obtained from product 2c by mild acetylation in 80% yield, m.p. 233-235 °C (from acetone), reported [5] m.p. 230 °C. IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 3410 (broad, OH). UV: \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.04), reported [10] \( \lambda_{\text{max}} = 253 \text{ nm} \) (log \( e \) = 4.03). IR: \( \nu_{\text{max}} \text{ cm}^{-1} \): 1690, 1710, 970, 920, 890 and 865. MS: \( m/e(\%) \): 300 (M\(^+\), C\(_{32}\)H\(_{48}\)O\(_4\)).
cm\(^{-1}\): 3400 (OH), 1730, 1270 (acetate) and 1710 (C=C). MS: m/e (%): 3575, 3450, 3370 (OH) and 1730 (acetate (C=C-C=O)). UV: \(\lambda_{\text{max}}\) 250 nm (EtOH), log \(\varepsilon\) 4.25. MS: m/e (%): 446 (1) (M+, C\(_{29}\)H\(_{46}\)O\(_4\)), 302 (53) (M+-H\(_2\)O), 286 (32) (M+-2H\(_2\)O), 271 (12) (M+-2H\(_2\)O + CH\(_3\)O) and 269 (M+-3H\(_2\)O).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\alpha\)-dienol-17-one (3f)

Dehydration of the diketonic compound (3e) by NaOH gave product 3f in 80% yield, m.p. 180 to 182 °C (acetone). Reported [16] m.p. 184-185 °C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3430 (OH), 1740 (acetate (C=C-C=O)). UV: \(\lambda_{\text{max}}\) 250 nm (EtOH), log \(\varepsilon\) 4.18. MS: m/e (%): 320 (22) (M+, C\(_{19}\)H\(_{28}\)O\(_4\)), 304 (5) (M+-H\(_2\)O), 286 (32) (M+-2H\(_2\)O), 271 (12) (M+-2H\(_2\)O + CH\(_3\)O) and 268 (M+-3H\(_2\)O).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\alpha\),6\(\beta\)-triol-17-one (4a)

It was prepared from androst-5-ene-3\(\beta\)-ol-17-one (4) in 40% yield, m.p. 270-272 °C (CHCl\(_3\)/MeOH). IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3575, 3450, 3370 (OH) and 1730 (five-membered >C=0). MS: m/e (%): 322 (2) (M+, C\(_{19}\)H\(_{29}\)O\(_4\)), 304 (5) (M+-H\(_2\)O), 286 (32) (M+-2H\(_2\)O), 271 (12) (M+-2H\(_2\)O + CH\(_3\)O) and 268 (M+-3H\(_2\)O).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\beta\),6\(\beta\)-triol-3,6-diacetate (4b)

Mild acetylation of the triol (4a) gave the diacetate derivative (4b) in 90% yield, m.p. 180 to 182 °C (acetone). Reported [17] m.p. 184-185 °C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3430 (OH), 1740 (acetate (C=C-O)), 1710, 1270 and 1240 (acetate groups). UV: \(\lambda_{\text{max}}\) 250 nm (EtOH), log \(\varepsilon\) 4.18. MS: m/e (%): 426 (M+, C\(_{29}\)H\(_{46}\)O\(_2\)).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\beta\),6\(\beta\)-triol-3,6-diacetate (4c)

It was prepared from androst-5-ene-3\(\beta\)-ol-17-one (4) in 40% yield, m.p. 270-272 °C (CHCl\(_3\)/MeOH). IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3575, 3450, 3370 (OH) and 1730 (five-membered >C=0). MS: m/e (%): 322 (2) (M+, C\(_{19}\)H\(_{29}\)O\(_4\)), 304 (5) (M+-H\(_2\)O), 286 (32) (M+-2H\(_2\)O), 271 (12) (M+-2H\(_2\)O + CH\(_3\)O) and 268 (M+-3H\(_2\)O).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\beta\),6\(\beta\)-triol-3,6-diacetate (4d)

Mild acetylation of the triol (4a) gave the diacetate derivative (4d) in 90% yield, m.p. 180 to 182 °C (acetone). Reported [17] m.p. 184-185 °C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3430 (OH), 1740 (acetate (C=C-O)), 1710, 1270 and 1240 (acetate groups). UV: \(\lambda_{\text{max}}\) 250 nm (EtOH), log \(\varepsilon\) 4.18. MS: m/e (%): 426 (M+, C\(_{29}\)H\(_{46}\)O\(_2\)).

5\(\alpha\)-Stigmastane-3\(\beta\),5\(\beta\),6\(\beta\)-triol-3,6-diacetate (4e)

Mild acetylation of the triol (4a) gave the diacetate derivative (4d) in 90% yield, m.p. 190-192 °C (acetone). Reported [17] m.p. 190-192 °C (acetone). IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3420 (OH), 1710 (acetate (C=C-O)) and 1740, 1270 (acetate). MS: m/e (%): 362 (8) (M+, C\(_{29}\)H\(_{30}\)O\(_4\)), 302 (53) (M+-AcOH) and 269 (M+-AcOH + H\(_2\)O + CH\(_3\)).
(>C=O). MS: m/e (%): 318 (5) M+, C₁₉H₂₆O₄ and 300 (1) (M+-H₂O).

Analysis: C₁₉H₂₆O₄
   Calcd  C 71.69  H 8.17,
   Found  C 72.00  H 8.78,

Androst-4-ene-3,6,17-trione (4f)

It was prepared by dehydration of product 4e in 80% yield, m.p. 222–224 °C. Reported [17] m.p. 223–225 °C. IR ν₁₅₂₅ cm⁻¹: 1740 (>C=O), 1670 and 1600 (–C=C–CO). UV: λₘ₅₅ 250 nm (EtOH), log ε 4.22. MS: m/e (%): 300 (30) (M+, C₁₉H₂₄O₃).