CONTRIBUTION TO THE CHEMISTRY OF SANGUINARINE AND CHELERYTHRINE

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A THESIS SUBMITTED FOR THE DEGREE OF

BACHELOR OF SCIENCE

UNIVERSITY OF WISCONSIN

1903

Contribution to the chemistry of Sanguinarine and Chelerythrine.

The rhizome and rootlets of Sanguinaria Canadensis, L. 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 1816 Dr.Bigelow, also called the attention of the medical profession to the properties of this plant.(3) Dr.Bigelow, 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 lead to its general use by the medical profession.

1.Pharm.Journ.and Trans.Vol.22,p.263.
2.Smith, Collections for an Essay towards a materia medica of the UnS.,1801-1804.
3.Pharm.Journ.and Trans.,Vol.22,p.263.
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.Journ.Pharm., vol.3,(1831),p.95; Pharm.Journ.and Trans. Vol.19,p.456; 22,p.263.

According to König and Tietz (7) the alkaloids of Sanguinaria embrace Sanguinarine, Chelerythrine, β and γ homochelidonine, and protopine. Later investigations of Fischer have confirmed these results. (8)

Of these alkaloids, sanguinarine, chelerythrine, and in part, protopine, are thrown down by ammonia, the others remaining in the ammonical 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. (9) 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 (10) 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 (11) as well as Gibb (12) thought chelerythrine, which had previously been isolated from celand-

7. Arch., 1893, vol.231, p.145.
8. Fischer, Inaugural dissertation, Marburg, 1900.
9. Annals Lyceum of Natural History, vol.2, p. 250.
10. Annalen d. Pharmacie, 1841, vol.31, p.241.
11. Silliman's Jour., September, 1855.
12. Pharm.Jour.and Trans., 1860, vol.19, p.454.

ine, to be identical with sanguinarine, but Schmidt (13) showed that a difference existed between the two. Hopp (14) found that Wayne's (15) puccine was nothing but impure sanguinarine, and demonstrated that Newbold's (16) sanguinaric acid was a mixture of sanguinarine with citric and malic acids. The investigations of Carpenter (17) indicate that Riegel's (18) unnamed alkaloid, found by him in 1845, was probably β-homochelidonine or protopine. König (19) 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 that 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.B.Power, F.W.Stecher mentions the isolation of an alkaloid with yellow salt forming properties, but due to the lack of time

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13. Jahresber., 1886, Vol. 21, p. 252
14. Amer. Journ. Pharm., 1875, Vol. 47, p. 183.
15. Ibid., 1866, Vol. 28, p. 521.
16. Ibid., 1866, Vol. 38, p. 496.
17. Ibid., 1879, vol. 51, p. 171.
18. Jahrb. f. p. Pharm. 1845, vol. 11, p. 102.
19. Chem. Centralbl., 1891, vol. 1, p. 321.

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 specimen of König's chelerythrine. Selle (20) 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(21) in opium. Schmidt believed and Hopfgartner(22) demonstrated, Eykmann's(23) macleyine, which he had obtained from Macleya cordata, to be identical with protopine. König found the same alkaloid in Sanguinaria.

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20. Inaugural. Dissertation, Erlangen, 1889.
21. Ann. d. Chem., Ergänzungsband, vol. 8, p. 318.
22. Monatshefte f. Chem., 1898, vol. 19, p. 179.
23. Rec. Trav. Chim. vol. 3, p. 182.

Experimental.

The material upon which this work was done consisted of the crude alkaloids manufactured according to special direction by Parke Davis & Co. of Detroit from one hundred pounds of Sanguinaria rhizomes. The method of manufacture corresponded in general to that mentioned by A.E.Kundert in a thesis for the degree of Pharmaceutical Graduate U.W.1901, and is in brief as follows:

The coarsely powdered drug is percolated with approximately 6% acetic acid, the percolate rendered ammoniacal and the purplish precipitate , consisting mainly of alkaloids, resins, and inorganic salts collected on a strainer. This pitate is further purified by repeated solution and reprecipitation and then dried onporous plates. Thus prepared the precipitate was in the form of brownish black lumps the al weight being about 1200 g.

Upon the alkaloids contained in the filtrate from the original ammoniacal precipitate no work was done beyond their separation and purification. This solution upon being treated in the manner described in the above mentioned thesis yielded protopine and β and γ -homochelidonine.

Preparation of Pure Sanguinarine and Chelerythrine from the Crude Alkaloids.

The main difficulty here met with was the elimination of

the reddish brown resin to which the purplish color of the precipitate is largely due. Since this resin is readily soluble in dilute acids, but is insoluble in water, its separation was finally accomplished by the fractional addition of acids, carefully avoiding an excess above the quantity necessary to form the water soluble salts of the bases. To this end the crude alkaloidal mass was triturated with double its weight of sand, this mixture transferred to a percolator without packing, moistened with 3% hydrochloric acid and allowed to macerate for about an hour. Water was then added until the percolate was practically colorless. Acid was again added and the operation repeated until the marc was free from alakloids. The alkaloids were now precipitated from the combined percolates by sodium carbonate, collected and dried. The sternutatory effect of the purplish precipitate, to which nearly all investigators on Sanguinaria call attention, seems to be mainly due to the resin, as the purified amorphous alkaloids appear to have no irritating effect on the mucous membranes. The partially purified alkaloids, which still had a light brown or yellowish color, were mixed with finely powdered marble and extracted with ether in a continuous extraction apparatus. Both Sanguinarine and Chelerythrine though readily soluble in ether while in the amorphous

condition are when crystalline almost insoluble in that solvent, and trouble was experienced with the Soxhlet apparatus, where alternate maceration and siphoning occurs, of crystallization taking place in the cylinder. Caldwell's apparatus, which allows the solvent to drip from the residue as fast as it runs through, was found to give better results.

The ether was then decanted from the crystallized alkaloids and allowed to evaporate spontaneously. The crystalline mass in the extraction bulb was washed with ether and dissolved in chloroform, alcohol added and the solution set aside to crystallize.

Upon standing and subsequent spontaneous evaporation, a mixture of chelerythrine and sanguinarine separated out, the former in the form of dense dark red crystals, the latter in wart like aggregations consisting of fine individual needles. The separation of chelerythrine and sanguinarine, although it can be accomplished by fractional crystallization from ethyl acetate or from a mixture of chloroform and alcohol in which sanguinarine is more soluble, is so easily achieved by mechanical separation that this is the preferable method. Sometimes the two forms are so intimately mixed that mechanical separation would be too tedious an operation. In that case the crust can be broken up, rotated for a moment with chloroform and then rapidly filtered. This process left behind on

the filter the most of the chelerythrine, for though both alkaloids, crystallized from solutions containing alcohol, are very soluble in chloroform, yet chelerythrine because of its compactness dissolves slower than sanguinarine.

Chelerythrine.

For many years the name Chelerythrine was used in chemical literature synonymously with sanguinarine and it was not until 1893 that researches by König and Tietz(1) proved that what had been variously termed chelerythrine or sanguinarine consisted in reality of two alkaloids differing in their composition, melting points, and color reactions. To the one which melted at 203° and yielded lemonyellow salts with acids the above investigators gave the name of chelerythrine. The other alkaloid melting at 213° and yielding blood red salts they called sanguinarine. The empirical formula for chelerythrine, crystallized from an alcoholic solution was determined by König and Tietz as $C_{23}H_{23}NO_5$ while the analysis of the salts indicated the composition $C_{21}H_{17}NO_4$. This difference was due to the presence of alcohol in the molecule of the free base; this is held very tenaciously not being given off at temperatures as high as 150°. The amorphous alkaloid prepared by precipitating it with sodium carbonate from a solu-

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1. Arch. d. Pharm. 231, p. 145.

tion of its salts was found by Fischer(1) to melt at 257°-264°. and Crystallized from toluol it melted at 263°-264° and showed the composition $(C_{21}H_{17}NO_4)_2H_2O + C_6H_5CH_3$ This latter work was repeated with the same results. The crystals obtained melted with decomposition at 262°-263° and lost 10.4% of their weight by heating for 4 1/2 hours in a water bath oven. 0.4823 g.lost 0.0503 g. corresponding to 10.4%. Calculated from the above formula for one-half molecule toluol, 10.1%. Using acetone as a solvent for the freshly precipitated alkaloid, granular crystals were obtained which lost no weight at 100° and melted at 251° with decomposition. Amorphous chelerythrine was dissolved in methyl alcohol (which gave no iodoform test for ethyl alcohol) and crystallized out in prismatic crystals melting at 203°. From a mixture of chloroform and methyl alcohol, similar crystals with the same melting point and showing no loss at 100°, were obtained. Adding dilute sulphuric acid and distilling, no ethyl alcohol could be detected in the distillate. Although no combustions of these crystals were made, it is safe to assume from the difference in melting point from the amorphous alkaloid that methyl alcohol was taken up, and that the compound corresponding to the compound from ethyl alcohol. From chloroform and alcohol colorless,

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1. Dissertation Marburg 1900.

rhombic plates were obtained which had the melting point of 203°. Pure chelerythrine was obtained with one crystallization by dissolving the mechanically-sorted impure alkaloid in a small quantity of chloroform by the aid of heat, transferring it to a narrow cylindrical vessel, and then carefully superposing an equal volume of ethyl alcohol on the surface of this concentrated solution. The well covered cylinder having been put in a quiet place to allow of a gradual diffusion of the liquids, well formed crystals in the shape of rhombic plates soon separated out, chelerythrine being much less soluble in alcohol than in chloroform. These crystals while still containing alcohol (determined by the iodoform test of the distillate, when the crystals were heated with acidulated water), generally also contained chloroform of crystallization, the amount of which however depending upon conditions which could not be determined or controlled. Upon exposure to air the crystals containing chloroform rapidly effloresced, losing their liquid of crystallization. This necessitated rapid manipulation after the crystals were removed from the mother liquids; the high results in some of the determinations reported below are probably due to consequent imperfect drying of the crystals.

I.0.20509 gms.lost at 100° 0.02775 gms. = 13.5 %

II.0.1435 gms.lost at 100° 0.~~3270~~ 0.0333 gms. = 23.28%

III.0.2180 gms.lost at 100° 0.0535 gms. = 24.5%

IV.0.2982 gms. no loss.

Calculated for $C_{21}H_{17}NO_4.C_2H_5OH + 1/2CHCl_3$ = 13.1%

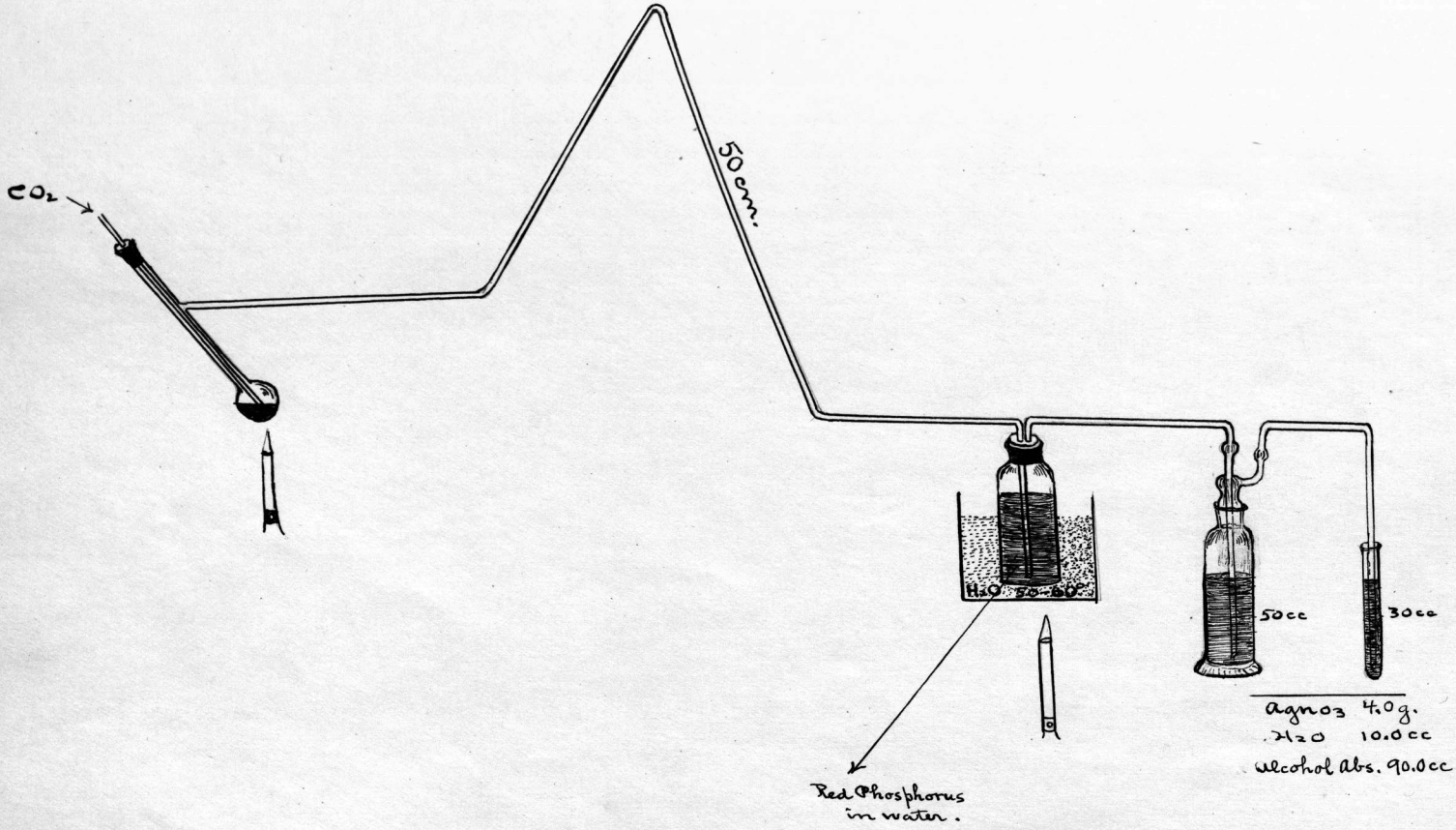
$C_{21}H_{17}NO_4.C_2H_5OH + CHCl_3$ = 23.2%

These results show that chelerythrine containing alcohol may crystallize with one -half molecule, with one molecule, or without any chloroform of crystallization. It is one of the few substances that crystallize with this liquid of crystallization. Chelerythrine is soluble in about 1300 parts of alcohol at 23°.

Methoxyl Determination.

Tietz had attempted to make a methoxyl determination of chelerythrine crystallized from alcoholic solution, but obtained discordant results, probably due to the presence of alcohol in his substance. Using the hydriodic acid salt, he obtained resluts pointing to two methoxyl groups.

To eliminate this disturbing factor, the amorphous alkaloid was prepared by precipitating a solution of the hydrochloride with sodium carbonate, collecting and washing the precipitate and then drying over calcium chloride and caustic potash under diminished pressure. This yellow tinted precipitate was very light and porous. Upon attempting to rub it up in a


CO_2
50cm.
H_2O 50-60°C
50cc
30cc
$AgNO_3$ 4.0g.
H_2O 10.0cc
Alcohol Abs. 90.0cc
Red Phosphorus
in water.

mortar it seemed to electrify very strongly and clung to everything with which it came in contact; it was therefore broken up into small pieces and used in this condition. A test showed it to be free from alcohol.

Zeisel's method was used with the modified apparatus as shown in the opposite sketch.

0.2815 gms. of alkaloid formed 0.3683 gms. AgI, corresponding to 17.3% OCH_3.

Calculated for $C_{19}H_{11}(OCH_3)_2NO_2$, 17.8%.

Upon following Ziesel's directions to stop the operation when the $AgNO_3$ solution had cleared up and the crystals had well formed, two very low results were obtained, one showing 4.4% and the other 4.5%, and it was not until the heating had been continued fully five hours after this clearing up had occurred that the above percentage was obtained. This indicates that where the reaction takes place very slowly it is well to continue the operation even after the end reaction seems to be indicated as shown by a subsided precipitate.

The hydriodic acid used was Merck's of sp.gr.1.70. It was found strongly contaminated with ethyl iodide, the odor of which could plainly be detected on heating. For purification it was boiled 10-12 hours with phosphorus in an

atmosphere of CO_2. To the bulb was a connected a reflux condenser supplied with water of a temperature of 70°-80°. The acid was then distilled over phosphorus in a current of carbon dioxide, the first and last portions being rejected. The acid so obtained was of a straw color and had a sp.gr.of 1.70. This was now placed in the modified Zeisel's apparatus and boiled until AgI was no longer formed.

Chelerythrine crystallized from chlo oform and methyl alcohol in short prismatic crystals that melted at 203°, and lost no weight at 100°. The same form of crystal, with the same melting point separated out when methyl alcohol was added to a chloroformic solution of the alkaloid containing ethyl alcohol. This indicates that the alkaloid has greater affinity for methyl than it has for ethyl alcohol.

Since the melting point of the above crystals from methyl alcohol was identical with that of chelerythrine containing ethyl alcohol, 0.2 gram of the former was rubbed up with dilute sulphuric acid and the aqueous solution distilled; the distillate gave no iodoform test for ethyl alcohol.

Since the crystals from methyl alcohol melted at the same temperature as those from ethyl alcohol, which latter had been proved to have taken up the elements of ethyl alcohol, it seems probable that the former had taken up methyl alcohol.

Also taking into consideration the fact that the amine base contains a carbonyl group, as proved below it was reasonable to suppose that the methyl alcohol had united with the carbonyl group to form a methoxyl and a hydroxyl group. If so, a methoxyl determination of the crystals from methyl alcohol should show the presence of three methoxyl groups. That this is actually the case is shown by the following determination::

0.1488 gms. gave 0.2727 gms. AgI corresponding to 24.17%

Calculated for $C_{19}H_{12}(OCH_3)_3NO_2$ = 24.54% OCH_3

Carbonyl Determination.

The tenacity with which this alkaloid held the alcohol led to the belief that it must be more strongly bound in the molecule than simply as alcohol of crystallization. This could be explained by assuming the presence of a carbonyl group whose double bond would split, one of them being satisfied by $-OC_2H_5$, the other by -OH. To form the phenyl hydrazine compound E. Fischer's method was used. 1 gm. of the amorphous alkaloid (which does not contain any alcohol) was suspended in water and placed in a bulb with a filtered solution of 1 gm. phenylhydrazine hydrochloride and 1/2 gm. crystallized sodium acetate in 10 gms. of water. This was allowed to stand 24 hours at ordinary temperature, but as no reaction seemed to have taken place, it was heated for 30 minutes on a boiling water bath. The tan colored insoluble compound was filtered, washed with water and dried. From hot alcohol in which it was very soluble it was deposited on cooling as tufts of fine needles which decomposed without melting at 150°. From the mother liquid on spontaneous evaporation it crystallized as microscopic cubes or small oblong prisms. Some of the feathery needles were redissolved in alcohol for further purification, but this did not seem practical as the solution on standing acquired a lemon yellow color and on spontaneous

evaporation left behind nothing but a yellow crust on the sides and bottom of the vessel. Two nitrogen determinations were made by Dumas' method, a previous determination having shown that the nitrogen of phenylhydrazine could not be determined by Kjeldahl's method.

I. 0.1137 gms. gave 10.4 cc nitrogen at 21.5° and 737.5 mm. b.p., corresponding to 10.4 % N.

II. 0.1316 gms. gave 10.6 cc nitrogen at 24.5° and 731 mm. b.p., corresponding to 9.17 % N.

Calculated for $C_{21}H_{17}NO_3(N.NHC_6H_5)$ N = 9.6%.

These results indicate that chelerythrine contains one C=O group and explains its behavior toward alcohol.

Hydroxyl Determination.

To determine if the remaining oxygen was present as alcoholic oxygen, the amorphous alkaloid was heated with acetic anhydride in the proportions of 1 gm. to 5 cc. After numerous attempts it was found that 3 hours heating on a boiling water bath gave the best results. On adding water after heating, an oily dark brown liquid settled to the bottom of a lemon yellow solution from which it was separated by decantation through a wetted filter. From the lemon yellow filtrate unchanged chelerythrine was obtained by adding sodium carbonate.

The oily liquid to which sodium carbonate was also added

gradually hardened and became lighter in color. It was broken up by means of a stirring rod and allowed to remain in the alkaline solution for a half or three quarters of an hour longer, then filtered and dried. After trying numerous solvents, acetone was chosen, and the solution poured into a narrow cylindrical vessel; upon evaporation of the solvent dark resinous impurities crawled up the sides of the container, while colorless prisms or plates, melting to a purple liquid at 253°, were deposited on the bottom. The solution while colored showed a decided fluorescence, but this disappeared upon purification of the compound. Crystallized from alcohol the substance also melts at 253° which excluded the possibility of its being the unchanged alkaloid. With dilute hydrochloric acid it gives no color and a lemon yellow color is but slowly developed with conc. sulphuric acid. Two attempts at determinations of acetyl radicals were made upon this compound but with negative results.

The compound is soluble in alcoholic potash (a 10% solution was used) with which it was boiled for one hour. It is not soluble in aqueous KOH. On adding phosphoric acid in excess it again separates out as a white flocculent ppt; this was filtered and washed until free from acid, dried and recrystallized from acetone. The melting point and color re-

action with conc. sulphuric acid was the same showing that no saponification had occurred. From the filtrate and washings no acetic acid could be volatilized although the temperature of the paraffin bath was raised to 160° and heating continued until the residue in the bulb was syrupy.

The attempt to form a benzoyl compound was also unsuccessful. Though the amorphous alkaloid was heated with an excess of benzoyl chloride in a sealed tube for four hours at 110-120°, nothing but the unchanged alkaloid could be obtained. Chelerythrine therefore, contains no hydroxyl groups, but heating with acetic acid anhydride produces a new chemical compound, the nature of which could not be determined for lack of time.

Attempts at the Preparation of a Methyl Iodide Addition Product.

The amorphous alkaloid was suspended in methyl alcohol, an excess of methyl iodide added and the mixture heated in a sealed tube for 5 hours at 110°-120°. Only the iodide and periodide of chelerythrine could be isolated. This result seems to indicate that chelerythrine is a quaternary base, although the chemical behavior of the base would hardly bear out such a conclusion.

Chelerythrine Salts.

The hydrochloride and hydrosulphate were prepared by adding an excess of the respective diluted acids to the free

base, dissolving the lemon yellow salts with the aid of heat and allowing the fine needle shaped crystals to separate out upon cooling. Both salts, though very readily soluble in pure water, are but very slightly soluble in acidulated water. Collected on a filter they were washed with alcohol, recrystallized from this solvent and air dried.

Neither the hydrochloride nor the hydrosulphate lost weight after heating for five hours in the water bath oven. Tietz(1) found that the hydrochloride, crystallized from alcohol, lost weight corresponding to 5 molecules of water of crystallization. The sulphate had never been prepared. The salts, when heated, darkened and were not completely soluble in water, evidently due to a slight decomposition. This probably accounts for the low results obtained in the following estimations which were made with the heated salt.

I. 0.16025 gms. gave 0.0784 $BaSO_4 \simeq 0.0329 g. H_2SO_4$ or 20.5%

II. 0.124 gms. gave 0.0595 $BaSO_4 \simeq 0.025 g. H_2SO_4$ or 20.16%

These results indicate that under the conditions, an acid salt must have been formed.

Calculated for $C_{21}H_{17}NO_4.H_2SO_4 = 22\%$

Calculated for $(C_{21}H_{17}NO_4)_2H_2SO_4 = 12.3\%$

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1. Arch. d. Pharm. 231, p. 161.

Sanguinarine.

As previously stated the first work of any real value in determining the composition of this alkaloid was done by König and Tietz.

Tietz gives its melting point as 213° and ascribes to it the formula $C_{20}H_{15}NO_4.H_2O$ while König reported its melting point to be 211° and proposed $C_{20}H_{15}NO_4$ $1/2C_2H_5OH$ as its formula. The results of Fischer's analyses agree with König's views.

There is no question that the alkaloid, melting at 211°, which I obtained from a solution in chloroform and alcohol contains alcohol which is, however, so bound in the molecule, that it cannot be driven off at 100°. To prove the presence of ethyl alcohol, some of the powdered alkaloid, which had been crystallized from chloroform and ethyl alcohol was introduced into a distilling bulb and an excess of dilute sulphuric acid added, theemixture then distilled and the distillate tested for alcohol by the iodoform test. Not only was the unmistakable odor of iodoform developed, but characteristic crystals of this substance separated out upon standing.

Unlike chelerythrine, sanguinarine does not crystallize with chloroform of crystallization, and the chloroform-ethyl alcohol solvent was not as satisfactory a crystallizing

medium. The crystals were never single but formed bundles consisting of individual short and rather thick needles. Well formed rhombic plates however, were obtained by the following method: The mechanically separated wart-like masses before mentioned were dissolved by the aid of a gentle heat and filtered into a weighing cylinder, an equal volume of methyl alcohol was then superposed as a layer on the surface of this concentrated solution, the stopper inserted, and the solution set carefully aside to crystallize. The plates which separated out, though tinted brown, were perfectly transparent lost no weight at 100°, lost their angles at about 200°, and melted at 225-226°.

Analyses show them to have the composition $C_{20}H_{15}NO_4 + CH_3OH$.

I. 0.1872 gms. gave 0.4737g CO_2 and 0.0787g H_2O

C 69.01% H 4.7%

II. 0.1876 gms. gave 0.4737g CO_2

C 68.86%

Calculated for $C_{20}H_{15}NO_4 + CH_3OH$

C 69.04% H. 5.2%

That the alkaloid has a stronger affinity for methyl than for ethyl alcohol is shown by the fact that the variety melting at 225-226° was formed when methyl alcohol was added

to a chloroformic solution of the crystals containing ethyl

The amorphous alkaloid was prepared as follows:

Pure alkaloid recrystallized several times from alcohol and melting sharply at 211° was triturated with a slight excess of 5% acetic acid and solution of the resulting salt effected by aid of gentle heat. Sodium carbonate was then added, the precipitate collected, well washed, and dried over calcium chloride under reduced pressure. This amorphous alkaloid gave the follwoing results upon analysis:

I.0.1667 gms.gave 0.4249 gms CO_2 and 0.0658 gms H

II.0.1756 " " 0.450 " " " 0.0666 " " 69.89% 4.2[illegible]%

III.0.180 " " 0.4615 " " " 0.0699 " " 69.92% 4.31%

IV.0.1724 " " 0.4397 " " " 0.0672 " " 69.60% 4.33%

V.(This alkaloid was formed without using any heat whatever).

0.1720 gms.gave 0.4391 gms.CO_2 and 0.664 gms.H 69.60% 4.22%

VI.0.4477 gms.analyzed by Kjeldahl's method required 4.33 cc. of sulphuric acid whose NH_3 factor is 0.00176, corresponding to 4.25% nitrogen.

Although these results agree very well among themselves, they do not agree with the formula $C_{20}H_{15}NO_4$, which requires H 4.5%, N 4.2%.

A satisfactory explanation of this difference could not

be found, but it may be due to partial decomposition for the amorphous alkaloid was found not to be entirely soluble in chloroform, leaving resinous traces on the paper when the solution was filtered. Chloroform does not take up the amorphous alkaloid with the readiness that might have been expected, heating even being necessary to effect solution; the addition of a few drops of either ethyl or methyl alcohol however, caused almost immediate solution to take place, due to the formation of the readily soluble ethyl or methyl alcohol compounds, which could afterwards be obtained from these solutions.

From toluol the amorphous alkaloid crystallized with great difficulty in microscopic granular crystals, highly refractive and rather impure. These lost no weight at 100 and melted with decomposition at 245°. Small cubical crystals melting with decomposition at 255° were obtained from acetone. These were soluble with great difficulty in chloroform, even in the boiling solvent.

Sanguinarine is soluble in about 600 parts of alcohol at 20°.

Methoxyl Determination.

Three determinations with the amorphous alkaloid were made and none of them, even after seven hours boiling, gave

more than traces of silver salt. It follows that since there is no methoxyl group present in the alkaloid itself, the crystals melting at 225-226° which analysis had determined to contain one molecule of methyl alcohol, (which is probably present as methoxyl and hydroxyl groups) should give results corresponding to one methoxyl. This is borne out by the following determination::

0.1770 gms. gave 0.1139gms. AgI corresponding to 8.48% OCH_3.

Calculated for $C_{20}H_{15}NO_4$ CH_3OH 8.49% OCH_3.

The operation was continued for 2 1/2 hours and proceeded very smoothly.

The only way in which the above result can be reconciled with the results found by Tietz is that what he considered as water-containing alkaloid, was in reality the alkaloid described by König and containing ethyl alcohol.

Carbonyl Determination.

Because of the readiness with which sanguinarine unites with ethyl or methyl alcohol, the firmness with which these substances are held, as well as the great differences in m.p., solubility etc. of the amorphous and the alcohol-containing base, sanguinarine like chelerythrine was suspected to contain a carbonyl group. To determine this point, the amorphous alkaloid was treated with phenylhydrazine hydrochloride in the

same manner as described under chelerythrine. The reaction not having taken place after 12 hours at ordinary temperatures, the mixture was placed on a boiling water-bath.

Here, as in previous work with these two alkaloids, it became evident that sanguinarine is much more sensitive and more easily decomposed than is chelerythrine, for after half an hour on the water bath a dark resinous mass was found floating in the aqueous liquid. Sanguinarine at this temperature in the presence of the reagent had evidently undergone entire decomposition as no crystalline substance could be obtained upon dissolving this mass in alcohol. After repeated trials the temperature 80-90° was found to give excellent results, the heating being continued for 15 minutes. The resulting compound was filtered from the phenylhydrazine solution, washed, dried and dissolved in hot ethyl alcohol. From this solvent, in which it is readily soluble, it deposited on cooling in short colorless needles that decomposed at 135°. They slowly acquired an orange yellow color even when kept in the dark in a well stoppered receptacle.

Analysis.

0.1101 gms. gave 10.2cc nitrogen at 26.0° and 737.5 m.m. b.p., corresponding to 10.1% N.

Calculated for $C_{20}H_{15}NO_3$(N.NHC_6H_5), = 9.9%.

Like chelerythrine, sanguinarine contains one carbonyl group.

Hydroxyl Determination.

Many attempts were made to form the acetyl compound before the temperature, at which the acetic anhydride would attack sanguinarine without completely decomposing the substance, was found. Chelerythrine could be heated with for several hours on a boiling water bath, but only one hour's exposure to this temperature decomposed sanguinarine. By starting at 70° and varying the time and temperature a series of attempts demonstrated that one hour at 80-90° gave the best results. Here as with chelerythrine there was always some sanguinarine acetate formed on adding water; this was filtered from the deep red oily liquid. This oily liquid also hardened and became brown when treated in the same manner as described under chelerythrine.

From ethyl acetate, which was found to be the best solvent, three distinct substances separated out. The one melting at 258° with decomposition and giving a scarlet color with acids was evidently the unchanged alkaloid. Another appeared in two crystalline forms, one a silvery mat of fine needles, the other, well formed slender prisms which became silvery upon being heated. Both of these forms melted with decomposition at 283°. They gave no color with dilute HCl, but seemed

to decompose with evolution of gas in conc.sulphuric acid, turning yellow while the acid was colored pink. The third substance separated in the form of acicular needles that blackened at 300°, but did not melt even at 330°. These gave an orange yellow color with conc.culphuric acid but none with dilute hydrochloric acid.

The needles, for which no melting point was obtained, were first used foran acetyl determination. They were boiled for one hour with 10% alcoholic potash in which they were very soluble. On acidifying with phosphoric acid, a white flocculent precipitate separated out which was filtered and washed free from acids, the filtrate and washings being distilled. No acid could be detected in any part of the distillate even though the bath was raised to 165° and distillation continued until the residue was syrupy. The precipitate on drying acquired a yellowish tint; it gave no color with dilute hydrochloric acid, but a lemon yellow tint with conc. sulphuric acid.

The crystals melting at 283° when treated as above described, likewise gave negative results for acetic acid. Boiling with the caustic potash solution has apparently no effect on the compound..

Two methods for making the benzoyl compound of sanguinarine were tried but without success. First the Schotten-

Bauman method, in which benzoyl chloride is used in dilute aqueous alkaline solution, was tried on the amorphous alkaloid. However, after neutralizing with sodium carbonate, only the alkaloid was recovered from the precipitate.

Then the amorphous alkaloid was heated in a sealed tube with an excess of benzoyl chloride for 3 hours at 100-110°. Here also only the unchanged alkaloid could be recovered.

Sanguinarine, therefore, contains no hydroxyl groups, but boiling with acetic anhydride breaks down the base into at least two different compounds, the study of which may throw further light on the composition of this alkaloid.

Incidental Result.

In standardizing volumetric solutions for nitrogen estimations by the Kjeldahl method, great difficulty was experienced, in determining the end reactions with N/10 tartaric acid, when iodoeosin was used as indicator. Thinking this might be due to the carbonate in the alkali, calcium hydroxide was added to remove it, but the color indications were no sharper. On trying N/10 oxalic and acetic acids the same unsatisfactory results were obtained showing that this indicator can not be used with these organic acids.

Attempt at Methyl Iodide Addition Product.

The attempt to form the methyl iodide addition product with sanguinarine also gave negative results. The amorphous alkaloid, suspended in methyl alcohol was mixed with an excess of methyl iodide and heated in a sealed tube for 3 hours at 100-110 .Only sanguinarine iodide and periodide could be isolated from the contents of the tube.

Sanguinarine Salts.

The hydrochloride, hydro sulphate and incidentally the hydriodide were made in the same manner described under the corresponding chelerythrine salts. Since the first and the third had already been prepared and described by Tietz, the hydrosulphate alone was more closely examined. Depending upon the conditions of the operation, scarlet needles would separate out containing various amounts of water of crystallization. The following shows results obtained on three different crops of crystals.

Sample A.

I.0.0559 gms.of salt lost at 100 0.0021 gms. 3.7%

II.0.1020 gms.of salt lost at 100 0.0033 gms 3.23%

Sample B.

I.0.1170 gms.of salt lost at 100 0.0063 gms 5.4%

II.0.1146 gms.of salt lost at 100 0.0062 gms. 5.4%

Sample C.

0.2154 gms. of salt lost at 100 . 0.1040 gms. 4.8%

The heated crystals had slightly decomposed and were no longer completely soluble in water.

Upon slow spontaneous evaporation of an alcoholoc solution well formed deep garnet red rhombohedral crystals separated out whereas, by rapid evaporation or by the cooling of a spontaneous solution, needle shaped crystals always resulted.

Conclusions.

Freshly prepared amorphous chelerythrine and sanguinarine both contain a carbonyl group, but no hydroxyl group.

Amorphous chelerythrine contains two methoxyl groups; amorphous sanguinarine contains none.

Both alkaloids combine with methyl and ethyl alcohol, with the formation of methoxyl or ethpxyl groups and probably oxyl groups.

The composition of both alkaloids depends upon the crystallizing medium.

Neither alkaloid forms methyl iodide addition compounds, thus acting like quaternary bases.

Chelerythrine can crystallize with toluol of crystallization and , when combined with alcohol, with chloroform of crystallization.

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This is to certify that the accompanying thesis on "Contribution to the Chemistry of Sanguinarine and Chelerythrine," has been written and the experimental work done by A.E.Kundert in partial fulfillment of the requirements of the University of Wisconsin for a baccaulaureate degree.

Respectfully,

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Madison, Wis.June 1, 1903.

Approved... Richard T. Fischer .....

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