Equilenin-3-oxyacetic Acid.—To a mixture of 1 g. of equilenin, 50 cc. of absolute ethanol and 3.5 cc. of ethyl chloroacetate was added a solution of 600 mg. of sodium in 20 cc. of ethanol. The mixture was refluxed for sixteen hours, when 1 g. of potassium hydroxide was added and the mixture refluxed for an additional hour. Upon dilution with water a white precipitate separated which was taken up in ether.

The water layer was acidified with hydrochloric acid and the white solid taken up in a large volume of ether. The ethereal extract was washed twice with sodium carbonate solution. Evaporation of the ether yielded about 200 mg. of unreacted equilenin. The sodium carbonate washings were acidified with hydrochloric acid and the precipitated solid collected and crystallized from acetone–ether as white needles, m. p. 233–236°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.2. Found: C, 73.7; H, 6.3.

The neutral fraction which separated upon first dilution of the reaction mixture with water was crystallized from aqueous acetone to give white crystals, m. p. 141.5–143°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 75.4; H, 7.1.

Hydrolysis of this neutral material with an excess of ethanolic potassium hydroxide yielded an acid which when crystallized from acetone–ether, m. p. 232–235°, gave no depression with equilenin-3-oxyacetic acid. The neutral product was very probably the ethyl ester.

With diazomethane equilenin-3-oxyacetic acid yielded a **methyl ester** which crystallized from acetone–methanol as white plates, m. p. 180–182°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 74.4; H, 6.5.

Hydrogenation of Equilenin-3-oxyacetic Acid.—A mixture of 800 mg. of equilenin-3-oxyacetic acid, 120 cc. of absolute ethanol, 500 mg. of Adams catalyst and 2 cc. of hydrochloric acid was shaken with hydrogen at two atm. at room temperature for five hours. The reaction products contained no appreciable acidic material. Crystallization from ether–pentane gave white needles, m. p. 144–146°, which gave no depression with a sample of 5,7,9-estratrienol-17(α), m. p. 144–146°.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.0; H, 9.5.

Summary

Equilenin derivatives upon mild oxidation with chromic anhydride yield 11-keto derivatives.

Catalytic hydrogenation of equilenin derivatives in acidic medium gives 5,7,9-estratrienol-17(α).

STATE COLLEGE, PENNA. RECEIVED SEPTEMBER 25, 1939

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

Sterols. LXXVII. The Oxidation of Pregnanetriol-3,4,20(α) and of Coprostanediol-3,4

BY RUSSELL E. MARKER, EUGENE L. WITTLE, LOUIS PLAMBECK, JR., EWALD ROHRMANN, JOHN KRUEGER AND PAUL R. ULSHAFER

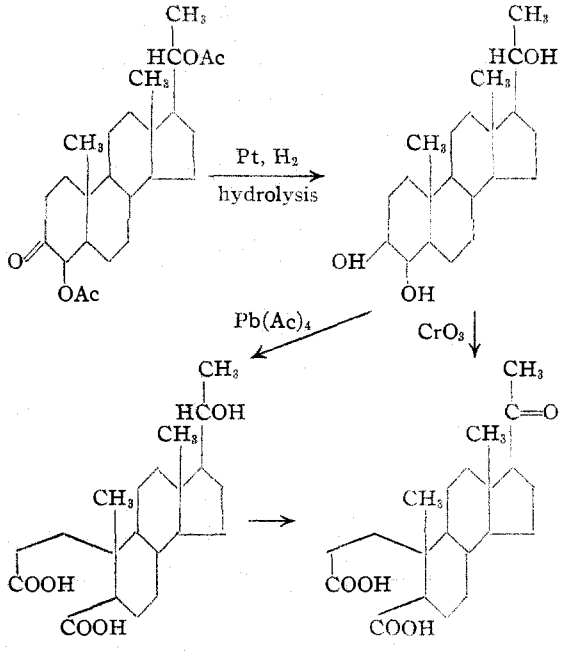
Gardner and Godden[1] oxidized coprosterol and coprostanone with cleavage of the 2,3-bond to a dicarboxylic acid of m. p. 247°. Windaus[2] confirmed Gardner and Godden's work and also oxidized *epi*-coprostanol with chromic oxide to the same acid. Windaus and Riemann[3] oxidized this dibasic acid to isolithobilianic acid which has been proved to have the carboxyl groups in the 2- and 3-positions. We have repeated the oxidation of coprostanone and obtained an acid of m. p. 247°, which appears to be the acid described above. The major oxidation product in the coprostane series, coprostane-2,3-dicarboxylic acid, is therefore formed by cleavage of the 2,3-bond.

On the other hand, oxidative degradations of compounds with the coprostane configuration in the bile acid series result in cleavage of the 3,4-bond as the major reaction. Wieland, Dane and Scholz[4] found that the oxidation of lithocholic acid proceeded with the formation of a 50% yield of lithobilianic acid and a 15% yield of isolithobilianic acid. Thus the oxidative cleavage in this compound took place chiefly at the 3,4-bond, and the substance formed by cleavage of the 2,3-bond was a by-product. Also J. Sawlewicz and T. Reichstein[5] obtained deoxybilianic acid as the major product in the oxidation of α-3-hydroxy-12-keto-cholanic acid. The same is true in the oxidation of other cholic acid derivatives.

Because the major oxidative cleavage in the bile acids of coprostane configuration is at the 3,4-bond, whereas the bile acids of the *allo* series are attacked at the 2,3-bond, it has been generally assumed that all coprostane and cholestane derivatives will behave in the same way. Confusion has resulted in the literature because of this

(1) Gardner and Godden, *Biochem. J.*, **7**, 588–595 (1913).
(2) Windaus, *Ber.*, **49**, 1724–1734 (1916).
(3) Windaus and Riemann, *Z. physiol. Chem.*, **126**, 277 (1923).
(4) Wieland, Dane and Scholz, *Z. physiol. Chem.*, **211**, 261–274 (1932).
(5) Sawlewicz and Reichstein, *Helv. Chim. Acta*, **20**, 992 (1937).

generally accepted but erroneous rule. Sobotka[6] gives the structure of the acid obtained by the oxidation of coprostanone as if a 3,4-cleavage had taken place in spite of the fact that Windaus[3] oxidized the side chain of this acid and obtained isolithobilianic acid, which could only have been formed if the first oxidation had resulted in a 2,3-cleavage in the coprostanone molecule.



Butenandt[7] oxidized pregnanedione with cleavage in ring A and obtained a dibasic acid to which he later assigned the 3,4-dicarboxylic acid structure.[8] We have repeated this oxidation and obtained the acid described by Butenandt. However, when pregnanetriol-3,4,20(α) (prepared by bromination of pregnanedione, followed by potassium acetate treatment, and finally by reduction and hydrolysis of the resulting ketoacetate) was oxidized, the major product was a ketodibasic acid (m. p. 216°), which was different from the acid of m. p. 270° (our melting point 281°) prepared by direct oxidation of pregnanedione with chromic anhydride. The same acid of m. p. 216° was obtained by lead tetraacetate oxidation followed by chromic anhydride treatment. Obviously the oxidation product of pregnanetriol-3,4,20(α) must have been obtained by cleavage of the 3,4-bond which lies between two hydroxyl groups.

(6) Sobotka, "Chemistry of the Sterids," Williams and Wilkins Co., Baltimore, Md., 1938, page 426.
(7) Butenandt, *Ber.*, **68**, 659 (1930).
(8) Butenandt and Schmidt, *ibid.*, **67**, 1893 (1934).

We also carried out an analogous series of reactions on coprostanone. This compound was brominated, and the 4-bromocoprostanone was converted to 4-acetoxycoprostanone by potassium acetate. The resulting compound, by catalytic reduction and hydrolysis, yielded 3,4-dihydroxycoprostane. This diol, on cold oxidation with chromic anhydride in acetic acid, yielded a 3,4-diacid, m. p. 217°, which was different from the 2,3-diacid, m. p. 247°, obtained as the major product of direct cleavage of coprostanone by chromic anhydride in acetic acid. This acid, the 3,4-coprostane-dicarboxylic acid, also gave a large depression in melting point with dihydro-Diels acid of m. p. 251°.

Thus, the point of cleavage of Ring A of the sterols on oxidation is highly dependent on the nature of the group attached to C-17, even though this group is far removed from the point of oxidative attack.

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Experimental Part

Pregnanetriol-3,4,20(α).—A suspension of 300 mg. of platinum oxide in a solution of 100 cc. of ether, 200 cc. of ethanol, and 1.7 g. of 4,20-diacetoxypregnanone-3, m. p. 250°, was shaken with hydrogen under 3 atm. pressure for four hours. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was crystallized once from dilute methanol to yield 1.4 g. of unsharply melting product. This diacetoxy-pregnanol gave only a slight precipitate when treated with digitonin in 95% ethanol, and when oxidized with excess chromic anhydride in acetic acid gave nearly a quantitative yield of the starting material, 4,20-diacetoxypregnanone-3, m. p. 250°.

A solution of 900 mg. of 4,20-diacetoxypregnanol-3 in 200 cc. of 95% ethanol was refluxed for two hours with a solution of 1.5 g. of potassium hydroxide in 75 cc. of 75% ethanol. The solution was poured into water and the hydrolyzed product was extracted with ether. The ethereal solution of the triol was washed with water and was then evaporated nearly to dryness. Pregnanetriol-3,4,20(α) crystallized from the concentrated solution in white plates of m. p. 182°. This triol gave no precipitate with digitonin. After recrystallization from ether and acetone it melted at 184°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.8; H, 10.8.

The triacetate was prepared by treatment of 100 mg. of triol with 3 cc. of pyridine and 2 cc. of acetic anhydride for two days. The solution was evaporated *in vacuo*, and the residue was dissolved in ether and dilute hydrochloric acid. The ether layer was washed with water and then with dilute potassium carbonate and finally was evaporated to

dryness. The residue, crystallized from methanol, yielded 75 mg. of triacetate of m. p. 181°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.0; H, 9.3.

Reduction of 4,20-Diacetoxypregnanone-3 with Aluminum Isopropylate.—A solution of 700 mg. of this compound, 1.0 g. of aluminum isopropylate and 100 cc. of dry isopropyl alcohol was refluxed in a fractionating column over a period of six hours while acetone was removed slowly. The solution was then poured into a mixture of ether and dilute hydrochloric acid. The ether was washed with water and then was evaporated to dryness. The residue on standing overnight with an alcoholic solution of digitonin gave no precipitate. It was not readily crystallized and was therefore converted to the triacetate by refluxing with 30 cc. of acetic anhydride for an hour. The solution was evaporated to dryness *in vacuo*, and the residue was crystallized from methanol to yield a product of m. p. 181°. The melting point could not be raised by repeated recrystallizations from alcohol.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.0; H, 9.4.

This triacetate gave no depression in melting point with the triacetate of the triol obtained by catalytic reduction.

Oxidation of Pregnanetriol-3,4,20(α).—To a solution of pregnanetriol-3,4,20(α) in 50 cc. of acetic acid at 25° was added a solution of 500 mg. of chromic anhydride in 25 cc. of 90% acetic acid. The solution was allowed to stand for one hour. It was then diluted with water and extracted with ether. The ethereal solution was washed with water and then was extracted with dilute potassium carbonate solution. The ethereal layer yielded a yellow oil which could not be crystallized. The potassium carbonate solution on acidification with dilute hydrochloric acid yielded a white solid of m. p. 212°. It was crystallized from dilute ethanol and dilute acetone to yield 75 mg. of acid of m. p. 216°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.2; H, 8.9. Found: C, 69.1; H, 8.6.

This acid gave a twenty degree depression in melting point with the 2,3-diacid of *allo*-pregnanone-20[9] of m. p. 218°, and melted at 180–220° when mixed with the 2,3-diacid of pregnanone-20 of m. p. 281° obtained by the direct oxidation of pregnanedione.[7]

The dimethyl ester of the 2,3-diacid of pregnanone-20 was prepared by treatment of the acid in ethereal solution with diazomethane. The solution was evaporated to dryness and the residue was crystallized from methanol to yield a substance of m. p. 87°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.4; H, 9.3. Found: C, 70.1; H, 9.6.

The oxime was prepared by refluxing a mixture of 50 mg. of this acid, m. p. 216°, 100 mg. of hydroxylamine hydrochloride, 150 mg. of sodium acetate and 25 cc. of ethanol for six hours. The solution was diluted with water, the oxime was filtered off and was crystallized from dilute acetone. The substance melted at 238°.

Anal. Calcd. for $C_{21}H_{33}O_5N$: C, 66.4; H, 8.8. Found: C, 66.2; H, 8.7.

3,4-Diacid of Pregnanol-20(α).—A solution of 100 mg. of pregnanetriol-3,4,20(α), and 200 mg. of lead tetraacetate in 25 cc. of acetic acid was allowed to stand for twenty-four hours at room temperature. The solution was poured into water, extracted with ether, and the ethereal solution was evaporated to dryness. The residue was taken up in 15 cc. of acetic acid and was treated with 10 cc. of 30% hydrogen peroxide for five hours on the steam-bath. The solution was poured into water and was extracted with ether. The ethereal solution was washed with water and was extracted with dilute potassium carbonate solution. The basic solution was then acidified and was extracted with ether. The ethereal solution after being washed with water was evaporated to dryness. The residue melted unsharply at 190–205°. After recrystallizations from dilute acetone and methanol, the substance melted at 231°. This acid (m. p. 231°) with the 3,4-diacid of pregnanone-20, m. p. 216°, melted at 185–200°.

Anal. Calcd. for $C_{21}H_{34}O_6$: C, 68.8; H, 9.4. Found: C, 68.8; H, 9.6.

Oxidation of the 3,4-Diacid of Pregnanol-20.—A solution of 200 mg. of this acid, m. p. 228°, in 50 cc. of glacial acetic acid was shaken at room temperature with 300 mg. of chromic anhydride in 25 cc. of 90% acetic acid for one hour. The solution was poured into 500 cc. of water and the product was extracted with ether. The ethereal solution was washed with water and then was evaporated to dryness. The residue was recrystallized twice from dilute acetone to yield 100 mg. of the 3,4-diacid of pregnanone-20 of m. p. 216°. This acid gave no depression in melting point with the acid of m. p. 216°, prepared by direct chromic anhydride oxidation of pregnanetriol-3,4,20(α).

4-Acetoxycoprostanone.—A solution of 20 g. of 4-bromocoprostanone,[10] in 200 cc. of glacial acetic acid containing 30 g. of fused potassium acetate was refluxed for two hours. The acetic acid was removed *in vacuo* and the organic material was extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, and then was evaporated to dryness. The residue was crystallized from alcohol and yielded 4-acetoxycoprostanone, m. p. 149°.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 78.3; H, 10.9. Found: C, 78.4; H, 10.9.

Coprostanediol-3,4.—A solution of 5 g. of 4-acetoxycoprostanone in 100 cc. of ether and 100 cc. of ethanol was shaken for three hours with 2.0 g. of platinum oxide catalyst under hydrogen at 3 atmospheres. The catalyst was filtered off and the solvent was removed by evaporation. The residue was hydrolyzed by refluxing for one hour with alcoholic potassium hydroxide. The product had a tendency to form a gel when crystallization was attempted. However, after sublimation in a high vacuum at 200° the diol could be crystallized from alcohol and melted at 185–188°. The product may contain some stereoisomer formed in the reduction.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 80.0; H, 12.0.

Coprostane Diacid-3,4.—To a solution of 4 g. of coprostanediol-3,4 in 100 cc. of glacial acetic acid at room temperature was added a solution of 5 g. of chromic oxide in

(9) Marker, Kamm and Jones, THIS JOURNAL, **59**, 1596 (1937).

(10) Butenandt, *Ber.*, **68**, 2094 (1935).

50 cc. of 90% acetic acid. After standing for fifteen minutes, water was added and the organic material was extracted with ether. The ethereal solution was washed well with water and dilute hydrochloric acid and then with dilute potassium hydroxide. The alkaline solution was acidified and extracted with ether. The ether solution was concentrated and pentane was added. This produced 2.4 g. of crystalline acid, m. p. 207–211°. Coprostane-3,4-dicarboxylic acid crystallized from methanol as large transparent rods, m. p. 217°. It gave a 15–20° depression in melting point with dihydro-Diels acid of m. p. 251°, and also with coprostane-2,3-dicarboxylic acid, m. p. 247°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Found: C, 74.8; H, 10.7.

The dimethyl ester was prepared with diazomethane in the usual way. It crystallized from methanol as large white flakes, m. p. 74°.

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.3; H, 10.7. Found: C, 75.6; H, 11.0.

Summary

Pregnanetriol-3,4,20(α) was oxidized to the 3,4-dicarboxylic acid of pregnanone-20, which was different from the dicarboxylic acid of pregnanone-20 formed by direct oxidation of pregnanedione. The latter acid must therefore be a 2,3-derivative.

Coprostanediol-3,4 was oxidized to a coprostane-dicarboxylic acid. This acid was different from the dicarboxylic acid obtained by direct oxidation of coprostanone.

The greater part of the oxidative fission of 3-substituted derivatives of the coprostane configuration (except those of the bile acid series) takes place at the 2,3-bond rather than at the 3,4-bond as has been generally assumed.

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[CONTRIBUTION FROM THE NICHOLS CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

The Preparation of Some Py-Amino Quinolines and Derivatives

BY R. R. RENSHAW[1] AND H. L. FRIEDMAN[2]

This paper describes the preparation of several py-amino quinolines and some of their derivatives. The amines were needed for a study of their coupling reactions with benzene diazonium chloride.[3] The 2-aminoquinoline was readily prepared by the sodamide reaction.[4]

Reduction of 3-nitroquinoline[5] gave the 3-aminoquinoline in small over-all yields. For better yields, Wibaut's[6] method was modified by preparing 3-bromoquinoline from quinoline, bromine and sulfur,[7] followed by conversion to the amine with concentrated ammonia and copper sulfate catalyst.[8]

Since it was found that 3-aminoquinoline forms the 4-azo derivative in the coupling reaction with benzenediazonium chloride,[3] an attempt was made to prepare the unknown 4-nitroquinoline. Anhydrous 3-acetylaminoquinoline was nitrated in concentrated sulfuric acid and the acetyl group removed by hydrolysis. A red nitro-amine was formed. An attempt to remove the amino group by diazotization and boiling in alcohol yielded only a nitro-ethoxy derivative. Attempted reduction to the known 3,4-diaminoquinoline[3] failed; the compound could not be reduced. It is tentatively postulated that 4-nitro-3-aminoquinoline was obtained, although the authors have never seen a quinoline compound with a nitro group in the 4 position recorded in the literature.

The 4-aminoquinoline and the 2,4-diaminoquinoline were prepared from the same material, the 2,4-quinoline-dicarboxylic acid.[9] Decarboxylation of the acid in boiling nitrobenzene gave excellent yields of cinchoninic acid which was converted through the acid chloride,[10] methyl ester,[11] and amide[12] to the amine[13] in an over-all yield of 68%. Similarly, it was found that starting with the 2,4-quinolinedicarboxylic acid, the 2,4-diaminoquinoline could be obtained by the same series of reactions in an over-all yield of 50%. The only method of preparation of the

(1) This paper is being published, following the death of Professor Renshaw, by his collaborator.

(2) Present address: Pyridium Corporation, Yonkers, New York.

(3) Renshaw, Friedman and Gajewski, THIS JOURNAL, **61**, 3322 (1939).

(4) Chichibabin, *et al.*, *J. Russ. Phys.-Chem. Soc.*, **46**, 1232 (1914); **50**, 554 (1918); *Ber.*, **58**, 803 (1925).

(5) Bargellini and Settimi, *Gass. chim. ital.*, **58**, 601 (1928).

(6) Jansen and Wibaut, *Rec. trav. chim.*, **56**, 709 (1937).

(7) Edinger, *J. prakt. Chem.*, **54**, 358 (1896).

(8) Maier-Bode, *Ber.*, **69**, 1536 (1936). Preparation of 3-aminopyridine from 3-bromopyridine.

(9) Pfitzinger, in Houben-Weyl, "Methoden," Vol. IV, 1924, p. 559.

(10) Spaeth and Spitzer, *Ber.*, **59**, 1484 (1926).

(11) Meyer, *Monatsh.*, **22**, 115 (1901).

(12) Wenzel, *ibid.*, **15**, 456 (1894).

(13) Wenzel, *ibid.*, **15**, 457 (1894).