tion and water, the ether evaporated, and the residue sublimed in high vacuum at 125°. After crystallization from 70% ethanol it melted at 118°.

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

Summary

Pregnenediol-3(β),20(α) and *allo*-pregnanediol-3(β),20(α) have been isolated from mares' pregnancy urine. Pregnenediol-3(β),20(α) upon oxidation gave progesterone and upon catalytic reduction gave *allo*-pregnanediol-3(β),20(α). β-Equistanol, previously obtained from stallion urine, has now been detected also in mares' pregnancy urine.

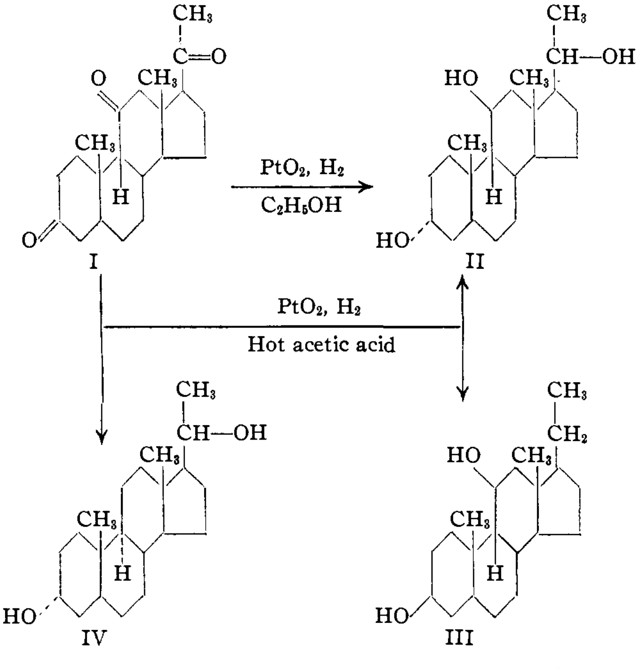
STATE COLLEGE, PENNA. RECEIVED MARCH 16, 1938

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

Sterols. XXXIX. The Reduction of Uranetrione

BY RUSSELL E. MARKER, EUGENE L. WITTLE AND THOMAS S. OAKWOOD

Uranetrione (I) is a 3,11,20-triketo-urane which has been found in previous work[1] to give uranedione (3,11-diketo-urane)[2] and pregnanedione when subjected to a series of reactions, the first step being catalytic reduction. In this paper a study of the reduction of uranetrione is presented.



Catalytic reduction of uranetrione (I) with platinum oxide in ethyl alcohol gave a product which on treatment with digitonin yielded a digitonide corresponding to approximately 10% of the product. The major unprecipitated fraction was found to contain a trihydroxy compound (II), as shown by the formation of a triacetate which is unaffected by further vigorous reduction or by chromic acid oxidation. This fraction, which did not precipitate with digitonin, was practically pure triol, showing that reduction of the carbonyl group at C-11 proceeded with the formation of only one of the two possible epimers. This behavior on reduction is therefore similar to that of the carbonyl group at C-20 which also gives only one epimer. The formation from uranetrione of a triol which forms a triacetate is in contrast to the reduction of a cortical steroid studied by Kendall.[3] His acid 1B (3-β-hydroxy-11-keto-aetio-*allo*-cholanic acid) was hydrogenated catalytically, and the resulting dihydroxy-aetio-*allo*-cholanic acid partially oxidized to give acid 1D (3-keto-11-hydroxy-aetio-*allo*-cholanic acid), which was stereoisomeric at C-11 with his dihydro acid 2. Acid 1D does not react with thionyl chloride or with acetylating reagents, and has a configuration at C-11 opposite to that of the natural cortical steroids.

According to our early prediction, uranetriol[1] now can be assigned definite stereochemical configurations. According to the arguments presented in an earlier paper,[1] a C-11α-hydroxyl group in a urane derivative is much more blocked than the epimeric C-11β-hydroxyl group, and, unlike the latter, will not form an acetate. Since triol (II), like uranetriol, forms a triacetate and does not precipitate with digitonin the configurations of the 3- and 11-hydroxyls in both these triols are established to be of the α- and β-configuration, respectively. The two triols, which

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

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

(3) Mason, Hoehn, McKenzie and Kendall, *J. Biol. Chem.*, **120**, 719 (1937).

are not identical, can therefore differ only in regard to the configuration of the hydroxyl group at C-20. By analogy with the pregnanediols, in which only 20α-hydroxyl groups occur naturally and only 20β-hydroxyl groups are formed on catalytic reduction, the configurations of uranetriol-(3α,11β,20α) and triol (II) (3α,11β,20β) are therefore established.

Reduction of uranetrione in hot acetic acid gave a product which was again separated with digitonin. The digitonide, corresponding in this case to approximately 20% of the product, gave on decomposition practically pure uranediol (III) which was identical with uranediol isolated from mares' pregnancy urine.[2] The diacetate prepared from diol (III) was also identical with uranediol diacetate. Thus in this case also the reduction of the carbonyl group at C-11 gave only the β- or natural configuration of the hydroxyl group. The fraction which did not precipitate digitonin was quite impure and could not be crystallized. It was treated with acetic anhydride and the product on crystallization gave the triacetate of triol (II) identical with that obtained from reduction of uranetrione (I) in ethyl alcohol.

The formation of uranediol suggests an alternate mechanism by which in previous work uranedione and pregnanedione were obtained. It now appears that vigorous reduction in hot acetic acid partially removed the carbonyl group at C-20 to form uranediol, and must have partially removed the carbonyl group at C-11, with inversion of the configuration at C-9 from a urane to a pregnane structure, to give pregnanediol (IV). The resulting carbinol mixture on oxidation gave a mixture of uranedione and pregnanedione. The formation of uranediol and pregnanediol could only have taken place in the first step of the transformation of uranetrione to uranedione and pregnanedione[1] as triol II, the other product of reduction, forms a triacetate which in the course of the other reactions to which the mixture was subjected could not give these two products.

It is to be noted that both carbonyl groups which were removed in the above reduction are alpha to a tertiary hydrogen; so the reduction is similar to that of 7-keto-cholesteryl chloride.[4]

Partial reduction of uranetrione in ethyl alcohol gave, besides some unchanged uranetrione, a product which precipitated digitonin (β-hydroxyl group at C-3) and gave an analysis corresponding to a hydroxy diketone $C_{21}H_{32}O_3$. It formed a monoacetate when treated with acetic anhydride. The reduction of uranetrione thus resembles that of the pregnanediones[5] in which the carbonyl group at C-3 is the first to undergo reduction.

In an attempt to isomerize uranediol (III) with sodium in boiling xylene to effect inversion at C-3 the compound was recovered largely in the original form and only a small amount of material not precipitated by digitonin could be obtained. Uranetriol, possessing an α-configuration at C-3, is also changed only slightly by this treatment. It thus appears that the urane compounds are more difficult to isomerize in this manner than those of the pregnane series.

Experimental Part

The Reduction of Uranetrione in Ethyl Alcohol.—A suspension of 50 mg. of platinum oxide in a solution of 500 mg. of uranetrione in 50 cc. of ether and 50 cc. of ethyl alcohol was shaken with hydrogen at 3 atmospheres pressure and 25° for five hours and then filtered to remove the catalyst. The filtrate was distilled until all of the ether was removed and then added to a solution of 300 mg. of digitonin in 50 cc. of ethyl alcohol and allowed to stand for four hours. The digitonide was collected and dried (250 mg.). The filtrate was evaporated to 10 cc. and diluted with 100 cc. of ether. The precipitated digitonin was filtered off and the filtrate after several washings with water was evaporated to dryness leaving a white solid which was very soluble in methyl and ethyl alcohols. It was crystallized from ether-pentane to yield 300 mg. of triol (II), m. p. 255°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.6; H, 10.6.

The triacetate, prepared by refluxing 50 mg. of this compound with 2 cc. of acetic anhydride for one-half an hour, was crystallized from methyl alcohol, m. p. 192°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.1; H, 9.2. Found: C, 70.2; H, 9.2.

This compound was treated with platinum oxide and hydrogen in acetic acid at 85° but was recovered unchanged. On treatment with an equal weight of chromic anhydride in acetic acid at 25° it was also recovered unchanged.

Reduction of Uranetrione in Hot Acetic Acid.—A suspension of 1 g. of platinum oxide in a solution of 100 cc. of glacial acetic acid containing 0.8 g. of uranetrione was shaken with hydrogen at 3 atmospheres and 85° for eight hours and then filtered from the catalyst while hot. The filtrate was evaporated to dryness in vacuum and the residue was dissolved in ether, washed with a sodium carbonate solution and water, and the solution was evaporated to dryness. The residue was dissolved in 50 cc. of alcohol and to it was added a solution of 1 g. of digitonin in 50 cc. of alcohol. After standing overnight the digitonide

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(4) Marker, Kamm, Fleming, Popkin and Wittle, THIS JOURNAL, **59**, 619 (1937).

(5) Marker, Kamm and Wittle, *ibid.*, **59**, 1841 (1937).

was collected, washed and dried (800 mg.) and heated for one hour on a steam-bath with 10 cc. of pyridine. The solution was diluted with 100 cc. of ether, filtered from digitonin, and the filtrate was washed with dilute hydrochloric acid until acid, and then with water. The ether was evaporated to dryness and the residue was crystallized from methyl alcohol to yield 150 mg. of uranediol, m. p. 215°. It gave no depression in melting point when mixed with uranediol (213°) isolated from mares' pregnancy urine.

The acetate was prepared from this compound in the usual manner, m. p. 160°. It gave no depression in melting point when mixed with uranediol diacetate.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.2; H, 10.1.

The filtrate from the digitonide was concentrated to 10 cc. and diluted with 100 cc. of ether to precipitate the excess digitonin. This was filtered off and the filtrate after several washings with water was evaporated to dryness and the remaining oil was found to resist crystallization. The solution was evaporated to dryness and the oily residue was converted to the acetate by refluxing it for one hour with 10 cc. of acetic anhydride and evaporating the solution in vacuum. The residue was crystallized from methyl alcohol to yield the triacetate of triol (II) m. p. 188°. It gave no depression in melting point with the triacetate of triol (II) obtained previously m. p. 192°.

Partial Reduction of Uranetrione in Alcohol.—A suspension of 200 mg. of platinum oxide in a solution of 300 mg. of uranetrione in 200 cc. of ethyl alcohol and 100 cc. of ether was shaken with hydrogen at 3 atmospheres and 25° for one hour and then filtered from the catalyst. The filtrate was distilled to remove the ether and then added to a solution of 2 g. of digitonin and allowed to stand for eight hours. The digitonide (200 mg.) was decomposed as usual, giving 50 mg. of white solid which was purified by crystallization from methyl alcohol, m. p. 225° (fibrous clusters).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 76.0; H, 9.7.

A portion of this compound was converted to the acetate which melted at 250° (from alcohol).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.7; H, 9.2. Found: C, 73.6; H, 9.2.

Attempted Isomerization of Uranediol.—Uranediol (150 mg.) was dissolved in 50 cc. of xylene, 2 g. of sodium was added and the mixture was refluxed for nine hours. The recovered product was dissolved in 50 cc. of ethyl alcohol and treated with 2 g. of digitonin. The digitonide was filtered off, dried and heated in pyridine for one hour. The solution was diluted with ether and filtered, and the filtrate yielded on evaporation a product which on crystallization from acetone gave 100 mg. of the original uranediol, m. p. 214°. The portion not precipitated by digitonin could not be crystallized to a pure product.

The authors wish to express their thanks to Parke, Davis & Co. of Detroit, Michigan, for a grant of funds supporting this work.

Summary

The reduction products of uranetrione were studied and found to be uranediol, a new triol and uranol-3β-dione-11,20.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

A New Fluorination Method

BY ALBERT L. HENNE

Principle of the Method.—This paper reports the use of nascent mercuric fluoride as a method for replacing one or several halogen atoms by fluorine in various types of compounds. In practice, the method consists in passing a stream of hydrogen fluoride through a well-stirred mixture of mercuric oxide and the substance to be fluorinated. The reaction between the acid and the oxide occurs instantly, and so also does the one between the mercuric fluoride so generated and the organic material. Since a great deal of heat is evolved, means must be provided to prevent the reaction from escaping control, and also to avoid the loss of volatile or easily destroyed reaction products. These means vary with the substances undergoing fluorination and therefore merely call for some ingenuity.

Dry and Nascent Mercuric Fluoride.—The use of anhydrous mercuric fluoride as a fluorinating agent has been described before.[1] It was pointed out at the time that only the anhydrous salt could be used, and this statement was verified repeatedly. Attempts to manufacture the dry salt by methods more conventional than the action of fluorine upon mercuric chloride forced the conclusion that aqueous reagents invariably would yield a dihydrated salt which could not be converted to the anhydrous salt because it always would lose hydrofluoric acid in preference to water. In an effort to circumvent this, mercuric oxide and hydrogen fluoride were allowed to react in an inert organic liquid. This reaction generates one molecule of mercuric fluoride and only one

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[1] Henne and Midgley, THIS JOURNAL, **58**, 884 (1936).