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Saponins and Sapogenins. IX. Oxidation of Echinocystic Acid and Derivatives

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Echinocystic acid, I, has been shown[1] to be a triterpenoid sapogenin of the empirical formula $C_{30}H_{48}O_4$ and to have as functional groups two hydroxyls, one carboxyl and a double bond. Because of the marked difference in the rates of hydrolysis of the two acetyl groups in the diacetate of echinocystic acid, it was assumed[1a] that one of the hydroxyl groups is primary and the other secondary. On attempting to prove this assumption by oxidation, it has been found to be incorrect.

Methyl echinocystate, II, on oxidation with dichromic acid at 25° was converted to a neutral compound, III, without the formation of acidic products. The oxidation product gave only a monoxime and one active hydrogen was found by a Zerewitinow determination. However, the compound was unchanged by attempted acetylation and benzoylation and the possibility that a rearrangement to a tertiary hydroxyl had taken place under the influence of the acid seemed to be excluded by the fact that the oxidation product could be distilled unchanged at 2.5 mm. Furthermore when methyl echinocystate was treated with the same concentrations of sulfuric and acetic acids used during the oxidation, the sole product obtained was a monoacetate of the methyl ester, VII, which was shown not to be a rearranged product by further acetylation to the diacetate and deacetylation to methyl echinocystate.

The answer to these seemingly contradictory results appeared when it was found that the oxidation product could be saponified readily in contrast to methyl echinocystate, which is resistant to alcoholic alkali. The product of saponification proved to be a neutral diketone, IV, having one less carbon atom than echinocystic acid. Both of the hydroxyl groups in echinocystic acid therefore are secondary and one is in a β-position to the carboxyl group. The formation of only monocarbonyl derivatives from a diketone in which one carbonyl group is β to a carboethoxy group has been noted[2] and the increased ease of saponification of carbomethoxy groups when β to a carbonyl group has been reported in the case of the methyl esters of glycyrrhetinic acid and ketoöleanolic acid[3] and of β-boswellic acid.[4] The active hydrogen shown by the Zerewitinow determination may be ascribed to enolization although the ferric chloride test for enols was negative. A direct proof that the oxidation product was indeed a diketomethyl ester was obtained when it was found that while Clemmensen reduction removed only one carbonyl group, the product, V, was saponifiable with loss of carbon dioxide to give VI.

It was of interest to determine which of the two hydroxyl groups was esterified in the direct esterification mentioned previously. Oxidation of the monoacetate, VII, with chromium tri-

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[1] (a) Bergsteinsson and Noller, THIS JOURNAL, **56**, 1403 (1934); (b) Noller, *ibid.*, **56**, 1582 (1934).

[2] Vorländer, *Ann.*, **294**, 264 (1897).

[3] Ruzicka, Leuenberger and Schellenberg, *Helv. Chim. Acta*, **20**, 1271 (1937).

[4] Simpson and Williams, *J. Chem. Soc.*, 686 (1938).

oxide in acetic acid solution gave a keto acetyl methyl ester, VIII, which did not form an oxime. On saponification it gave a hydroxy ketone, IX, with loss of carbon dioxide. Oxidation of the hydroxy ketone gave the same diketone, IV, obtained by the saponification of the oxidation product of methyl echinocystate. It was proved, therefore, that the more readily esterifiable hydroxyl group was that which was not β to the carboxyl group.

With the above information in hand it was obvious that one should be able to obtain the decarboxylated diketone, IV, by direct oxidation of echinocystic acid. Such, however, was found to be not the case. Oxidation gave a decarboxylated diketone, X, but the physical properties were entirely different from those of the product obtained through the methyl ester. It had a high positive rotation instead of a high negative rotation, the melting point was about 20° higher, and a mixed melting point of the two showed a marked depression.

The most plausible explanation of these results seemed to be that a racemization of the asymmetric tertiary carbon atom to which the carbomethoxy group had been attached had taken place under the influence of the alkali during the saponification of the diketo methyl ester. This hypothesis was disproved by the following series of reactions, all of which were carried out under acid conditions. Echinocystic acid was converted to the monoacetate, XI, by means of acetic acid and sodium acetate. This monoacetate on oxidation gave the acetate of a hydroxy ketone, XII, with loss of carbon dioxide. The acetyl group was removed by acid alcoholysis to give the hydroxy ketone, IX, identical with that obtained by the alkaline saponification of the acetyl keto methyl ester, VIII. Any rearrangement, therefore, takes place only during the oxidation of free echinocystic acid and *this rearrangement is prevented either by methylation of the carboxyl group or by acetylation of the hydroxyl group which is not β to it.* While it is difficult to see what type of rearrangement would be prevented by esterification of either a hydroxyl or a carboxyl group, it is equally difficult to see how this mutual effect could exist if the hydroxyl and carboxyl groups were not relatively near to each other. Since the other hydroxyl group is β to the carboxyl group, all of the functional groups must be relatively near each other, a conclusion previously drawn from the measurement of the area of monomolecular films of echinocystic acid and its derivatives.[5,6]

Previous work[1,5] has shown that echinocystic acid must be closely related in structure to other triterpenoids such as oleanolic acid and hederagenin, since selenium dehydrogenation yields the same naphthalene and picene derivatives. The isolation of the same trimethylnaphthol may be considered as strong evidence that one of the hydroxyl groups occupies the same position in all of these compounds. The non-reactivity of the double bond and the resistance of the methyl esters to saponification would indicate that these groups are located in echinocystic acid similarly to the same groups in hederagenin and oleanolic acid. Further evidence along this line has now been obtained by the preparation of a bromolactone diacetate, XIII, and of a hydrogen peroxide oxidation product of the methyl ester diacetate, XIV, reactions characteristic of oleanolic acid and hederagenin.[7]

In view of the inability of the more widely discussed formulas to explain completely certain experimental facts concerning the better known triterpenoids,[8] it does not seem of value to discuss the behavior of echinocystic acid in terms of these formulas, especially since it has not been shown to be interconvertible with these compounds. Echinocystic acid resembles β-boswellic acid in that both are β-hydroxy acids[4] and in that the hydroxyl, carboxyl and double bond of β-boswellic acid appear to be near each other.[9] We believe, however, that it is unlikely that echinocystic acid has its carboxyl in the 1-position and one hydroxyl in the 2-position as postulated for β-boswellic acid, since echinocystic acid readily loses both the carboxyl and hydroxyl on heating above 300°. and if this hydroxyl were in the 2-position one would not expect to obtain the 2-hydroxy-1,5,6-trimethylnaphthalene or the 1,2,-5,6-tetramethylnaphthalene on selenium dehy-

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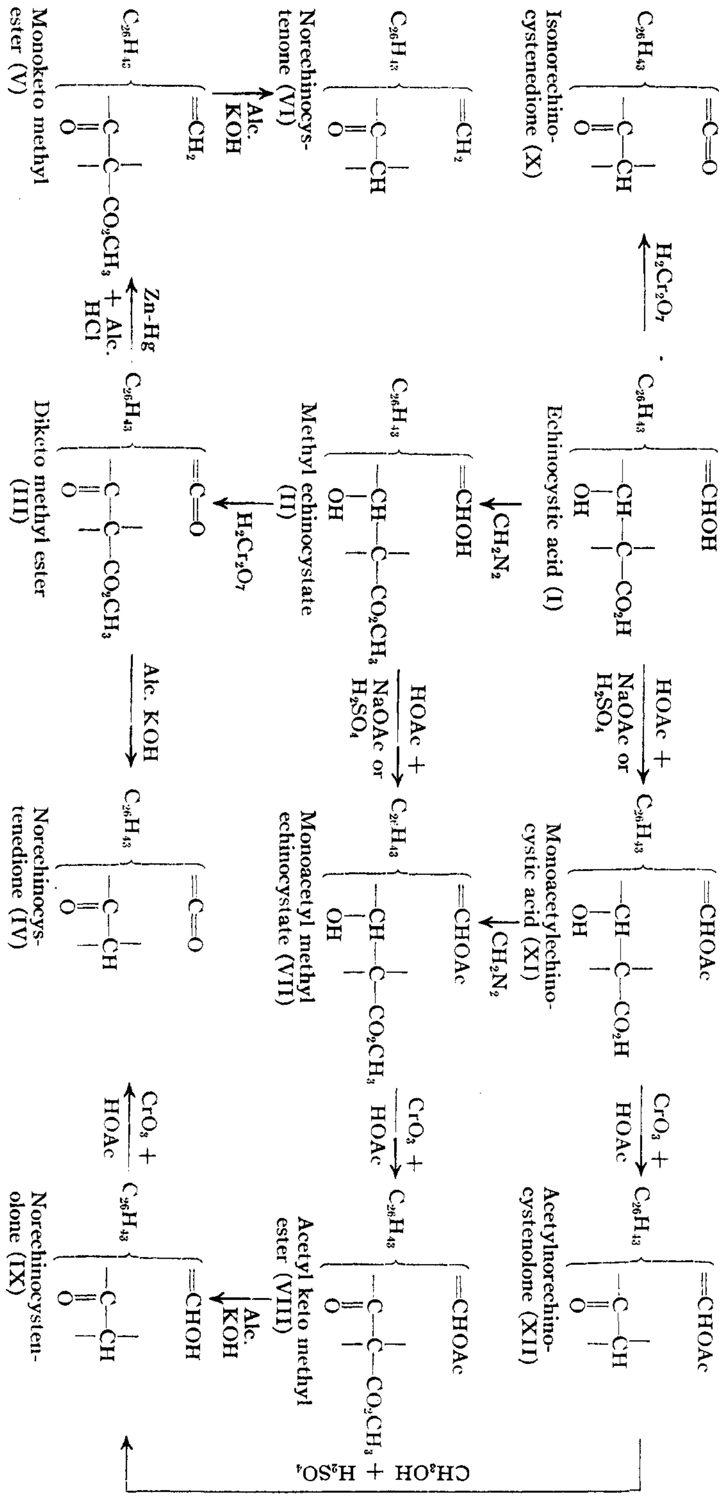
(5) Noller, This Journal, **60**, 1938 (1938).

(6) The experimental evidence of Kitasato [*Acta Phytochim. (Japan)*, **10**, 199 (1937)] for placing the carboxyl group of hederagenin and oleanolic acid at the union of the A and B rings has been shown to be in error [Kitasato, *ibid.*, **10**, 239 (1938); Ruzicka and Sluys-Veer, *Helv. Chim. Acta*, **21**, 1371 (1938)].

(7) Winterstein and Wiegand, *Z. physiol. Chem.*, **199**, 46 (1931); Kitasato and Sone, *Acta Phytochim. (Japan)*, **6**, 199 (1932); Ruzicka and Cohen, *Helv. Chim. Acta*, **20**, 804 (1937).

(8) Haworth, *Ann. Reports Prog. Chem.*, **34**, 327 (1937); Beynon, Sharples and Spring, *J. Chem. Soc.*, 1233 (1938); Beynon, Heilbron and Spring, *Nature*, **142**, 434 (1938); Simpson, *J. Chem. Soc.*, 1313 (1938); Ruzicka, Cohen, Furter and Sluys-Veer, *Helv. Chim. Acta* **21**, 1735 (1938).

(9) Simpson and Williams, *J. Chem. Soc.*, 1712 (1938).



drogenation. One cannot help but wonder, of course, whether the results of selenium dehydrogenation may not be leading chemists astray in their speculations on the structure of this class of compounds.

Two points concerning the physical properties of this series of compounds are worthy of special mention. The first is the rather disconcerting tendency to exist in two crystal forms. Thus two compounds having different melting points but apparently the same chemical properties have been obtained in the case of the diketo methyl ester, III, the monoacetyl methyl ester, VII, the acetyl keto methyl ester, VIII, and norechinocystenolone, IX. In no case did one form cause a lowering of the melting point of the other.

The second point of interest concerns the specific rotation, since most of the compounds can be placed into three groups, the members of each group having approximately the same rotation. Using the values for the green line of mercury, echinocystic acid,[1a] methyl echinocystate[1a] and their monoacetyl derivatives, VII and XI, made by direct esterification, have specific rotations from +33 to +41°; that is, esterification of the carboxyl group or of the hydroxyl which is not β to it has little effect on the rotation. Diacetylechinocystic acid,[1a] its methyl ester,[1a] the monoketo methyl ester, V, and its acetyl derivative, VIII, have specific rotations from −15 to −18°; that is, either esterification of the β-hydroxyl group or its oxidation to a keto group produces a marked decrease in rotation, the esterification of the other hydroxyl group or of the carboxyl group again being without effect. The positive rotations are evidently caused by hydrogen bond formation between the hydrogen of the β-hydroxyl group and the carbonyl group of the carboxyl. The change must be due entirely to a change in the contribution of the carbon atom to which the carboxyl group is united since destruction of the asymmetry of the adjacent carbon atom by oxidation of the secondary hydroxyl to a carbonyl group has no greater effect than acetylation of the hydroxyl group, unless racemization takes place during acetylation. Norechinocystenolone, IX, and norechinocystenedione, IV, have rotations of

−106 and −115°, decarboxylation producing a very marked change. Here again it appears that the carbon atom to which a secondary hydroxyl group is attached, this time the one not β to the carboxyl group, makes very little contribution to the total rotation since oxidation to the carbonyl group has comparatively little effect. Two compounds do not fall quite into line with the above observations. The diketo methyl ester, III, has a rotation of −1.6° instead of an expected rotation of about −15°, or if one takes into account the 11° difference between IV and IX, of −26°. Similarly acetylnorechinocystenolone, XII, has a rotation of −65° instead of −106°, the value for the deacetylated compound. Most surprising of all is the high positive rotation of +103° for the isomeric norechinocystenedione, X. This may be due to racemization of the carbon atom which carried the carboxyl group, since norechinocystadienol in which this carbon atom carries a double bond has a rotation of +100°.

It is of interest to note that no such marked changes in rotation have been observed for hederagenin and oleanolic acid or their derivatives including the decarboxylated compounds. On the other hand, the change in rotation, using the series of higher rotation, in going from β-boswellic acid or its methyl ester to their acetates[9] is in the same direction and equal to that on acetylating the β-hydroxyl group of echinocystic acid. The change in going from methyl β-boswellate to nor-β-boswellenone, however, is much less than that from methyl echinocystate, II, to norechinocystenolone, IX.

Experimental

Diketo Methyl Ester, III.—To a solution of 10.4 g. of methyl echinocystate[1a] in 250 cc. of glacial acetic acid at room temperature was added with stirring 29 g. of a solution of 60 g. of crystalline sodium dichromate and 80 g. of concentrated sulfuric acid in 270 g. of water.[10] After standing for thirty minutes the excess dichromic acid was destroyed by the addition of methyl alcohol, the solution heated to 100° and water added to turbidity. After cooling and allowing to crystallize, the precipitate was filtered and washed with water until white. The product weighed 9.5 g. and melted at 161–167°. The crude product was dissolved in ether and the solution extracted with 10% aqueous sodium hydroxide. Practically nothing separated on acidifying the alkaline wash. After evaporation of the ether, the residue was crystallized twice from methyl alcohol when it melted at 166–168°; $[\alpha]^{23}\text{D}$ +1.6°, $[\alpha]^{23}_{546}$ −1.6° in dioxane.

Anal.[11] Calcd. for $C_{31}H_{46}O_4$: C, 77.13; H, 9.61; one OH, 3.52. Found: C, 76.98, 77.16; H, 9.60, 9.60; OH (by Zerewitinow), 3.45, 3.50.

A positive test for unsaturation was obtained with tetranitromethane. The ferric chloride and Zappi[12] tests for enolic hydroxyl were negative as was Connor's test[13] for an active methylene group. After boiling with acetic anhydride and sodium acetate, heating in benzene solution with benzoyl chloride and pyridine or distillation at 2.5 mm., the compound was recovered unchanged.

An **oxime** was prepared by adding 1 g. of the oxidation product to a solution of 0.5 g. of hydroxylamine hydrochloride in 1 cc. of water and 2 cc. of 10% sodium hydroxide. Sufficient methyl alcohol was added until everything was in solution at the boiling point and the solution refluxed for one and one-half hours. The solution was concentrated and the insoluble portion crystallized from methyl alcohol, after which it sintered at 254° and melted at 257.5–259.5°; $[\alpha]^{21}\text{D}$ −50.0°, $[\alpha]^{21}_{546}$ −61.8° in dioxane.

Anal. Calcd. for a monoxime, $C_{31}H_{47}O_4N$: C, 74.80; H, 9.52; N, 2.81. Found: C, 74.51, 74.52; H, 9.51, 9.51; N, 3.07, 2.76.

A **phenylhydrazone** was obtained by adding to a solution of 0.5 g. of the oxidation product in methyl alcohol, a solution of 1 g. of phenylhydrazine hydrochloride and 1.5 g. of sodium acetate in 4 cc. of water and refluxing. About two minutes after adding the phenylhydrazine solution a canary-yellow solid started to separate. After refluxing for two hours and standing overnight, the precipitate was crystallized from methyl alcohol. On heating in a melting-point tube the substance liquefied at 178° and then vaporized explosively without visible products of decomposition. Two more crystallizations raised the melting point to 179.5° with the same type of decomposition; $[\alpha]^{20}\text{D}$ −60.4, $[\alpha]^{20}_{546}$ −97.7 in dioxane.

Anal. Calcd. for a monophenylhydrazone, $C_{37}H_{50}O_3N_2$: C, 77.85; H, 8.83; N, 4.92. Found: C, 73.45; H, 8.84; N, 4.75.

The low value found for carbon probably is due to the behavior of the compound on heating. It is surprising that a hydrazone should be so highly colored.

The oxidation product could not be made to condense with *o*-phenylenediamine or with benzaldehyde. On shaking a solution in ethyl alcohol with hydrogen in the presence of platinum for several days, the absorption of hydrogen did not appear to be greater than would be caused by slow leaks and diffusion through the rubber tubing. On concentrating the alcohol, however, a product was obtained which melted at 189–193° and after two recrystallizations from methyl alcohol at 192–194°. This product gave an oxime which melted at 260–263° and no lowering of the melting point occurred when mixed with the oxime of the original oxidation product. On mixing the material, m. p. 192–194°, with the oxidation product, m. p. 166–168°, a melting point of 168–189° was obtained. Apparently the oxidation product exists in two crystal forms.

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[10] Kiliani and Merk, *Ber.*, **34**, 3564 (1901).

[11] All carbon, hydrogen and nitrogen analyses are by Dr. A. Schoeller, Berlin.

[12] Zappi, *Bull. soc. chim.*, [4] **51**, 54 (1932).

[13] Connor, This Journal, **58**, 1131 (1936).

Attempts to oxidize methyl echinocystate with acetone and aluminum isopropoxide or aluminum tertiary butoxide did not lead to a pure product.

Norechinocystenedione, IV.—A solution of 2 g. of the diketo methyl ester, III, and 4 g. of potassium hydroxide in 75 cc. of 95% alcohol was refluxed for five hours. Almost immediately after heating, the solution turned a deep reddish-orange color. The solution was concentrated to 35 cc. under reduced pressure and 300 cc. of water added. The resulting suspension was extracted with ether and the clear orange-colored water layer acidified, when the solution became colorless and about 0.02 g. of a white precipitate formed. This precipitate was rather sticky and turned orange again on treating with alkali. It was not further investigated. The colorless ether layer was evaporated and the residue, weighing 1.92 g., was dissolved in hot methyl alcohol. On cooling, glassy beads were formed which crystallized after standing for several days and melted at 184–192°. After four recrystallizations from methyl alcohol there was obtained 0.64 g., m. p. 210–212°; $[\alpha]^{24}_{\rm D}$ −92.7°; $[\alpha]^{24}_{546}$ −115.3° in dioxane. This material did not change color on treating with alkali.

Anal. Calcd. for $C_{29}H_{44}O_2$: C, 82.03; H, 10.43. Found: C, 82.01; H, 10.45.

Monoketo Methyl Ester, V.—Of the various modifications of the Clemmensen reduction that were tried, the following procedure gave the best results. To a solution of 3 g. of the diketo methyl ester, III, in 200 cc. of 95% ethyl alcohol was added 25 g. of mossy zinc which had previously been amalgamated with 5 g. of mercuric chloride. Hydrogen chloride was passed in continuously while the mixture was refluxed for thirty-five hours. After evaporation to 70 cc. under reduced pressure and filtering, there was obtained 2.5 g., m. p. 176–187°. After five crystallizations from methyl alcohol there was obtained 0.91 g., m. p. 209–212°; $[\alpha]^{22}_{\rm D}$ −10.3°, $[\alpha]^{22}_{546}$ −15.0° in dioxane.

Anal. Calcd. for $C_{31}H_{48}O_3$: C, 79.43; H, 10.33; one OH, 3.63. Found: C, 79.13, 79.28; H, 10.22, 10.31; OH, 3.59, 3.45.

On attempting to acetylate and form an oxime by the usual procedures, only unchanged starting material was recovered. A positive test for unsaturation was obtained with tetranitromethane but tests for enolic hydroxyl were negative.

Norechinocystenone, VI.—A solution of 1.3 g. of the Clemmensen reduction product, V, and 4 g. of potassium hydroxide in 75 cc. of 95% alcohol was refluxed for four hours. In contrast to the saponification of the diketo methyl ester, III, the solution remained colorless. Water was added to the boiling solution to turbidity and after cooling 0.93 g. of material, m. p. 217–224°, was obtained. Six crystallizations from methyl alcohol gave a product melting at 230–233°.

Anal. Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.30. Found: C, 84.58; H, 11.24.

Monoacetyl Methyl Echinocystate, VII.—To a solution of 8 g. of methyl echinocystate, II, in 250 cc. of glacial acetic acid was added with stirring a solution of 5 cc. of concentrated sulfuric acid and 5 cc. of water. After standing for three hours at room temperature the acetic acid was removed under reduced pressure until a pasty mass of crystals was obtained. Filtration gave 3.2 g. of material, m. p. 200–204°, and on adding water to the mother liquor an additional lot was obtained. After two crystallizations from methyl alcohol it melted at 205–208°; $[\alpha]^{22}_{\rm D}$ +27°, $[\alpha]^{22}_{546}$ +32.8° in dioxane.

Anal. Calcd. for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91; acetyl, 8.13. Found: C, 74.70; H, 9.80; acetyl, 8.55, 8.25.

Acetylation with acetic anhydride gave the diacetyl methyl ester and acid alcoholysis regenerated methyl echinocystate.

Monoacetylation was carried out also by refluxing 11 g. of methyl echinocystate and 1 g. of fused sodium acetate in 100 cc. of glacial acetic acid for twelve hours. After concentrating under reduced pressure to 25 cc., filtering and crystallizing three times from methyl alcohol there was obtained 4.6 g. of a product, m. p. 170–171°; $[\alpha]^{21}_{\rm D}$ +29.1°, $[\alpha]^{21}_{546}$ +34.6° in dioxane. A mixed melting point with the product, m. p. 205–208°, melted at 173–203°. A sample of the product, m. p. 170–171°, which had stood for five months was found to melt at 170–199°. Three crystallizations from methyl alcohol raised the melting point to 206–209°. The monoacetate evidently exists in two crystalline forms, the higher melting being the more stable. As shown below, both products gave the same acetyl keto methyl ester on oxidation.

Acetyl Keto Methyl Ester, VIII.—To a solution of 2.5 g. of the monoacetyl methyl ester, m. p. 169–171°, in 25 cc. of glacial acetic acid was added 0.38 g. of chromium trioxide. After stirring for five hours at room temperature all of the chromium trioxide had been used and the solution was heated and water added at the boiling point until turbid. After cooling, the precipitate was filtered and dried, dissolved in ether and extracted with 10% aqueous potassium hydroxide. No acid fraction was obtained. Evaporation of the ether and crystallization of the residue from methyl alcohol gave 1.32 g., m. p. 200–203°. Three recrystallizations raised the melting point to 203–205°; $[\alpha]^{21}_{\rm D}$ −9.8°; $[\alpha]^{21}_{546}$ −17.7° in dioxane.

Anal. Calcd. for $C_{33}H_{50}O_5$: C, 75.24; H, 9.57. Found: C, 75.21; H, 9.65.

The compound showed an unusual behavior during Zerewitinow determinations. After thirty minutes' reaction the volumes of methane evolved corresponded in two determinations to 4.75 and 4.83% of hydroxyl but methane was still being evolved slowly so that after four hours the methane in three determinations corresponded to 7.0, 6.5 and 6.7% of hydroxyl. The value calculated for one hydroxyl is 3.23 and for two 6.46%.

The compound gave a positive test with tetranitromethane but negative tests for enol. No oxime could be obtained by the usual procedure.

Oxidation of the monoacetyl methyl ester of m. p. 206–209° gave a product identical with the above as shown by melting point and mixed melting point determinations.

On refluxing this oxidation product for two hours with acetic anhydride and sodium acetate, a compound was obtained melting after four crystallizations at 229–232°. Also in one oxidation of the monoacetyl methyl ester a crude product melting at 220–245° was obtained which, after crystallization from methyl alcohol, methyl alcohol and benzene, and 80% aqueous acetic acid, melted at

231–234°. A mixed melting point with the compound from the acetylation mixture showed no depression and with the oxidation product of m. p. 203–205°, the mixed melting point was 203–230°. The rotation of the higher melting compound was $[\alpha]^{20}_{\mathrm{D}}$ −9.0° and $[\alpha]^{20}_{546}$ −16.8° in dioxane, the same as that of the lower melting compound within experimental error. Apparently here again the compound is dimorphous.

Norechinocystenolone, IX.—A solution of 1.5 g. of the acetyl keto ester, VIII, m. p. 201–204°, and 5 g. of potassium hydroxide in 150 cc. of ethyl alcohol was refluxed for three and one-half hours. The orange colored solution was concentrated to 70 cc. and 150 cc. of ether and 300 cc. of water added. After shaking, the colored alkaline layer was separated and gave on adding excess acid a very small colorless precipitate which was not further investigated. The colorless ether solution was evaporated and the residue crystallized from methyl alcohol, giving 0.75 g., m. p. 222–225°. After four more crystallizations the melting point remained constant at 230–233°; $[\alpha]^{21}_{\mathrm{D}}$ −86.7°, $[\alpha]^{21}_{546}$ −106.0° in dioxane.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.88; one OH, 4.01. Found: C, 81.92; H, 10.74; OH (by Zerewitinow), 2.7.

The compound gave a positive test for unsaturation with tetranitromethane and negative tests for enolic hydroxyl.

In another saponification carried out under the same conditions, the product from the first crystallization melted at 216–220°. After nine recrystallizations the melting point reached 268–271°. A mixed melting point with the product, m. p. 230–233°, melted at 231–270°. Although no further attempt was made to establish the chemical identity of these compounds, they are apparently dimorphs.

To a solution of 0.67 g. of the compound, m. p. 230–233°, in 25 cc. of glacial acetic acid was added with stirring a solution of 0.084 g. of chromium trioxide in 5 cc. of water. After standing for three hours at room temperature the solution was heated to boiling and water added until turbid. After cooling, the precipitate was filtered, dried and crystallized from methyl alcohol when it melted at 207–211°. After three recrystallizations the melting point remained constant at 210–212°; $[\alpha]^{25}_{\mathrm{D}}$ −93.7°, $[\alpha]^{25}_{546}$ −116.8°. A mixed melting point with the starting material, IX, melted at 202–208° whereas no depression in the melting point was observed on mixing with norechinocystenedione, IV, m. p. 209–212°.

Isonorechinocystenedione, X.—To a solution of 0.5 g. of echinocystic acid in 25 cc. of glacial acetic acid at 25° was added 2.9 g. of Kiliani's dichromic acid mixture.[10] A green gum separated on shaking. After standing for one-half hour, the excess dichromic acid was destroyed by the addition of methyl alcohol, a small amount of water was added and the mixture heated to boiling until all was in solution. More water was added at the boiling point until the solution remained turbid, and after cooling the solid was filtered and washed with water. It was dried, dissolved in ether and shaken with 5% sodium hydroxide solution. No precipitate formed on acidifying the alkaline layer. The ether solution was dried over potassium carbonate, the ether removed and the residue crystallized three times from methyl alcohol when it melted at 230–233°; $[\alpha]^{22}_{\mathrm{D}}$ +85.6°, $[\alpha]^{22}_{546}$ +103.2° in dioxane. A mixture with norechinocystenedione, IV, m. p. 210–212°, melted at 184–198°.

Anal. Calcd. for $C_{29}H_{44}O_2$: C, 82.03; H, 10.43; one OH, 4.11. Found: C, 82.42, 82.34; H, 10.53, 10.45; OH, 1.96.

Monoacetylechinocystic Acid, XI.—This compound was prepared from echinocystic acid by the same procedure used to prepare monoacetyl methyl echinocystate, VII, except that the product was crystallized from toluene; m. p. 270–273°, $[\alpha]^{28}_{546}$ +37.1° in alcohol.

Anal. Calcd. for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79; neut. equiv., 514.7. Found: C, 74.34; H, 9.74; neut. equiv., 509.9, 512.9.

Reaction with diazomethane and purification usually gave the monoacetyl methyl echinocystate, VII, of m. p. 170–171° although occasionally the ester melting at 205–208° was obtained.

Acetylnorechinocystenolone, XII.—To a solution of 3 g. of monoacetylechinocystic acid, XI, in 150 cc. of glacial acetic acid was added 0.38 g. of chromium trioxide in 10 cc. of water with stirring and the solution allowed to stand for one hour. At the end of this time it had become green and was heated to boiling and water added to turbidity. After cooling, filtering and crystallizing from methyl alcohol the product melted at 194–197° and two recrystallizations raised the melting point to 204–207°; $[\alpha]^{24}_{\mathrm{D}}$ −55.9°; $[\alpha]^{24}_{546}$ −65.1° in dioxane.

Anal. Calcd. for $C_{31}H_{48}O_3$: C, 79.43; H, 10.33. Found: C, 78.89; H, 10.31.

A solution of 0.4 g. of the above product and 1 cc. of concentrated sulfuric acid in 50 cc. of methyl alcohol was placed in a distillation flask fitted with a separatory funnel. Methyl alcohol and methyl acetate were slowly distilled, keeping the volume constant by the addition of 100 cc. of methyl alcohol over a period of two and one-half hours, the final volume of the solution being about 25 cc. A large volume of water was added and the solid crystallized from methyl alcohol; m. p. 228–234°. After two recrystallizations it melted at 231–234°; $[\alpha]^{24}_{\mathrm{D}}$ −87.4, $[\alpha]^{24}_{546}$ −107.5 in dioxane. A mixed melting point with norechinocystenolone, IX, m. p. 230–233°, gave no depression. The product of the alkaline saponification of acetyl norechinocystenolone, XII, had identical properties. Oxidation of the deacetylated product gave a compound indistinguishable from norechinocystenedione, IV.

Bromolactone of Diacetylechinocystic Acid, XIII.—Two grams of diacetylechinocystic acid was dissolved in 30 cc. of hot methyl alcohol, the solution cooled to room temperature, and 0.63 g. of bromine in 20 cc. of carbon tetrachloride added over a period of five minutes. After standing for ten minutes longer 250 cc. of ether was added and the solution washed with water and alkali. The ether layer was concentrated to dryness and the glassy residue crystallized from methyl alcohol; m. p. 185–192°. After three recrystallizations the melting point was 184–190°; $[\alpha]^{22}_{\mathrm{D}}$ +8.5°, $[\alpha]^{22}_{546}$ +12.1° in dioxane. The tetranitromethane test for the double bond was negative.

Anal. Calcd. for $C_{34}H_{51}O_6Br$: C, 64.24; H, 8.09; Br, 12.57. Found: C, 64.27; H, 8.37; Br, 12.62, 12.40.

Hydrogen Peroxide Oxidation of Methyl Diacetylechinocystate, XIV.—To a solution of 2.1 g. of methyl diacetylechinocystate in 70 cc. of glacial acetic acid at 70° was added with stirring a solution of 17.5 cc. of 30% hydrogen peroxide in 17.5 cc. of glacial acetic acid. The resulting solution was heated at 80° for one hour, then heated to boiling and water added to turbidity. After cooling, filtering and crystallizing from methyl alcohol, the product melted at 211–214°. Two recrystallizations raised the melting point to 215–217.5°; $[\alpha]^{22}_{D}$ −74.2°, $[\alpha]^{22}_{546}$ −87.6° in dioxane.

Anal. Calcd. for $C_{35}H_{54}O_7$: C, 71.64; H, 9.27. Found: C, 71.47; H, 9.18.

The tetranitromethane test was negative. On attempting to acetylate the compound or to form an oxime, it was recovered unchanged.

Summary

It has been shown by oxidation that both hydroxyl groups in the triterpenoid sapogenin, echinocystic acid, are secondary and that one is β to the carboxyl group since a diketone is formed with loss of carbon dioxide. If the carboxyl group is esterified before oxidation a diketo ester is obtained which on saponification loses carbon dioxide and yields a diketone different from that formed by the direct oxidation of echinocystic acid. If one oxidizes the monoacetyl derivative of echinocystic acid in which the hydroxyl group of echinocystic acid which is not β to the carboxyl group is esterified, a monoketoacetyl derivative is formed with loss of carbon dioxide. Removal of the acetyl group by acid alcoholysis followed by oxidation yields a diketone identical with that from the methyl ester but different from that derived from the free acid. Since the esterification of the carboxyl group or of the hydroxyl group which is not β to it prevents a rearrangement, it is concluded that both hydroxyl groups and the carboxyl group must be relatively near each other.

The preparation of a bromolactone and of a hydrogen peroxide oxidation product gives additional evidence for the close relationship of echinocystic acid to hederagenin and oleanolic acid.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Jacobsen Reaction. VI.[1] Ethyltrimethylbenzenes

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In previous papers of this series, several tetrasubstituted benzenes have been investigated with respect to their behavior when subjected to the conditions of the Jacobsen rearrangement. The results may be summed up briefly as follows: of the chlorotrimethylbenzenes studied, 5- and 6-chloropseudocumenes rearranged to 3-chloropseudocumene, while the last-mentioned compound, as well as chloromesitylene and 4-chlorohemimellithene, were not rearranged by sulfuric acid but merely sulfonated. When rearrangement of these chloro compounds occurred, it was entirely intramolecular and resulted merely in the migration of a chlorine atom. The two bromotrimethylbenzenes which were studied presented a somewhat different picture in that 5-bromopseudocumene rearranged to the 3-bromo compound and at the same time there was an intermolecular transfer of bromine leading to tribromopseudocumene. In the case of bromomesitylene, the rearrangement was entirely of the intermolecular type and the products were mesitylene and polybromomesitylenes. The tetramethylbenzenes showed both types of rearrangement, durene and isodurene giving prehnitene as the main product by intramolecular rearrangement, but at the same time there were formed smaller amounts of pseudocumene and hexamethylbenzene by intermolecular transfer of methyl groups. Prehnitene was not rearranged by sulfuric acid, but merely sulfonated. The accumulated results of previous studies indicated that in the monohalotetramethylbenzenes, the decreasing ease of migration was $Br > CH_3 > Cl$, while in the monohalotrimethylbenzenes, the order was $Br > Cl > CH_3$. Moreover, when any tetra substituted benzene did rearrange intramolecularly, the main product was always a tetrasubstituted benzene in which the substituents were oriented in the 1,2,3,4-positions.

Since slight changes in the nature of the sub-

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[1] Polymethylbenzenes. XXIV. Paper XXIII, THIS JOURNAL, **61**, 284 (1939). Paper V on the Jacobsen Reaction, *J. Org. Chem.*, **2**, 112 (1937).

[2] Abstracted from a thesis by Matthew A. Kiess, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, November, 1938.