The formula $C_{21}H_{23}NO_5$ requires C = 68.292%; H = 6.23%.
The formula $(C_{21}H_{23}NO_5.HCl)_2PtCl_4$ requires Pt = 17.00%.

From these data it is concluded that the base in question is *γ-homocheledonine.*

A few crystals were also separated mechanically which began to soften at 155° C. and were completely melted at 159–160° C. Although no analytical data were obtained the melting point shows that these crystals consisted of *β-homochelidonine.*

By repeatedly converting the larger part of the total alkaloids into hydrochloride and fractionating, then converting into free base, followed by repeated fractional crystallization from alcohol or a mixture of alcohol and acetic ether there was obtained a base which was white in the free state and also formed white salts. The melting point of the free base was 206–207° C.

An elementary analysis of this base gave the following results:

0.1731 Gm. of substance yielded 0.0925 Gm. of H_2O and 0.4292 Gm. of CO_2, corresponding to 5.93% H and 67.6% C. The formula $C_{20}H_{19}O_6N$ requires C = 67.98%; H = 5.38%.

These results show that the base in question is *protopine.*

Circumstances made it impossible to investigate these interesting alkaloids further, but the fact that there was present a considerable amount of a base which in the free state is white but which forms pale yellow salts is perhaps sufficient evidence to justify the conclusion that *chelerythrine* is also present.

SUMMARY.

The leaves of *Bocconia frutescens* L. contain at least four alkaloids. By elementary analysis and melting point determination two of these were identified as *γ-homochelidonine* and *protopine*, respectively.

A third one agrees in melting point with *β-homochelidonine.* Judging from the color (white) of the free base and the yellow color of its salts a fourth one is believed to be *chelerythrine.*

On account of the size of the leaves and their high alkaloidal content this plant is probably the best known source of protopine.

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AMMONIUM ACETYL SALICYLATE "AMMON-ASPIRIN" $C_6H_4OCOCH_3COONH_4$.

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In order to produce a new chemical for the drug trade that would give simultaneously the physiological effects of commercial Aspirin and Aromatic Spirit of Ammonia, work was begun on the preparation of the ammonium salt of aspirin, namely, ammonium acetyl salicylate. Commercial aspirin, it should be recalled, is acetyl salicylate. This new chemical, will when taken internally in five-grain

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tablets dissociate readily into free ammonia and acetyl salicylic acid, thus giving simultaneously the physiological effects of commercial aspirin and aromatic spirit of ammonia.

Ammonium acetyl salicylate is most economically prepared from phenol as the base. From phenol the acetyl salicylic acid(1, 2, 3) is prepared and by its interaction with concentrated ammonium hydroxide solution the ammonium derivative is formed.

One hundred pounds of phenol, U. S. P grade, is melted in a standard phenol fusion kettle. One hundred and ten pounds of caustic soda solution, one pound sodium hydroxide to 1.5 pounds of water, previously prepared in a caustic pan, is then slowly added to the molten phenol and gently stirred; the reaction taking place forms sodium phenolate:

$$C_6H_5OH + NaOH \longrightarrow H_2O + C_6H_5ONa$$

The solution is evaporated to dryness in a stirred vacuum pan, or better in a vacuum drum dryer. The product must be completely dried. The dried sodium phenolate is charged into a stirred jacketed autoclave and carbon dioxide is run in slowly, keeping the temperature below 50° C. by water cooling. The carbon dioxide under pressure must be first dried by passing it through 66° Bé. sulphuric acid. This operation forms sodium phenol carbonate:

$$C_6H_5ONa + CO_2 \longrightarrow C_6H_5ONaCOONa + C_6H_5OH$$

In the same autoclave the carbon dioxide pressure is then raised to 125 pounds and the temperature is raised to 130° C. for six hours. This forms crude sodium salicylate:

$$C_6H_5ONaCOOH$$

The sodium salicylate is then purified by dissolving it in hot water, boiling the solution, and adding the following chemicals in succession: dilute sulphuric acid added to acidity, then 3% stannous chloride, then 1% aluminum, 4% carbon and finally sodium carbonate to neutrality. The impurities are thus removed, absorbed and adsorbed. The solution is filtered through a wooden filter press. To the clear filtrate dilute sulphuric acid (1:5) is added to precipitate the salicylic acid. The contents are cooled, contrifuged, and the crystals washed with cold water. The salicylic acid crystals are then dried on paper or cloth at not over 60° C.

The phenol used must be free from creosols. The salicylic acid can be recovered from the waste and wash liquors. A trace of iron will give the salicylic acid crystals a purple color. Consequently, the apparatus used in the manufacturing processes must not be of iron.

Acetyl salicylate can now be formed either from the salicylic acid just prepared or preferably from the sodium salicylate previously prepared after careful purification. Acetyl chloride is added to a hot saturated solution of the purified salicylic acid or its sodium salt and agitated. On cooling in crystallizers, acetyl salicylate crystallizes out in fine needles:

$$C_6H_4OHCOOH + CH_3COCl \longrightarrow C_6H_4OCOCH_3COOH + HCl$$

or

$$C_6H_4ONaCOOH + CH_3COCl \longrightarrow C_6H_4OCOCH_3COOH + NaCl$$

Fifty-seven pounds of acetyl chloride to one pound of salicylic acid or fifty pounds of acetyl chloride to one pound of sodium salicylate.

Acetyl salicylate is rather insoluble in cold water (one part in about one hundred parts of cold water) but very soluble in concentrated ammonium hydroxide. To sixty pounds of hot water (60° C.) in a mixer having a strong agitator drive forty pounds of concentrated ammonium hydroxide (94%) is added and then one hundred pounds of acetyl salicylate is added with vigorous stirring. There is a large heat evolved in the solution and reaction, and the crystals will tend to cake if the acetyl salicylate crystals are not added slowly with vigorous agitation of the solution. The crystals will go completely into solution on strong agitation forming a slight yellowish red syrupy liquid. On cooling in a crystallizer fine prismatic crystals of ammonium acetyl salicylate settle out. The contents are placed in a centrifuge basket and centrifuged. The crystals are washed with a little cold water containing some ammonium hydroxide to prevent hydrolysis and dried with blotting paper or on cloth at not over 50° C.

$$C_6H_4OCOCH_3COOH + NH_4OH \longrightarrow C_6H_4OCOCH_3COONH_4 + H_2O$$

or

$$C_9H_8O_4 + NH_4OH \longrightarrow C_9H_{11}O_4N + H_2O$$

The mother liquor from the centrifuge is evaporated down to saturation in a vacuum evaporator at a high vacuum and placed in a crystallizer for a second crop of acetyl ammonium salicylate crystals. The contents are again centrifuged and the crystals dried as before. This process of evaporating down to saturation of the mother liquor is continued in the same fashion until most all of the acetyl ammonium salicylate crystals has separated out.

In the last stage of the commercial preparation of Ammon-Aspirin, where acetyl salicylate is dissolved in the ammonium hydroxide solution, care must be taken in not adding a greater proportion of ammonium hydroxide then specified, for greater difficulty will then be encountered in crystallizing out the salt, due to the great solubility of acetyl ammonium salicylate in ammonium hydroxide.

Ammonium acetyl salicylate will decompose at temperatures above 70° C. liberating ammonia and hydrolyzing the acetyl group to acetic acid. Consequently the mother liquors from the crystallization cannot be evaporated in atmospheric evaporators at elevated temperatures, but only in high vacuum evaporators. Great care must also be taken in not permitting any water to be added to the ammoniacal ammonium acetyl salicylate solutions as dilution with water causes salicylic acid to precipitate out.

Ammonium acetyl salicylate is difficultly soluble in cold water, more readily soluble in hot water, soluble in cold alcohol and very soluble in ammonium hydroxide. It is a white crystalline compound and decomposes at temperatures above 70° C. into acetyl salicylate, salicylic acid and phenols. The acetyl radical hydrolyzes readily into acetic acid leaving an hydroxyl radical in its place on the phenyl group. In alkaline solutions it dissociates readily into acetyl salicylate and free ammonia, the ammonia forming ammonium hydroxide with the alkali.

Ammonium acetyl salicylate is practically odorless and has a slight sour taste. Due to the alkalinity of the intestines ammonium acetyl salicylate disso-

ciates when taken internally into acetyl salicylate (aspirin) and ammonia. A five-grain tablet of this compound will yield on complete dissociation in the intestines 4.5 grains of aspirin and 0.5 grains of free ammonia or 1.0 grain of ammonium hydroxide. The ammonium ion acts as a counterirritant and as a stimulant. By the liberation of this volatile and diffusible ammonia the action of this ammonium compound extends deeply. The ammonia is absorbed by the system and is converted into urea.

Ammon-Aspirin is non-poisonous. It can be taken internally with the same ease as ordinary aspirin. The proper dose is in 5-grain tablets. It has the same effect on the human system as a mixture of ordinary aspirin and aromatic spirits of ammonia, or free ammonium hydroxide in the same proportions. It has the advantage of being a simple white crystalline compound containing both aspirin and ammonia in combination. If desired to increase the ammonia content of each tablet for greater effect on the central nervous system a little ammonium carbonate can be added to the ammonium acetyl salicylate before the tablets are made up.

REFERENCES.

(1) Thorp, "Dictionary Applied Chemistry."
(2) Dammar, *Chem. Tech. der Neuzeit*, 1, 683.
(3) *Chemical Age*, 1, 79.
(4) U. S. Patent 1,217,882, Feb. 27, 1917.

BIOASSAY OF ACONITE AND ITS PREPARATIONS. I. LETHAL DOSE OF ACONITINE TO RATS.*

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The bioassay of aconite and its galenical preparations has been proposed by a number of investigators since Squibb (8), in 1882, proposed the determination of the minimum concentration just capable of producing the characteristic tingling of the human tongue when held in the mouth for 5 to 10 minutes. Taylor (12) showed the quantitative possibilities of the method, but other investigators have not been favorably impressed, claiming that the personal equation plays too great a part in the assay results. A series of publications from Haskell's laboratory (2) discuss the seasonal variation of guinea-pigs and develop a modification of the Hatcher cat method used for the assay of digitalis, which is claimed to give consistent results in the biosasay of aconite. Jauregui (4), in a critical study of various bioassay methods for aconite, presents a few data to substantiate his belief that more consistent results may be obtained with cats under artificial respiration, although the guinea-pig method of bioassay, originally proposed by Githens and Vanderkleed (1), is also considered reliable. Roth (6) found that the guinea-pig method was more satisfactory than the Squibb test. Various factors affecting the

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[2] Resigned from the Government service August 1928.