Keto-Steroids, I
Conversion of Diosgenin to 6β-Methylpregn-4-ene-6α,20-diol-3,16-dione
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Diosgenin, 5α-(25R)-Spirostane-3β,5,6β-triol, 5α-Pregnane-3β,5β,6β,16β,20α-pentol

The reaction of diosgenin (1) with hydrogen peroxide/formic acid was investigated. As a result of this work, 5α-(25R)-spirostane-3β,5,6β-triol (2) was prepared in 79% yield and 5α-pregnane-3β,5,6β,16β,20α-pentol (3) in 80% yield. The pentol (3) was oxidised to 5α-pregnane-3β,5,16β,20α-tetrol-6-one (5) without forming its 16β,20α-isopropylidenedi-oxoy derivative (4). Reaction of product 5 with CH₃MgI to give 6-methylpregnane deriva-
tive was unsuccessful. Therefore, product 7 was oxidatively degraded by H₂O₂/HCOOH to the 16-keto pregnane derivative (13) and its structure was proved through its transforma-
tion to 6β-methylpregn-4-ene-6α,20α-diol-3,16-dione (15).

The importance of the steroid sapogenin, diosgenin as a main precursor in the steroid hormone industry is well known. Diosgenin is converted by Marker degradation [1] to all types of adrenocortical and sex hormones through its transformation to the intermediate compound, pregn-5,16-diene-3β-ol-20-one. It is reported [2] that the introduction of a methyl group at position six in pregnane compounds increases their progesterational activity, this stimu-
lated us to seek a feasible and superior method for the preparation of 6-keto diosgenin derivatives which could be converted to the intermediate 6-methyl pregnane compounds. This work deals with the results obtained on oxidation and side-
chain degradation of diosgenin with performic acid, in addition to some other reactions.

In 1954 Romo and his collaborators reported [3] that treatment of diosgenin in tetrahydrofuran with performic acid yielded 5α-spirostan-3β,5,6β-triol (2) in 79% yield. When we repeated this method exactly in the same manner [3] on diosgenin, an additional product, C₂₇H₄₀O₈ was obtained in 20% yield and identified as 5α-pregnane-3β,5,6β,16β,20α-pentol, POL (3) beside the expected triol (2). By studying the difference in ratio of formic acid and hydrogen peroxide to diosgenin and varying the time of reaction, we found that for 0.012 mole diosgenin dissolved in tetrahydrofuran when treated with formic acid/hydrogen peroxide (1.07/0.09 mole) and shaken for 6 h at room temperature resulted in the formation of the triol (2) only in 98% yield, but when the quantity of formic acid/hydro-
gen peroxide was double (2.14/0.18 mole) and increasing the time of reaction to 48 h resulted in the formation of pentol (3) in 97% yield. This result concerning the selective oxidation of diosgenin to give either the triol (2) or the pentol POL (3) is feasible and superior to the previous reported meth-
ods for their preparation [3–5]. The compound POL was first prepared by Miki et al. [4] from dios-
genin in 70% yield using performic acid and known to exhibit pharmacological activities since it blocks the electrolyte activity of aldosterone [4]. Selective oxidation of the secondary hydroxyl group (β-axial) at C-6 in POL (3) to give the corresponding 6-keto product was carried out by Miki et al. [4] by pro-
tecting the two hydroxyl groups at C-20 and C-16 via the formation of the 16β,20α-isopropylidene-
dioxy of POL (4), followed by its oxidation with N-bromosuccinimide in aqueous methanol/ether mixture to yield the 3β,5-dihydroxy-16β,20α-isopropylidenedioxy-5α-pregnan-6-one which on treatment with aqueous acetic acid gave 6-keto pentol (5). We found that this last 6-keto product could be formed directly in one step (70% yield) by allowing POL to react with N-bromosuccinimide in 1:2 molar ratio, in a mixture of dioxane/water (30:70).

Our attempt to introduce a methyl group at position six of the 6-keto product (5), its unreported triacetate C₂₇H₄₈O₈ (6) or its isopropylidenedioxy derivative via the reaction with methyl magnesium iodide was unsuccessful. Therefore, 5α-(25R)-spirol-

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stane-3β,5-diol-6-one (7) was allowed to react with methyl magnesium iodide to yield the known compound 6β-methyl-5α-(25R)-spirostane-3β,5,6α-triol (8), cf. Scheme, reported previously by Petrow et al. [5] through the action of perbenzoic acid on diosgenin acetate to give 5α,6α-epoxide followed by treatment with periodic acid to form 5α,6β-diol-3-acetate. This product was transformed to 6-keto with Sarett oxidation and finally with methyl magnesium iodide then dilute sulphuric acid to yield the desired product (8).

\[
\begin{align*}
\text{Ac} & \quad \text{CH}_3 \\
\text{Methylene} & \quad \text{OH} \\
\text{OAc} & \quad \text{CH}_3 \\
\end{align*}
\]

Oxidation of 8 with Jone's reagent yielded the keto-spirostane compound (9) which on treatment with methanolic potassium hydroxide solution resulted in the selective elimination of the tertiary hydroxylic group at C-5 and formation of the \(\alpha,\beta\)-unsaturated ketone (10).

Compound 8 was acetylated to give the monoacetate derivative (11) which on treatment with thionyl chloride in pyridine (Darzen's method) eliminated both the tertiary hydroxyl groups at C-5 and C-6 and formed the diene (12).

Degradation of the spirostane product (8) with performic acid resulted in the formation of a pregnane compound (13), \(\text{C}_{22}\text{H}_{36}\text{O}_5\), m.p. 272–275 °C, \(\text{M}^+, m/e 380\). Its IR spectrum showed a strong band at 1750 cm\(^{-1}\) with no indication of the four absorption bands characteristic of the spiroketal sidechain [6]. To be certain that the band at 1750 cm\(^{-1}\) is not due to the H–COO – as a result of the formation of formate ester, the degradative product was refluxed with alcoholic potassium hydroxide for six hrs where the starting material was recovered unchanged, based on this fact it was drawn that this IR band at 1750 cm\(^{-1}\) is mostly due to the presence of a ketonic group at C-16. This product showed no absorption in the UV region indicating the absence of any chromophore.

In the product isolated from this degradation process (13), there are three possibilities for the location of the carbonyl group which might be at C-3 or C-16 or C-20. Position three is excluded because refluxing this compound with alcoholic potassium hydroxide did not yield the 4-ene-3-one due to the facile elimination of the 5α–OH group in the presence of the 3-keto group (no absorption in the UV region). The presence of the keto group at position 20 is also excluded based on H\(^1\)NMR (no signal appeared around \(\delta 2.0\) for CH\(_3\)-CO–). Based on the previous spectral data [7] and that of the following reactions, this degraded compound was considered to be 6β-methyl-5α-pregnane-3β,5,6α, 20α-tetrol-16-one (13). Oxidation of this product with Jone's reagent resulted in the formation of the diketone product (14) which on its treatment with alcoholic potassium hydroxide selectively eliminated the C-5 tertiary hydroxyl group and not the C-6 one to form product (15).

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. NMR spectra were taken at 60 MHz with a Varian T-60 A instrument in CDCl\(_3\) using trimethyl silane as the internal standard. Ultraviolet spectra were recorded on CE 595 double beam digital Ultraviolet spectrophotometer.
5α-(25R)-Spirostane-3β,5,6β-triol (2)

Diosgenin (1) (5 g, 0.012 mole) in THF (65 ml) and HCOOH (90%, 45 ml, 1.07 mole) were heated in a steam-bath for 15 min, then cooled to room temperature. H₂O₂ (30% v/v, 10 ml, 0.09 mole) was added, followed by shaking for 6 h, after which cold H₂O (100 ml) was added, the formate ppt. formed was filtered, dissolved in MeOH 125 ml and KOH (50%, 6.5 ml), refluxed for 30 min, cooled, acidified with AcOH and H₂O₂ (200 ml) was added. The formed product 2 was filtered (5.3 g, 98% yield) which was crystallized from MeOH to give colourless plates, m.p. 282–284 °C (Me₂CO). IR r™ cm⁻¹: 3570 (OH), 1710, 1240 bands for (>C=C<), 960, 920, 880 and 860 (spirostane side-chain).

Degradation of diosgenin (1) to 5α-pregnane-3β,5,6β,16β,20α-pentol (3)

Diosgenin (1), (5 g, 0.012 mole) in THF (65 ml) and HCOOH (90%, 90 ml, 2.14 mole) was heated on a steam-bath for 15 min, cooled, treated with H₂O₂ (30% v/v, 20 ml, 0.18 mole) and stirred for 48 h. Water as then added (100 ml), after the reaction with CH₃Cl and evaporation, the formate of compound 3 was obtained, dissolved in MeOH (125 ml) and KOH (50%, 6.5 ml), and the solution was refluxed for 30 min. cooled. The substance was extracted with CH₃Cl after acidification with AcOH and H₂O₂. Evaporation of the CH₃Cl extract gave 3.5 g of the same crude compound. Crystallization from MeOH gave colourless plates, m.p. 250–252 °C, reported [4] 252 °C. MS: m/e (%): 342(5) (M⁺, C₂H₆O₄); 262(10) (M⁺-2O); 239(4) (M⁺-3O); 125(10) (M⁺-3H₂O) and 139(100) (ring F ions [9]).

Oxidation of 5α-pregnane-3β,5,6β,16β,20α-pentol (3) with NBS

Compound 3 (1 g, 0.0026 mole) in a mixture of dioxane/water (30:70) was treated with NBS (0.96g, 0.0054 mole), shocked for 30 min, then sodium metabisulphate soln (10%) was added, followed by extraction with CH₂Cl₂ and then H₂O. Evaporation of the CH₂Cl₂ extract gave one g of 3. The aqueous layer after concentration gave 3.5 g of the same crude compound.

Reaction of 16β,20α-isopropylideneoxy-5α-pregnane-3β,5,6β-triol (4) with NBS

A solution of 4 (1 g, 0.024 mole) in a mixture of dioxane/water (90:10) was shaken with NBS (1.3 g 0.009 moles for 3-5 min, then sodium metabisulphate solution was added to give amorphous precipitate (950 mg, 95% yield), m.p. 282–284 °C (MeOH), undepressed by a sample of compound 5.

6β-Methyl-5α-(25R)-spirostane-3β,5,6α-triol (8)

Compound 7 (5 g, 0.01 mole) in THF (500 ml) was added to a solution of CH₃MgI (Mg 0.3 g, 0.1 mole; CH₃I, 20 g, 0.14 mole in ether 50 ml), refluxed for 3 h, decomposed after cooling with NH₄Cl solution, extracted with CH₂Cl₂ and processed to give 6-methyl spirostane product (8) (3.5 g, 70% yield), m.p. 273–275 °C.

6β-Methyl-5α-(25R)-spirost-4-en-6α-ol-3-one (9)

To product 9 (0.5 g, 0.001 mole) in MeOH (100 ml) was added KOH (15%, 7.5 ml) and refluxed for 2 h. The reaction mixture was then concentrated in vacuo (to 50 ml), H₂O was added to give compound 10 in 90% yield (0.45 g); m.p. 228–228 °C (EtOH). Reported [5] m.p. 225–235 °C, IR v™ cm⁻¹: 3400 (OH), 1700 (C=O), 920, 880 and 820 (spirostane side-chain). MS: m/e (M⁺-3H₂O): 462(5) (M⁺, C₃H₂O₄); 426(4) (M⁺-2H₂O); 408(3) (M⁺-3H₂O); 393(5) (M⁺-3H₂O+CH₃), and 139(100) (ring F ions [9]).

6β-Methyl-5α-(25R)-spirost-4-en-6α-ol-3-one (10)

To product 9 (0.5 g, 0.001 mole) in MeOH (150 ml) was added KOH (15%, 7.5 ml) and refluxed for 2 h. The reaction mixture was then concentrated in vacuo (to 50 ml), H₂O was added to give compound 10 in 90% yield (0.45 g); m.p. 228–228 °C (EtOH). Reported [5] m.p. 225–235 °C, IR v™ cm⁻¹: 3400 (OH), 1700 (C=O), 920, 880 and 820 (spirostane side-chain). MS: m/e (M⁺-3H₂O): 462(5) (M⁺, C₃H₂O₄); 426(4) (M⁺-2H₂O); 408(3) (M⁺-3H₂O); 393(5) (M⁺-3H₂O+CH₃), and 139(100) (ring F ions [9]).

6β-Methyl-5α-(25R)-spirostane-3β,5,6α-triol-3-acetate (11)

To a solution of pentol (3) (5 g, 0.01 mole) in dry Me₂CO (70 ml) was added freshly distilled boron trifluoride etherate (37%, 0.5 ml) and stirred at room temperature for one h. The deposited crystals were filtered, washed with Me₂CO and dried to give product 4 (4 g, 80% yield), m.p. 272–274 °C (MeOH). Reported [4] m.p. 268–269 °C, IR v™ cm⁻¹: 3430 (OH), 1120, 1000, 910, and 845 (characteristic bands for 16β,20α-isopropylidene) [4].
(acetate bands), 960, 920, 890 and 865 (spirostane bands). MS, m/e (%): 504(10) (M+, C_{30}H_{44}O_{4}).

H^1 NMR: δ 2.02 (3H, s, CH$_3$COO).

Reaction of 6β-methyl-5α-(25R)-spirostane-3β,5,6α-triol-3-acetate (11) with thionyl chloride

To a solution of compound 11 (0.5 g, 0.001 mole) in pyridine (15 ml) was added SOCl$_2$ (5 ml) dropwise at 0 °C and left for 10 min at room temperature. Then processed to give product 12 as fine needles (0.15 g, 70% yield, m.p. 238-241 °C, methanol). IR v/cm$^{-1}$: 1770 and 1245 (acetate bands), 960, 920, 890 and 865 (spirostane bands). MS, m/e: 468 (M+, C$_{30}$H$_{44}$O$_4$). UV: $\lambda_{max}$ 285 (ε 19,850).

6β-Methyl-5α-pregnane-3β,6α,20α-tetrol-16-one (13)

To a solution of product 8 (2 g, 0.048 mole), in THF (25 ml) was added HCOOH (90%, 216 ml, 5.16 mole) and heated on a steam-bath for 15 min, cooled at room temperature then H$_2$O$_2$ (30% v/v 24 ml, 0.23 mole) was added under stirring and left on water-bath for 48 h. The formate derivative was extracted with CHCl$_3$ after the addition of H$_2$O$_2$, dissolved in MeOH (25 ml), treated with KOH (50%, 10 ml), refluxed for one h, cooled, acidiﬁed with AcOH and (100 ml) was added to give a colourless precipitate (A). The ﬁlterate was extracted with CHCl$_3$ to give fraction (B). Fractions (A) and (B) were identical (1.5 g) and chromatographed on a column of silica gel (60 g, 2 x 150 cm). Elution with CHCl$_3$ gave 100 mg of the starting material 8. The next fraction also eluted with CHCl$_3$ gave 400 mg of 13, m.p. 272-275 °C (CHCl$_3$). Elution with CHCl$_3$ containing 1% MeOH gave 0.5 g of unidentified mixture. IR $\nu_{max}$ cm$^{-1}$: 3460 (OH, broad) 1750 (>C=O in five mernbered ring). MS, m/e (%): 380(5) (M+, C$_{22}$H$_{36}$O$_5$). H^1 NMR: δ 0.70 (6H, s), 1.4 (6H, d), 2.4 (1H, s), 2.6 (1H, s), 4.8 (1H, s) and 5.15 (1H, s).

Treatment of 6β-methyl-5α-pregnane-3β,6α,20α-tetrol-16-one (13) with alcoholic potassium hydroxide

To compound 13 (5 mg) in MeOH (15 ml) was added aqueous KOH (15%; 0.8 ml) and reﬂuxed for 6 h. Processing of the reaction gave the starting material 13 m.p. 270-273 °C (identical IR spectra).

6β-Methyl-5α-pregnane-5,6α,20α-triol-3,16-dione (14)

A solution of product 13 (0.5 g, 0.0013 mole) in dry Me$_2$CO (100 ml) was cooled to 0 °C and treated with Jone’s [11] reagent (2 ml). It gave product 14 (400 mg, 80% yield), m.p. 262-264 °C (acetone). IR $\nu_{max}$ cm$^{-1}$: 3570, 3780 (OH), 1750 (>C=O of ring D) and 1715 (>C=O of ring A).

6β-Methyl-pregn-4-ene-6α,20α-diol-3,16-dione (15)

Compound 14 (70 mg, 0.001 mole) in MeOH (20 ml) was dehydrated with aqueous KOH (15%, 1 ml) as described before and processed to give 50 mg of product 15, m.p. 292-294 °C (EtOH). IR $\nu_{max}$ cm$^{-1}$: 3440 (OH, broad), 1770 (>C=O of ring D), 1670 (C=C-C=O) and 1610 (>C=C<). UV: $\lambda_{max}$ 239 (ε 12,500). MS, m/e (%): 362(5) (M+, C$_{22}$H$_{34}$O$_4$).