

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XXIV. Norechinocystenol-A and Norechinocystenone-A

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It has been reported previously¹ that Clemmensen reduction of norechinocystenone-B² or of norechinocystendione gives a hydrocarbon identical with oleanene III, obtained by Winterstein and Stein³ from oleanolic acid. This was the first direct indication that echinocystic acid and oleanolic acid have the same carbon skeleton. Since the preparations of oleanene III from echinocystic acid and from oleanolic acid involve a Clemmensen reduction, which Winterstein and Stein³ have shown produces a molecular rearrangement, it was considered desirable to attempt to interrelate the two compounds by other methods.

In the monoacetyl derivative of methyl echinocystate prepared by direct esterification, the hydroxyl group acetylated is the one which is not " β " to the carboxyl group⁴ and apparently occupies the same position in the carbon skeleton as the hydroxyl group in oleanolic acid, as evidenced by the fact that both echinocystic acid and oleanolic acid give hydroxyagathalene on selenium dehydrogenation.⁵ Oxidation of this monoacetyl methyl echinocystate gives the monoacetyl monoketo ester.⁴ If the carbonyl group of the keto ester could be replaced by a methylene group one should obtain a compound identical or isomeric with acetyl methyl oleanolate. Wolff-Kishner reduction seemed the most promising since it would avoid the isomerizations taking place on Clemmensen reduction. All attempts to prepare a semicarbazone failed so a direct reduction with hydrazine hydrate and sodium ethylate⁶ was carried out. Analysis of the product and the formation and analysis of an acetyl derivative showed that not only had the carbonyl group been reduced to methylene but the carboxyl group was eliminated and the acetyl group alcoholized. To confirm this conclusion, acetylnorechinocystenone⁴ was subjected to the same treatment and an identical product obtained. This compound, which has been named "norechinocystenol-A," is isomeric with oleanol⁷ but not identical with it.

It was conceivable that norechinocystenol-A is epimeric with oleanol. Accordingly the former compound was oxidized to the ketone and com-

pared with oleanone but again the two compounds were found to be different. The new compound has been named "norechinocystenone-A." The difference in structures may arise from a difference in constitution or configuration of the carbon skeletons of oleanolic acid and echinocystic acid or to molecular rearrangements taking place during the Wolff-Kishner reductions or the decarboxylation reactions.

Attempts to carry out a Clemmensen reduction of norechinocystenolone resulted in the formation of a resin which could not be purified and from which no pure derivative could be obtained.

Experimental

Norechinocystenol-A.—A mixture of 0.93 g. of the acetyl keto methyl ester derived from echinocystic acid,⁴ 5 cc. of hydrazine hydrate and 1 g. of metallic sodium dissolved in 35 cc. of absolute alcohol was heated in a sealed tube at 200° for eight hours.⁶ The contents were poured into a large volume of water and the insoluble material extracted with ether. The ether solution was washed with barium hydroxide solution and water and dried over sodium sulfate. Evaporation of the ether gave a product which was recrystallized from methanol to a constant melting point of 188–191°. The product is only slightly soluble in ligroin, fairly soluble in toluene and very soluble in dioxane, acetone, chloroform and ether; $[\alpha]_D^{20} + 15.1^\circ$ in chloroform. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.40; H, 11.71. Found: C, 83.91, 83.96; H, 11.91, 11.83.

Reduction of 0.23 g. of acetylnorechinocystenone⁴ by the above procedure gave a product which after two crystallizations from methanol melted at 187–189°. A mixture with the above product showed no depression in melting point. The reported melting point of oleanol is 216–220° and $[\alpha]_D^{20} + 59.1^\circ$ in chloroform.⁷

Reaction of 0.30 g. of norechinocystenol-A with 1 cc. of acetic anhydride in 2 cc. of pyridine, precipitation in water and crystallization from methanol gave the acetate melting at 217–220°; $[\alpha]_D^{20} + 21.6^\circ$ in chloroform. *Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.54; H, 10.87. The reported melting point for oleanol acetate is 209–210° and $[\alpha]_D^{20} + 44.7^\circ$ in chloroform.⁷

Norechinocystenone-A.—A solution of 0.11 g. of norechinocystenol-A in glacial acetic acid was oxidized at 50° with a solution of 0.18 g. of chromium trioxide in glacial acetic acid. After standing one hour, 2 cc. of methanol was added to destroy the excess chromium trioxide and the product was precipitated by adding a large volume of water. The precipitate was collected in ether and the ether solution washed with alkali, dried and the solvent evaporated. The residue was crystallized twice from methanol and then from 95% ethanol to give a product melting at 159–162°; $[\alpha]_D^{20} + 30.8^\circ$ in chloroform. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.81; H, 11.30. Found: C, 84.98; H, 11.14. A mixture with an equal amount of oleanone,⁸ m. p. 170–173°, melted at 157°. The melting point of oleanone has been reported to be 167–169°⁸ and 168–172°⁹ and $[\alpha]_D^{20} + 95.8^\circ$ in chloroform.³

Summary

Norechinocystenol-A has been prepared by removing the carboxyl group of echinocystic acid and the hydroxyl group " β " to the carboxyl group. It is not identical with oleanol prepared

(8) Bilham and Kon, *J. Chem. Soc.*, 1469 (1940).

(1) Todd, Harris and Noller, *THIS JOURNAL*, **68**, 1624 (1940).

(2) This compound previously has been called simply "norechinocystenone." The carbonyl group is derived from the hydroxyl group in echinocystic acid which is " β " to the carboxyl group. The designation "B" has been added to distinguish it from norechinocystenone-A in which the carbonyl group is derived from the hydroxyl group in echinocystic acid which is not " β " to the carboxyl group.

(3) Winterstein and Stein, *Ann.*, **502**, 223 (1933).

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

(5) Ruzicka and co-workers, *Helv. Chim. Acta*, **17**, 442 (1934); **19**, 1391 (1936); Noller, *THIS JOURNAL*, **56**, 1582 (1934).

(6) Longwell and Wintersteiner, *ibid.*, **62**, 200 (1940).

(7) Winterstein and Stein, *Z. physiol. Chem.*, **202**, 229 (1931).

by the decarboxylation of oleanolic acid. Oxidation of norechinocystenol-A gives the ketone norechinocystenone-A, which is different from oleanone

prepared by the decarboxylation and dehydrogenation of oleanolic acid.

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Alkyl Sulfites—Cyclohexyl Sulfite

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In 1931 Voss and Blanke¹ reported the preparation of alkyl sulfites in high yields from primary and in fair yields from secondary alcohols. They also reported a yield of 54% of cyclohexyl sulfite—b. p. 182° (19 mm.), $n_{D}^{18.7}$ 1.4865; S 13.16% (calcd. 13.02%). At about the same time Kitasato and Sone² reported that cyclohexyl sulfite made in the presence of pyridine boiled at 55° (12 mm.), which would appear to be too low for the boiling point of this ester.

Later, Carré and Libermann³ cast doubt on the isolability of cyclohexyl sulfite, stating that cyclohexene was the only reaction product of cyclohexanol with thionyl chloride. The criticism of Carré and Libermann was countered by a subsequent report of Voss and Wachs⁴ reasserting the isolation of cyclohexyl sulfite in a 42% yield, b. p. 173–173.5° at 14.5 mm.; $n_{D}^{17.3}$ 1.48497; S, 12.85%. Finally, Carré and Libermann⁵ made the categorical statement that "the new experiments have confirmed our previous results: the reaction of thionyl chloride with cyclohexanol gives mainly cyclohexene, with only a small quantity of cyclohexyl sulfite which we were unable to distil under vacuum without decomposition."

Having prepared cyclohexyl sulfite in these laboratories at three different times during the past twelve years and tested the products at intervals for stability, we concluded that, if properly prepared, the ester is stable over long periods of time. It distills within a very narrow range under a fairly good vacuum and always smells of sulfur dioxide and cyclohexene.

The procedure for the preparation of *n*-butyl sulfite given in "Organic Syntheses"⁶ is not applicable to secondary alkyl sulfités. Following the reaction, distillation gives some olefin and the unchanged alcohol. Voss and Blanke obtained fair yields of secondary alkyl sulfités only by displacing the hydrogen chloride in the course of its liberation during the reaction with a stream of carbon dioxide. This elimination of hydrogen chloride appears to be of significance in driving the esterification to completion.

We have been able to improve the process, and

consequently the yields, by carrying out the reaction under reduced pressure. Using the vacuum obtainable by an ordinary water pump, it was demonstrated that the halogen acid is removed quite successfully and excellent yields of both secondary and primary sulfités are obtained from the corresponding alcohols.

Since in the process for *n*-butyl sulfite referred to above 3–5% of butyl chloride is formed we chose a lower reaction temperature in order to minimize chloride formation. At the recommended temperatures (10–20°), the reaction proceeds quite rapidly, giving the high yields desired.

The following experimental work relating to improvements in the technique of preparing sulfités in general is submitted in order to clarify the situation regarding cyclohexyl sulfite.

Experimental

The apparatus consisted of a four-necked flask carrying an efficient reflux condenser, a thermometer for following the reaction temperature, a dropping funnel and an agitator revolving in a lubricated rubber sleeve⁷ for operation under vacuum.

Cyclohexyl Sulfite.—Two hundred grams of anhydrous cyclohexanol was charged into the reaction flask and cooled with agitation to incipient crystallization (25°). Vacuum was applied (24") and 121 g. of freshly distilled thionyl chloride was slowly dropped in. As the addition progressed and the cyclohexanol liquefied, the reaction temperature was lowered gradually. When about one-half of the thionyl chloride had been added (time fifteen minutes) the temperature had fallen to 15°. At this point, further addition of thionyl chloride induced the evolution of hydrogen chloride which further lowered the temperature. External cooling was discontinued when the temperature had fallen to 5° and addition of the rest of the chloride was regulated to maintain this temperature and the pressure given. Total addition time was forty-five minutes. The vacuum was now increased to 30" in order to expedite the more complete elimination of hydrogen chloride which in turn lowered still further the temperature (0°). After a short time the flask was immersed in a water-bath and the temperature raised slowly to 55°, taking a half-hour for this operation. After an additional reaction time of a half-hour at 55°, vacuum was broken off and the liquid was transferred into a distillation flask with an attached Vigreux column. After separating a small amount of low boiling liquid under partial vacuum, the main fraction was distilled using a high vacuum pump. The distillate weighed 217 g. and boiled constantly at 134–136° at 3 mm. The low boiling fraction upon refractionation gave 11 g. of unreacted cyclohexanol. The yield of cyclohexyl sulfite was therefore 93.5% on cyclohexanol consumed and 86% on thionyl chloride used. There was evidence of evolution of

(1) Voss and Blanke, *Ann.*, **485**, 272 (1931).

(2) Kitasato and Sone, *Ber.*, **64**, 1142 (1931).

(3) Carré and Libermann, *Bull. soc. chim.*, [5] **2**, 160 (1935).

(4) Voss and Wachs, *Ber.*, **68**, 1939 (1935).

(5) Carré and Libermann, *Bull. soc. chim.*, [5] **3**, 144 (1936).

(6) "Organic Syntheses," Coll. Vol. II, 1943, p. 112.

(7) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Vol. 21, p. 40.