THE ALKALOIDS OF SANGUINARIA CANADENSIS

by

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The Alkaloids of Sanguinaria Canadensis.

History.

The rhizome and rootlets of Sanguinaria Canadensis have been used for centuries by the Indians of North America, both as a medicine, and as a paint and dyeing agent. (1)

The first mention of the drug in scientific literature seems to have been made by B. Smith,(2) (1801-04)who called attention to its emetic properties. In 1803 Dr. Downey of Maryland, and in 1816 Dr. Bigelow, also called the attention of the medical profession to the properties of this plant (3). Dr. Bigelow, in 1816, examined the root chemically, finding a peculiar "resin," of an orange color. Dr. Fitzgerald Bird (1822) published an inaugural dissertation on the root in which mention was made of a deep orange red "resin".(4) Dr. Dana in 1819 (5) made a chemical investigation but there seems to be considerable confusion as to the exact date of the publication of his results (6). The discovery of an alkaloid called by him sanguinarina brought the drug into prominence and led to its general use by the medical profession.

Official recognition.

The first Pharmacopoeia (1820) recognized Sanguinaria in the form of a tincture.

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1) Pharm. Journ. and Trans., vol. 22, p. 263.
2) Smith, Collections for an essay towards a materia medica of the U.S., 1801-1804.
3) Pharm. Journ. and Trans., vol. 22, p 263.

Synonyms.

The generic name Sanguinaria is derived from "sanguis" (blood) from the blood red color of the juice which flows from its rhizome and petioles when wounded. The specific name, Canadensis, was applied to it by Linne to mark its habitat. Moench applied the specific name acaulis; others that have been given it are, grandiflora, stenopetala, vernalis and Virginiana (7).

Among the common names by which it is known are, bloodroot, puccoon, Indian turmeric, Indian puccoon, red root, beth root, tetterwort, Indian red paint, and pauson (8).

Botany.

Sanguinaria Canadensis belongs to the natural order Papaveraceae. According to Gray (9) it is " a low perennial, with thick, prostrate, premorse rootstalks, surcharged with red-orange, acrid juice; sending up in earliest spring a rounded, palmate-lobed, leaf, and a one-flowered naked scape. Flower white, handsome, the bud erect, the petals not crumpled, sepals 2, petals 8-12, spatulate, oblong, the inner narrower.

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4) Pharm. Journ. and Trans., vol. 19, p. 456.
5) Jahresber., 1855, p. 51. Can. Ber. d. Pharm., 1860, p. 60. Proc. A. P. A., vol. 48, p. 258.
6) Amer. Jour. Pharm. vol. 3 (1831), p. 95. Pharm. Jour. and Trans. vol. 19, p. 456; 22, p. 263.
7) Hooker and Jackson, Index Kewensis, 1895, part 4, p. 797.
8) Pharm. Jour. and Trans. vol. 22, p. 264.
9) Gray, Lessons, 1887, p. 58.

Stamens about 24, style short, stigma two grooved. Pod oblong, turgid, 1 celled, 2 valved. Seeds with a large crest."

Habitat.

It is a native of Canada and the United States though allied species have also been found in the Argentine Republic (10) and in Chile (11).

Description.

The rhizome is 5-10 cm. long, and 1 cm. thick, horizontal, slightly branched, cylindrical, and faintly annulate by leaf scars. In the fresh state it is fleshy and, after drying, is reddish-brown, longitudinally wrinkled, breaks with a short fracture of a slightly waxy appearance. The thin rootlets are mainly on the lower side, and in the commercial article, mostly broken off, short remnants, or scars only remaining. Bloodroot yields a pale grayish-red irritating powder, with a slight, heavy odor, and a persistent, bitter, acrid taste (12). As adulterations may be mentioned Helonias rhizome (13) and turmeric root (14).

Chemical Constituents.

According to König and Tietz (15) the alkaloids of Sanguinaria embrace Sanguinarine, Chelerythrine, β and γ

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10) Proc. A. P. A., 1876, vol. 24, p. 762.
11) Proc. A. P. A., 1876, vol. 24, p. 765.
12) N. D., 5th ed., p. 1408.
13) Pharm Jour. , vol. 57, p. 21.
14) Proc. A. P. A., vol. 23, p. 510.
15) Arch., 1893, vol. 231, p. 145.

homochelidonine, and protopine. Later investigations of Fischer have confirmed these results (16).

Of these alkaloids, sanguinarine, chelerythrine, and in part, protopine, are thrown down by ammonia, the others remaining in the ammoniacal liquid. As previously mentioned, Dana was the first to attempt a definite alkaloidal investigation. His method for obtaining sanguinarine consisted of precipitating it with ammonia, from a dilute acetic or hydrochloric acid infusion of the root, and subsequently purifying the precipitate (17). By this method, according to our present knowledge, chelerythrine and protopine, as well as sanguinarine, would be thrown down, so that Dana's alkaloid was undoubtedly a mixture of the three. Probst (18) obtained sanguinarine by passing hydrochloric acid gas into an ethereal tincture of the root, and precipitating the alkaloid with ammonia, subsequently purifying with ether and charcoal. This method also must have yielded a mixture of several alkaloids. Both Probst and Schiel (19) as well as Gibb (20) thought chelerythrine, which had previously been isolated from celandine, to be identical with sanguinarine, but Schmidt (21) showed that a difference existed between the two.

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16) Fischer, Inaugural dissertation, Marburg, 1900.
17) Annals Lyceum of Natural History, vol. 2, p. 250
18) Annalen d. Pharmacie, 1841, vol. 31, p. 241.
19) Silliman's Jour., September, 1855.
20) Pharm Jour. and Trans., 1860, vol. 19, p. 454.
21) Jahresber., 1886, vol. 21, p. 252.

Hopp (22) found that Wayne's (23) puccine was nothing but impure sanguinarine, and demonstrated that Newbold's (24) sanguinaric acid was a mixture of sanguinarine with citric and malic acids. The investigations of Carpenter (25) indicate that Riegel's (26) unnamed alkaloid, found by him in 1845, was probably either β-homochelidonine or protopine. König (27) was the first to show positively that the substance variously known as chelerythrine and sanguinarine consisted in reality of a mixture of two, and possibly three, alkaloids, one of which, to which he gave the name sanguinarine, formed bright red salts, while the other, which received the name of chelerythrine, yielded salts of a pure yellow color.

It is of interest to note that as early as 1887, in a thesis for the degree of Graduate in Pharmacy, on Sanguinaria, carried out at the University of Wisconsin under the direction of F. W. Power, F. W. Stecher mentions the isolation of an alkaloid with yellow salt forming properties, but due to the lack of time the investigation was not extended and never was published in any journal. An examination of the specimen in question, kept in the museum of the school of Pharmacy, showed that the investigators had in hand an almost pure

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22) Amer. Jour. Pharm., 1875, vol. 47, p. 193.
23) Ibid., 1856, vol. 28, p. 521.
24) Ibid., 1866, vol, 38, p. 496.
25) Ibid.,1879, vol. 51, P. 171.
26) Jahrbuch f. p. Pharm., 1845, vol. 11, p. 102.
27) Chem. Centralb., 1891, vol. 1, p. 321.

specimen of König's chelerythrine. Selle(28) isolated from Chelidonium majus, β-homochelidonine, in colorless monoclinic crystals melting at 159 ° and α-homochelidonine in large colorless crystals melting at 182 °. To these alkaloids he gave the formula $C_{21}H_{21}NO_5$. König found β-homochelidonine in Sanguinaria; he also found another alkaloid of the same formula which crystallized in the rhombic system and melted at 170°. This alkaloid he called γ-homochelidonine. Wintgen claimed that they were identical while Fischer came to the conclusion that β- and γ-homochelidonine were physical isomers. Protopine was first found by Hesse(29) in opium. Schmidt believed and Hopfgartner (30) demonstrated, Eykmann's(31) macleyine, which he had obtained from Macleya cordata, to be identical with protopine. König found the alkaloid in Sanguinaria.

Experimental.

Four thousand grams of commercial powdered sanguinaria were exhausted in a percolator, with 5 % aqueous acetic acid. The precipitate (A), formed upon rendering the tincture alkaline with ammonia, was collected upon a strainer, and washed with water until the washings were colorless. The filtrate (B) and those washings, which upon acidulation with hydrochloric

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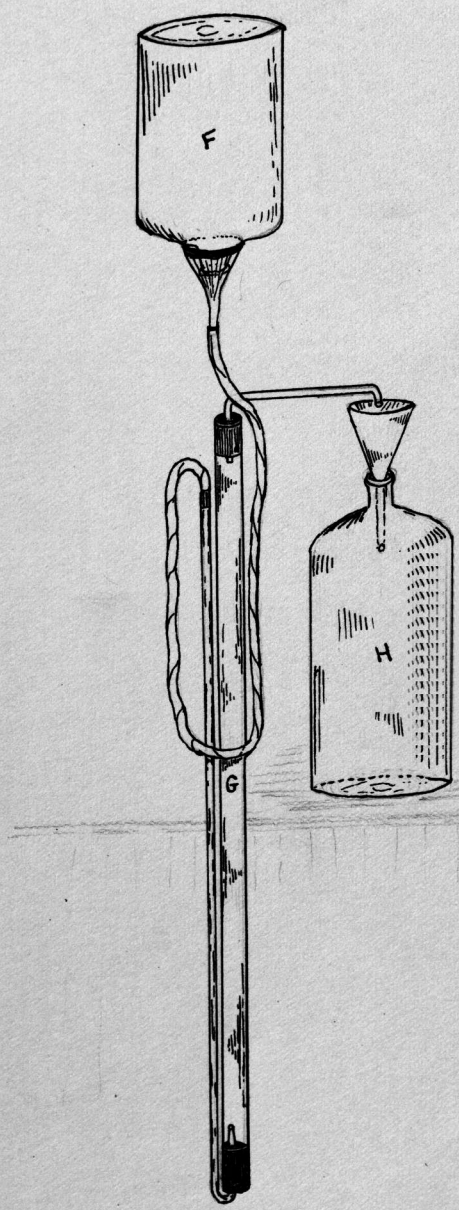
28) Inaugural dissertation, Erlangen, 1889.
29) Ann. d. Chem., Ergänzungsband, vol. 8, p. 318.
30) Monatshefte f. Chem., 1898, vol. 19, p. 179.
31) Rec. Trav. Chim. vol. 3, p. 182.

G was made of hard glass tubing about 35 cm. in diameter with perforated corks in each end. The lower cork was gelatine coated. This cylinder was nearly filled with chloroform and was then connected with the upper funnel by means of glass and rubber tubing. Into this funnel was inserted the neck of the inverted bottle F, which was filled with the ammoniacal liquid (B). The pressure was regulated by adjusting the height of F, until (B) was forced out in small bubbles through the constricted orifice of the bent glass tubing. From receiver H it was again transferred to F until after acidifying with hydrochloric acid and it gave no precipitate with Meyer's reagent.


F
H
G

acid, gave a precipitate with Meyer's reagent, were acidulated with acetic acid, and evaporated on a water bath to a syrupy consistency, ammonia again added until alkaline, and then extracted with chloroform, in the apparatus shown in the sketch. The chloroform was recovered by distillation, and the alkaloids freed from the resinous matter by adding water and then hydrochloric acid until the solution was faintly acid. After filtering the liquid, the alkaloids were precipitated with sodium carbonate and shaken out with ether. From this ethereal solution besides almost colorless crystals of β Homochelidonine, clusters of colorless prismatic crystals were deposited. These were probably impure protopine, as they gave a purple color with concentrated sulphuric acid, and had a melting point of 180°.

The washed precipitate (A) was dissolved by the aid of dilute acetic acid, just enough of the acid being used to accomplish the solution, and the liquid then largely diluted with water. Considerable resin of a dark brown color remained behind, while the dilution caused the separation of still more. This was filtered out, washed till washings were nearly colorless, the filtrate and washings again treated with ammonia, and the process repeated, until the ammonia precipitate was completely soluble in dilute acetic acid. The purified precipitate amounted to about 4 % of the weight of the crude drug. It was extracted with ether, in a Soxhlet apparatus, until a solution of the residue in dilute hydrochloric acid

gave but little precipitate with Mayer's reagent. From the weight of the insoluble portion it was determined that 63.7 % of this purified precipitate (A) had dissolved in ether. As the amount of alkaloids obtained from (B) was small the yield of total alkaloids was not much above the 2.9 % obtained from the purified precipitate (A).

The ethereal solution was evaporated to dryness on a water bath, and the mixture of alkaloids so obtained, digested with alcohol, the solution decanted, and filtered. (Filtrate C). The almost colorless residue was dissolved in chloroform and alcohol (Solution D) in which it was completely soluble, with the exception of a small quantity of grayish-blue powder. This upon incineration left practically no ash, and was insoluble in water and hydrochloric acid. To separate the sanguinarine and the chelerythrine, the method used was to dissolve the mixture of alkaloids in chloroform and alcohol, and after partially purified crystals had been obtained, to recrystallize them from ethyl acetate. Sanguinarine seemed to be much more soluble in ethyl acetate than is chelerythrine and after a certain degree of purity had been established, not much difficulty was experienced in separating the two by means of this solvent. Sanguinarine melting at 211° was obtained from ethyl acetate in acicular crystals. They all had a pinkish tint, the color being probably due to the readiness with which the alkaloid combines with the carbon dioxide of the

air. Chelerythrine crystallized from ethyl acetate in colorless rhombic crystals melting at 200° (uncorrected).

Sanguinarine forms the scarlet hydrochloride when a crystal is dropped into dilute hydrochloric acid. This red color is so persistent, that chelerythrine, melting at 190°, still had a decided orange tint when added to the hydrochloric acid. Chelerythrine when pure forms the lemon yellow hydrochloride and the degree of purity of the two alkaloids was primarily ascertained by the colors given with hydrochloric acid. Though no quantitative separation was attempted the indications point to a much larger ratio for s than the possible 20 % of total alkaloids, stated terbeck and Murrill.(32). Fischer noticed that wh thrine was precipitated in such a manner as to deprive it of its alcohol of crystallization, the melting point rose from 203° to 263°-264°. To determine if this also held true in the case of sanguinarine, some of the pure alkaloid was dissolved in dilute acetic acid and re-precipitated by sodium carbonate. The melting point of the amorphous alkaloid was found to be 255°-260°. On account of lack of time the investigations were concluded, but will be continued from this po near future.

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32) Merck's report, vol. 9, p. 451.

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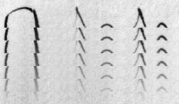

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