Power (F. B.)

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Read before the American Pharmaceutical Association, Milwaukee, August 28, 1884.

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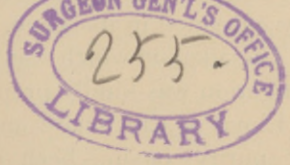

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HYDRASTINE.

By Prof. Frederick B. Power, Ph. D.

The alkaloid hydrastine was observed by Durand,* of Philadelphia, as early as 1851, but, although its alkaline nature was noticed, he did not succeed in preparing it in a pure state. It was afterward more closely examined by J. D. Perrins,† of Worcester, England, in 1862, who first separated it from Hydrastis canadensis in a relatively pure form, and described some of its reactions, but did not institute an elementary analysis. The following year it was analyzed and some of its other properties noticed by F. Mahla,‡ of Chicago, who assigned to it the empirical formula $C_{22}H_{24}NO_6$. From Mahla's analytical results the formula $C_{22}H_{23}NO_6$ has been deducted by Kraut, and this has since been generally accepted.

The investigation undertaken by me had primarily for its object the verification of the empirical formula of the alkaloid and the determination of its crystalline form, but, as opportunity permitted, was afterward considerably extended in its scope.

The alkaloid which was employed for the present investigation was kindly prepared for me by Professor J. U. Lloyd of Cincinnati, and represented a substance of rare purity, having been precipitated and crystallized about thirty consecutive times. To the kindness and liberality of Professor Lloyd, I am also indebted for the method employed by him in the preparation of the alkaloid, which is as follows:

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* Amer. Journ. Pharm. 23, 112.

† Pharm. Journ. Trans. (2) 3, 546.

‡ Silliman's Amer. Journ. Vol. 36, No. CVI., p. 57.

PROCESS OF MANUFACTURE.

One thousand pounds of powdered Hydrastis canadensis were properly moistened with alcohol, packed in a suitable percolator, and percolation then conducted with the use of officinal alcohol as a menstruum. Sulphuric acid, in strong excess, was added to the percolate, and, after four hours, the supernatant liquid filtered from the mass of crystals of sulphate of berberine ($C_{20} H_{17} NO_4 . H_2 SO_4$). To this filtrate ammonia water was added until it showed but a slightly acid reaction, then strained to separate the precipitated sulphate of ammonium, distilled to a syrupy consistence, and the residue poured into ten times its bulk of cold water. After twenty-four hours the precipitated resinous substances, oils, etc., were separated from the liquid by filtration, the filtrate being an impure solution of sulphate of hydrastine. Ammonia water, in decided excess, was then added to this resultant liquid, and the precipitate of impure hydrastine collected and dried. It was then digested with one-hundred times its weight of cold water, to which sulphuric acid was carefully added to *slight* acid reaction, and, after twenty-four hours, filtered. The filtrate was again precipitated with excess of ammonia water, the precipitate collected on a strainer and dried. This precipitate was powdered and extracted with boiling alcohol, from which impure, dark yellow crystals of hydrastine separated when the alcoholic solution was cooled. The crystals were purified by repeated crystallization from boiling alcohol. In order to obtain the hydrastine perfectly colorless, when in the form of large crystals, many crystallizations are necessary. Small crystals appear to be white, when in

reality they are considerably colored, and which is partly due to the fact that they are prone to become opaque from the presence of numerous fractures.

CRYSTALLINE FORM.

For the determination of the crystalline form of the alkaloid some carefully selected and handsomely developed crystals were also furnished me by Professor Lloyd. By the crystallization of relatively small amounts, the faces of the crystals are rarely, if ever, perfectly developed, and, even when operating upon larger quantities, this is also frequently the case, from the fact that the crystals almost invariably form with their lateral surfaces attached to the sides of the crystallizing vessel.

The crystals, which attain a maximum length of from eight to ten millimeters, have the form of four-sided prisms (Fig. I. and II.), and apparently belong to the ortho-rhombic system, although the goniometer at my disposal did not admit of the exact measurement of the angles. The drawings here presented, which represent typical crystals, were formed by making an orthographic projection, and the angles may be said to be as geometrically accurate as is possible to obtain them without absolute measurements. In Fig. II. the terminal faces are shown to be very perfectly developed, while Fig. I. represents a crystal as viewed somewhat from the side and from above, the terminal faces not so symmetrically developed, and therefore having a somewhat more complicated form. It is interesting to observe that when both ends of the crystals are developed, as shown in Fig. I., the corresponding terminal faces of opposite ends are invariably inclined to each other at an angle of exactly 90 degrees.

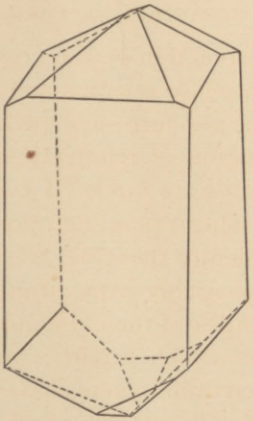

FIG. 1.

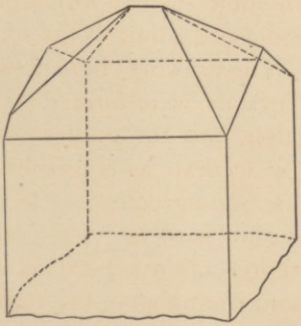

FIG. 2.

CRYSTALS OF HYDRASTINE

PHYSICAL PROPERTIES.

The crystals of hydrastine are anhydrous, and, when pure, perfectly colorless and very brilliant. They fuse at 132° C. (Mahla, *loc. cit.* states 135° C.), to a light amber-colored liquid. When heated on platinum-foil they decompose with the evolution of empyreumatic, inflammable vapors, reminding, as Mahla had previously observed, somewhat of carbolic acid, and leaving a large amount of ash, which burns slowly away at a red heat.

Hydrastine is insoluble in water and in petroleum benzine, these liquids leaving, after prolonged contact with the alkaloid, no perceptible residue upon evaporation, and the aqueous liquid is not affected by potassio-mercuric iodide; it is soluble, however, in dilute acids and in chloroform, benzol, ether and alcohol.

The degree of solubility in the four latter liquids was determined by digesting the alkaloid with the solvent in closed tubes for several days, at a temperature of 15° C., with frequent agitation, filtering into tubes provided with tightly-fitting stoppers, and, after weighing, evaporating to dryness, and finally drying the product at 100° C. The relative solubility is then calculated by the formula $\frac{a-b}{b}$, where a represents the amount of solution employed, and b the amount of residue left upon evaporation. 4.858 grams of the chloroform solution gave 1.765 grams of alkaloid; 5.688 grams of benzol solution gave 0.340 grams; 5.068 grams of ether solution gave 0.060 grams; and 4.487 grams of alcohol solution gave 0.037 grams of alkaloid. One part of alkaloid is therefore soluble in 1.75 parts of chloroform, in 15.70 parts of benzol, in 83.46 parts of ether, and in 120.27 parts of alcohol. It is naturally much more

freely soluble in these liquids when hot, but to what extent I did not attempt to determine.

Through the kindness of Prof. Flückiger, of Strasburg, I have ascertained the action of hydrastine upon polarized light, as determined by the Polaristrobometer of Wild. Ten parts of the alkaloid, dissolved in 97 parts of chloroform, deviate the polarized ray, in sodium light, with a column of 100 millimeters—17°; with a column of 50 millimeters—8, 5°. From these data I have calculated the *specific rotation* to be $(a)D = -170°$, as deduced from the following formula:

$$(a)D = \frac{a\ V}{l\ K}$$

where a=the angle of rotation in sodium light, or—17°.

V=the volume of liquid, or 100 C. Cm.

l=the length of the applied column of liquid, expressed in decimeters, or 1.

K=the weighed amount of substance, or 10 grams,

or $$(a)D = \frac{100\ a}{l.\ c.}$$

where c represents the number of grams of substance in 100 C. Cm. of solution, or 10.

From the *specific* rotation, the *molecular* rotation may then be calculated according to the formula of Krecké, which expresses the angle of rotation effected by an equal number of molecules in unity of volume, when a ray of light passes through a layer of 1 millimeter in thickness.

$$[M] = \frac{P\,[a]}{100}$$

$$[M] = -674{,}9°,$$

where P represents the molecular weight of hydrastine, or $C_{22}\ H_{23}\ NO_6 = 397$, and $[a]$ its specific rotation, or— 170°.

CHEMICAL EXAMINATION AND ANALYSIS.

The crystals of hydrastine are affected in the following manner by reagents:

Concentrated sulphuric acid produces a yellow color, which, in contact with a crystal of potassium bichromate, becomes brown.

Concentrated sulphuric acid, on warming, produces a bright red color.

Concentrated nitric acid produces, in the cold, a yellow color, changing to reddish-yellow.

Concentrated hydrochloric acid gives no coloration, either in the cold or upon warming.

Concentrated sulphuric acid and molybdate of ammonium gives an olive-green color, which appears to be its most characteristic test.

The solution of the hydrochlorate is affected as follows by reagents:

Ammonia water and the fixed alkalies give a white, curdy precipitate, sparingly soluble in excess; potassium iodide, potassio-mercuric iodide, potassium ferrocyanide, potassium sulphocyanide, mercuric chloride and tannic acid produce white precipitates; iodine in potassium iodide, a light brown precipitate; potassium bichromate, a yellow precipitate; picric acid, a bright yellow precipitate; platinic chloride, an orange yellow precipitate; auric chloride, a deep yellowish-red precipitate.

The ultimate analysis of the alkaloid was performed by its combustion with oxide of copper, in a tube pro-

vided with a glowing copper spiral. 0.2600 gram of hydrastine gave 0.6360 gram CO_2 = 66.69 per cent. C., and 0.1315 gram H_2O = 5.61 per cent. H.

Since Mahla estimated the nitrogen by burning with soda-lime, and subsequently converting the ammonia into the platinum double salt, it is therefore of interest to compare the result which I have obtained by Dumas' method, by the direct estimation of the volume of nitrogen gas.

0.648 gram of hydrastine when burned with oxide of copper in an atmosphere of CO_2, and the gas led over a glowing copper spiral, afforded 21 c. cm of nitrogen. The percentage is then calculated according to the following formula:

$$G = \frac{V}{1+0.00367t} \cdot \frac{B-f}{760} \cdot 0{,}001256$$

where G=the weight of nitrogen sought.

V=the observed volume of gas in cubic centimeters, or 16.

0.00367=the coefficient of expansion of the gas for each degree centigrade.

t=the temperature of the gas, or 16° C.

f=the tension of aqueous vapor at the temperature t, or 13.536 millimeters.

B=the barometric pressure, or 737.2 millimeters.

0.001256=the weight of one cubic centimeter of nitrogen, expressed in grams, at 0° C, and under 760 m. m pressure.

G is then equal to 3.46.

Calculated for $C_{22}H_{23}NO_6$	Found Power.	Found Mahla.	
C=66.48 per cent.	66.69 per ct.	66.69	66.38
H= 5.79 per cent.	5.61 per ct.	6.01	5.69
N= 3.53 per cent.	3.46 per ct.	3.83	3.76
O=24.20 per cent.	——	——	——
100.			

The results of both our analyses are seen to agree quite closely with the accepted formula, which may therefore now be presumed to be correct. It is also quite evident that there is no simple relationship between hydrastine and the alkaloid berberine, $C_{20}H_{17}NO_4$, such as exists, e.g., between the associate alkaloids, morphine and codeine, or caffeine and theobromine.

Mahla prepared the *hydrochlorate of hydrastine*, and obtained it in the form of an uncrystallizable, white, gum-like substance, which can readily be powdered, and is easily soluble both in water and alcohol. This salt was found to contain 8.46 per cent. HCl, and has therefore the formula $C_{22}H_{23}NO_6 . HCl$., which requires 8.42 per cent. HCl.

From the hydrochlorate Mahla prepared and analyzed the *platinum double salt*, and obtained therefrom 16.17 per cent. of platinum. This salt has therefore the formula $(C_{22}H_{23}NO_6 . HCl_4) + PtCl_4$, which requires 16.15 per cent. of platinum.

An analysis of both of these salts, prepared by myself, confirms the correctness of these results, and need not therefore be repeated.

Since, however, the sulphate and the gold double salt have not to my knowledge hitherto been analyzed, I have prepared and analyzed both of these. The *sul-*

phate of hydrastine is amorphous,* and of a light brownish color, but affords a nearly white powder. For analysis it was dried at 100° C. 1.0625 grams of the sulphate gave 0.2916 gram $BaSO_4$ = 0.1227 H_2SO_4, or 11.54 per cent. The formula $(C_{22}H_{23}NO_6)_2H_2SO_4$ requires 10.98 per cent. H_2SO_4.

The *gold double salt* was prepared from the hydrochlorate by precipitation with auric chloride. It is of a deep yellowish-red color, quite hygroscopic, and fuses at the temperature of the water-bath to a reddish liquid, which, upon cooling, becomes brittle and resinous in appearance.

0.3310 gram of hydrastine-gold chloride, dried at 100° C., gave 0.0560 gram of metallic gold, or 16.92 per cent. The formula $(C_{22}H_{23}NO_6 . HCl)_2 AuCl_3$ requires 16.78 per cent. of gold. I attempted to prepare the *nitrate* by dissolving the alkaloid in warm dilute nitric acid, but as decomposition appeared to ensue, it was afterward formed by the decomposition of the sulphate with barium nitrate. As obtained in this way the salt was found to be uncrystallizable, resembling in appearance the sulphate and hydrochlorate.

The *acetate* may readily be prepared in solution by dissolving the alkaloid in acetic acid, but upon evaporation, even with an excess of acid, it finally becomes decomposed, with the separation of the alkaloid.

With the hope that some of the salts of hydrastine with the organic acids might be crystallizable, weighed portions of the alkaloid were dissolved in warm alco-

* It may be stated that the *crystallized* sulphate of hydrastine advertised by some manufacturers is simply the acid sulphate of the yellow alkaloid berberine, $C_{20}H_{17}NO_4 . H_2SO_4$, to which the name hydrastine is persistently misapplied.

hol and mixed with alcoholic solutions of citric, tartaric, oxalic, salicylic and benzoic acids respectively, in the proper theoretical proportions. The solutions after admixture retained a slightly acid reaction, and, after standing for some time, well developed crystals were separated, differing in each case in appearance according to the acid employed, but upon examination they were found to be insoluble in water, either hot or cold, and to consist simply of the pure alkaloid. I then attempted to prepare the citrate and tartrate by adding to the warm alcoholic solutions of hydrastine aqueous solutions of citric and tartaric acids, in the proper molecular proportions to form neutral salts, but upon the evaporation of solutions the alkaloid again became separated. The conclusion may therefore be drawn from these experiments that hydrastine is not only a very weak base, but also incapable of forming any crystallizable simple salts.

After these experiments had been made, a commercial preparation termed "*soluble citrate of hydrastine*" was brought to my notice, which was examined with the following result. It is a light yellowish-gray, amorphous powder, readily soluble in water, with the exception of a small amount of resinous matter, and affording, after filtration, a bright, pale yellowish solution, having a strongly acid reaction. The amount of pure alkaloid which it contained was determined by precipitating the aqueous solution with ammonia water, in slight excess, and extracting the alkaloid with successive portions of chloroform until the aqueous liquid, after acidulation, was no longer affected by potassio-mercuric iodide. 0.9160 gram of the salt, dried at 100° C., afforded 0.1025 gram of hydrastine, or 11.19

per cent. This would correspond to the proportion of one molecule of alkaloid to fifteen molecules of citric acid, or one part by weight of alkaloid to eight parts of acid=11.19 per cent.

$$\underbrace{C_{22}H_{23}NO_6}_{397} : \underbrace{15\ C_6H_8O_7 . H_2O}_{3150} = 1:8$$

A neutral salt $(C_{22}H_{23}NO_6)_3 + C_6H_8O_7 . H_2O$, would require the proportion of about five parts of alkaloid to one part of acid. The permanence and solubility of this commercial preparation is therefore easily explained by the very large excess of citric acid employed.

In order to ascertain whether hydrastine is capable of yielding a hydro compound, five grams of the alkaloid were dissolved in dilute sulphuric acid, and subjected for about two days to the action of nascent hydrogen, as developed from metallic zinc and platinum. The liquid was then filtered, precipitated by ammonia water, in slight excess, and the precipitate, after washing, dissolved in hot alcohol, and allowed to crystallize. The crystals are insoluble in water, and closely resemble in appearance those of hydrastine, but possess a slightly yellowish tint, which could not be removed by repeated crystallization. The melting point also lies close to that of hydrastine, being observed at 131° C. I have not as yet subjected these crystals to ultimate analysis, but have formed therefrom and analyzed the hydrochlorate. The latter, like the hydrochlorate of hydrastine, is amorphous, and remains, by the evaporation of its solution, in the form of a transparent, yellowish varnish, yielding, however, a nearly white powder, freely soluble in water. After drying at 100° C., 0.7830

gram of substance gave 0.2560 gram AgCl=0.0651 gram H Cl., or 8.31 per cent.

This result would therefore indicate that a *hydro-hydrastine* is thereby formed, by the absorption of four atoms of hydrogen, and is analogous in composition to hydro-berberine, C_{20} H_{21} NO_4 (Ann. Chem. Pharm. Suppl., 2, 191).

Calculated for $C_{22}H_{27}NO_6$ HCl.	Found.
HCl=8.34 per cent.	8.31 per cent.

With iodine and bromine, hydrastine also enters into combination, which is best effected by the use of chloroform solutions, but the products of this reaction, which, in the case of bromine, is attended by the development of considerable heat, I have not yet further examined. The iodine compound has been obtained in a crystalline form.

Since Mahla has stated (*loc. cit.*) that hydrastine is not affected by a dilute solution of potassa, even by prolonged boiling therewith, I have not repeated this experiment, but its decomposition by fusing with potassium hydroxide has afforded me products of considerable interest.

Ten grams of the alkaloid, reduced to powder, were brought into about four times its weight of fusing potassium hydroxide, contained in a silver dish, when a considerable amount of unpleasant, inflammable vapors were evolved, and the mass assumed an uniform yellowish brown color. This was dissolved in water, dilute sulphuric acid in slight excess added, and the liquid distilled. In the distillate formic acid was detected. The residual acid liquid, contained in the flask, was then shaken with ether, the etherial liquid separated and al-

lowed to evaporate, when a considerable amount of a crystalline acid was obtained, corresponding in all of its reactions to protocatechuic acid, $C_7 H_6 O_4$. Thus its aqueous solution, even when very dilute, affords with ferric chloride a deep bluish-green color, and upon the subsequent addition of a very small quantity of a highly dilute solution of sodium carbonate a beautiful blue color is produced. No other acids appear to be formed by this reaction. It may be stated, however, that protocatechuic acid is likewise formed, under the same circumstances, from the alkaloid berberine, as well as from many other substances.

In order to determine, if possible, with which class of organic bases hydrastine may be grouped, whether primary, secondary, or tertiary, it was subjected to the action of ethyl iodide. Ten grams of the alkaloid, in alcoholic solution, were heated for several hours with twenty grams of freshly prepared ethyl iodide on a water bath, in a flask provided with an inverted condensor. In the beginning of the operation a considerable amount of hydriodic acid was evolved. The liquid contained in the flask, after heating for several hours, was of a yellowish color, and no longer separated any crystals upon cooling. Upon the evaporation of the liquid a deep reddish-yellow syrup was obtained, which, upon being treated with alcohol, separated a considerable amount of a white crystalline powder. This was collected on a filter, washed with a little alcohol, and being observed to be be quite freely soluble in water, it was dissolved in the latter. From the warm aqueous solution it separates, upon cooling, in small, nearly colorless, crystalline scales. The alcoholic liquid obtained from the first separation of the crys-

tals was of a reddish-yellow color, and was allowed to evaporate nearly to dryness. This residue was then treated with boiling water, which completely dissolved it, but upon evaporation an amorphous residue was again obtained. Upon treating this, however, again with alcohol, an amorphous, dark-colored substance became dissolved, leaving an additional amount of a purely white salt, which was afterward purified by crystallization from hot water. The crystals are anhydrous, and fuse at about 183° C., but become decomposed at a considerably lower temperature. After drying at 100° C., the salt was analyzed with the following result:

I. 0.7480 gram of the salt gave 0.3280 gram Ag I= 0.1786 gram HI, or 23.80 per cent.

II. 0.3075 gram of the salt gave 0.1320 gram Ag I= 0.0719 gram HI, or 23.38 per cent.

Calculated for $C_{22}H_{22}(C_2H_5)NO_6.HI$.	Found.	
	I.	II.
HI=23.14%	23.87%	23.38%.

This crystalline compound is therefore evidently the *hydriodate of ethyl-hydrastine*, formed by the substitution of one atom of hydrogen by the ethyl radical, and hydrastine may be considered, with a considerable degree of probability, as a secondary or imide base. In this respect, according to Henry* and Bernheimer,† it occupies an analogous position to berberine, since they obtained from the latter mono-ethyl and methyl derivatives, while, according to Perrins and

* Ann. Chem. Pharm. 115, p. 132.

† Gazz. Chim. Ital. xiii. p. 329–342.

Schmidt,* in the case of berberine, the simple hydriodate of the base is thereby formed.

That the crystalline compound obtained from hydrastine is really an ethyl derivate is evident, not only from the analysis, but I have also prepared the simple hydriodate by dissolving the alkaloid in freshly prepared hydriodic acid. As thus obtained it is an amorphous substance, and very easily decomposed.

In concluding this investigation, a few words may be said regarding the supposed third alkaloid of Hydrastis canadensis, the so-called *xanthopuccine*. The presence of such an alkaloid was first intimated by A. K. Hale,† afterward confirmed by John C. Burt,‡ and finally by Herman Lerchen,§ who endowed it with a name. The very peculiar properties, for an alkaloid, which were ascribed to this substance by Mr. Burt, would render it extremely interesting, since he states (*loc. cit.*, p. 482) that "the hydrochlorate solution gave with ferric chloride a dark brown to black solution, and with potassium ferrocyanide a greenish blue solution, while the fact of its precipitating lead acetate is not quite so remarkable, in view of the sparing solubility of lead chloride."

With a desire to examine this substance more carefully, I applied to Prof. Lloyd for a specimen of it, and was not greatly surprised to learn from him that in working upon thousands of pounds of Hydrastis, he had never been able to obtain it.

UNIVERSITY OF WISCONSIN, August, 1884.

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* Ber. der. deutsch. Chem. Ges., 1883, p. 2,589.

† Amer. Journ. Pharm., 1873, p. 247.

‡ Ibid, 1875, p. 481.

§ Ibid, 1878, p. 470.