TESTOSTERONE AND 17-METHYLTESTOSTERONE FROM HYODEOXYCHOLIC ACID*

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ABSTRACT

The preparation of the title compounds from hyodeoxycholic acid is described. A modified Oppenauer oxidation using alumina in place of conventional alkoxide catalyst is outlined.

The development of methods(1) for the conversion of the 3α,6α-dihydroxy groups of hyodeoxycholic acid (3α,6α-dihydroxy-5β-cholan-24-oic acid) (I) into the Δ^4-3-keto moiety, a feature unique in its prevalence amongst steroidal sex and corticoidal hormones opened the way for utilization of this important hog-bile constituent. The transformation of (I) into progesterone was described earlier from these laboratories(2). The present report is a logical extension of these studies to include the preparation of the analogous male sex hormone, testosterone and its synthetic homologue, 17-methyltestosterone (VIII).

Enol acetylation of the diacetate of (II), obtained(2) from (I) in 55% yield by Meystre-Miescher degradation, was

(I)
(II)
(III)
(IV)
(a) R = H
(b) R = Ac
(c) R = Ts
(V)
Testosterone
(VI)
(VII)
(a) R = H
(b) R = Ts
(VIII)
Methyltestosterone

carried out in carbon tetrachloride with acetic anhydride-perchloric acid mixture for 1.25 hours, following the procedure of Barton et al(3), the reaction being monitored by saponification value determinations. Longer reaction periods had a deleterious effect on the yield probably due to the further action of the acetic anhydride on the enol acetate(4). An attempt was also made to establish the optimum conditions for enol acetylation by iodine value determinations. This, however, gave erratic results presumably due to the instability of the α-iodoketone formed during estimation.

In view of the geometrical isomers anticipated on the formation of the Δ^{17}-double bond (5), no attempt was made to isolate the triacetate (III), which was directly ozonized in situ in a 1:1 mixture of carbon tetrachloride and aqueous acetic acid (95% v/v). Reductive decomposition of the ozonide with zinc dust, followed by saponification then gave 3α,6α-dihydroxy-5β-androstan-17-one (IVa) in ca 87% yield, characterized as its diacetate (IVb).

The conversion of the 3α,6α-dihydroxy groups of (IVa) into the Δ^{5}-3β-hydroxy moiety, a precursor of the Δ^{4}-3-keto grouping was effected following the method described

earlier(2) in these laboratories. Tosylation of (IVa) in pyridine with p-toluenesulfonyl chloride gave, in quantitative yield, the ditosylate (IVc), which was heated with potassium acetate in aqueous dimethylformamide at 100° for 4.5 hours. Saponification and chromatographic purification then afforded the known 3β-hydroxyandrost-5-en-17-one (dehydroepiandrosterone) (V) (34% overall yield from II), convertible to testosterone by well established methods(6).

The synthesis of the higher homologue, 17-methyltestosterone (VIII) from (V) was accomplished via Grignard and Oppenauer reactions. Addition of methylmagnesium iodide in ether to the ketone (V) was initially reported by Ruzicka et al(7) to give 17-methylandrost-5-en-3β,17β-diol (VI), the yield (57%) being subsequently improved(8) to 74% by the simple expedient of using a ten-fold excess of the Grignard reagent. In the present work, it was found that the cheaper reagent methylmagnesium chloride could be readily prepared in ca 90% yield in tetrahydrofuran from magnesium and methyl chloride using catalytic amounts of methyl iodide and when this was reacted with (V), the 17α-methyldiol (VI) could be obtained in optimized yield of

ca 80%. A similar result was obtained with the corresponding acetate of (V). With methyllithium in ether, the addition reaction was very rapid (30 min) but the yield (70%) was somewhat diminished. The final step in the projected transformation was completed by Oppenauer oxidation with aluminium isopropoxide and methylisobutyl ketone or preferably cyclohexanone as the hydrogen acceptor to furnish 17-methyltestosterone in optimized yields of 72 and 88% respectively.

An interesting modification was discovered during the course of these investigations and consisted in the use of activated alumina in place of the conventional alkoxide catalyst. Thus, the diol (VI), on treatment with cyclohexanone and alumina (3g/g steroid) in refluxing toluene for 1 hour was smoothly converted into methyltestosterone (VIII) in 80% yield, taking into consideration a 17% recovery of starting material. The heterogeneous oxidation, though closely related to, is mechanistically different from the Oppenauer reaction with aluminium alkoxide, which involves a quasi six-membered cyclic transition state (9). It is unlikely that such an activated complex obtains with the alumina-catalysed oxidation, which presumably entails

coadsorption of the diol (VI) and cyclohexanone on the active surfaces of the catalyst with subsequent hydrogen transfer from the steroid-donor to the ketone-acceptor. In this respect, the reaction is reminiscent, in general, of the heterogeneously catalysed transfer hydrogenations, studied extensively by Braude, Linstead et al(10) and in particular, of the Raney nickel catalysed oxidations(11) with cyclohexanone and the recently reported(12), (13) oxidation-reduction reactions at alumina surfaces.

In an alternative route to the diol (VI) from the dihydroxyketone (IVa), the sequence of reactions was reversed i.e. the C-17 side-chain was elaborated preparatory to the construction of the Δ^5-3β-hydroxy grouping. Treatment of (IVa) with methylmagnesium chloride in tetrahydrofuran under conditions identical to those used with hydroxy-ketone (V), surprisingly gave a comparatively low yield (45 vs 80%) of the triol (VIIa). A priori, this was ascribed to the poor solubility of (IVa) in the reaction medium, particularly as some (12%) recovery of the starting material was made. However, this could hardly have been the reason, since replacement of (IVa) by its diacetate (IVb), which is quite soluble in tetrahydrofuran and gives a soluble Grignard complex, still failed to improve the yield.

Presumably, this is another manifestation of long range conformational effects first described by Barton et al(14). Tosylation of the triol (VIIa) with pyridine and tosyl chloride at 0 - 5° and subsequent dehydrotosylation of the resultant ditosylate (VIIb), as described above with (IVc), furnished the unsaturated diol (VI) in 45% yield, identical with the material prepared by the alternative route, described above. The isolation of pure (VI), in this instance was a matter of considerably difficulty and was best achieved by conversion to and regeneration from its oxalic acid adduct(15).

EXPERIMENTAL(16)

3α,6α-Dihydroxy-5β-pregnan-20-one 3,6-diacetate

A solution of 20.5 g of 3α,6α-dihydroxy-5β-pregnan-20-one (II) in 50 ml of dry pyridine and 40 ml of acetic anhydride was heated on the steam bath for 2 hours. On cooling, water was carefully added whereupon an oil separated out, which solidified on standing in the refrigerator overnight. Filtration gave 25.9 g (100%) of crude diacetate, mp 126 - 132°, which was used as such in the following experiments. A slightly purer product mp 130 - 133° was obtained in quantitative yield by carrying out the reaction at room temperature for 24 hours.

3α,6α-Dihydroxy-5β-androstan-17-one (IVa)

A stock solution of acetylating mixture was prepared by dissolving 0.2 ml of 70 - 72% perchloric acid in 5 ml of acetic anhydride.

Five ml of this solution in 50 ml of carbon tetrachloride was mixed with 5 g of diacetoxy-20-ketone and allowed to stand at room temperature for 1.25 hours. It was washed with 25 ml of ice-cold 10% sodium hydroxide solution, then with saturated sodium bicarbonate solution and finally with water. The resulting solution (ca 125 ml) was diluted with an equal volume of dilute (95% v/v) aqueous acetic acid and ozonized at 12 - 15° (bath temp) for 1.25 hours by the passage of a stream of oxygen and 3% ozone at the rate of 10 litres per hour. The absorption of ozone in the beginning is almost complete, none being detected in the exit gases. As the reaction proceeds, the yellow colour of the solution gradually fades and disappears completely after 35 minutes. At the end, the solution acquires a very faint blue tinge. The ozonide was decomposed at 5 - 10° by the addition of a little hydroquinone and 15 g of zinc dust over a period of 15 minutes. The mixture was then allowed to stand at room temperature for 1 hour, filtered and the filtrate evaporated to dryness in vacuo on the steam bath. The residue was then taken up in benzene and washed several times with water until free from acid. Evaporation of the dried (Na_2SO_4) benzene extracts gave 4.75 g of dark-coloured viscous gum. The latter was dissolved in a solution of 5 g of potassium hydroxide in 75 ml methanol and 25 ml water and heated under reflux on the steam bath for 1.5 hours. After removal of the bulk of the solvents in vacuo, the residue was diluted with saturated sodium chloride solution and extracted exhaustively (seven times) with chloroform. Evaporation of the dried (Na_2SO_4)chloroform solution gave 3.2 g (87%) of a yellowish solid, mp 218 - 238° decomp. Crystallization from ethyl acetate (charcoal) gave the pure dihydroxy-17-ketone (IVa) as colourless needles mp 246 - 250°, $[\alpha]_D^{29}$ + 53° (c, 1.675, dioxane) (Lit(17): mp 246 - 249°).

Anal Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; O, 15.66%.
Found: C, 74.46; H, 9.97; O, 15.63%.

The use of diol (I) in place of the corresponding diacetate in the above series of reactions gave a considerably inferior yield (ca 15%) of the 17-ketone (IVa).

The diacetate of (IVa) was prepared by acetylating 1.25 g of the dihydroxy-17-ketone in 3 ml of anhydrous pyridine and 3 ml of acetic anhydride at room temperature for 24 hours. The crude diacetate (IVb) mp 134 - 137° obtained in near quantitative yield was crystallized twice from hexane to give rosettes of needles, mp 141 - 143° $[\alpha]_D^{26}$ + 65° (c, 1.034, dioxane).

Anal Calcd for $C_{23}H_{34}O_5$: C, 70.76; H, 8.71; O, 20.51%. Found C, 70.58; H, 8.70; O, 20.70%.

3α,6α-Dihydroxy-5β-androstan-17-one 3,6-ditosylate (IVc)

To a suspension of 5 g of the diol (IVa) in 25 ml of anhydrous pyridine was added 9 g of p-toluenesulfonyl chloride. There was evolution of heat and within 5 minutes, a clear solution resulted. After keeping the solution at room temperature for 24 hours protected from moisture and light, it was cooled in an ice bath and the excess chloride decomposed by controlled addition of water. The mixture was then diluted with a large volume of water and refrigerated overnight. An oil initially separated out, which on scratching from time to time gradually solidified. The colourless solid was filtered off, washed with water and dried at 50 - 55°/10 mm for 24 hours. The crude ditosylate (IVc), thus obtained weighed 10.0 g (100%) and showed mp 158 - 159° decomp. A single crystallization from a mixture of benzene and hexane gave the analytical sample mp 158 - 159° decomp, $[\alpha]_D^{27}$ + 40° (c, 1.768, dioxane).

Anal Calcd for $C_{33}H_{42}O_7S_2$: C, 64.47; H, 6.89; O, 18.22; S, 10.43%. Found: C, 64.42; H, 6.92; O, 18.24; S, 10.42%.

3β-Hydroxyandrost-5-en-17-one (dehydroepiandrosterone) (V)

A solution of 9.9 g of the preceding ditosylate (IVc) and 15 g of potassium acetate in 80 ml of dimethylformamide and 20 ml of water was heated on the steam bath for 4.5 hours. After removal of solvents in vacuo on a boiling water bath, the residue was dissolved in a solution of 10 g of potassium hydroxide in 50 ml of methanol and 20 ml of water and heated under reflux for 1.5 hours. After the removal of the bulk of solvent in vacuo, the residue was diluted with water and extracted several times with chloroform. The organic extracts were combined, washed once with water, dried (Na_2SO_4) and evaporated in vacuo to leave 4.8 g of a dark-coloured viscous gum,

λ_{max}^{EtOH} 227 mμ ($E_{1cm}^{1\%}$ 66), λ_{max}^{EtOH} 234 mμ ($E_{1cm}^{1\%}$ 69),

$\lambda_{inflection}^{EtOH}$ 243 mμ ($E_{1cm}^{1\%}$ 44), indicating ca 10% $\Delta^{3,5}$-diene content.

For purification, the gum was dissolved in a mixture of hexane and benzene and adsorbed on a column of activated alumina (300 g). The ethyl acetate eluates were collected in three portions of 500 ml each. The middle fraction on evaporation left 2.5 g of a pale yellow gum, which was crystallized first from a mixture of benzene and hexane and then from aqueous methanol to yield 1.9g of dehydroepiandrosterone (V) as colourless needles, mp 148 - 151° undepressed on admixture with an authentic sample.

17-Methyl-5β-androstane-3α,6α,17β-triol (VIIa)

Through a stirred suspension of 4 g of magnesium in 50 ml of tetrahydrofuran, methyl chloride gas predried by passage through a tube of "Drierite" was bubbled. 0.25 ml of methyl iodide was added and the stirring continued. Within a couple of minutes, the reaction initiated and the solution turned pale green and then grey. Bubbling of gas was continued for 1 hour; heat was evolved and the solution refluxed gently. A clear grey solution resulted,

when all the magnesium had reacted. Titration indicated ca 90% yield of methylmagnesium chloride. No reaction occurred even after 2 hours reflux, in the absence of methyl iodide.

To the above stirred solution of methylmagnesium chloride, a suspension of 3 g of the dihydroxy-17-ketone (IVa) in 50 ml of tetrahydrofuran was slowly added over 10 minutes. Once again, there was evolution of heat and the mixture refluxed gently. Half-way through the addition, the mixture became too thick to be stirred; 20 ml of tetrahydrofuran was therefore added, an additional 25 ml being used for rinsing. The mixture was stirred at room temperature for 2 hours and then heated under reflux for 24 hours. At the end of this period, the Gilman colour Test I(18) was strongly positive, while the Zimmerman test(19) was faint. After cooling in an ice-bath and decomposing the Grignard complexes by dropwise addition of 5 ml of water, the mixture was poured into a large volume of water and the solution acidified with concentrated hydrochloric acid. Since no solid separated, the solution was saturated with sodium chloride and extracted exhaustively with chloroform. The combined coloured chloroform extracts were washed with very dilute (2%) sodium hydroxide solution, whereupon the colour was discharged. Evaporation in vacuo left 2.9 g of a colourless frothy material. The latter was dissolved in methanol, the solution diluted with a large volume of ethyl acetate and distilled until crystallization set in. After cooling in the refrigerator for 70 hours, 1.79 g of colourless solid, mp 226 - 230° (prior sintering) was filtered off. Recrystallization from the same mixture of solvents gave 1.41 g (45%) of pure triol (VIIa) as colourless needles mp 230 - 232°, $[\alpha]_D^{26}$ - 23° (c, 0.649, dioxane) (Lit(17): mp 219 - 221° for a slightly impure sample).

Anal Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63; O, 14.89%
Found: C, 74.27; H, 10.61; O, 15.10%.

Evaporation of the mother liquors from the first crystallization gave 0.9 g of a greyish frothy material, which upon trituration with ethyl acetate at room temperature solidified to afford 0.35 g (12%) of starting material, mp and mixed mp 246 - 249°.

Nearly the same yield (48%) of the triol (VIIa) was obtained when 3α,6α-dihydroxy-5β-androstan-17-one 3,6-diacetate was used in place of the corresponding dihydroxy compound (IVa) in the above Grignard reaction.

17-Methyl-5β-androstane-3α,6α,17β-triol 3,6-ditosylate (VIIb)

A solution of 0.5 g of triol (VIIa) in 4 ml of anhydrous pyridine was treated with 0.8 g of p-toluenesulfonyl chloride and allowed to stand at room temperature for 24 hours, protected from moisture and light. On cooling, the excess acid chloride was decomposed by careful dropwise addition of water. Subsequently, the mixture was diluted with a large volume of water, whereupon an oil separated out, which gradually solidified after refrigeration over a prolonged period (ca 2 weeks) of time. Filtration gave 1.01 g of a colourless solid, mp 145 - 146° decomp (prior sintering). Crystallization from ether gave 0.55 g of the pure ditosylate (VIIc), mp 144 - 145° decomp, $[\alpha]_D^{26}$ - 11° (c, 0.849, dioxane).

Anal Calcd for $C_{34}H_{46}O_7S_2$: C, 64.73; H, 7.35; O, 17.75; S, 10.16%. Found: C, 64.70; H, 7.49; O, 17.98; S, 10.22%.

Purification of 17-Methylandrost-5-ene-3β,17β-diol (VI) by conversion to and regeneration from its oxalic acid adduct

The experiment was carried out to establish optimum conditions for the purification of the diol (VI) via its oxalic acid adduct. 2 g of authentic (VI) was dissolved in 45 ml of ethylene dichloride by heating under reflux. The clear solution was then cooled to 60 - 65° (bath temperature), mixed with 0.6 g of anhydrous oxalic acid and shaken by hand for 10 minutes at that temperature. Crystallization proceeded very rapidly and was completed at room temperature overnight to yield 2.03 g of adduct, mp 177 - 178° decomp. To cleave the adduct, a suspension of the latter in 40 ml of water was heated, with occasional shaking, at 70 - 80°

(bath temperature) for 30 minutes. After cooling to room temperature, the colourless solid was filtered off, washed and dried at 65°/10 mm for 18 hours. The diol (VI) thus recovered weighed 1.66 g (94% recovery based on the adduct) and had mp 200 - 203°.

17-Methylandrost-5-ene-3β,17β-diol (VI)

A.
By Dehydrotosylation of (VIIb)

3.2 g of the triol (VIIa) was tosylated in 30 ml of anhydrous pyridine with 5.1 g of p-toluenesulfonyl chloride for 24 hours as described above. The crude tosylate isolated by chloroform extractions was a frothy material (6.2 g; 98%), which was used as such in the dehydrotosylation step.

A solution of the crude tosylate in 50 ml of dimethylformamide was mixed with a solution of 9.3 g of potassium acetate in 5 ml of water and heated on a steam bath for 5 hours. After removal of the bulk of the solvents in vacuo, the residence was poured into a large volume of water, whereupon a colourless solid separated out. After refrigeration overnight, 3.1 g of solid was recovered by filtration. The crude dehydrotosylated product was then saponified with 1 g of potassium hydroxide in 45 ml of methanol and 5 ml of water at reflux temperature for 1.5 hours. After removal of the bulk of the solvents in vacuo, the residue was diluted with water and kept overnight in the refrigerator. Filtration gave 2.76 g of a colourless solid, mp 185 - 190°,

λ_{max}^{EtOH} 228 mu ($E_{1cm}^{1\%}$ 64), λ_{max}^{EtOH} 235 mu ($E_{1cm}^{1\%}$ 68),

λ_{max}^{EtOH} 234 mu ($E_{1cm}^{1\%}$ 45), indicating ca 10% $\Delta^{3,5}$-diene content.

The above material was adsorbed on a column of neutral deactivated alumina (300 g). The benzene-ethyl acetate (1:1) eluated were collected in two fractions of 600 ml and 1 l. The second fraction on evaporation to dryness in vacuo gave 2.45 g of a colourless solid. Attempts to purify

latter by repeated crystallizations were unavailing. The reconstituted material was therefore dissolved in 40 ml of ethylene dichloride at reflux temperature, the solution cooled to 60 - 65° (bath temperature) and while being stirred, mixed with 0.8 g of powdered anhydrous oxalic acid. Crystallization set in immediately. The mixture was stirred at the above temperature for 10 minutes, then cooled overnight in the refrigerator and filtered to give 2.3 g of crude oxalic acid adduct mp 135 - 140°. For cleavage of the adduct, a stirred suspension of the latter in 50 ml of water was heated at 70 - 80° (bath temperature), for 30 minutes, then cooled in the refrigerator for 24 hours and filtered. 1.78 g of a colourless solid, mp 192 - 197° were thus recovered. Crystallization from ethyl acetate followed by recrystallization from aqueous methanol furnished 1.36 g (45%) of pure methylandrostenediol (VI) as a colourless solid, mp and mixed mp 197 - 201°, $[\alpha]_D^{30}$ - 74° ± 4 (c, 1.105, ethanol) (Lit(7): mp 204°).

B.
By Action of Methyllithium on Dehydroepiandrosterone Acetate

A solution of 2 g of dehydroepiandrosterone acetate in 50 ml of anhydrous ether was added in one lot to a stirred 50 ml solution of 0.66N methyllithium in ether. A colourless precipitate was immediately formed, with evolution of heat. After ca 30 minutes, the Gilman colour Test I(18) was negative, while the Zimmerman test(19) was faint. The mixture was then poured into a large volume of cold water and ether evaporated in an air stream in situ. After acidification with dilute (10%) hydrochloric acid, the colourless solid was filtered off, washed with water and dried at 70°/ 10 mm for 16 hours. It weighed 1.82 g (98%), mp 185 - 195° and showed a very faint Zimmerman test. Crystallization from ethyl acetate (charcoal) gave 1.28 g (70%) of colourless crystals, mp and mixed mp 198 - 202°.

C.
By Action of Methylmagnesium Chloride on Dehydroepiandrosterone

A solution of 3 g of dehydroepiandrosterone (V) in 30 ml of tetrahydrofuran was added dropwise over 3.75 hours to a well-stirred solution of methylmagnesium chloride [prepared from 4 g magnesium as described above in the preparation of the triol (VIIa)] in 50 ml of tetrahydrofuran at room temperature, an addition 10 ml of solvent being used for rinsing. The reaction mixture was allowed to stir

at room temperature for another hour and then heated under reflux for 23 hours. The cooled mixture was poured into 1 l of cold water, acidified with hydrochloric acid and refrigerated overnight. Filtration gave 3.06 g of solid, mp 191 - 198°, which upon crystallization from ethyl acetate furnished 2.35 g (74%) of pure 17α-methyldiol (VI) mp and mixed mp 200 - 203°. The residue from evaporation of the mother liquor to dryness in vacuo, was dissolved in chloroform, the solution diluted with hexane and concentrated on the steam bath until crystallization commenced. The resultant solid (0.36 g), mp 185 - 195° was crystallized in a similar manner from a mixture of chloroform and benzene and finally from ethyl acetate to give an additional 183 mg of (VI), mp 199 - 203° (total yield, 80%).

Exactly the same yield of diol (VI) was obtained when 3 g of dehydroepiandrosterone acetate was used in the above Griganrd reaction, in place of dehydroepiandrosterone.

17-Methyl-17β-hydroxyandrost-4-en-3-one (17-Methyltestosterone) (VIII).

A.

Oppenauer Oxidation of (VI)

A solution of 10 g of diol (VI), 155 ml of toluene and 35 ml of cyclohexanone was heated to boiling and 35 ml of solvent was removed by distillation. To this hot solution, 2.0 g of aluminum isopropoxide was added rapidly and the mixture stirred and heated under reflux for one hour, with exclusion of moisture. To the slightly cooled (95°) reaction mixture, 3 ml of water was added and the stirring continued for 15 minutes. The precipitated aluminum hydroxide was removed by filtration and the filter cake washed with toluene. The combined filtrate and washings, on evaporation to dryness in vacuo on a boiling water bath left 12.4 g of a colourless solid, which was vigorously slurried with 75 ml of hexane for 1 hour and then refrigerated for 3 hours. The finely divided precipitate was filtered, washed with a little cold hexane and dried to give 9.20 g (92%) of crude (VIII), mp 159 - 163°. For crystallization, this material was dissolved in 35 ml of boiling ethyl acetate, the solution diluted with 175 ml of hot isooctane and refrigerated for 24 hours. The colourless needles were filtered, washed with a small amount of

isooctane and dried to give 8.67 g (87%) of 17-methyltestosterone, mp and mixed mp 164 - 166° λ_{max}^{EtOH} 241 mu (ε, 16,300)

Lit(20): mp 161.5 - 164.5°).

Using methylisobutyl ketone (350 ml) alone (without toluene) in place of cyclohexanone and aluminium isopropoxide (6 g) in the above run, the yield was 72%.

B.

Oxidation of (VI) using Alumina and Cyclohexanone

A solution of 4.83 g of diol (VI) in 190 ml of toluene and 38 ml of cyclohexanone was heated to boiling and 42 ml of solvent was removed by distillation. Activated alumina (15 g) was added and the vigorously stirred mixture distilled until a further 33 ml of solvent was collected. The mixture was then stirred and heated under reflux for an additional hour. After addition of water it was filtered and the filter cake washed well with hot chloroform. Evaporation of the filtrate in vacuo left 17.7 g of a pale yellow oil, which was dissolved in hexane and cooled. The colourless solid was filtered, washed with cold hexane and dried to give 4.12 g of crude (VIII), mp 136 - 148°, λ_{max}^{EtOH} 241 mu ($E_{1cm}^{1\%}$ 432, indicating purity of ca 78%).

The mother liquor was steam distilled for 2 hours, cooled and filtered to give an additional 0.94 g of crude product, λ_{max}^{EtOH} 241 mu ($E_{1cm}^{1\%}$ 385). The two crops were combined (5.01 g), dissolved in benzene and chromatographed on a column of 400 g of neutral deactivated alumina. Elution with benzene-ethyl acetate (2:1) and evaporation gave 1.7 g of a colourless solid, mp 147 - 161° λ_{max}^{EtOH} 241 mu ($E_{1cm}^{1\%}$ 410), which upon crystallization from a mixture of 8 ml of ethyl acetate and 40 ml of isooctane furnished 1.41 g of methyltestosterone as colourless needles, mp 164 - 166° λ_{max}^{EtOH} 241 mu (ε max 16,300). Elution with benzene-ethyl acetate (1:1) and evaporation gave 1.95 g of a colourless

solid, mp 160 - 165° λ_{max}^{EtOH} 240 mu ($E_{1cm}^{1\%}$ 450), which was crystallized from a mixture of 12 ml of ethyl acetate and 50 ml of isooctane to give an additional 1.75 g of 17-methyltestosterone as colourless needles, mp and mixed mp 165 - 166°. Elution with ethyl acetate and evaporation gave 0.85 g of starting diol (VI) as a colourless solid, mp 199 - 201°, raised to 201 - 203° upon crystallization from ethyl acetate. A mixture melting point with starting material was not depressed.

The total yield of 17-methyltestosterone is thus 3.16 g (80%) taking into consideration a 0.85 g (17%) recovery of starting material.

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