[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXXX. 3,6-Diketo Sterols and their Reduction Products*

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Saturated 3,6-diketo steroids may be prepared by zinc–acetic acid reduction of Δ^4-3,6-diketones using the method of Windaus.[1] The unsaturated ketones have been prepared in a variety of ways, the best of which is the direct chromic acid oxidation of the free 3-hydroxy-Δ^5-compounds.[1] We have previously[2] indicated a simplification of the preparation as applied to chlorogenone and *allo*-pregnanetrione-3,6,20. This has now been extended to the preparation of sitostanedione-3,6,[3,4] stigmastenedione,[3] dehydro-*allo*-hyodesoxycholic acid[5] and dehydro-*bis-nor-allo*-hyodesoxycholic acid.[6] It has also been found that acetylation of the 3 and 6 hydroxyls is sufficient to protect the first two rings during oxidation of the side-chain with chromic acid[6] in the case of cholestanediol-3,6. *nor-allo*-Hyodesoxycholic acid has now been obtained in this manner from sitostanediol-3,6.

Reduction of the 3,6-diketo compounds with Adams catalyst and hydrogen in acetic acid solution gave the corresponding 3(β),6(β)-diols. In this manner pregnanetriol-3(β),6(β),20(β) was prepared from pregnanetrione-3,6,20, sitostanediol-3(β),6(β) was prepared from sitostanedione-3,6 and from stigmastenedione-3,6; *allo*-hyodesoxycholic acid was prepared from dehydro-*allo*-hyodesoxycholic acid and *bis-nor-allo*-hyodesoxycholic acid was prepared from the dehydro-*bis-nor*-cholenic acid.

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Experimental Part

Sitostanedione-3,6 from Sitosterol.—A solution of 50 g of sitosterol in 2500 cc. of acetic acid was oxidized with 50 g. of chromic acid at 15–20°. The solution was allowed to stand for one hour. At the end of this time, 100 g. of zinc dust and 150 cc. of water was added and the solution was refluxed for four hours. The zinc was filtered and the product was extracted with water and ether. The ethereal solution was washed well with water and with sodium hydroxide solution to free it of acids. Upon evaporation of the ether, the product crystallized. It was crystallized from ether and from acetone, m. p. 196–199°, yield 26 g.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.2; H, 11.3. Found: C, 81.5; H, 11.2.

Sitostanediol-3(β),6(β) from Sitostanedione-3,6.—A solution of 10 g. of sitostanedione-3,6 in 500 cc. of acetic acid was hydrogenated by shaking with 1 g. of platinum oxide catalyst under a pressure of 45 pounds of hydrogen for ninety minutes. The catalyst was filtered and the filtrate was distilled *in vacuo*. The residue was crystallized from acetone, m. p. 204–206°, yield 8.8 g.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.5; H, 12.1. Found: C, 80.7; H, 12.3.

Upon refluxing with acetic anhydride it gave a product which was crystallized from methanol, m. p. 111–113°.

Anal. Calcd. for $C_{33}H_{56}O_4$: C, 76.7; H, 10.9. Found: C, 76.9; H, 11.0.

Stigmastenedione-3,6 from Stigmasterol.—To a solution of 2 g. of stigmasterol in 300 cc. of acetic acid at 20–22° was added a solution of 2 g. of chromic anhydride in 50 cc. of 90% acetic acid. After standing for one hour, 10 g. of zinc dust was added and the product was refluxed for four hours. The zinc was filtered and the product was extracted with ether. The ethereal solution was washed well with sodium hydroxide. The ether was evaporated and the residue crystallized from acetone and from ether, m. p. 194–196°, yield 1.1 g.; mixed with sitostanedione-3,6, m. p. 196–199°, it melted at 178–185°.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.6; H, 10.9. Found: C, 81.7; H, 11.1.

Reduction of Stigmastenedione-3,6 to Sitostanediol-3(β),6(β).—To a solution of 200 mg. of Δ^{22}-sitostenedione-3,6 in 100 cc. of acetic acid was added 200 mg. of platinum oxide catalyst and the mixture was shaken for two hours under hydrogen at 45 pounds pressure. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was crystallized from acetone, m. p. 204–206°. When mixed with sitostanediol-3(β),6(β), m. p. 204–206° (from sitostanedione-3,6), it gave no depression in melting point, yield 160 mg.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.5; H, 12.1. Found: C, 80.8; H, 12.4.

When refluxed with acetic anhydride it gave a diacetate, which was crystallized from methanol, m. p. 111–113°. When mixed with sitostanediol-3(β),6(β) diacetate, m. p. 111–113°, it gave no depression in melting point.

Anal. Calcd. for $C_{33}H_{56}O_4$: C, 76.7; H, 10.9. Found: C, 76.6; H, 10.9.

Oxidation of Sitostanediol-3(β),6(β) Diacetate to *nor-allo*-Hyodesoxycholic Acid.—To a solution of 8 g. of the diacetate of sitostanediol-3(β),6(β) in 300 cc. of acetic acid was added a solution of 18 g. of chromic anhydride in 18 cc. of water and 80 cc. of acetic acid. The product was heated on a steam-bath at 90–95° for five hours. Water was added and the product was extracted with ether. The

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(1) Windaus, *Ber.*, **39**, 2249 (1906).

(2) Marker, Jones, Turner and Rohrmann, THIS JOURNAL, **62**, 3006 (1940).

(3) Fernholz, *Ann.*, **508**, 215 (1934).

(4) Pickard and Yates, *J. Chem. Soc.*, **93**, 1928 (1908).

(5) Windaus, *Ann.*, **447**, 233 (1926).

(6) Marker, Krueger, Adams and Jones, THIS JOURNAL, **62**, 645 (1940).

acetic acid was removed by washing with water. The ethereal solution was extracted with potassium hydroxide solution. The alkaline layer was warmed for thirty minutes on a steam-bath to hydrolyze the acetoxy groups. It was then acidified with hydrochloric acid, extracted with ether and converted to the sodium salt which is quite insoluble. This was filtered, decomposed with dilute hydrochloric acid and crystallized from slightly diluted methanol and finally from methanol, m. p. 226–229°, yield 150 mg. When mixed with *nor-allo*-hyodesoxycholic acid, m. p. 226–229°, it gave no depression in melting point.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 73.0; H, 10.1. Found: C, 72.8; H, 10.2.

Conversion of 3-Hydroxy-5-cholenic Acid to Dehydro-*allo*-hyodesoxycholic Acid.—To a solution of 5 g. of Δ^5-3-hydroxy-cholenic acid in 500 cc. of acetic acid at 20° was added a solution of 5 g. of chromic anhydride in 50 cc. of 90% acetic acid. After one hour, 15 g. of zinc dust and 15 cc. of water were added and the product was refluxed for four hours. The zinc was filtered and the solvent was removed to about 100 cc. It was well extracted with ether and the acetic acid was removed by washing with water. The solvent was removed and the residue was crystallized from methyl alcohol, m. p. 206–209°; yield 2.1 g. Mixed with dehydro-*allo*-hyodesoxycholic acid prepared from hyodesoxycholic acid, it gave no depression in melting point.

To a solution of 1.5 g. of dehydro-*allo*-hyodesoxycholic acid in 50 cc. of acetic acid was added 500 mg. of platinum oxide catalyst. The product was shaken under an atmosphere of hydrogen for two hours at 45 pounds pressure. The catalyst was filtered and the residue after removal of the solvent was crystallized from ethyl acetate, m. p. 280°. Mixed with *allo*-hyodesoxycholic acid, prepared from hyodesoxycholic acid, m. p. 278–280°, it gave no depression in melting point.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.4; H, 10.3. Found: C, 73.6; H, 10.3.

Conversion of 3-Hydroxy-5-*bis-nor*-cholenic Acid to Dehydro-*bis-nor-allo*-hyodesoxycholic Acid.—To a solution of 3 g. of 3-hydroxy-Δ^5-*bis-nor*-cholenic acid (from stigmasterol) in 300 cc. of acetic acid at 20° was added a solution of 3 g. of chromic acid in 30 cc. of 90% acetic acid. After standing for one hour, 10 g. of zinc dust and 10 cc. of water was added and the product was refluxed for four hours. The zinc was filtered and the solvent was removed to 50 cc. It was well extracted with ether. The solvent was freed of acetic acid by washing well with water. The ether was removed and the residue was crystallized from ethyl alcohol, m. p. 244–247°, yield 650 mg.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.3; H, 8.9. Found: C, 73.0; H, 8.9.

***bis-nor-allo*-Hyodesoxycholic Acid.**—A mixture of 500 mg. of dehydro-*bis-nor-allo*-hyodesoxycholic acid, prepared above, 500 mg. of platinum oxide catalyst and 100 cc. of acetic acid was shaken with hydrogen at 45 pounds pressure for one hour. The catalyst was filtered, the solvent removed and the residue crystallized from methanol, m. p. 258–260°. It gave no depression in melting point when mixed with *bis-nor-allo*-hyodesoxycholic acid which was prepared by the Wieland degradation of *allo*-hyodesoxycholic acid.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.5; H, 10.0. Found: C, 72.8; H, 10.2.

***allo*-Pregnanetriol-3(β),6(β),20(β).**—A mixture of 400 mg. of *allo*-pregnanetrione-3,6,20 (prepared by the chromic acid oxidation of Δ^5-pregnenol-3(β)-one-20 followed by zinc reduction[2]), 100 mg. of platinum oxide catalyst and 75 cc. of acetic acid was shaken with hydrogen at room temperature and 3 atmospheres pressure for one hour. The catalyst was filtered and the solvent was evaporated *in vacuo*. The residue was crystallized from acetone, m. p. 222–224°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.0; H, 10.9.

Treatment of this material with hot acetic anhydride gave a triacetate which melted at 163–165° after crystallization from methanol.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.2; H, 9.1.

Summary

Various 3,6-diketo steroids have been prepared by direct oxidation of the Δ^5-steroid with chromic acid, followed by reduction with zinc dust in acetic acid. Their platinum oxide reduction products have been studied.

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