

THE ALKALOIDS OF GLAUCIUM FLAVUM.

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A Thesis submitted for the Degree of
GRADUATE IN PHARMACY,
Two Years Course.

UNIVERSITY OF WISCONSIN

1902

The Alkaloids of Glaucium flavum.

* Glaucium Flavum (Crantz), the yellow horned or sea poppy, natural order Papaveraceae, is one of the many species of the genus Glaucium. The Index Kewensis (10) mentions five synonyms of this species:

Glaucium fulvum (Sim.)

Glaucium glaucum (Moench)

Glaucium littorah (Salish)

Glaucium luteum (Scop)

Glaucium tricolor (Godi.)

The same authority also mentions sixteen allied species of the genus Glaucium with their various habitats and the synonyms of each:

Glaucium aleppicum (Boiss & Hausk) Arabia.

Glaucium calycinum (Boiss) Persia.

Glaucium cappadocicum (Boiss) Cappadocic.

Glaucium contortuplicatum (Boiss) Persia.

Glaucium elegans (Fisch) Persia.

Glaucium fimbrilligerum (Boiss.) Turkestan and Afganistan.

Glaucium Fischeri (Beruh) Persia.

Glaucium grandiflorum (Boiss & Huett) Asia Minor and Persia.

Glaucium leiscarpus (Boiss) Asia Minor and Persia.

Glaucium lytoioderna (Maxim) China.

Glaucium oxylobum (Boiss and Buhse) Persia

Glaucium persicum (D.C.) Prussia.

Glaucium Serpieri (Helt) Graecia.

Glaucium squandgerium (Kai.& Kir.) Central Asia.

Glaucium vitelbinum (Boiss & Buhse) Persia.

Of these allied species *Glaucium aleppicum*, has one synonym:

Glaucium refractum (J.Gay ex Boiss)

Glaucium corniculatum has six synonyms:

Glaucium auranticum (Morti.)

Glaucium Aureum (C.Koch.)

Glaucium intermedium (Fink.)

Glaucium phoenicium (Crantz)

Glaucium rubrum (Sibtle)

Glaucium tricolor (Beruli ex Sprang.)

Glaucium elegans has two synonyms:

Glaucium pumilum (Boiss)

Glaucium squamigerum (Bunge)

Glaucium flavum is a stout rigid and branching shrub growing two to three feet high. The leaves are thick, ovate or oblong, three to eight inches long and one to two inches wide, scruffy, the basal and lowest cauline petioled, the upper sessile, clasping, all pinnatifid, the divisions toothed.

In July and August it bears handsome yellow flowers which are axillary and terminal, one to two inches broad; sepals scruffy. The flowers are followed by narrowly linear capsules, six to twelve inches long, tipped with the persistent stigma. The capsules open in two valves leaving two fine linear placentae, forming a thin dry substance in which the many minute seeds are more or less imbedded. (18)

Glaucium flavum is a native of Europe where it is widely distributed as a weed in maritime regions, especially along the Mediterranean and west coast to Scandinavia. Also found in waste places over England. The species grows most luxuriantly in low sandy places along sea coasts. (18-19-20-21-22)
~~It has been introduced~~
It has been introduced into this country, growing in waste places along Long Island and southward near the coast of Virginia. (15)

Although *Glaucium flavum* has been used as a popular remedy for many centuries it has only recently found its way into the scientific materia medica. We find it mentioned in Galen's (131-200 A.D.) writings under the name of Mekon Keratites. Gerald, an old English writer, refers to the medicinal use of the plant as follows: (19)
"The root boiled in water with the consumption of one halfe, and drunke, provokethe urine, and openeth the stopping of the liver. The seed taken in the

quantitie of a spoonefull looseth the belly gently. The juice mixed with honie and meale inundifieth old, rotten and filthie ulcers. The leaves and flowres put into unguents or salves appropriate for greene woundes, digest them, that is, bring them to white matter with perfect guitture or saines."

The plant is mentioned as being medicinal in Gray's
(18)
Supplement 1847 and in Fernie's "Herbal SSimples" page 441.
(31)
Barlase says: "In Scilly Islands the root of the sea poppy is so much valued for removing pains in breast, stomach and intestines, as well as so good for disordered lungs, whilst so much better there than other places, that the apothecaries of Cornwall send thither for it, and some persons plant these roots in their gardens at Cornwall and will not part with them
(18)
under six pence per root." J. Wicliffe Peck describes the plant as having a distinctly sedative action. He found that the plant was gathered in Devonshire in August and September, when the flowers and capsules were in all stages of size and development, and dried, forming a drug having the Anglo Saxon name of "deigan" meaning "to dry". When used for pains a poultice was made by the aid of boiling water and a handful of the drug. When intended for internal use a "pinch" of the drug was put in a teacup and boiling water poured over it. A teaspoonful of the cold tea was stated to cause children to

have a night of quiet peaceful slumber.

Mrs. Pratt, in her "Flowering Plants of Great Britian", speaks of the plant as highly acrid and dangerous, and says the root is reputed to cause madness if eaten. In Germany this plant as well as the related species *Glaucium corniculatum* is used as a popular remedy for diabetis, being one of the ingredients of a compound tea or infusion. ⁽¹³⁾ This latter use led ⁽¹⁷⁾ Marpmann to make a clinical investigation of its efficiency upon which he reported in 1898. Using the fluid extract he obtained very favorable results in diabetis. Fischer and Becker ⁽¹⁶⁾ found it an efficient remedy in carcinoma of the stomach and glands. Helt ⁽¹⁷⁾ confirms the statement of Marpmann. He found that after fourteen days of treatment the blood of the patient becomes richer in haemoglobin and the number of red blood corpuscles is increased in a degree not attained by treatment with iron. After three weeks of treatment the amount of sugar excreted is reduced, and, in many cases, disappears.

According to analyses by Cloez ⁽²⁾ the seeds of *Glaucium flavum* lose 8 percent of moisture when dried in an oven, and when dried contain 42 1/2 percent of a succative oil, which can be used as an aliment or for burning. In the ordinary state, by pressure, the seeds yield 32 percent of this oil. The

marc or residue constitutes a valuable manure, giving, on analysis 6 percent of nitrogen and an ash rich in phosphate of lime. Landerer⁽⁴⁾ states that an extract of *Glaucium flavum*, which has a strong narcotic odor and a bitter taste, is sometimes put on the market as an adulterant of opium.

The earliest chemical investigation of *Glaucium flavum* was made by Probst⁽¹⁾ in 1839, who mentions the following constituents: 1. an acrid alkaloid called by him Glaucine, 2. a bitter alkaloid which he called Glaucopicrin, 3. chelerythrine, 4. Glaucic acid identical with Fumaric acid, 5. a bluish coloring matter called Glaucolin, 6. a yellow coloring matter of the flowers. Glaucine, which was found only in the herb, was obtained by precipitating the clarified juice with lead salts; removing the excess of lead with hydrogen sulphide and precipitating the alkaloids from the neutral solution with oak bark decoction. The precipitate while still moist was treated with alcohol and milk of lime; the excess of lime removed with carbon dioxide, the alcohol evaporated and the residue washed with water leaving a fairly white alkaloidal residue. The alkaloid was recrystallized from hot water. So purified it was obtained in small scaly crystals. From ethereal solutions a sticky, turpentine like mass resulted. Probst describes it as melting below the boiling point of water and having a bitter

acid taste. It dissolves readily in ether and alcohol, also in water especially when hot. Heating glaucine with sulphuric acid an indigo violet solution is obtained.

Glaucopictin, according to Probst, is contained only in the root. He describes it as white granular crystals soluble in water and alcohol, less soluble in ether and having a bitter taste. It neutralizes acids forming white, bitter salts.

Chelerythrine (Probst) was also found only in the root. He describes it as forming pure, white, transparent crystals, yielding salts of an intense red color. Battandier⁽⁹⁾ in 1892, while working on the leaves of *Glaucium luteum* to discover the best method of extracting glaucine, was induced to examine *Glaucium corniculatum*, variety *phoenicium*, for the same alkaloids. To his surprise he found fumarine instead. Finding this alkaloid in a plant of Papaveraceae he considered it additional argument for combining this order with the Fumariaceae.

Three years later, in 1895, Battandier⁽¹⁴⁾ reports isolating fumarine from *Glaucium luteum*. He claims the glaucine obtained by Probst contained small quantities of fumarine which gave the violet color with cold sulphuric acid.

In 1892 Battandier⁽¹⁶⁾ published his method for preparing glaucine hydrobromide which was as follows: The concentrated juice of the leaves of *Glaucium luteum* are extracted

with ammonia and petroleum ether, the petroleum ether taken up with dilute acetic acid, and this solution precipitated with ammonia. Glaucine precipitates as a sticky mass. If dissolved in 95 percent alcohol and this solution saturated with an aqueous solution of hydrobromic acid, the glaucine hydrobromide crystallizes out immediately, the brown impurities remaining in the mother liquor. On redissolving in boiling alcohol it crystallizes in beautiful, rose colored, prismatic needles. Battandier⁽¹⁶⁾ also gave the following reactions for glaucine. With concentrated sulphuric acid a sky-blue color which turns to violet on standing. The violet tint is immediately produced when the glaucine is impure. To 10cc of sulphuric acid add four drops of mercuric nitrate solution and shake. Upon dropping a few small crystals of glaucine into the solution an intense green color is produced gradually changing to red.

Richard Fischer⁽²⁶⁻³²⁾ in 1901 studied the alkaloids of *Glaucium flavum*, isolating glaucine and protopine in a pure state. He obtained the former in large, well developed, colorless crystals belonging to the rhombic system and melting at 119-120°, readily soluble in alcohol, acetic ether, ether and chloroform; very slightly soluble in water, benzol and toluol. Glaucine is a very weak monacid base, but forms

crystallizable salts with strong mineral acids. The hydrochloride and hydrobromide were prepared and analyzed, the former crystallizing with three molecules of water of crystallization. A crystalline mercury salt was also prepared, melting at 130-140°. Glaucine is optically strongly active, a five percent alcoholic solution giving $(\alpha)_d = +113.3$. The base gives very delicate and characteristic tests with general alkaloidal reagents. Its empirical formula was determined to be $C_{27}H_{23}NO_4$. It is a tertiary base containing four methoxyl groups. The compound $C_{17}H_{13}(OH)_4N$, of which glaucine is the tetramethyl ester was prepared and described.

EL Schmidt⁽²⁴⁾ in 1901 reports the results of H. Meyer's investigations on the pharmacological action of glaucine hydrochloride. According to this, glaucine differs from the other poppy alkaloids. It resembles chelidonine, α and β homochelidonine, chelerythrine and hydrastine in its action on the transversely striped muscles, which upon application of the poison, immediately become fixed and immovable, while the sensibility ceases entirely. In its action on the circulatory organs glaucine hydrochloride resembles chelerythrine, weakening the heart and apparently also the arteries. In its action on the central nervous system glaucine hydrochloride resembles narcotine. On frogs a mild narcosis of the brain results

combined with an increase in reflex irritability. On mammals the narcosis is plain but slight. The characteristic effects, however, are the violent epileptic cramps which continue periodically at short intervals and result in death if the quantity of poison is sufficient. The reflex irritability of the spinal cord remains unchanged or is slightly lowered (as in the case of protopine).

Marpmann⁽²³⁾ in 1900 estimated the total alkaloidal content and water content of the herb and root of *Glaucium corniculatum* during different months. He found the alkaloidal content was greatest in spring before blossoming and in the fall after blossoming. The alkaloids were estimated with N/100 acid and alkali using phenolphthalein as an indicator.

Experimental.

The material for this work consisted of 1150 grams of dried herb and 500 grams of the dried root of *Glaucium flavum*, grown at Ann Arbor, Michigan, and kindly donated by Professor Schlotterbeck of the University of Michigan.

The herb in a No.30 powder was percolated with 2 1/2 percent acetic acid, the percolate made alkaline with ammonia whereby a precipitate formed which was removed by decantation and filtration. The precipitate, which gave an alkaloidal reaction with Mayer's reagent, was dried and extracted with ether in a Soxlet apparatus; an amorphous mass resulted upon complete evaporation of the ether, which, on account of lack of time was not further worked up.

The ammoniacal filtrate was allowed to run in a thin stream through a special chloroform extraction apparatus until it gave no further test for alkaloids with Mayer's reagent. The chloroform was distilled off nearly to dryness and set aside and allowed to evaporate spontaneously; an amorphous mass resulted which was taken up with 5 percent acetic acid and shaken out with ether(a) and then with chloroform(b). The solution was then made neutral with sodium bicarbonate and shaken out with chloroform(c), which took out all the alkaloids.

From(a) the ether was distilled off nearly to dryness.

Upon complete evaporation of the ether a crystalline residue remained, which, after purification, was identified as protopine by its melting point (206-207°), as well as by its characteristic color reactions.

From (B) the chloroform was distilled off nearly to dryness and then allowed to stand until completely evaporated; an amorphous residue resulted which was taken up with 5 percent acetic acid, made alkaline with potassium carbonate, and shaken out with ether. The ether was allowed to evaporate to dryness. The residue consisted of numerous crystals imbedded in a brown, amorphous magma, which latter, when treated with alcohol(D), dissolved, leaving the almost colorless crystals behind. These crystals, dissolved in a mixture of equal parts of alcohol and chloroform, separated out, upon evaporation of the solvent, in the characteristic, transparent prisms of protopine.

The alcoholic mother liquor(D) was treated in the following manner: The alcohol was allowed to evaporate to dryness; the residue was taken up with five percent acetic acid, made alkaline with potassium carbonate, and shaken out with ether. The ethereal solution was allowed to evaporate partly and was then inoculated with a protopine crystal to insure a nearly complete separation of any protopine that might have been dissolved by the alcohol. The solution was then allowed to stand several

hours when it was filtered from the few protopine crystals that had formed. Into the ethereal filtrate hydrochloric acid gas was passed; a thick, gelatinous, slightly pinkish precipitate formed, which was filtered off and dissolved in acidulated (HCl) water and digested for an hour with animal charcoal. The almost colorless filtrate was rendered strongly acid with hydrochloric acid and allowed to cool. A heavy precipitate separated out as a mass of fine needles which were identified as glaucine hydrochloride by comparison with a known sample. The salt was separated from the mother liquor by filtration and then washed with water containing a little hydrochloric acid, leaving a pure white crystalline residue, which, when dried formed a horny mass. This dried mass was dissolved in water, made alkaline with potassium bicarbonate, and shaken out with ether. The ethereal solution was filtered into a tared Erlenmeyer flask, evaporated to dryness and weighed. Considering the residue nearly pure glaucine the amount of N/1 sulphuric acid V.S. necessary to neutralize it, was calculated and added. A crystalline mass separated out, which was dissolved by a gentle heat; the solution placed in a desiccator and allowed to evaporate completely. After many futile attempts at purifying the reddish crystalline mass which resulted by the use of various solvents (alcohol, water, alcohol and ether) it was taken

up with alcohol and digested with animal charcoal for half an hour. The filtrate was evaporated to a small bulk, and ethyl acetate added, causing a heavy white precipitate which was redissolved by heating. Upon cooling, many fine, feathery, colorless crystals separated out, which were soluble in water and gave precipitates with barium chloride and Mayer's reagent. Since the crystals also gave the characteristic color reactions for glaucine, they were undoubtedly pure glaucine sulphate.

From (C) the chloroform was removed by evaporation. An amorphous residue resulted which was taken up with 5 percent acetic acid, made alkaline with potassium carbonate, and shaken out with ether. The ethereal solution was evaporated to dryness whereby a crystalline residue resulted to which alcohol was added. The alcohol dissolved out all the coloring matter and left a pure, white, crystalline, alkaloidal residue which was identified as protopine.

A portion of the powdered herb was macerated with 5 percent acetic acid, dried and then percolated with alcohol until the percolate no longer gave an alkaloidal reaction with Mayer's reagent. Upon standing for some time colorless crystals (e) deposited on the sides of the flask, which were collected and examined. They were insoluble in alcohol, readily soluble in water. Heated to 305° in a melting point tube they remained

unchanged, but upon heating to a higher temperature on a platinum foil they liquified and then volatilized without charring or burning. Upon heating with a solution of sodium hydroxide no odor of ammonia was evolved. Fused with solid sodium hydroxide or metallic potassium, a green color resulted. Fusing with metallic potassium, taking up the fused mass with water, adding a mixture of ferrous and ferric salt and acidulating with hydrochloric acid, no blue color appeared, showing the absence of nitrogen in the compound.

The filtrate from (e) was evaporated to dryness, leaving an amorphous residue which was taken up with 5 percent acetic acid, made alkaline with ammonia. A precipitate formed which was separated by filtration, but which upon testing gave no alkaloidal reaction. The ammoniacal filtrate was shaken out with chloroform and the chloroform evaporated to dryness; the amorphous residue was taken up with 5 percent acetic acid, made alkaline with potassium carbonate, and shaken out with ether. Upon evaporation of the ether numerous crystals formed distributed through a brown varnish like mass. Treated with alcohol the latter dissolved leaving almost pure crystals of protopine.

The alcoholic mother liquor from these crystals was allowed to evaporate to dryness; an amorphous residue resulted which was taken up with dilute hydrobromic acid where upon

a crystalline mass separated out. This was removed by filtration and dissolved in alcohol and then digested for half an hour with animal charcoal. The nearly colorless filtrate was set aside and allowed to evaporate spontaneously. Small colorless, needle shaped crystals separated out which were identified as glaucine hydrobromide by comparison with a known sample of the salt.

The powdered root, treated in an identical manner as the first portion of the herb, yielded small quantities of proto-pine from the ethereal(a) and chloroformic(B) shakings from acid solution; a considerable quantity from the chloroformic shaking of a neutral solution. Though the time was too limited to work up the last residues, from the results obtained, the presence of appreciable quantities of glaucine or of any other alkaloid in the root is very doubtful.

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Approved. Richard Fischer.....

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