[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

The Preparation and Hydrolysis of Some Alpha-Hydroxyanthraquinone Glycosides[1,2]

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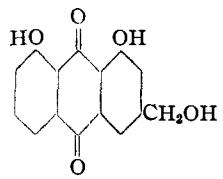
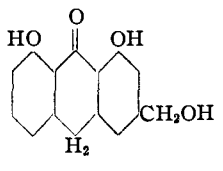
For a long time barbaloin was regarded as a *d*-arabinoside of aloe-emodin (Formula I) on the basis of Léger's discovery that it could be hydrolyzed to aloe-emodin and *d*-arabinose.[3] However, the reaction does not proceed as would be expected for a glycoside, being extremely slow and giving very poor yields of the reaction products, the most part of the material apparently being converted into a red substance of unknown constitution. Léger suggested as an alternative that barbaloin might have an ether rather than a glycoside structure. This does not seem reasonable as such a formulation would give barbaloin a potential aldehyde group. Although barbaloin readily reduces Fehling's solution and Tollens' reagent, it does not give a phenylhydrazine derivative.[4]

More recently, it has been found that barbaloin on heating with an aqueous solution of borax gives aloe-emodin-9-anthrone (Formula II).[5]

On the basis of this result, Hauser[5a] regards barbaloin as an ether of *d*-arabinose and aloe-emodin-9-anthranol and Rosenthaler[5b] formulates it as the arabinoside of the same anthranol. However, the absence of the anthrone from the product of acid hydrolysis argues against both of these views. Cahn and Simonsen[6] regard barbaloin as a hexahydroanthracene derivative, but their formula requires too many assumptions to be accepted without further evidence. At present, we can only say that no structure as yet suggested for barbaloin seems to fit all of the known facts.



I



II

Hoping to obtain more evidence on this problem, we have started a study of the synthesis and reactions of compounds of known structure related to the various formulas proposed for barbaloin. To start, we have prepared α-hydroxyanthraquinone-β-*d*-glucoside and β-*d*-arabinoside and have measured their rates of hydrolysis in hydrochloric acid, potassium hydroxide and borax solutions. In no case was there observed any resemblance to barbaloin.

Experimental

α - Hydroxyanthraquinone - tetraacetyl - β - *d* - glucoside.—This was prepared by the method of Müller,[7] as yellow needles from ethyl acetate, m. p. 212–212.5°.[8] Müller gives m. p. 200°.

Anal. Calcd. for $C_{28}H_{26}O_{12}$: C, 60.62; H, 4.73. Found: C, 60.83; H, 4.82.

α-Hydroxyanthraquinone-β-*d*-glucoside.—A suspension of 2.5 g. of α-hydroxyanthraquinone-tetraacetyl-β-*d*-glucoside in 400 cc. of alcohol was treated with a solution of 12.5 g. of potassium hydroxide in 200 cc. of alcohol, with vigorous stirring. After fifteen minutes of stirring, the solid was filtered out and crystallized from a 2:1 alcohol–glacial acetic acid mixture, followed by a short digestion with alcohol; yield, 1.6 g. (92%) of yellow needles, m. p. 232.2–232.8°.

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.16; H, 4.70. Found: C, 62.29; H, 4.55.

Acetobromo-*d*-arabinose.—Two and one-half grams of *d*-arabinose was acetylated with acetic anhydride and sodium acetate. On extraction with chloroform and evaporation, a thick sirup was obtained. This was treated with 11 g. of a cold 33% solution of hydrobromic acid in glacial acetic acid, allowed to stand for two hours, diluted with 80 cc. of ice water and extracted with ether. The ether solution was washed with cold 5% sodium bicarbonate solution followed by ice water and then dried over anhydrous sodium sulfate. On evaporation of the ether under reduced pressure, 1.3 g. (23%) of colorless needles, m. p. 134°, was obtained. Chavanne[9] gives m. p. 137°.

α - Hydroxyanthraquinone - triacetyl - β - *d* - arabinoside.—A mixture of 0.7 g. of α-hydroxyanthraquinone, 1.7 g. of bromoaceto-*d*-arabinose and 1.4 g. of silver oxide in 7 cc. of quinoline was shaken for fifteen minutes. After standing for two hours, it was treated with chloroform and filtered. The chloroform solution was shaken with 5% sulfuric acid, followed by ice water, and then dried over calcium chloride. The sirup obtained on removal of the chloroform under reduced pressure was crystallized from

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(2) The major part of this investigation was made possible by a grant to the senior author from a fund given to Washington University by the Rockefeller Foundation for research in science.

(3) Léger, *Ann. chim.*, [9] **6**, 318 (1916).

(4) Rosenthaler, *Pharm. Acta Helv.*, **4**, No. 9 (1929).

(5) (a) Hauser, *ibid.*, **6**, 79 (1931); (b) Rosenthaler, *ibid.*, **9**, 9 (1934); (c) McDonnell and Gardner, THIS JOURNAL, **56**, 1246 (1934).

(6) Cahn and Simonsen, *J. Chem. Soc.*, 2573 (1932).

(7) Müller, *Ber.*, **62**, 2793 (1929).

(8) All melting points in this paper are corrected.

(9) Chavanne, *Compt. rend.*, **134**, 661 (1902).

alcohol; yield 0.85 g. (55%). A small portion was further recrystallized from alcohol for analysis, m. p. 189.2–189.4°.

Anal. Calcd. for $C_{25}H_{32}O_{10}$: C, 62.22; H, 4.60. Found: C, 62.62; H, 4.69.

α-Hydroxyanthraquinone-β-d-arabinoside.—A suspension of 0.4 g. of α-hydroxyanthraquinone-triacetyl-β-d-arabinoside and 2.5 g. of anhydrous potassium carbonate in 30 cc. of absolute alcohol was shaken for ten minutes and immediately filtered. The filtrate was acidified with one drop of glacial acetic acid and then concentrated to 5 cc., from which 0.19 g. (64%) of yellow needles separated on cooling, m. p. 203–203.5°.

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.52. Found: C, 64.02; H, 4.62.

Preparation of the Samples for Hydrolysis.—Since both glucosides are insoluble in water, it was thought best to carry out the hydrolysis experiments on material ground to uniform fineness. The glucoside was ground in an agate mortar and passed through a standard 100 mesh screen. The arabinoside was similarly ground but was passed through a smaller screen which allowed nearly all of the ground glucoside to pass and so must have been approximately 100 mesh.

Acid Hydrolysis.—A suspension of the glucoside or the arabinoside in the proportion of 0.0250 g. of the glucoside or 0.0231 g. of the arabinoside to 5 cc. of 0.050 *N* hydrochloric acid was heated in a boiling water-bath under a reflux condenser for the desired period of time. At the end of the heating, the flask was plunged into an ice-bath and allowed to cool for ten or fifteen minutes to permit the finely divided material to coagulate. The precipitate was then transferred to a weighed Pregl filter tube and dried for fifteen minutes at 105° in a current of air, in a Pregl regenerating block. The degree of hydrolysis was calculated by the equation

$$R = S(1 - \alpha) + \alpha S(A/G) \qquad (1)$$

where α is the fraction hydrolyzed, R the residue remaining, S the weight of sample taken and A and G are the molecular weights of α-hydroxyanthraquinone and the glycoside, respectively. Substituting the proper molecular weights for the glucoside this may be reduced to

$$\alpha = 2.383(1 - (R/S)) \qquad (2)$$

and for the arabinoside

$$\alpha = 2.197(1 - (R/S)) \qquad (3)$$

Alkaline Hydrolysis.—The same quantities of the glucosides were heated in a boiling water-bath with 5 cc. of 0.050 *N* potassium hydroxide. In the case of the glucoside, the alkaline solution was filtered directly after cooling and all of the α-hydroxyanthraquinone remained in solution. In a few experiments, the solution was acidified with hydrochloric acid after the completion of the period of heating and the α-hydroxyanthraquinone weighed with the unchanged glucoside. The results of the two methods were in good agreement. As the arabinoside was found to be somewhat soluble in 0.050 *N* potassium hydroxide, its solutions were cooled and acidified at the end of the heating, and the arabinoside and α-hydroxyanthraquinone filtered off together. Calculations were made in this case by the formula (3) used for the acid hydrolysis.

Borax Hydrolysis.—Borax was crystallized three times from water and dried over deliquescent sodium bromide. For each hydrolysis there were used 0.500 g. of borax and 5 cc. of water with 0.0250 g. of the glucoside or 0.0231 g. of the arabinoside. The solution was heated as before in the boiling water-bath for the desired period of time, cooled in an ice-bath, acidified with the calculated quantity of *N* hydrochloric acid and the precipitate transferred, dried and weighed. The results were calculated as described for the acid hydrolysis. The borax solution showed a *p*H of 9.4 with phthalein red at 40°.

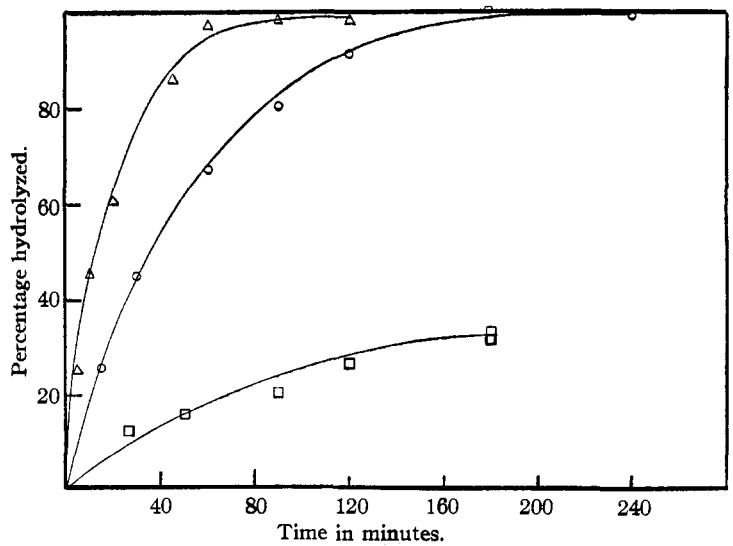

Fig. 1.—Hydrolysis of glucoside.

Results and Discussion

The results obtained on the hydrolysis of α-hydroxyanthraquinone-β-d-glucoside are shown graphically in Fig. 1 and those for the arabinoside in Fig. 2. It will be noted that in both cases the alkaline hydrolysis is most rapid, borax slowest and hydrochloric acid intermediate. With each of these reagents, the arabinoside was hydrolyzed much more rapidly than the glucoside.

There must also be considered, of course, the possibility that the reactions might be more complex than a simple hydrolysis. For this reason, the aglycone was isolated after each type of hydrolysis. In the case of the glucoside, the product in no case melted below 194–195° and, when mixed with α-hydroxyanthraquinone (m. p. 198–199°), there was no depression. In the case of the arabinoside, the same was true in hydrochloric

acid and borax solutions, but, on carrying the hydrolysis to completion in potassium hydroxide solution, the product obtained on acidifying with hydrochloric acid melted at 174–177°. A mixture with equal quantities of α-hydroxyanthraquinone melted at 186–188°, indicating that the product was largely α-hydroxyanthraquinone.

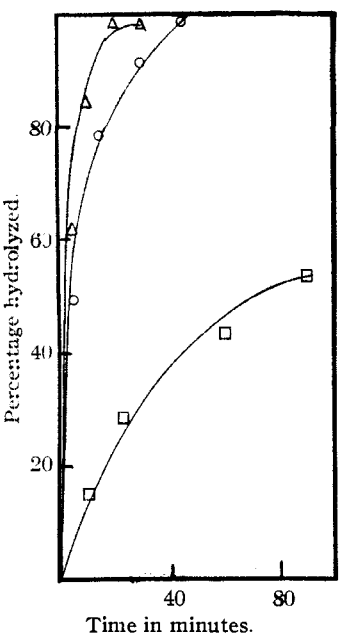

Fig. 2.—Hydrolysis of arabinoside: ⊙, HCl; △, KOH; ⊡, borax.

Since it is difficult to obtain α-hydroxyanthraquinone-β-*d*-arabinoside in large quantities for an extensive study, an attempt was made to determine the action of *d*-arabinose on α-hydroxyanthraquinone in alkaline solution under the conditions of the hydrolysis experiments. Since it has been shown that anthraquinone can be reduced by glucose in alkaline solution to anthrone,[10] it was regarded as quite possible that a similar reaction might be taking place in this case. As a trial experiment, a mixture of 0.1 g. of α-hydroxyanthraquinone, 0.1 g. of *d*-arabinose and 20 cc. of 0.050 *N* potassium hydroxide was heated on the boiling water-bath for one hour. On acidifying with hydrochloric acid, there was obtained a dark brown material melting at 140–155°. The only identifiable product that could be isolated was 0.04 g. of α-hydroxyanthraquinone, m. p. 194–195°, and giving no depression on mixing with an authentic sample. We regard it as extremely probable that the product obtained on the alkaline hydrolysis of the arabinoside is mostly α-hydroxyanthraquinone contaminated with a small amount of the anthrone.

Certainly there is nothing in any of these reactions that suggests any analogy with barbaloin. We must conclude that, in so far as reasoning by analogy is permissible, the data here presented offer definite evidence against the Léger arabinoside formula for barbaloin.

Summary

1. The hydrolysis of α-hydroxyanthraquinone-β-*d*-glucoside and β-*d*-arabinoside in hydrochloric acid, potassium hydroxide and borax solutions has been studied.

2. The hydrolysis of both compounds takes place in order of increasing velocity with borax, hydrochloric acid and potassium hydroxide.

3. The arabinoside is hydrolyzed more rapidly than the glucoside.

4. These measurements indicate that barbaloin cannot be an aloe-emodin-*d*-arabinoside.

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(10) Perkin, U. S. Patent 1,375,972, April 26, 1921.