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

Sterols. LXXXV. Oxidation of Sarsasapogenin Acetate with Potassium Permanganate

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Although the oxidative degradation of the side chain of the steroidal sapogenins using chromic anhydride has been rather extensively investigated, especially with sarsasapogenin, only a few studies have been reported concerning the effect of other oxidizing agents upon the side chain. Several investigators[1,2,3] have studied the action of nitric acid on the side chain and observed that this reagent tends to yield C_{22} lactones. Simpson and Jacobs[2] observed that the side chain of sarsasapogenin is inert to sodium hypobromite. We have substantiated this observation. This is in accordance with the apparent inertness of the side chain in alkaline solutions.

With the hope of gaining further information concerning the nature of the side chain, we have made a brief study of the action of potassium permanganate on sarsasapogenin acetate.

Sarsasapogenin acetate, when treated with potassium permanganate in acetic acid solution at 20°, is readily oxidized to yield the C_{22} keto acid,[4] the C_{22} lactone[5] and sarsasapogenoic acid. Almost identical results were obtained when the reaction was carried out at 50–70°. We find that sarsasapogenoic acid acetate and the C_{22} lactone acetate are relatively inert to potassium permanganate in acetic acid and appear to give none of the C_{22} keto acid. The C_{19} dibasic acid[6] was not encountered in the permanganate oxidation, indicating that permanganate under the conditions used has less tendency to further oxidize a ketonic carbonyl group with subsequent ring rupture than is the case with chromic anhydride.

In striking contrast to the action of permanganate on sarsasapogenin acetate in acid solution is the great stability of the sapogenin to this reagent in neutral or alkaline medium. Sarsasapogenin acetate was unaffected by heating with potassium permanganate in a pyridine–aqueous sodium carbonate medium. The substance also was unaffected by boiling with a pyridine solution of potassium permanganate. These results show further that the sapogenin side chain is non-reactive in alkaline or neutral medium in contrast to its reactivity in acidic medium.[7]

The results on the oxidation of sarsasapogenin acetate with permanganate raise some interesting questions relative to the mechanism of the side chain oxidation. The great ease of the formation of the C_{22} keto acid, the lactone and sarsasapogenoic acid and the fact that neither the lactone nor the C_{22} keto acid are formed from permanganate oxidation of sarsasapogenoic acid,[8] suggests that the oxidation may proceed through the formation of two intermediates. The extreme lability of these intermediates to further oxidation apparently results in carbon–carbon cleavages under relatively mild conditions.

We wish to thank Parke, Davis and Company for their generous help and assistance in the various phases of this work.

Experimental Part[9]

To a solution of 1 g. of sarsasapogenin acetate in 100 cc. of acetic acid at 20° was added 50 cc. of 1 *N* aqueous potassium permanganate solution. The temperature was maintained at 18 to 20° for fifteen hours, after which the mixture was diluted with water and extracted with ether. The ethereal extract was washed well with water and then with 3% sodium hydroxide solution.

Evaporation of the ether solution containing the neutral products gave a sirup which was hydrolyzed with hot ethanolic potassium hydroxide. Dilution of the resulting solution with water gave a slight precipitate which was taken up in ether and discarded. The aqueous alkaline solution was acidified with hydrochloric acid and the precipitated material taken up in ether. After sublimation in high vacuum at 160–180° the product was crystallized from ether–pentane to give white needles, m. p. 198–200°. This gave no depression with an authentic sample of sarsasapogenin lactone, m. p. 198.5–200°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.7. Found: C, 76.2; H, 10.0.

The sodium hydroxide washings containing the acidic fraction from the oxidation was heated on the steam-bath for fifteen minutes to complete the hydrolysis. Acidification of the cooled solution with hydrochloric acid yielded a white solid which was taken up in ether and crystallized from this solvent to give 225 mg. of white crystals. The product was recrystallized from methanol to give a product,

(1) Windaus and Linsert, *Z. physiol. Chem.*, **147**, 275 (1925).
(2) Simpson and Jacobs, *J. Biol. Chem.*, **109**, 573 (1935).
(3) Simpson and Jacobs, *ibid.*, **110**, 565 (1935).
(4) Marker and Rohrmann, THIS JOURNAL, **61**, 1285 (1939).
(5) Farmer and Kon, *J. Chem. Soc.*, 414 (1937).
(6) Marker and Rohrmann, THIS JOURNAL, **61**, 2722 (1939).
(7) Marker and Rohrmann, *ibid.*, **61**, 846 (1939).
(8) Marker and Rohrmann, *ibid.*, **61**, 2072 (1939).
(9) Micro-analyses by Dr. John R. Adams, Jr., of this Laboratory.

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

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS, PENNSYLVANIA STATE COLLEGE, AND THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY]

Sterols. LXXXVI. Desoxotestosterone and its Conversion to Testosterone

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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).