$\Delta^{16,17}$-Pregnenedione-3,20 from Diketo Acid (VIII).—To a solution of 250 mg. of diketo acid in 20 cc. of acetic acid was added a solution of 250 mg. of chromic anhydride in 5 cc. of 80% acetic acid. After standing at 25° for seventy-five minutes water was added and the precipitated solid taken up in ether and washed with water and potassium hydroxide solution. Evaporation of the ether gave a product which crystallized from acetone as white plates, m. p. 199–201°. This gave no depression with a sample of $\Delta^{16,17}$-pregnenedione-3,20, m. p. 200–202°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.1; H, 9.5.

The acidic fraction yielded some unchanged diketo acid.

Oxidation of Diacetate of Dihydropseudosarsasapogenin, (a) At 90°.—To a solution of 4 g. of dihydropseudosarsasapogenin diacetate in 100 cc. of acetic acid heated at 90° was added with stirring over a course of one hour 8 g. of chromic anhydride in 40 cc. of 80% acetic acid. The mixture was heated for an additional hour after which ethanol was added and the mixture evaporated *in vacuo* to a volume of about 75 cc. Water was added and the precipitated solids taken up in ether. The ethereal solution was washed with water and 3% sodium hydroxide. The aqueous alkaline layer was heated on the steam-bath for twenty minutes and the acids precipitated with hydrochloric acid. The acidic product was crystallized from chloroform as white crystals, m. p. 220–223°. This gave no depression with an authentic sample of 3-hydroxy-*etio*-bilianic acid, m. p. 220–222°. The yield was 1.4 g.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.4; H, 8.9. Found: C, 67.3; H, 8.8.

Hydrolysis of the "neutral fraction" gave only additional amounts of the above bilianic acid. There was no noticeable neutral material.

(b) At Room Temperature.—To a solution of 2 g. of dihydropseudosarsasapogenin diacetate in 100 cc. of acetic acid was added 2 g. of chromic anhydride in 20 cc. of 80% acetic acid. After standing at 25–28° for two hours, water was added and the precipitated solid taken up in ether. The ethereal solution was washed with water and 3% sodium hydroxide solution. The acidic fraction was hydrolyzed and worked up as under (a). The product crystallized from chloroform as small white crystals, m. p. 219–222°. This gave no depression with a sample of 3-hydroxy-*etio*-bilianic acid, m. p. 220–222°.

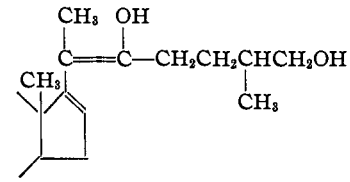
The neutral fraction was crystallized from aqueous methanol to give white plates, m. p. 143–145°. This gave no depression with a sample of pregnenol-3-(*β*)-one-20 acetate, m. p. 144–146°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.7; H, 9.4.

When the reaction was carried out below 20° the only neutral product which could be isolated (after alkaline hydrolysis) was dihydropseudosarsasapogenin.

Summary

Evidence has been presented indicating that pseudosarsasapogenin probably has the structure (or one of its equivalents)



STATE COLLEGE, PENNA. RECEIVED DECEMBER 26, 1939

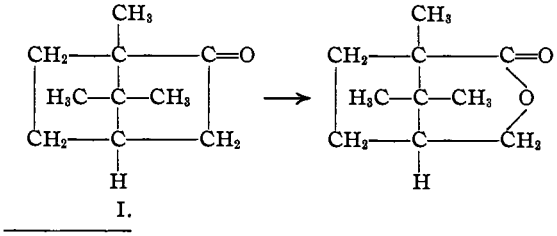
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XC. Oxidation Products of Sarsasapogenin. Pregnanetriol-3,16,20

BY RUSSELL E. MARKER, EWALD ROHRMANN, HARRY M. CROOKS, EUGENE L. WITTLE, ELDON M. JONES AND D. L. TURNER

In a recent publication the conversion of sarsasapogenin to pregnane derivatives was described.[1] This degradation involved the isomerization of sarsasapogenin to pseudosarsasapogenin, the oxidation of this substance to $\Delta^{16,17}$-pregnenedione-3,20 and the subsequent reduction of this to pregnanedione-3,20 and the various pregnanediols.

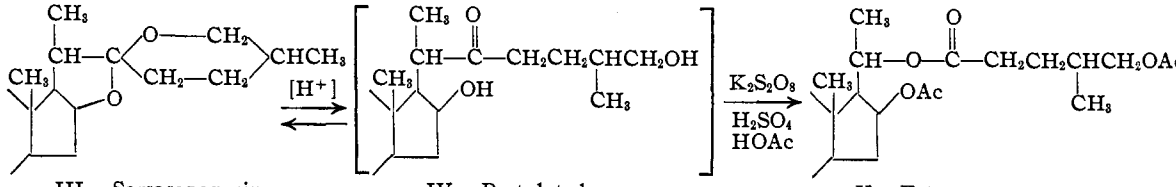
The fact that sarsasapogenin (III) appears to have a potential ketone group which is very reactive in the presence of acids[2] suggested a method of directly converting the substance to a pregnane derivative in one step, namely, by a persulfate oxidation. It is well known that persulfates in the presence of sulfuric acid readily react with polycyclic ketones to yield lactones. A typical example of this type of oxidation is the conversion of camphor (I) to α-campholide (II).[3] Ruzicka and Stoll[4] carried out similar oxidations in a lig-



I.

(1) Marker and Rohrmann, THIS JOURNAL, **62**, 518 (1940).
(2) Marker and Rohrmann, *ibid.*, **61**, 846 (1939).
(3) Baeyer and Villiger, *Ber.*, **32**, 3630 (1899).
(4) Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

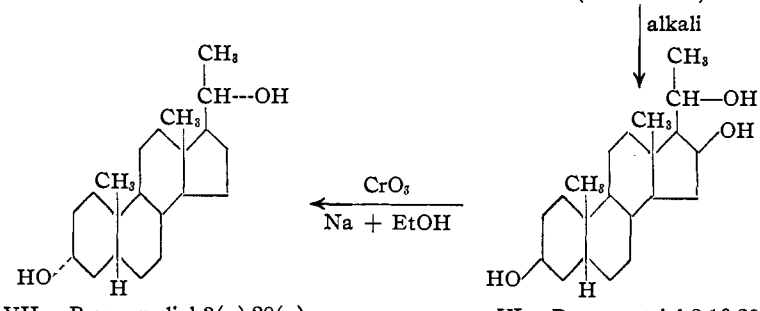
roin medium to obtain good yields of lactones. Rollett and Bratke[5] carried out the oxidations in an aqueous acetic acid medium in the presence of a small amount of sulfuric acid.



III. Sarsasapogenin (Marker and Rohrmann)

IV. Postulated intermediate

V. Ester (not isolated)



VII. Pregnanediol-3(α),20(α)

VI. Pregnanetriol-3,16,20

Using this latter procedure we have carried out the oxidation of sarsasapogenin acetate with potassium persulfate and have obtained a substance after alkaline hydrolysis of the composition $C_{21}H_{36}O_3$ (VI). This substance forms an acetate and a benzoate which appear to be *tris* derivatives. The substance contains no ketonic groups. Mild oxidation of the substance with chromic anhydride followed by removal of the acidic products with alkali and subsequent reduction of the neutral fraction with sodium and ethanol gave pregnanediol-3(α),20(α) (VII). This indicates that the original substance was pregnanetriol-3,16,20 (VI) since by a similar procedure *allo*-pregnanetriol-3,16,20 has been converted to *allo*-pregnanedione-3,20.[6,7] When the neutral fraction from the persulfate oxidation was oxidized with chromic anhydride (without prior alkaline hydrolysis), the only product which was obtained on subsequent hydrolysis was pregnanetriol-3,16,20. This indicates that all of the hydroxyl groups are esterified in the course of the oxidation.

The ease with which this conversion of sarsasapogenin to pregnanetriol-3,16,20 takes place raises many interesting questions in regards to the mechanism of the cleavage. It appears that all of the facts are in complete accordance with the ketone spiro acetal structure of the sapogenin side chain as is indicated in the suggested mechanism given in the accompanying chart. The postulated intermediates IV and V were not isolated.

epi-Sarsasapogenin acetate on oxidation with persulfate yielded a triol having the *epi* configuration at C-3. The persulfate oxidation of sarsasapogenin acetate yields an appreciable acidic fraction which we have not investigated as yet.

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

Experimental Part[8]

Pregnanetriol-3(β),16,20 from Sarsasapogenin Acetate.—A mixture of 1 g. of sarsasapogenin acetate, 4 g. of potassium persulfate, 150 cc. of 90% acetic acid and 1 cc. of concentrated sulfuric acid was refluxed for two hours. Water was added and the precipitated solid taken up in ether and washed with water and 3% sodium hydroxide. The ether was evaporated and the residual material was hydrolyzed with ethanolic potassium hydroxide. Water was added to the alkaline solution and the precipitated solid taken up in ether and crystallized from ether–pentane as small white crystals, m. p. 223–226°. The yields varied from 20 to 40% in different runs.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 75.0, 74.8; H, 10.6, 11.0.

With benzoyl chloride in pyridine the product gave a **benzoate** which was crystallized from methanol as white prisms, m. p. 185–187°.

Anal. Calcd. for $C_{42}H_{48}O_6$: C, 77.7; H, 7.5. Found: C, 77.9; H, 7.5.

With boiling acetic anhydride the substance gave a **triacetate** which crystallized from dilute ethanol as white crystals, m. p. 108–111°.

(5) Rollett and Bratke, *Monatsh.*, **43**, 685 (1922).

(6) Marker, Kamm, Wittle, Oakwood and Lawson, THIS JOURNAL, **60**, 1067 (1938).

(7) Marker and Wittle, *ibid.*, **61**, 855 (1939).

(8) Microanalyses by Dr. John R. Adams, Jr., of this Laboratory.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 69.8; H, 9.1.

Pregnanetriol-3(α),16,20 from *epi*-Sarsasapogenin.—*epi*-Sarsasapogenin acetate was treated with potassium persulfate as described above. After hydrolysis with ethanolic potassium hydroxide the neutral fraction yielded a substance which crystallized from ether to give white crystals, m. p. 206–207°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.9; H, 10.7.

With benzoyl chloride in pyridine the product gave a **benzoate** which crystallized from aqueous acetone as small white needles, m. p. 153–155°.

Anal. Calcd. for $C_{42}H_{48}O_6$: C, 77.7; H, 7.5. Found: C, 77.3; H, 7.4.

Conversion of Pregnanetriol-3(β),16,20 to Pregnanediol-3(α),20(α).—To a solution of 900 mg. of pregnanetriol in 35 cc. of acetic acid was added slowly a solution of 400 mg. of chromic anhydride in 5 cc. of water and 15 cc. of acetic acid. The solution was allowed to stand at room temperature for twenty minutes and then diluted with water and the product taken up in ether. The ether solution was washed with sodium hydroxide solution and water and evaporated to dryness to give a colorless neutral oil which was dissolved in 200 cc. of boiling absolute ethanol and reduced with 10 g. of sodium. Water was then added and the neutral fraction extracted with ether. The ether solution was washed with water and evaporated to leave a yellow oily residue which was dissolved in 10 cc. of acetone and allowed to stand overnight. The product which crystallized from the solution was purified by further recrystallization from acetone to give pregnanediol-3(α),-20(α), m. p. 235–238°. It gave no depression with a sample of pregnanediol-3(α),20(α), m. p. 236–239°. It gave a depression of 20° with the original pregnanetriol.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.7; H, 11.2.

Treatment with acetic anhydride gave the **diacetate** of **pregnanediol-3(α),20(α)**, m. p. 177–179°, which gave no depression of the melting point with the known diacetate, m. p. 178–180°.

Summary

Sarsasapogenin has been converted to pregnanetriol-3,16,20 by persulfate oxidation.

STATE COLLEGE, PENNA. RECEIVED DECEMBER 26, 1939

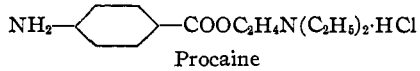
[CONTRIBUTION FROM THE LABORATORY OF G. D. SEARLE & CO., AND DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY, UNIVERSITY OF LOUISVILLE]

Heterocyclic Local Anesthetics. Carbazole, Dibenzofuran and Dibenzothiophene Derivatives[1]

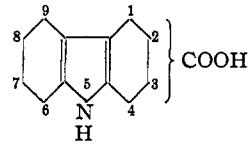
BY ROBERT R. BURTNER AND GERHARD LEHMANN

In any study of local anesthetics of the procaine type one is impressed by the fact that most of the structural variations have been focused upon the amino alcohol portion of the molecule. The effect of alkylation of the nuclear amino group has been studied, and in a few instances useful drugs have resulted, whereas the introduction of an aryl group in this position has received little or no attention.

The carbazole carboxylic acids offered a readily available group of starting materials of the latter type with the interesting variation involving the carbon–carbon bond between the two benzene nuclei.



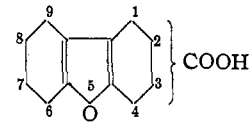
Procaine



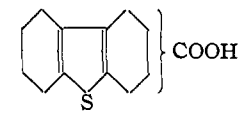
Carbazolecarboxylic acid

Previous investigation of a series of esters of carbazole-N-(or 5)-carboxylic acid by Knoefel[2] led to some rather active compounds of low toxicity. In the present study a series of dialkylaminoalkyl esters of the isomeric carbazolecarboxylic acids was prepared with suitable variations involving the alcohol portion of the molecule as well as nuclear substituents.

Seeking to determine the effect of replacement of the heterocyclic element by oxygen and sulfur an analogous series of esters of dibenzofuran and dibenzothiophenecarboxylic acids was investigated.



Dibenzofurancarboxylic acid



Dibenzothiophenecarboxylic acid

In order to study the effect of the carbon–carbon bond between the two benzene nuclei on the activity of compounds of this type, the correspond-

(1) Presented before the Medicinal Section of the American Chemical Society at the Baltimore Meeting, April, 1939.

(2) Knoefel, *J. Pharmacol.*, **47**, 69 (1933).