m. p. 286–288° dec. This gave no depression with a sample of the C_{22} keto acid previously described, m. p. 285–287°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 72.6; H, 9.7.

The filtrate remaining after removal of the above acid was evaporated and the sirup crystallized from aqueous acetone to give 150 mg. of white crystals, m. p. 185°. The product was recrystallized from ether–pentane as white plates, m. p. 186–188°. This gave no depression with an authentic sample of sarsasapogenoic acid, m. p. 187–189°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.4; H, 9.7.

Similar results were obtained when the oxidation was carried out at 50–70° for two hours.

A solution of sarsasapogenoic acid acetate in acetic acid when treated with aqueous potassium permanganate for three hours at 25° gave no evidence of oxidation. Some oxidation appeared to take place at 70–80° but the only product which could be isolated after mild alkaline hydrolysis was sarsasapogenoic acid.

A solution of sarsasapogenin lactone acetate in acetic acid when heated with aqueous potassium permanganate for one hour and then allowed to stand at 25° for eight hours yielded no acidic products and the lactone acetate was recovered essentially unchanged.

A solution of 1 g. of sarsasapogenin acetate in 50 cc. of pyridine was mixed with a solution of 1 g. of potassium permanganate and 2 g. of sodium carbonate in 30 cc. of water and 20 cc. of pyridine. After heating for one hour at 70° there was no evidence of oxidation. Sarsasapogenin acetate when refluxed for two hours with a pyridine solution of potassium permanganate showed no noticeable evidence of oxidation.

Summary

1. Sarsasapogenin acetate upon oxidation with potassium permanganate yields the C_{22} keto acid, the C_{22} lactone and sarsasapogenoic acid.

STATE COLLEGE, PENNA. RECEIVED NOVEMBER 22, 1939

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Sterols. LXXXVI. Desoxotestosterone and its Conversion to Testosterone

BY R. E. MARKER, E. L. WITTLE AND B. F. TULLAR

Various isomers and epimers of testosterone, such as $\Delta^{5,6}$-androstenol-17-one-3, dehydroandrosterone, *cis*-testosterone, etc., have been prepared in an attempt to obtain greater hormone activity or to learn more of the specificity of testosterone. In this connection it seemed of interest to prepare less oxygenated substances, such as desoxotestosterone and desoxoandrostenedione, which might be converted to testosterone or related substances by oxidation within the body and thus show hormone activity. That such an oxidation is conceivable might be expected from the ease of preparation of 7-keto-cholesteryl acetate from cholesteryl acetate in the laboratory and in the present work by a similar conversion of desoxotestosterone to testosterone. This paper describes the preparation of desoxotestosterone and related experiments.

The starting material, cholesterol, was converted to $\Delta^{5,6}$-cholestene by known processes[1] and after protection of the double bond by bromine the latter compound was oxidized by chromic acid to remove the side-chain. The $\Delta^{5,6}$-androstenone-17 so formed was isolated from the oxidation mixture as the insoluble semicarbazone and the carbonyl group was then regenerated by hydrolysis with dilute sulfuric acid. The insolubility of cholestene dibromide in acetic acid during the oxidation was overcome by the use of carbon tetrachloride and this procedure, together with the absence of substituents in ring A of the sterol molecule, facilitated the oxidation. Reduction of $\Delta^{5,6}$-androstenone-17 with sodium and alcohol gave the hydroxy compound (I) which was converted to the hydrochloride by treatment with dry hydrogen chloride in the cold. Regeneration of the double bond by refluxing this compound with alcoholic potassium acetate gave a mixture of desoxotestosterone (II) and the original $\Delta^{5,6}$-androstenol-17 (I), the former predominating. This mixture could not be separated by direct crystallization, recalling the preparation of the so-called "*allo*"-cholesterol, m. p. 117°,[2] by this method, a substance which was later shown to be a mixture of the true *allo*-cholesterol and cholesterol.[3]

The hydroxy compounds were separated by crystallization of the acetates prepared from this mixture and hydrolysis of the pure acetates. While these isomeric acetates show a depression in melting point when mixed, the hydroxy com-

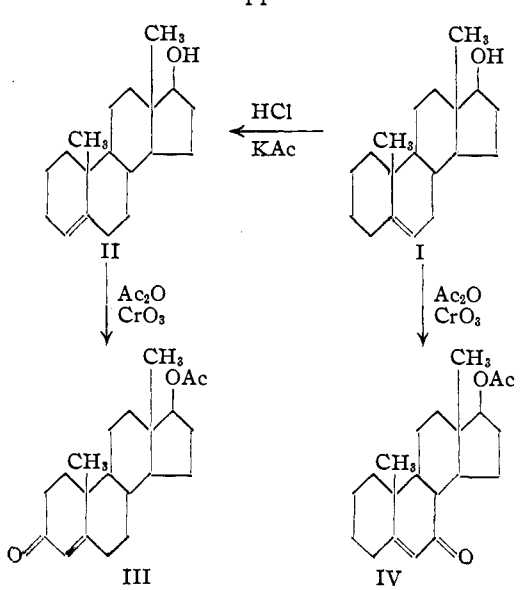
(1) Mauthner, *Monatsh.*, **28**, 1113 (1907); **30**, 635 (1909).

(2) Windaus, *Ann.*, **453**, 101 (1927).

(3) Schoenheimer and Evans, *J. Biol. Chem.*, **114**, 567 (1936).

pounds (I) and (II) do not. $\Delta^{4,5}$-Androstenone-17 was prepared from desoxotestosterone (II) by oxidation of the hydroxyl group to a carbonyl group while protecting the double bond with bromine. It was also prepared by isomerization of the double bond of $\Delta^{5,6}$-androstenone-17 with hydrogen chloride but the resulting mixture of isomers was difficult to separate by crystallization due to the low melting point and greater solubility. These isomeric carbonyl compounds are similar to the acetates in showing a depression in melting point when mixed.

While a double bond such as in neo-cholestene ($\Delta^{2,3}$-cholestene) is completely split into a dibasic acid by chromic acid oxidation, a more highly substituted bond as in cholesteryl acetate is attacked at the α-methylene position to give 7-keto compounds.[4] Thus $\Delta^{4,5}$-cholestene can be converted to cholestenone on oxidation.[5] An analogous oxidation was carried out with desoxotestosterone (II) after acetylation of the hydroxyl group and gave a mixture from which testosterone could be isolated readily. In a repetition of this oxidation, using $\Delta^{4,5}$-androstenol-17 acetate contaminated with some $\Delta^{5,6}$-androstenol-17 acetate, a small amount of an isomer of testosterone acetate was also obtained. The position of the carbonyl group was not definitely known but the compound was regarded as a 6 or 7 keto-androstenol-17 acetate. Since this work was completed an abstract appeared[6] in which 7-keto-$\Delta^{5,6}$-androstenol-17 acetate (IV) was prepared from $\Delta^{5,6}$-androstenol-17 acetate by an oxidation similar to those of the present work. The melting points recorded for 7-keto-$\Delta^{5,6}$-androstenol-17 and the acetate are identical with those of the compound obtained in this work and thus identify it as the 7-keto compound (IV). An oxidation of desoxotestosterone without the protection of the hydroxyl group, or of $\Delta^{4,5}$-androstenone-17, yielded androstenedione in an analogous manner.



(4) Mauthner and Suido, *Monatsh.*, **17**, 593 (1896).
(5) Grasshof, *Z. physiol. Chem.*, **223**, 249 (1934).
(6) Kuwada and Tutihasi, *C. A.*, **33**, 8209 (1939).

Experimental

The Oxidation of $\Delta^{5,6}$-Cholestene Dibromide.—In a 12-liter flask was placed 230 g. of cholestene dibromide and 500 cc. of carbon tetrachloride. When solution was completed, 8 liters of glacial acetic acid was added and the solution was warmed to 45° with stirring. To this stirred solution at 48–50° was added dropwise a stirred solution of 320 g. of chromic anhydride in 350 cc. of water and 800 cc. of acetic acid, over a period of four to five hours. The solution was stirred at 50° for six hours and then cooled with cold water or ice to 30°. Ethyl alcohol (250 cc.) was then added slowly to this stirred solution in about one-half hour and the acetic acid was then removed under reduced pressure until the volume of the solution had been reduced about one-half. During the evaporation the temperature of the solution was kept at 40–45°. The solution was cooled slightly and the unchanged dibromide was filtered off and dried. The filtrate was then further concentrated under reduced pressure at 40° until only a small quantity of acetic acid remained. This residue was diluted with 4 l. of water and 2.5 l. of ether and stirred until all the material was in solution; the water layer was then separated and extracted with 2.5 l. of ether. The combined ether solutions were washed well with 2 l. of water, 3 l. of water containing 300 cc. of concd. hydrochloric acid, and twice with 1.5 l. of salt water, sufficient salt to cause rapid separation of the layers. The ether solution was evaporated to dryness, the last ether being taken off cautiously to avoid undue heat and one liter of acetic acid was then added to the residue with 5 g. of powdered zinc dust. The solution was stirred vigorously and heated to 95° on the steam-bath, when 45 g. of zinc was added to this stirred solution in small portions over a period of forty-five minutes. The solution now was filtered from the caked zinc and this was washed well with acetic acid; the acetic filtrate was evaporated to dryness on the steam-bath and the residue dissolved in two liters of ether. The ether solution was washed twice with water and the acid fraction extracted with 5% sodium hydroxide solution, until all acids were removed. The ether was evaporated to dryness and the residue steam distilled to remove the volatile products. The product was redissolved in ether and the water separated. The ether was evaporated to dryness and the residue dissolved in 200 cc. of 95% ethyl alcohol; 5 g. of semicarbazide hydrochloride and 6 g. of sodium acetate were added, the solution was refluxed on the steam-bath for four hours, and the alcohol concentrated to one-half volume. The

solution was cooled and diluted with 500 cc. of ether. After shaking the suspension for about one-half hour with cooling, 200 cc. of water was added, the solution was shaken and cooled in a salt-ice-bath and filtered with suction. The white solid was washed well with water and then ether. It was refluxed with 50 cc. of alcohol for one hour, cooled, filtered and air dried, yielding 5 g. of white, powdered semicarbazone, m. p. 285–287°.

Anal. Calcd. for $C_{20}H_{31}N_3O$: C, 72.8; H, 9.5. Found: C, 73.0; H, 9.6.

$\Delta^{5,6}$-Androstenone-17.—A solution of 6.7 g. of $\Delta^{5,6}$-androstenone-17 semicarbazone, m. p. 280–285°, in 500 cc. of 95% ethyl alcohol, 35 cc. of concentrated sulfuric acid and 35 cc. of water was refluxed for two and one-half hours on the steam-bath. The solution was diluted with water and the organic product was extracted with ether. The ether solution was washed well with water and sodium bicarbonate until alkaline and evaporated to dryness. The residue was purified by distillation at 80° in a molecular still and crystallization from dilute alcohol to yield 3 g. of $\Delta^{5,6}$-androstenone-17, m. p. 100–105°. This on further purification had m. p. 105–107°.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.7; H, 10.4. Found: C, 83.5; H, 10.4.

$\Delta^{5,6}$-Androstenol-17.—A solution of 1.7 g. of $\Delta^{5,6}$-androstenone-17 in 26 cc. of refluxing *n*-propyl alcohol was treated with 2.5 g. of sodium in small portions for one-half hour. The solution was poured into water and the white solid was filtered off. This was crystallized from methyl alcohol to yield 1.4 g. of $\Delta^{5,6}$-androstenol-17, m. p. 163–165°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.1; H, 11.0. Found: C, 83.0; H, 11.3.

$\Delta^{5,6}$-Androstenol-17 Acetate.—$\Delta^{5,6}$-Androstenol-17 was refluxed for one hour with excess acetic anhydride and then the solution was evaporated to dryness under reduced pressure. The residue was dissolved in hot methyl alcohol and allowed to crystallize, m. p. 133–135°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.4. Found: C, 80.0; H, 10.5.

Hydrolysis of this acetate gave the original hydroxy compound.

$\Delta^{4,5}$-Androstenol-17 Acetate.—A stream of dry hydrogen chloride was bubbled through a solution of 1 g. of $\Delta^{5,6}$-androstenol-17 in chloroform, cooled to 0°, for several hours. The cold solution was allowed to stand for several hours and then carefully evaporated to dryness under reduced pressure. The white solid hydrochloride was dissolved in ethyl alcohol and refluxed for six hours with 4 g. of fused potassium acetate. The solution was poured into water and the hydroxy compound was filtered off and dried. This product consisted of a mixture of $\Delta^{4,5}$- and $\Delta^{5,6}$-androstenols, m. p. 150–155°, which could not be separated by crystallization. The total product was converted to the acetate by refluxing it with acetic anhydride for two hours. Crystallization of the acetate effected a separation into a small amount of the less soluble $\Delta^{5,6}$-androstenol-17 acetate, m. p. 133–135°, and a larger amount of the $\Delta^{4,5}$-androstenol-17 acetate, m. p. 97–100°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.4. Found: C, 79.2; H, 10.1.

A mixture of these two acetates gave a depression in melting points, 72–82°.

$\Delta^{4,5}$-Androstenol-17.—A solution of 500 mg. of $\Delta^{4,5}$-androstenol-17 acetate, m. p. 97–100°, in 25 cc. of methyl alcohol was refluxed for one-half hour with a solution of 1 g. of potassium hydroxide in 10 cc. of 50% methanol. The solution was then diluted with water and the product extracted with ether. The ether solution was washed with water and evaporated to dryness. The hydroxy compound was purified by crystallization from methanol, m. p. 146–149°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.1; H, 11.0. Found: C, 83.0; H, 11.0.

This product gave no depression in melting point with the $\Delta^{5,6}$-androstenol-17, m. p. 163–165°, but a melting range between the two melting points.

$\Delta^{4,5}$-Androstenone-17.—A solution of 200 mg. of $\Delta^{4,5}$-androstenol-17 in 100 cc. of acetic acid was treated with bromine in acetic acid until saturated and then a solution of 300 mg. of chromic anhydride in 20 cc. of 90% acetic acid was added with shaking. The solution was allowed to stand at room temperature for one hour and then treated with 5 g. of zinc dust on the steam-bath. The solution was filtered, poured into water and the product extracted with ether. The ether solution was washed well with water and dilute alkali and evaporated to dryness. The residue was distilled in a molecular still under reduced pressure and then crystallized from dilute methyl alcohol, m. p. 78–80°.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.7; H, 10.4. Found: C, 83.4; H, 10.7.

This ketone gave a depression in melting point, 60–65°, when mixed with $\Delta^{5,6}$-androstenone-17.

Testosterone.—To a solution of 2 g. of $\Delta^{4,5}$-androstenol-17 acetate in 75 cc. of glacial acetic acid at 50° was added a solution of 2 g. of chromic anhydride in 25 cc. of 90% acetic acid over a period of one hour. The solution was poured into water and the product was extracted with ether. The ether solution was washed well with water and dilute sodium carbonate solution and then evaporated to dryness. The remaining oil, which showed a high androgenic activity, was treated with Girard's reagent to separate the ketonic fraction. The crude ketones were treated with warm alcoholic hydrochloric acid to remove the acetate radical and then distilled in a molecular still at 0.01 mm. pressure. Crystallization of the product so obtained from ether–pentane or dilute methyl alcohol gave testosterone, m. p. 148–150°, which gave no depression in melting point with the known product.

7-Keto-$\Delta^{5,6}$-androstenol-17 Acetate.—From the neutral product of an oxidation similar to that above using $\Delta^{4,5}$-androstenol-17 acetate contaminated with some $\Delta^{5,6}$-androstenol-17 acetate a small amount of a second crystalline acetate was obtained. It was purified by crystallization from methyl alcohol, in which it is not very soluble, m. p. 215–217°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.29; H, 9.17. Found: C, 76.30; H, 9.31.

Hydrolysis of this acetate with alcoholic hydrogen

chloride at 80° for several hours yielded the corresponding hydroxy compound, m. p. 141.5–142.5°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.2; H, 9.68. Found: C, 79.7; H, 9.89.

This hydroxy ketone was further characterized by the orange colored 2,4-dinitrophenylhydrazone, m. p. 230–232°, which it formed.

Anal. Calcd. for $C_{25}H_{32}N_4O_5$: C, 64.0; H, 6.89. Found: C, 63.2; H, 6.99.

Androstenedione.—To a solution of 2.5 g. of $\Delta^{4,5}$-androstenol-17 in 200 cc. of acetic acid was added at 35–45° and with stirring a solution of 3 g. of chromic acid in 50 cc. of 90% acetic acid. The addition required one-half hour and the solution was then kept at 45° for one-half hour. The solution was poured into water and the product was extracted with ether. The ether solution was washed well with sodium carbonate solution and water and concentrated to a small volume. On cooling this solution for some time crystals formed and were filtered. They were recrystallized from ether to yield androstenedione, m. p. 168–170°, identical with the known product.

Summary

Cholestene dibromide was oxidized to $\Delta^{5,6}$-androstenone-17 which was converted to desoxotestosterone acetate and $\Delta^{4,5}$-androstenone-17. These new compounds on oxidation were converted to testosterone acetate and androstenedione. An isomeric 7-keto-$\Delta^{5,6}$-androstenol-17 was also obtained.

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NOTES

An Attempted Synthesis of Morphenol

BY ALFRED BURGER AND S. AVAKIAN

A recent announcement by Gilman and Cheney[1] that these authors are studying the closure of a six-membered ring between positions 1 and 9 in dibenzofuran types prompts us to report unsuccessful attempts to synthesize methylmorphenol through 6-methoxy-9-hydroxy-phenanthrylene oxide and subsequent selective reduction of the 9-hydroxy group. 4-Methoxy-dibenzofuran-1-acetic acid was treated with (a) concentrated sulfuric acid, (b) 85% sulfuric acid, (c) anhydrous hydrogen fluoride at room temperature,[2] and (d) stannic chloride in the cold, and at the boiling point of the condensing agent. The acid chloride was treated with aluminum chloride in ice-cold benzene (e), and the acid bromide with aluminum chloride in nitrobenzene solution at room temperature (f), and with boiling stannic chloride (g), but none of these reactions yielded phenanthrene derivatives. It is possible that Gilman and his coworkers will achieve ring closure by using compounds containing strongly *para*-orienting groups in position 6 of the dibenzofuran system.[1]

Since the distance between sulfur and carbon atoms is greater than that between oxygen and carbon atoms, the positions 1 and 9 in dibenzothiophene should be closer to each other than in dibenzofuran, and ring closure should be easier in the dibenzothiophene series. In investigating the effect of substituting sulfur atoms for —CH=CH— groups in polycyclic aromatic systems we are now studying the intramolecular dehydration and decarboxylation of 1-carboxy-dibenzothiophene-9-acetic acid, which should lead to derivatives of 4,5-phenanthrylene sulfide, a possible isoester of pyrene.

Experimental

4-Methoxydibenzofuran-1-carboxylic acid[3] was converted into the chloride by the action of thionyl chloride. The acid chloride crystallized from benzene–ligroin as colorless needles, m. p. 162.5–163.5°. The yield was 93%.

Anal. Calcd. for $C_{14}H_9ClO_3$: C, 64.48; H, 3.48. Found: C, 64.22; H, 3.62.

The acid chloride was stirred with an ethereal solution of diazomethane for sixteen hours. The diazo ketone crystallized out. Recrystallization from benzene–petroleum ether rendered yellow crystals, m. p. 150–151° (dec.). The yield was 86%.

Anal. Calcd. for $C_{15}H_{11}N_2O_3$: C, 67.39; H, 4.15. Found: C, 67.50; H, 4.00.

The diazo ketone was treated with ammonium hydroxide in dioxane solution according to Arndt and Eistert.[3,4] 4-Methoxydibenzofuran-1-acetamide crystallized from ethanol as colorless needles, m. p. 203°. The yield was 75%.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.14 Found: C, 70.93; H, 5.34.

(1) Gilman and Cheney, THIS JOURNAL, **61**, 3149 (1939).
(2) Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).
(3) Gilman, Parker, Bailie and Brown, *ibid.*, **61**, 2836 (1939).
(4) Arndt and Eistert, *Ber.*, **68**, 200 (1935).