

taining a C-3 hydroxyl group of the proper configuration are not precipitated by digitonin.^{4,7} It thus may even be questionable whether precipitation by digitonin has the same significance for the steroid sapogenins as for the sterols.

Summary

1. The solubility of the digitonides of steroid sapogenins varies considerably and is much greater than that of the digitonides of cholesterol and β -cholestanol. Thus the solubility product of the digitonide of sarsasapogenin, which is known to be the less soluble of two epimeric forms, is practically the same as that of the digitonide of *epi*-dihydrocholesterol, which ordinarily is considered as not precipitable by digitonin.

(7) Dimroth, *Ber.*, **69**, 1123 (1936); Reichstein and Gätzi, *Helv. Chim. Acta*, **21**, 1185 (1938).

2. Gitogenin digitonide has a smaller solubility product than sarsasapogenin digitonide and hence gitogenin provisionally must be considered as being the epimer that is precipitated by digitonin.

3. The digitonide of chlorogenin has a much larger solubility product than that of sarsasapogenin and until its epimer is prepared and shown to give a more soluble digitonide, chlorogenin must be considered as the isomer not precipitable by digitonin.

4. It has been shown that the solubility products of steroid digitonides vary so widely that qualitative tests for precipitation are without meaning unless the behavior of both isomers can be compared.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS

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

Sterols. LXXI. Urane Derivatives

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In papers XXIX¹ and XXXVII² of this series the isolation from mares' pregnancy urine of uranetriol and uranediol was described. These substances were shown to possess hydroxyl groups at C-11 and both compounds were converted to the same parent hydrocarbon, urane (I), which is believed to differ from pregnane in the configuration at C-9.

In spite of the close relationship^{1,2,3} existing between uranetriol and uranediol, they nevertheless show some unusual and striking differences. We have pointed out previously the fact that on the basis of precipitability with digitonin uranetriol is a 3- α while uranediol is a 3- β compound. There is also a pronounced difference in the reaction of bromouranetriol and bromouranediol with pyridine, the former yielding urentriol directly while the latter gives largely pyridinium salt which yields urenedione upon destructive distillation. The fact that on the debromination of bromouranediol only one product was obtained suggests that the bromine occupied the C-4 position. Although it appears that the double bond in urentriol and urenedione may be in the

4,5-position, no definite proof of this point has as yet been obtained.

In the catalytic hydrogenation of uranedione-3,11 (V) the carbonyl group at C-3 is much more easily reduced than that at C-11 and consequently the preparation of uraneol-3(β)-one-11 (VIII) is possible. There was no noticeable *epi* fraction obtained in this reduction. The same product was formed by the reduction of uranedione with aluminum isopropylate. Oxidation of the product with an excess of chromic anhydride gave uranedione.

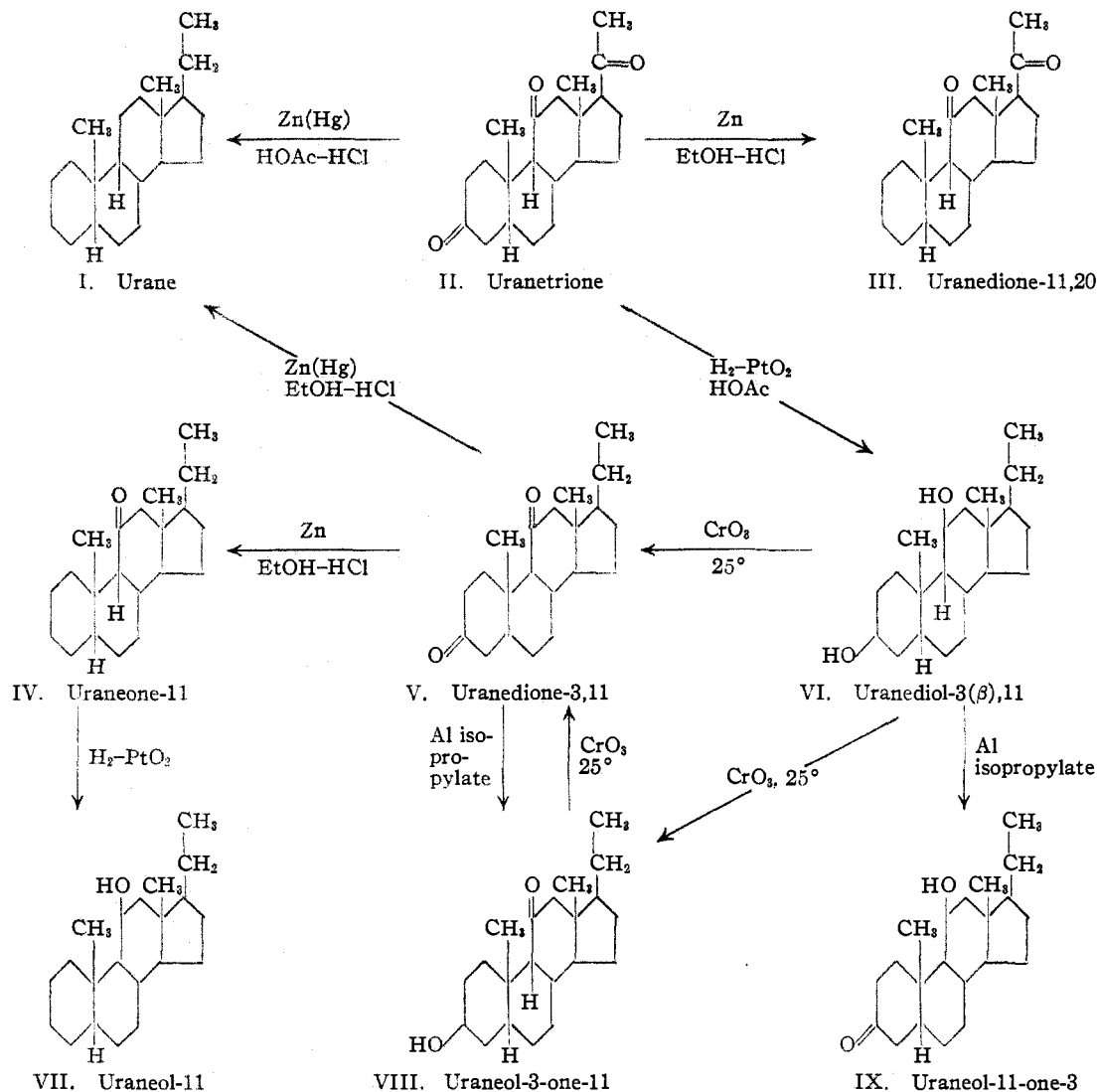
Uranediol on partial oxidation with chromic anhydride yielded some uraneol-3(β)-one-11 (VIII) in addition to uranedione. No uraneol-11-one-3 was isolated from the oxidation. In the oxidation of uranediol with aluminum isopropylate, however, the oxidation proceeds readily at C-3 and the only ketonic product obtained was uraneol-11-one-3 (IX). This product formed a monoacetate and a monosemicarbazone.

By the Clemmensen reduction of uranedione-3,11 with amalgamated zinc in ethanol solution, an almost quantitative yield of uraneone-11 (IV) was obtained. This product formed no semicarbazone, but on catalytic hydrogenation yielded uraneol-11 (VII) which formed a monoace-

(1) Marker, Kamm, Oakwood, Wittie and Lawson, *THIS JOURNAL*, **60**, 1061 (1938).

(2) Marker, Rohrmann and Wittie, *ibid.*, **60**, 1561 (1938).

(3) Marker, Wittie and Oakwood, *ibid.*, **60**, 1567 (1938).



tate. When the Clemmensen reduction was carried out with amalgamated zinc, the main product of the reaction was the hydrocarbon, urane (I).

The Clemmensen reduction of uranetrione (II) with unamalgamated zinc in ethanol solution yielded a diketone which is undoubtedly uranedione-11,20 (III).

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Experimental Part

Bromouranedione-3,11.—To a solution of 2 g. of uranedione in 40 cc. of acetic acid acidified with 3 drops of 48% hydrobromic acid was added 6.3 cc. of 1.05 *M* bromine in

acetic acid. White crystals separated toward the end of the reaction. The reaction mixture was diluted carefully with water and the crystalline solid collected, washed and crystallized from ether to give compact white crystals, *m. p.* 202–203° dec.

Anal. Calcd. for $C_{21}H_{31}O_2Br$: C, 63.8; H, 7.9. Found: C, 63.4; H, 7.8.

Reaction of Bromouranedione-3,11 with Pyridine.—A mixture of 1.7 g. of bromouranedione-3,11 and 45 cc. of dry pyridine was refluxed for three and one-half hours. Small white plates separated shortly after refluxing was started. These were collected, washed with pyridine and ethanol and dried. The product did not melt below 300°; yield 1.5 g.

Anal. Calcd. for $C_{26}H_{38}O_2$: C, 65.8; H, 7.65. Found: C, 66.1; H, 7.7.

Decomposition of Pyridinium Salt of Bromouranedione-3,11.—The pyridinium salt (1.4 g.) was placed in a glass retort and heated at 5–10 mm. pressure until no more material distilled over. The reaction product was sub-

limes in high vacuum at 90–110°. The sublimate was taken up in ether and the pyridine salts removed by washing with dilute hydrochloric acid and water. The ether was evaporated and the product crystallized from aqueous acetone as white needles, m. p. 168–170°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 80.2; H, 9.6. Found: C, 80.5; H, 9.6.

Uraneol-3(β)-one-11 from Uranedione-3,11. (a) By Aluminum Isopropylate Reduction.—A mixture of 700 mg. of uranedione, 1.5 g. of aluminum isopropylate (aged, powder) and 50 cc. of isopropyl alcohol was refluxed for fifteen hours. The solvent was distilled off over a period of one hour. The residue was shaken with dilute hydrochloric acid and extracted with ether. The ether was evaporated and the residue dissolved in 20 cc. of hot 95% ethanol and precipitated with a solution of 1 g. of digitonin and 60 cc. of 85% ethanol. A white precipitate separated at once. After standing for two hours this was collected, washed with ethanol, dried and decomposed with pyridine. The product was crystallized from acetone as compact white crystals, m. p. 205–207°. The product gave a 25° depression with uranediol-3(β),11.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.5; H, 11.0.

When refluxed for twenty minutes with acetic anhydride, the product gave an acetate which crystallized from aqueous acetone as white needles, m. p. 170.5–172°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.8; H, 10.3.

The *epi* fraction could not be separated readily from unchanged uranedione.

(b) **By Catalytic Hydrogenation.**—A mixture of 400 mg. of uranedione, 300 mg. of Adams catalyst and 120 cc. of absolute ethanol was shaken with hydrogen at 25° and 3 atmospheres pressure for two hours. The mixture was filtered and the filtrate evaporated to a volume of 75 cc. To this hot solution a solution of 1 g. of digitonin in 50 cc. of 95% ethanol was added and the mixture allowed to stand for twelve hours. The digitonide was filtered, washed, dried and decomposed with pyridine. The ether soluble material was crystallized from methanol as white crystals, m. p. 205–208°. This gave no depression with the product obtained by the aluminum isopropylate reduction of uranedione.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.2; H, 10.9.

Oxidation of the diol with chromic anhydride in acetic acid at 25° for one hour yielded a product which crystallized from aqueous acetone as white plates, m. p. 174–177°. This gave no depression with a sample of uranedione, m. p. 175–177°.

The *epi* fraction from the hydrogenation was negligible and was not investigated further.

Uraneol-3-one-11 by Oxidation of Uranediol.—About 5 g. of impure uranediol-3(β),11 obtained from mares pregnancy urine was oxidized in acetic acid at room temperature with 1.5 g. of chromic anhydride. The oxidation mixture which would not crystallize readily was adsorbed in a tower of alumina from benzene-ligroin solution and eluted with benzene. The product was crystallized from ethyl acetate and acetone to give compact white crystals,

m. p. 207–209°. This gave no depression with previously prepared samples.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.4, 79.2; H, 10.9, 10.7.

The product was recovered unchanged upon treatment with semicarbazide acetate under the usual conditions.

On refluxing with acetic anhydride the product gave an acetate which crystallized from aqueous acetone as white crystals, m. p. 170°. This gave no depression with the acetate of uraneol-3(β)-one-11.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.6; H, 10.1.

Uraneol-11-one-3.—A mixture of 1 g. of uranediol, 2 g. of aluminum isopropylate, 15 cc. of cyclohexanone and 50 cc. of dry toluene was refluxed for ten hours. The mixture was cooled, diluted with ether, washed with water and the solvent distilled with steam. The residual oil was treated with 2 g. of Girard's reagent to give approximately 250 mg. of crude ketones. The product was crystallized from ether-pentane as fine white needles, m. p. 169.5–171°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.1; H, 10.9.

When refluxed for thirty minutes with an excess of acetic anhydride the product gave an acetate which crystallized from aqueous acetone as small white plates, m. p. 195–197°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.8; H, 10.1.

When treated with semicarbazide acetate in boiling 80% ethanol for one hour the product yielded a semicarbazone which crystallized from dilute ethanol as small white crystals, m. p. 251–253° dec.

Anal. Calcd. for $C_{22}H_{37}O_2N_3$: C, 70.3; H, 9.9. Found: C, 70.5; H, 10.0.

Uraneone-11.—To a boiling mixture of 600 mg. of uranedione-3,11, 60 cc. of 95% ethanol and 10 g. of 20-mesh zinc was added 8 cc. of concentrated hydrochloric acid over a period of three hours. The solution was decanted into water and the mixture extracted with ether. Evaporation of the ether gave a product which crystallized from acetone as white needles, m. p. 135–136.5°, yield 500 mg.

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.4; H, 11.3. Found: C, 83.5; H, 11.5.

The product was recovered unchanged after treatment with semicarbazide acetate for one hour.

Hydrogenation of Uraneone-11.—A mixture of 275 mg. of uraneone-11, 120 cc. of acetic acid and 500 mg. of Adams catalyst was shaken with hydrogen at 3 atmospheres pressure, at 25° for seven hours. The mixture was filtered and the reduction product sublimed in high vacuum at 80–100°. The sublimate was crystallized repeatedly from methanol to give white crystals which melted poorly at 110°.

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.8; H, 11.9. Found: C, 82.5; H, 12.0.

With boiling acetic anhydride the product yielded an acetate which crystallized from aqueous acetone as fine white needles, m. p. 140–142°.

Anal. Calcd. for $C_{23}H_{38}O$: C, 79.7; H, 11.1. Found: C, 80.0; H, 11.1.

Uranedione-11,20.—Uranetrione (600 mg.) was reduced by the Clemmensen method as described for uranedione-3,11. After sublimation in high vacuum, the product was crystallized from ether-pentane as white needles, m. p. 199–201°.

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

Summary

The following reactions of urane derivatives have been observed:

1. Uranedione on partial oxidation with chromic anhydride yielded uraneol-3(β)-one-11. Urane-

diol on oxidation with aluminum isopropylate gave uraneol-11-one-3.

2. Mild catalytic hydrogenation of uranedione-3,11 gave uraneol-3(β)-one-11. Similar results were obtained on mild reduction with aluminum isopropylate.

3. Mild Clemmensen reduction of uranedione-3,11 gave uranone-11. Vigorous reduction gave urane. Mild Clemmensen reduction of uranetrione gave uranedione-11,20.

4. Uranedione has been prepared from bromouranedione.

STATE COLLEGE, PENNA.

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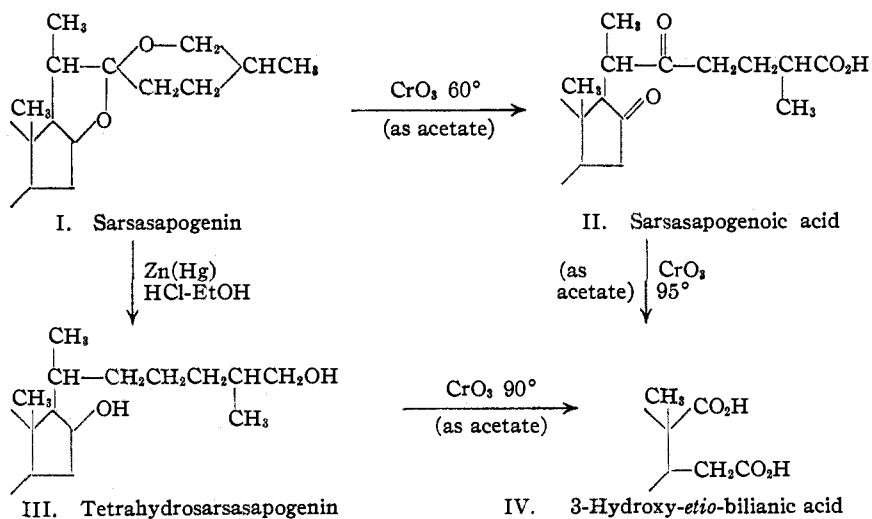
Sterols. LXXII. Oxidation Products of Sarsasapogenin. C_{19} Dibasic Acid

BY RUSSELL E. MARKER AND EWALD ROHRMANN

The fact that sarsasapogenin contains a substituent at C-16 and has by indirect methods been degraded to *etio*-bilianic acid¹ suggests that 3-hydroxy-*etio*-bilianic acid might be expected among the acidic products obtained by the direct oxidation of sarsasapogenin acetate with chromic anhydride.

In extending our investigation of the acidic products from the chromic anhydride oxidation of sarsasapogenin acetate (conducted at 85°), we have isolated from the hydrolyzed acidic fraction in addition to the C_{22} keto acid previously reported² a dibasic hydroxy acid of the composition $C_{19}H_{30}O_5$. The acid gives a dimethyl ester with diazomethane. The resulting dimethyl ester was characterized further by the formation of an acetate. Treatment of the acid with acetic anhydride either by refluxing or by the pyridine method resulted in the formation of an acetate anhydride of the composition $C_{21}H_{30}O_5$ which upon alkaline hydrolysis yielded the original acid.

Mild oxidation of the acid followed by Clemmensen reduction yielded a desoxy acid of the composition $C_{19}H_{30}O_4$, m. p. 232°. With acetic anhydride the desoxy acid yielded an anhydride, m. p. 207°. Although no direct comparison was made, the desoxy acid is very probably identical with *etio*-bilianic acid first reported by Wieland³ and co-workers, who reported a melting point of 228° for the acid and 206° for the anhydride.



(1) Farmer and Kon, *J. Chem. Soc.*, 414 (1937).

(2) Marker and Rohrmann, *THIS JOURNAL*, 61, 1285 (1939).

(3) Wieland, Schlichting and Jacobi, *Z. physiol. Chem.*, 161, 80 (1926).