[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XXV. Norechinocystenedione and Isonorechinocystenedione

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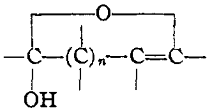
Oxidation of methyl echinocystate gives a diketomethyl ester which on saponification loses carbon dioxide to give norechinocystenedione. If echinocystic acid is oxidized directly, an isomeric product, "isonorechinocystenedione," is obtained.[3] While norechinocystenedione behaves normally, giving a dioxime, the ultraviolet absorption spectrum of isonorechinocystenedione does not show a maximum typical of a carbonyl group. However, it does react with hydroxylamine to give a product, the analysis of which corresponds to that of a monoxime. Alcoholic alkali converts isonorechinocystenedione into norechinocystenedione.[4]

As a working hypothesis, it was suggested[4] that the isodione might contain the structure of a hemiacetal of the monoenol form of a diketone, *i. e.*,



$$\overbrace{-\underset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}-(\underset{|}{\overset{|}{\mathrm{C}}})_n-\underset{|}{\mathrm{C}}=\underset{|}{\overset{|}{\mathrm{C}}}-}^{\mathrm{O}}$$

where *n* probably is 1 or 2.

Accordingly various possible reactions of a hemiacetal were attempted. Refluxing with acetic anhydride and pyridine for periods up to eight hours gave only starting material. With acetic anhydride and potassium acetate, however, the isodione was converted into norechinocystenedione. Prolonged refluxing with methyl alcoholic or ethyl alcoholic hydrogen chloride also converted the isodione to norechinocystenedione. After reaction with methyl iodide and silver oxide, the isodione was recovered for the most part unchanged although some resinous material was formed. In an effort to prepare a mercaptol, the isodione was refluxed with ethyl alcoholic hydrogen chloride containing butyl mercaptan. This treatment resulted in the formation of a new product which, however, was free of sulfur. The new compound forms only a monoxime and analyses indicate that the new compound is isomeric with the isodione and norechinocystenedione. It does not react with acetic anhydride and pyridine, indicating that no hydroxyl group has been formed by reduction, nor is it affected by boiling with alcoholic potassium hydroxide. The ultraviolet absorption spectrum (Fig. 1) shows a maximum at 252 mμ of high intensity (log ϵ = 4.0) which is characteristic of a double bond conjugated with a carbonyl group. The conjugation explains the formation of a monoxime since α,β-unsaturated ketones in the triterpenoid series may not react with carbonyl reagents.[5] The fact that the double bond migrates to a position of conjugation under comparatively mild conditions has an important bearing on the structure of echinocystic acid.[6]

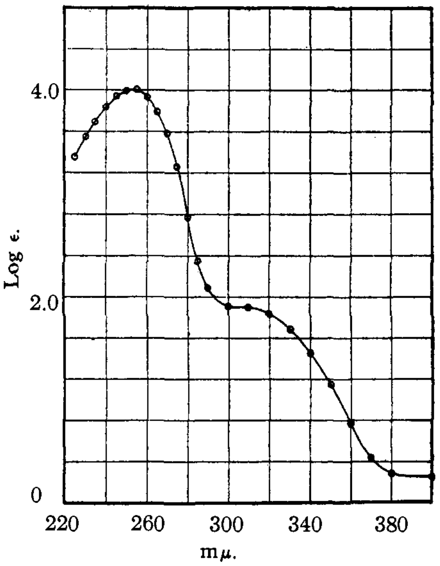


Fig. 1.—Ultraviolet absorption spectrum of conjugated norechinocystenedione.

Neither butyl mercaptan nor alcoholic hydrogen chloride alone will bring about the reaction, the combined action of hydrogen chloride and butyl mercaptan being required. We are not aware of any similar action of mercaptans and we have no ideas concerning the mode of action. Norechinocystenedione shows exactly the same behavior giving the same compound which will be called "conjugated norechinocystenedione," or simply "conjugated dione."

The absorption spectra of solutions of norechinocystenedione previously reported[4] were anomalous in that the intensity of the band at 300 mμ was too high (log ϵ = 2.75) and an unexplained maximum appeared at 250 mμ (Curve I, Fig. 2). The conversion of the nordione by butyl mercaptan to a compound containing a conjugated system indicated that the second maximum might be due to the presence of the conjugated dione as an impurity. Repeated crystallization of the nordione lowered the first maximum to log ϵ = 1.98 and shifted it slightly to 294 mμ, while the second maximum disappeared entirely (Curve II, Fig. 2).

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[3] White and Noller, THIS JOURNAL, **61**, 983 (1939).

[4] Jones Todd and Noller, *ibid.*, **61**, 2421 (1939).

[5] Voss, Klein and Lauer, *Ber.*, **70**, 122 (1937); Ruzicka and Cohen, *Helv. Chim. Acta*, **20**, 804 (1937); Spring and Vickerstaff, *J. Chem. Soc.*, 650 (1934), 249 (1937); *cf.* Kuhn and Brockmann, *Ann.*, **516**, 115 (1935).

[6] See paper XXVII, THIS JOURNAL, **66**, 1269 (1944).

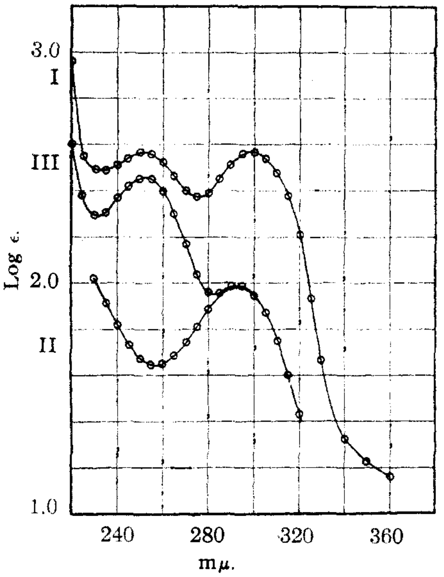

Fig. 2.—Ultraviolet absorption spectrum of impure norechinocystenedione (I), of pure norechinocystenedione (II), and of a 1:50 mixture of conjugated norechinocystenedione with norechinocystenedione (III).

The impurity, however, is not the conjugated dione as shown by Curve III, Fig. 2, which indicates the absorption of a mixture of one part conjugated dione and fifty parts of nordione. Although a second maximum is introduced, the intensity of the first maximum is not raised appreciably. This conclusion was confirmed by subjecting the nordione to prolonged treatment with alkali. No conjugated dione could be isolated but only a small amount of isonordione, indicating that the conversion of isodione to nordione is reversible. It has not been possible to isolate any other compound from the mother liquors and the nature of the impurity remains unknown. It has been found also that some nordione can be isolated from the mother liquors from the isolation of the isodione obtained by the direct oxidation of echinocystic acid.

Experimental

Isomerization of Isonorechinocystenedione to Norechinocystenedione.—A solution of 1.6 g. of isodione[3] in 30 cc. of acetic anhydride containing 1 g. of fused potassium acetate was refluxed for five hours. To the dark brown solution was added 50 cc. of methanol to destroy the excess acetic anhydride. The solution stood overnight and then was warmed gently on the steam-bath to insure complete reaction. Decoloration with Norite and concentration to a small volume did not result in crystallization, so the solution was poured into a large volume of water, precipitating a brown amorphous material which weighed 0.7 g. and melted at 170–192°. This material was crystallized from methanol four times and gave 0.2 g. of bright rod-like material melting at 203–205°. No depression of melting point was observed when mixed with norechinocystenedione; $[\alpha]^{29}\text{D}$ −94.2°, $[\alpha]^{28}_{546}$ −113° in dioxane. *Anal.* Calcd. for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 81.70; H, 10.02. No other crystalline product could be isolated from the mother liquors.

The *dioxime* was prepared by dissolving 0.8 g. of the acetic anhydride product in 225 cc. of 95% ethanol containing 0.49 g. of hydroxylamine hydrochloride and 0.61 g. of fused potassium acetate and refluxing for three hours. Dilution with water gave a product which after four crystallizations from methyl alcohol melted at 246–249° with decomposition when placed in a preheated bath at 225°; $[\alpha]^{23}\text{D}$ −127° in dioxane. *Anal.* Calcd. for $C_{29}H_{46}O_2N_2$: C, 76.60; H, 10.20; N, 6.16. Found: C, 76.57; H, 10.60; N, 5.77. No depression in melting point was observed when mixed with the dioxime of norechinocystenedione: $[\alpha]^{25}\text{D}$ −128°, $[\alpha]^{25}_{546}$ −136° in dioxane.

In the early work depressions on mixing the acetic anhydride product with the nordione were observed but an exhaustive investigation of more highly purified products has shown conclusively that the two products are identical. Besides the failure to obtain depressions in mixed melting point determinations on the compounds and their oximes and the identity of optical rotations, identical solubility behavior and crystal form has been observed. Moreover, crystals of the acetic anhydride product and of the nordione each show two indices of refraction which are identical for both, namely, $n^{20}\text{D}$ 1.546 and 1.582.

A solution of 0.6 g. of isodione in 20 cc. of pyridine containing 3 cc. of acetic anhydride was refluxed eight hours. Precipitation by water gave material which after three crystallizations from methanol melted at 210–217° and showed no depression in melting point when mixed with isodione. A second fraction from the mother liquor also proved to be identical with the starting material.

Through a refluxing solution of 1.2 g. of isodione in 150 cc. of absolute ethyl alcohol was passed a continuous stream of dry hydrogen chloride for sixteen hours. Concentration and dilution with water gave 1.1 g. of material which after four crystallizations from methanol melted at 201–205°; $[\alpha]^{25}\text{D}$ −90.0 in dioxane. No depression in melting point was observed on mixing with norechinocystenedione.

Refluxing a solution of 0.8 g. of isodione in 150 cc. of absolute methanol containing 3% hydrogen chloride for seventeen hours gave 0.65 g. of material which was difficult to purify. After many crystallizations from methyl alcohol a small quantity of material was obtained which melted at 199–203° and showed no depression in melting point when mixed with norechinocystenedione.

To a solution of 0.6 g. of isodione in 100 cc. of anhydrous dioxane was added 3 cc. of methyl iodide and 0.5 g. of silver oxide, and the suspension refluxed for twenty-four hours. At the end of each hour 0.2 g. of silver oxide was added, and at the end of every three hours about 2 cc. of methyl iodide was added. Concentration, filtration of silver salts, and evaporation of the solution to dryness gave a residue which was crystallized from methanol three times. The product melted at 212–217° and showed no melting point depression when mixed with the isodione. Material obtained from the mother liquid melted at 183–189° and was quite resinous.

A solution of 1 g. of norechinocystenedione and 0.4 g. of potassium hydroxide in 75 cc. of 95% ethyl alcohol was refluxed for thirty-four hours. Concentration and precipitation by water gave a product which on crystallization from methanol gave a mixture of two definite crystalline compounds. The crystals were large enough to be separated mechanically. The large yellow resinous crystals were crystallized from methyl alcohol four times and gave 0.42 g. of material melting at 203–206° which did not depress the melting point of norechinocystenedione. The small round white colony-like crystals were crystallized from methanol and yielded 0.08 g. of material which melted at 210–215° and did not depress the melting point of isodione. About 0.2 g. of the mixed crystals was obtained in which the crystals were so small that they could not be separated mechanically. Separation by fractional crystallization alone was not successful. From the mother liquors of the preparation of isodione by the direct oxidation of echinocystic acid, a mixture of two crystalline products has been obtained which likewise proved to be isodione and nordione.

Isomerization of Isonorechinocystenedione and Norechinocystenedione to Conjugated Norechinocystenedione.

—To a solution of 3 g. of isodione in 275 cc. of absolute ethyl alcohol was added 2 cc. of *n*-butyl mercaptan. The solution was refluxed for sixteen hours during which time dry hydrogen chloride was bubbled through continuously. Evaporation to 50 cc. and precipitation by pouring into ice, and water gave 1.87 g. of amorphous material which was washed repeatedly with hot water. Five crystallizations from methanol including decolorization with Norite gave a product melting at 236–242°; $[\alpha]^{25}\text{D}$ +45.3°; $[\alpha]^{26}_{546}$ +56.1° in chloroform. *Anal.* Calcd. for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 82.01; H, 10.74.

A strong positive test for unsaturation was obtained with tetranitromethane. The compound contained no sulfur as was shown by testing for sulfide ion after fusion with sodium. Treatment with cold acetic anhydride and pyridine or refluxing four hours with acetic anhydride and potassium acetate gave only the unchanged conjugated dione.

An **oxime** was prepared by refluxing 0.96 g. of conjugated dione, 0.49 g. of hydroxylamine hydrochloride, and 1.23 g. of fused potassium acetate in 125 cc. of methanol for five hours. On cooling 0.61 g. of crystalline material was obtained which, after four crystallizations from methyl alcohol, melted with decomposition at 269–271° when placed in a heated bath at 250°; $[\alpha]^{25}\text{D}$ −23.4° in dioxane. Although there is no depression in decomposition point on mixing with the oxime of isodione, the rotation of the latter compound is $[\alpha]^{26}\text{D}$ +22.0°, $[\alpha]^{26}_{546}$ +28.2° in dioxane. *Anal.* Calcd. for a monoxime, $C_{29}H_{45}O_2N$: C, 79.22; H, 10.32; N, 3.18. Found: C, 79.00; H, 10.16; N, 3.90.

Treatment of 0.52 g. of nordione in 60 cc. of absolute ethyl alcohol and 1 cc. of *n*-butyl mercaptan with hydrogen chloride as described previously for the isodione gave a product which melted at 236–242°, $[\alpha]^{22}\text{D}$ +42.7° in dioxane, and showed no depression in melting point when mixed with conjugated dione.

Refluxing 1 g. of isodione with 1 cc. of *n*-butyl mercaptan in 100 cc. of 95% ethyl alcohol for sixteen hours without the addition of hydrogen chloride yielded material on concentration which melted at 219–225° and showed no melting point depression on mixing with isodione. The mother liquors gave only isodione.

A solution of 0.110 g. of conjugated dione and 0.3 g. of potassium hydroxide in 30 cc. of 95% ethyl alcohol was refluxed for four hours. Water was added to the hot solution to turbidity, and on cooling a white crystalline product was obtained which after two crystallizations from methyl alcohol melted at 234–242° and showed no melting point depression on mixing with the starting material.

Absorption Spectra.—The absorption spectrum of the conjugated dione was determined first by Dr. R. Norman Jones in the Chemical Laboratory of Harvard University, using a quartz spectrograph in conjunction with a Hilger Spekker photometer and we wish to express our appreciation of his help. This work has been duplicated and the other spectra obtained using a Beckman quartz photoelectric spectrophotometer.

Summary

1. Treatment of isonorechinocystenedione with either alcoholic hydrogen chloride, acetic anhydride and potassium acetate, or alcoholic potassium hydroxide leads to isomerization to norechinocystenedione. Prolonged action of alcoholic potassium hydroxide on pure norechinocystenedione gives some isonorechinocystenedione indicating that the conversion of isodione to nordione is reversible

2. Prolonged treatment of either isodione or nordione with alcoholic hydrogen chloride in the presence of butyl mercaptan gives a new isomer designated as "conjugated norechinocystenedione" in which the double bond has become conjugated with one of the carbonyl groups as shown by the ultraviolet absorption spectrum.

3. The abnormally high absorption and the second maximum reported previously for the nordione are due to an impurity. That this impurity is not conjugated nordione is indicated by the fact that the absorption curve of the impure compound cannot be duplicated by mixtures of nordione and conjugated nordione.

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Saponins and Sapogenins. XXVI. The Conversion of Echinocystic Acid into Oleanolic Acid

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While it has been possible to show that echinocystic acid and oleanolic acid have the same carbon skeleton,[1] attempts to interrelate the compounds more closely were unsuccessful.[2] The indications, however, are that echinocystic acid differs from oleanolic acid in having an additional hydroxyl group β to the carboxyl group. If it were possible to replace the β-hydroxyl group in echinocystic acid by hydrogen under conditions which did not involve rearrangement, one would expect to obtain oleanolic acid. Among various procedures which have been tried to bring this about, an attempt was made to replace the β-hydroxyl group by iodine using the series of reactions worked out by Helferich[3] for the sugars, namely, formation of the methanesulfonyl (mesyl) derivative and reaction with sodium iodide to replace the methanesulfonate group by iodine. It was expected that it would be possible to remove the iodine from an iodo derivative by reduction.

For this purpose the monoacetyl derivative of methyl echinocystate prepared by direct esterification with acetic acid was used as a starting point. In this compound the hydroxyl group which is not β to the carboxyl group is acetylated while the β-hydroxyl group is free.[4] Reaction with methanesulfonyl chloride in pyridine gave methyl acetylmesylechinocystate. When this

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(1) Todd, Harris and Noller, THIS JOURNAL, **62**, 1624 (1940).

(2) Harris and Noller, *ibid.*, **66**, 1005 (1944).

(3) Helferich, *Ber.*, **71**, 712 (1938).

(4) White and Noller, THIS JOURNAL, **61**, 983 (1939).