step is proportional to the initial concentration of the iodine. As the net reaction is the decomposition of ethylene oxide into carbon monoxide and methane, this mechanism may be represented formally by

$$(CH_2)_2O + I_2 = XI + YI \quad (1)$$
$$XI + YI = CO + CH_4 + I_2 \quad (2)$$

in which (2) is assumed to be the slow step.

All attempts to isolate the intermediate products failed because at lower temperatures the reaction rates are changed so that most of the iodine is in form of the free element. However, a few possibilities may be eliminated by comparing the observed decomposition rate with the rate of formation of iodine from several reactions. The reaction between methyl iodide and hydrogen iodide as calculated from Ogg's data[7] is definitely too fast to account for the observed results. Furthermore, it is mainly a first-order reaction at these temperatures because the second term in his rate law accounts for the major portion of the reaction. However, our observed results definitely require a second-order reaction. The reaction between methylene iodide and hydrogen iodide was also found to be too fast. It is reasonable to assume that hydrogen iodide is one of the intermediates involved in the decomposition mechanism. However, the results of a test of this made by adding a small amount of hydrogen iodide to the reaction mixture would be inconclusive due to the fact that hydrogen iodide alone causes some catalysis of the decomposition of ethylene oxide.

(7) Ogg, THIS JOURNAL, **56**, 526 (1934).

Summary

It has been shown that the decomposition of ethylene oxide into methane and carbon monoxide above 350° is catalyzed by iodine. Throughout the major portion of the reaction the rate is a constant which is determined by the square of the pressure of iodine originally added. Although it was not found possible to identify the intermediate stages it was shown that the results are in accordance with the theory of compensating reactions discussed in an earlier paper.

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

Sterols. XIV. Pyroandrosterone and Derivatives

BY RUSSELL E. MARKER, OLIVER KAMM, DAVID M. JONES AND LAWSON W. MIXON

The oxidation of beta-cholestanol by means of chromic acid gives a dicarboxylic acid[1] which when heated with acetic anhydride followed by pyrolysis is converted to pyrocholestanone, in which the first ring has lost one carbon atom and becomes a five-membered ring.

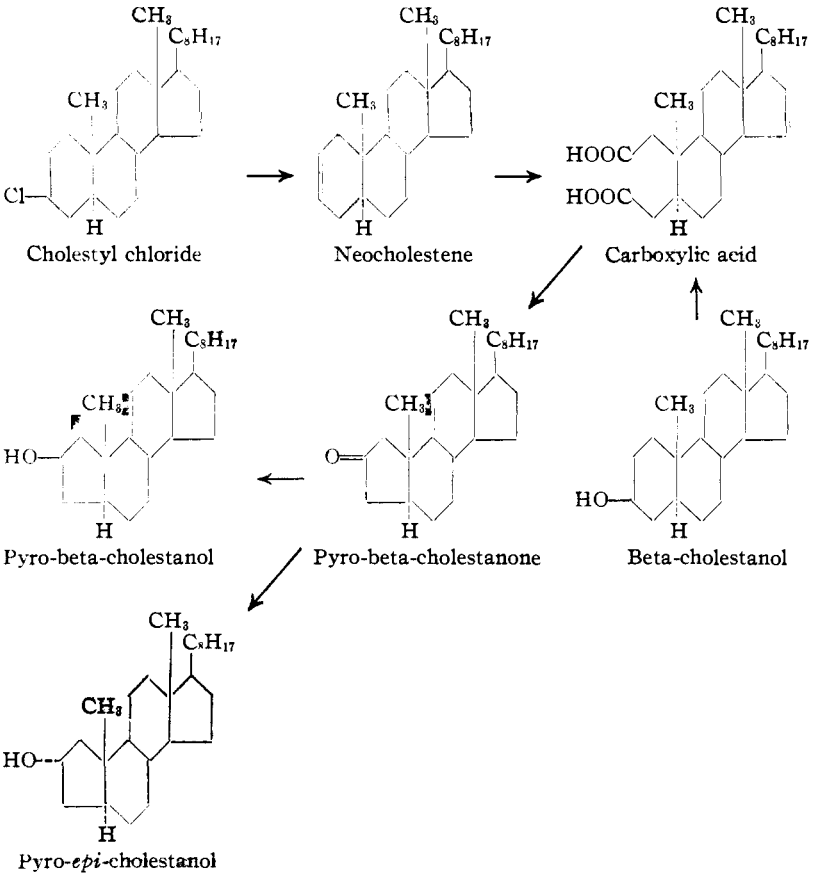
In order to determine the position of the double bond in neocholestene, which is formed by treating cholestyl chloride with quinoline, we oxidized this product both by chromic acid and by ozonolysis, obtaining the same dicarboxylic acid as when beta-cholestanol is oxidized. This shows that the double bond in neocholestene lies in the Δ-2 position.

The dicarboxylic acid from β-cholestanol was pyrolyzed to pyrocholestanone. Upon reduction of pyrocholestanone with sodium–alcohol, a mixture of pyro-beta-cholestanol and pyro-*epi*-cholestanol was obtained in the ratio of 3:1. The components were separated by means of digitonin, the compound of pyro-beta-cholestanol precipitating, whereas the *epi* form did not form a digitonide. Reduction of pyrocholestanone with aluminum isopropylate produced principally the *epi* form in the ratio of 2:1.

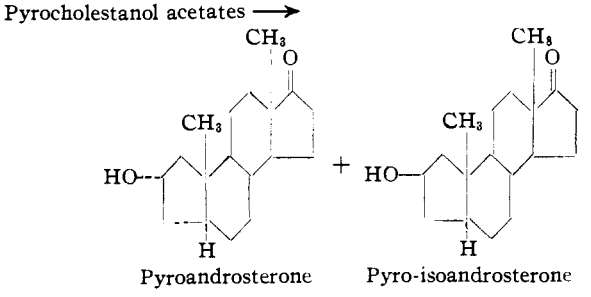
During the course of this work it was found that contrary to the generally accepted belief that only carbinols of the sterol series having the —OH group of the cholesterol configuration form insoluble complexes with digitonin, pyrocholestanone, a ketone, gave a heavy precipitate with digitonin in ethyl alcohol. This was also the case with β-cholestanone.

To produce pyroandrosterone derivatives for testing androgenic activity, the side chain of a mixture of the acetates of pyro-beta-cholestanol and pyro-*epi*-cholestanol (aluminum isopropylate) was oxidized with chromic acid. A mixture of

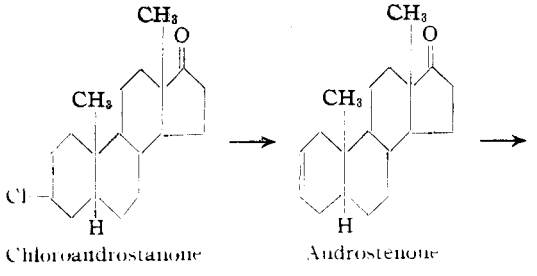
(1) Windaus and Uibrig, *Ber.*, **47**, 2387 (1914).

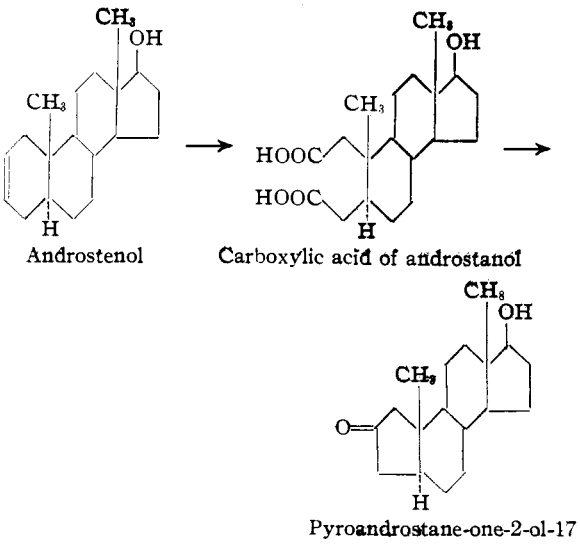


pyroandrosterone and pyro-isoandrosterone was obtained which was separated by means of digitonin precipitation.



We also prepared pyroandrostane-one-2-ol-17 from 3-chloroandrostanone, by splitting out hydrogen chloride to form androstene-2-one-17. This





product was reduced to androstenol, the acetate of which was ozonized to the dicarboxylic acid. This acid was pyrolyzed to pyroandrostane-one-2-ol-17.

Experimental

Ozonolysis of Neocholestene.—Neocholestene was prepared by the method of Mauthner[2] by heating cholestyl

(2) Mauthner, *Monatsh.*, **30**, 643 (1909).

chloride with quinoline. A solution of 2 g. of neocholestene in 200 cc. of chloroform was cooled and ozone was passed through it for an hour. The chloroform was partially evaporated under reduced pressure. Acetic acid was added and the mixture was heated on the steam-bath for two hours. The solution was cooled and a solution of 2 g. of chromic anhydride in 50 cc. of acetic acid was added. After stirring for an hour the mixture was diluted with water and extracted with ether. The product was crystallized from acetic acid, m. p. 193°. A mixture with the acid obtained by chromium oxide oxidation of beta-cholestanol gave no depression in melting point.

The oxidation of neocholestene by chromic acid in acetic acid gave the same dicarboxylic acid as was obtained by ozonolysis.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 75.1; H, 10.7. Found: C, 74.7; H, 10.6.

Pyrolysis of Dicarboxylic Acid from Neocholestene to Pyrocholestanone.—A solution of 5.5 g. of the acid in acetic anhydride was heated slowly to 250°, distilling off the excess acetic anhydride. The ketone was then distilled at 250° at 5 mm. pressure. The distillate was recrystallized from ethyl alcohol; m. p. 98°; yield 3 g.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.8; H, 11.7. Found: C, 83.9; H, 11.8.

Pyro-*epi*-cholestanol and Pyro-beta-cholestanol.—To a solution of 3 g. of pyrocholestanone in 19 cc. of dry isopropyl alcohol was added 2 g. of distilled aluminum isopropylate. The solution was refluxed for seven hours, then slowly distilled until the volume was approximately half that of the original mixture. This was treated with a hot solution of 1.6 g. of potassium hydroxide in 25 cc. of methyl alcohol and allowed to stand for one hour. The mixture was then poured into 200 cc. of water and extracted with ether. The product after evaporation of the ether was dissolved in 20 cc. of hot alcohol and added to a solution of 7 g. of digitonin in 175 cc. of alcohol. After standing overnight the precipitate was filtered and dried. The digitonide was decomposed by warming with 30 cc. of pyridine until dissolved, when the solution was diluted with 300 cc. of ether. The digitonin was filtered and the pyridine removed by washing with acid. The ether was evaporated and the residue was recrystallized from dilute alcohol, m. p. 130°. This was pyro-beta-cholestanol.

Anal. Calcd. for $C_{26}H_{46}O$: C, 83.4; H, 12.3. Found: C, 83.6; H, 12.3.

The filtrate from the digitonide was evaporated to dryness. Ether was added and the digitonin was filtered. The ether was evaporated and the residue recrystallized from dilute alcohol, m. p. 155°. This was pyro-*epi*-cholestanol.

Anal. Calcd. for $C_{26}H_{46}O$: C, 83.4; H, 12.3. Found: C, 83.7; H, 12.1.

In the above experiment the *epi* form predominated in the ratio of 2:1, whereas when the reduction of pyrocholestanone was carried out by sodium in alcohol and the products separated by the above method the pyro-beta-cholestanol predominated in the ratio of about 3:1.

Acetate of Pyro-*epi*-cholestanol.—A solution of 200 mg. of pyro-*epi*-cholestanol in 10 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was distilled under reduced pressure and the residue was crystallized from dilute alcohol; m. p. 96°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.8; H, 11.5. Found: C, 80.9; H, 11.8.

Acetate of Pyro-beta-cholestanol.—A solution of 200 mg. of pyro-beta-cholestanol in 10 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was evaporated under reduced pressure and the residue was crystallized from dilute alcohol, m. p. 77°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.8; H, 11.5. Found: C, 80.3; H, 11.3.

***epi*-Pyroandrosterone.**—The reduction of 81 g. of pyrocholestanone by means of aluminum isopropylate was carried out as previously described. The mixture was acetylated without separation of the two isomers. The crude mixed acetates were dissolved in 3500 cc. of acetic acid and heated to 90°. The product was stirred at this temperature and a solution of 80 g. of chromic acid in 50 cc. of water and 250 cc. of acetic acid added over a period of forty-five minutes. The solution was stirred six hours at 90°, cooled and the excess chromium oxide destroyed by the addition of alcohol. The acetic acid was distilled under reduced pressure and the residue dissolved in ether and water. The ether was washed free of acids with 10% sodium hydroxide solution. The ether solution was evaporated and the residue was steam distilled. The product was extracted with ether. After evaporation of the ether, the residue was dissolved in 200 cc. of alcohol, cooled, and filtered from the unoxidized acetates. The filtrate was treated with semicarbazide acetate. The semicarbazone was hydrolyzed with sulfuric acid in alcohol, followed by hydrolysis of the acetate group by alcoholic sodium hydroxide.

The mixture of pyroandrosterones was treated with digitonin in alcohol, the solid was filtered, and the filtrate was evaporated to dryness. The residue was taken up in ether and filtered. The carbinol-ketone was then further purified by making its half succinic ester, dissolving this in sodium carbonate and extracting with ether. The sodium salt of the half-succinic ester was then hydrolyzed and extracted with ether. The residue after evaporation of the ether was crystallized from petroleum ether, m. p. 124°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.0; H, 10.2.

Semicarbazone of Pyroandrosterone.—The semicarbazone was prepared by treating pyroandrosterone in alcohol with semicarbazide acetate. This was crystallized from alcohol, m. p. 250°.

Anal. Calcd. for $C_{19}H_{31}N_3O_2$: C, 68.4; H, 9.5. Found: C, 68.4; H, 9.4.

Acetate of Pyroandrosterone.—Pyroandrosterone acetate (50 mg.) was prepared by refluxing pyroandrosterone with 5 cc. of acetic anhydride. The acetic anhydride was distilled at reduced pressure and the product was crystallized from petroleum ether, m. p. 102°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.0; H, 9.4.

Androstenone.—A solution of 15 g. of 3-chloroandrostanone was refluxed with 100 cc. of quinoline for three hours.

Ether was added and the quinoline was removed by shaking with hydrochloric acid. The residue after removal of the ether was distilled under high vacuum at 110°. The sublimate was then crystallized from dilute alcohol, m. p. 102°.

Anal. Calcd. for $C_{19}H_{28}O$; C, 83.8; H, 10.4. Found: C, 84.1; H, 10.3.

Androstenol.—To 60 cc. of propyl alcohol was added 0.5 g. of androstenone and the solution brought to a boil. Small pieces of sodium were added until no more dissolved. The solution was cooled, water was added and the product was extracted with ether. The residue after distillation of the ether was recrystallized from petroleum ether, m. p. 165°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.1; H, 11.0. Found: C, 83.2; H, 11.2.

Acetate of Androstenol.—A mixture of 1.5 g. of androstenol and 10 cc. of acetic anhydride was refluxed one hour. The solvent was removed by vacuum distillation and the residue crystallized from petroleum ether, m. p. 96°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 80.0; H, 10.1.

Dicarboxylic Acid from Androstenol.—A solution of 1 g. of androstenol acetate in 100 cc. of chloroform was cooled to 0° and ozonized with a 4% ozone–oxygen stream. The solvent was distilled and the residue was taken up in 50 cc. of acetic acid which contained 5 cc. of water. The solution was heated on a steam-bath for one hour, and after cooling to room temperature a dilute solution of chromic oxide in acetic acid was added. It was then warmed to 60° for one hour. The solvent was evaporated and the residue was taken up in water and extracted with ether. The ether solution was extracted with 10% sodium carbonate solution until free of acids. The alkaline solution was acidified and the free acid was extracted with ether. The ether was removed and the residue was dissolved in 40 cc. of ethyl alcohol containing 3 g. of sodium hydroxide. The mixture was refluxed for one hour, cooled, and acidified with hydrochloric acid. The acid was extracted with ether, the ether was distilled and the residue was crystallized from acetone, m. p. 273°.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.4; H, 9.0. Found: C, 67.8; H, 9.2.

Pyroandrostanone-2-ol-17.—The acetylation and ozonolysis as described above was carried out with 4.2 g. of androstenol, obtaining the dicarboxylic acid. The acid was dissolved in 40 cc. of acetic anhydride which was distilled over a period of one hour. The residue was heated to 250° for one hour during which time a small amount of gas was evolved. The residue was then distilled using a pressure of 4 mm. The distillate was dissolved in alcoholic sodium hydroxide and refluxed for thirty minutes. After the addition of water, the product was extracted with ether. The ether was distilled and the residue was sublimed under high vacuum at 135°. The sublimate was crystallized from a mixture of petroleum ether and ethyl acetate, m. p. 197°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.1; H, 10.2. Found: C, 77.5; H, 10.4.

Semicarbazone of Pyroandrostanone-2-ol-17.—The semicarbazone was prepared in alcohol with semicarbazide acetate. It was recrystallized from alcohol, m. p. 238°.

Anal. Calcd. for $C_{19}H_{31}O_2N_3$: C, 68.4; H, 9.4. Found: C, 68.7; H, 9.6.

Summary

The double bonds in neocholestene and androstenone are in the 2,3-position. Upon reduction of pyrocholestanone with sodium in alcohol or with aluminum isopropylate, a mixture of *epi*-pyrocholestanol and beta-pyrocholestanol is formed. The mixture is separated by digitonin precipitation of beta-pyrocholestanol. The oxidation of the side chain of pyrocholestanol produces pyroandrosterone. Pyroandrostanol-17-one-2 was prepared by the pyrolysis of the acid resulting from the ozonolysis of androstenol.

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