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The Products of Hydrolysis of Cascara Resin

THE PRODUCTS OF HYDROLYSIS OF CASCARA RESIN

BY

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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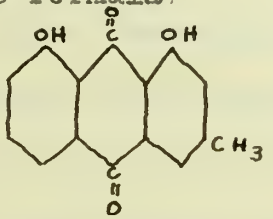
I wish to express my appreciation to Dr. Geroge D. Beal under whose direction, and advice this work has been carried out. The success and results obtained are due largely to his helpfulness and suggestions given in carrying out the experimental work of this paper.

I. HISTORICAL.

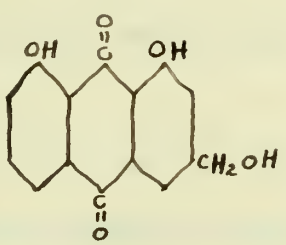
Since the latter part of the eighteenth century, there have been described various naturally occurring dyestuffs which are yellow in the free state and give red colors with alkalies. The preparations, of these dyestuffs, by early workers, were not chemical individuals.

In 1858 De La Rue and Miller[1] isolated pure emodin, and in 1875 Schmidt[2] distilled aloes with zinc dust, obtaining a-methyl anthracene. This was the first real evidence of the structure of these compounds, and remained so until 1911, when Fischer and Sappers, and Fischer, Falco, and Gross[4] were able to prove that the hydrocarbon obtained from chrysophanic acid was B-methyl anthracene.

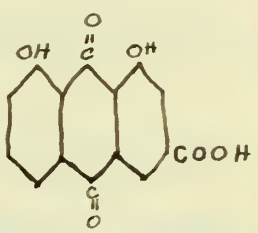
Oesterle has shown that the substance usually associated with chrysophanic acid was emodin-monomethyl-ether. He was also able to prove that chrysophanic acid, aloe-emodin and rhein were different stages in the oxidation of the same hydroxymethyl-anthraquinone, represented by the formula.



Chrysophanic Acid

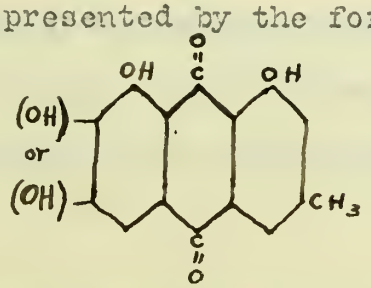


Aloe-emodin



Rhein

while emodin is a trihydroxy-methyl anthraquinone, the structure of which is probably represented by the formula.



Cascara, Rumex, Rhubarb, Frangula, Senna, and Aloes are the best known members of the group of drugs which are supposed to owe their medicinal properties to the fact that they all contain some derivative of these methyl anthraquinones.

Aloe-emodin from the nature of its reduction products, seems to be a derivative of B-methyl anthracene. It is obtained from the ether extract of the drug and crystallizes in orange-red needles, melting at 224°. Ether, hot alcohol, benzene, ammonia, and the fixed alkalies dissolve it the last two solutions having a deep red color.

The principal derivative is chrysammic acid, obtained on heating with nitric acid. This forms yellow plates or monoclinic prisms, and is soluble in alcohol and ether, but almost insoluble in water.

Chrysophanic acid on reduction with zinc dust yields B-methyl anthracene. It is also obtained from the ether and petroleum ether extracts of the drugs containing it. It forms golden plates melting at 198° when pure, and is soluble in dilute solutions of the alkali hydroxides; rather sparingly soluble in ether and alcohol, but quite soluble in benzene and chloroform.

By heating with strong ammonia, or even on long standing with this reagent, it forms mono-amino chrysophanic acid; and on warming with concentrated nitric acid a tetranitro derivative is formed.

Rhein may be obtained by extracting the drug resins containing it with dilute solutions of alkali carbonates, or by oxidizing aloe-emodin with chromic acid. It forms small yellow needles melting at 321°, and is of a distinctly acid character, slightly soluble in or-

ganic solvents, but forming solutions of the characteristic red color with concentrated sulfuric acid, ammonia, and the fixed alkali carbonates and hydroxides.

Emodin on reduction with zinc dust yields B-methyl anthracene. It may be extracted from the plant by alcohol, and separated from the ether solution of the resin so obtained by extraction with sodium carbonate. It crystallizes from glacial acetic acid in orange-red needles; and is soluble in ammonia, the alkali carbonates and hydroxides and concentrated sulfuric acid with a red color.

Emodin-mono-methyl-ether has practically the same solubilities as chrysophanic acid, with which it is closely associated.

Dohme and Englehardt stated that cascara does not contain emodin, but a glucoside, yielding emodin on hydrolysis. The glucoside was prepared by first extracting the drug with chloroform to remove the fat, and then with 80 per cent alcohol. The alcohol was distilled off, and the residual extract dissolved in water and precipitated with lead subacetate. This precipitate was decomposed by hydrogen sulphide, and the filtrate evaporated. A hard brownish-red substance was obtained, which could only be crystallized with great difficulty. A few dark red needles were obtained, melting at 237° C. They stated that it was not emodin, since it gave no purplish color with caustic potash, and that it was a glucoside characteristic of the drug.

No proof of the purity of the crystals was given. It would be expected that any impurity present would modify the color reaction. From this it would appear that these crystals were impure emodin. No

proof is furnished of the glucosidal character of this substance and no tests for sugars were made previous to or after hydrolysis.

Le Prince, stated that he isolated from the bark emodin, chrysophanic acid, and chrysarobin. He extracted the chrysarobin from the crude product by means of acetic acid, and its melting point was 165°-170° C, and it was not analyzed.

The chrysophanic acid was separated by Le Prince by using a large volume of acetic acid. It melted at 160° - 162° C and gave the theoretically required figures on analysis. Chrysophanic acid is known to melt at 190° C and is insoluble in ammonia. These results indicate that substances allied to emodin were present, but their identity cannot be considered definitely established.

The only definite principle isolated from cascara bark, the identity of which can be considered established, is emodin. The statement of the existence in the bark of chrysophanic acid, chrysarobin, or glucosides yielding on hydrolysis emodin, chrysophanic acid, or rhamnetin, is not supported by satisfactory experimental evidence.

Jowetts made a detailed examination of the constituents of the bark, especial attention being directed to the results already obtained. Where definite substances were isolated, their purity was established, if possible, by chemical methods.

The details of the experimental work are somewhat extended, so only a summary of the results will be given. In addition to emodin, an isomeric substance was isolated, melting at 183° C but insoluble in ammonia. Its acetyl derivative melted at 168° C.

Glucose was also proved to occur in the bark, and a substance which, on treatment with acid, yielded syringic acid. The nature of the compound yielding the acid could not be ascertained.

No evidence could be obtained of the existence of chrysophanic acid or chrysarobin in the bark, or of glucosides yielding on hydrolysis emodin, chrysophanic acid or rhamnetin. It was found that emodin, although insoluble in water, was soluble in the aqueous extract of the bark, and that it was extracted from such a solution only slowly and with difficulty by shaking with the immiscible solvents, such as benzene, ether or chloroform. On the other hand after treatment with acids, the water-soluble substances were decomposed with formation of insoluble resins, and the emodin was very readily extracted from such a mixture. If the aqueous extract is repeatedly shaken with chloroform or ether, and then hydrolyzed, not more than traces of emodin were found.

The bark contained about two per cent of fat which consisted of rhamnol arachidate, free arachidic acid, and substances yielding on hydrolysis linolic acid and myristic acid. The name rhamnol has been assigned to the alcohol $C_{20}H_{34}O$ melting at 135° - 136° C, which is combined with arachidic acid in cascara.

It was thought that emodin was not the active principle of the drug, but that the active principle was contained in that portion of the lead subacetate precipitate extracted by ethyl acetate, and which is soluble in water and in alcohol. No crystalline product was isolated, and therefore no clue could be obtained as to the chemical nature of the active principle.

II. EXPERIMENTAL.

The author's attention was directed towards the products of the hydrolysis of cascara resin by results obtained by other students working with Dr. Beal. When cascara was exhausted in a percolator of the ordinary type, the extract being concentrated by almost continuous heating on the steam bath an excellent yield of emodin was obtained on extracting the dried resin with ether. When another, and much larger, portion of drug was extracted in the Lloyd apparatus, in which the extract after having been rapidly concentrated was immediately chilled and kept cold, the yield of emodin obtained from the resin by direct extraction was very much smaller.

It was thought that the difference in yield might be explained by assuming the presence in the drug of an emodin containing glucoside, or other derivative, which was extracted in either instance by the alcohol, but in the one case was broken down by the continuous heating, yielding emodin which was easily extracted by ether.

The material used for the examination was cascara bark, obtained through Fuller, Morrison and Company, Wholesale Druggists, of Chicago. The drug as received was in the form of quills, and was ground to about number twenty powder in a Hance mill. The drug used in this study amounted, when ground, to 4810 grams. This was moistened with alcohol, placed in the percolator of a Lloyd Extraction Apparatus, covered with 95% alcohol, and allowed to macerate twenty-four hours, after which percolation was begun, and continued until the drug was completely exhausted.

Concentration of the percolate was carried out in the concentrator

of the extraction apparatus, and was continuous during the extraction. This concentrator is of a type making use of the principle of surface evaporation while the tendency is for the heavier concentrate to be carried by gravity to the lower portion of the concentrator, thus removing it from the heated zone. The extract is never exposed to heat for any period longer than one minute, and is in addition rapidly cooled by a water jacket surrounding the apparatus immediately below the heater. This short period of heating, coupled with rapid cooling, and the fact that the extract is at no time, brought in contact with air, leads one to believe that the extract as thus obtained must surely represent most closely the actual nature of the extractives as they are present in the tissues before extraction.

The extract obtained, representing the total alcohol soluble material of the bark, was reddish brown in color, thick and syrupy. This was mixed with enough alcohol to make a liquid having the viscosity of a rather thin syrup, and sufficient 37°/o hydrochloric acid added to give an actual acid concentration of one per cent. The flask was placed on a steam cone, with a large funnel in the neck of the flask to restrict circulation of air and loss of solvent, and heated at such a rate that the alcohol simmered gently. The heating was continued for twenty-four hours, twice replenishing the alcohol lost by evaporation. At the end of that period the alcohol remaining was distilled off until a thick viscous extract remained, and this, while still warm, was poured into a large volume of water contained in a stone jar, the water being vigorously stirred by means of a blast of air. The precipitate obtained was a dense, sticky mass, dark brown

in color. This was filtered from an orange yellow liquid, washed with water, and allowed to dry spontaneously. The extract was precipitated in two portions, a total of about one hundred grams of water insoluble material being precipitated.

The orange yellow filtrate, on standing in closed containers, deposited gradually a lemon yellow precipitate. This was filtered, and the filtrate evaporated to a small volume under diminished pressure.

A. WATER INSOLUBLE MATTER. The precipitated resin after being air dried, was broken into small fragments and placed in the inner tube of a large Soxhlet extraction apparatus, where it was extracted with ether. The resin during this extraction, possible due to the presence of a small amount of water, gradually cohered into a gummy mass, only slightly permeable to the ether. When this stage was reached, the resin was removed, dried and again powdered, then returned to the extraction apparatus and the extraction with ether completed. The resin, after the ether failed to dissolve more material, was dissolved in alcohol, hydrolysed a second time with one per cent hydrochloric acid, and precipitated and extracted with ether as before.

Since the anthraquinone derivatives present in the ether extract would differ in acidity by reason of variation in the number of hydroxyl and carboxyl groups present, the ether solution was shaken with solutions of progressively increasing basicity in order to effect a partial separation. Accordingly the ether extract was shaken in turn with solutions of ammonium carbonate, sodium carbonate and sodium hydroxide.

. Ammonium Carbonate Extract. Shaking the ether extract with 5% ammonium carbonate yielded a deep red solution. This extraction was repeated until the ammonium carbonate solution became only slightly colored. The extracts thus obtained were combined and acidified with hydrochloric acid, forming a yellow precipitate, rather small in volume. The precipitate thus obtained was crystallized in part from alcohol and partly from glacial acetic acid. The crystals were dried in air and melted at 248° C, uncorrected.

An acetyl derivative was prepared by refluxing with acetic anhydride and fused sodium acetate for one hour. On cooling the solution lemon yellow crystals appeared. These were recrystallized from glacial acetic acid in yellow needles, which after drying melted at 197° C, uncorrected. This corresponds to the melting point and appearance of triacetyl emodin as given in the literature.

The filtrate from the acidified ammonium carbonate extracts was shaken out with ether and the extract saved, but not examined.

Sodium Carbonate Extract. The ether extract was then shaken out with 5% sodium carbonate giving a deep red solution. The extraction was repeated until the sodium carbonate was only slightly colored. The extracts obtained were combined and acidified with sulphuric acid, forming an orange yellow precipitate, large in volume. The precipitate thus obtained was filtered and recrystallized from glacial acetic acid. The melting point of this precipitate was 250° - 255° C, from the first sample, and 248° C, from the second sample. The precipitate was completely soluble in dilute ammonia with a characteris-

tic purplish-red coloration. An acetyl derivative prepared as above gave the yellow needles melting at 197° C, corresponding to triacetyl emodin.

The filtrate from the acidified sodium carbonate extracts was shaken out with ether and the ether extract saved.

Sodium Hydroxide Extract. The ether extract was shaken out with a 5% solution of sodium hydroxide until fresh portions of alkali added took on only a slight color. The neutral solution after these extractions was saved, but not examined. The extracts obtained were combined and acidified with sulphuric acid, forming a dark brown precipitate, very small in volume. The precipitate was recrystallized from glacial acetic acid. On attempting to determine the melting point of this material, it darkened greatly and apparently decomposed, making it impossible to observe the true melting point. The value lies above 260° C.

The filtrate was shaken out with ether and the ether extract saved, but not examined.

B. WATER SOLUBLE MATTER. The filtrate from the hydrolized resin was filtered and neutralized with barium carbonate, and filtered again. The filtrate was evaporated, under diminished pressure, to a small volume and filtered.

The precipitates obtained were dried and united, and extracted in a Soxhlet apparatus with ethyl ether. The ether extract was shaken out successively with 5% solutions of ammonium carbonate, sodium carbonate and sodium hydroxide. From the ammonium carbonate extract, after acidifying, only a small amount of amorphous red resin was obtained. The sodium carbonate extract yielded emodin which was re-

crystallized from glacial acetic acid and was identical with that described above. The sodium hydroxide extract yielded a yellow substance, which on crystallization from glacial acetic acid formed a golden yellow substance characteristic of a mixture of chrysophanic acid and emodin-mono-methyl-ether.

The filtrate was treated with lead acetate and a precipitate, large in volume, was formed. This precipitate was filtered off and saved. The filtrate was treated with hydrogen sulphide to remove the excess lead, and the lead sulphide filtered off. This solution was evaporated for further examination, but during the evaporation the solution caramelized, making identification of the sugars impossible.

III.- SUMMARY.

Powdered cascara was extracted under such conditions that the extract could be concentrated with the minimum amount of exposure of the concentrated material to heat, thus avoiding decomposition.

The extract so obtained was hydrolysed in alcoholic solution by means of one per cent hydrochloric acid.

The resin precipitated from this solution showed the presence of a much larger amount of emodin than the unhydrolysed extract.

The presence of sugar in the filtrate from the hydrolysed resin was shown, but the sugar was not identified.

From the results obtained it is concluded that a portion, at least, of the anthraquinone derivatives are present as glucosides, or in some other combined form.

The work is being continued by the author.

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