much narrower compared with those found in the region near the cortex. For instance, the width of a medullary ray cell near the cambium will be about 0.010 mm., while the width of the cell in the same ray near the cortext will be 0.020 mm.

REFERENCES TO LITERATURE.

1. A Text-Book of Botany and Pharmacognosy. Fourth Edition. By Henry Kraemer. P. 524.
2. J. Moeller. *Pharm. Post,* 1890 (23), p. 237.
3. Kommentar zur achten Ausgabe der Osterreichischen Pharmakopoe. By August v. Vogl. 2te Band. 1908. P. 282.
4. Lehrbuch der Pharmakognosie, by George Karsten and Friedrich Oltmans. 2te Auflage. 1909. P. 133.

Date.

THE CRYSTALLINE ALKALOID OF CALYCANTHUS GLAUCUS.

(Fourth Paper.)

SOME SALTS OF A NEW QUATERNARY BASE OBTAINED BY METHYLATION OF ISOCALYCANTHINE.

H. M. GORDIN.

It was shown in the last paper on this subject[1] that anhydrous isocalycanthine has the formula $C_{11}H_{14}N_2$, and that when recrystallized from a mixture of acetone and water it contains some water of crystallization the exact amount of which is difficult to determine, owing to the extreme slowness with which this water is given off. When the alkaloid is kept in vacuo over sulphuric acid, the loss of the water of crystallization is at first quite fast, but very soon slackens down to such an extent that it can be observed only when working with considerable quantities and weighing every month or two. I have now been keeping 1.9862 gm. of the alkaloid in vacuo over sulphuric acid for about twenty months. So far the loss amounts to 0.0894 gm. and the weight has not changed within the last two months. Supposing there will be no further loss, the amount of water of crystallization found would be 4.5 per cent, corresponding to half a molecule H_2O.

Calculated for $C_{11}H_{14}N_2.\frac{1}{2}H_2O$, 4.92 per cent. H_2O.

It was also shown in that paper that besides a CH_3N group, isocalycanthine contains an NH group, since when treated with nitrous acid, it given an insoluble nitrosamine. It was therefore expected that it would react with one molecule of methyl iodide to form a teritary methyliscocalycanthine of the formula $C_{11}H_{13}(CH_3)N_2$, and with two molecules of methyl iodide to form a neutral quatternary methiodide of the formula $C_{11}H_{13}(CH_3)N_2.CH_3I$. A large number of experiments showed, however, that whether the methyl iodide is in excess or the alkaloid is in excess, whether the reaction takes place in the cold or at 100° under pressure, in no case is either of the expected substances formed. Under all conditions so far tried the reaction products are as follows: About 35 per cent of the isocalycanthine taken takes no part in the reaction, and can be recovered unchanged; about 35 per cent of the iso calycanthine is converted into its hydriodide, while the rest is transformed into a new quaternary iodide having the entirely unexpected formula

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[1] J. Am. Chem. Soc., 31, 1305.

$C_{24}H_{28}N_3IO.H_2O$. The relative quantities of these substances were determined by the following procedure. The whole of the reaction product, obtained after evaporating the methyl alcohol and the excess of methyl iodide to dryness, as described below, was taken up with dilute acetic acid (about 6%). The acid easily dissolves the unchanged isocalycanthine, but takes up only a small amount of the isocalycanthine hydriodide produced in the reaction, and still less of the new quaternary iodide which is very difficulty soluble in water or weak acids. From the acid solution the free unchanged isocalycanthine was obtained by precipitation with ammonia. From 10 gm. isocalycanthine taken about 3.5 gm. were recovered unchanged. The residue left after the treatment with the acetic acid was rubbed up with concentrated ammonia, which liberates the isocalycanthine left after the second treatment with acetic acid consisted of the new quaternary iodide. After standing over night, the ammoniacal liquid was sucked off, the residue washed with a little water, and then again treated with dilute acetic acid. In the new acid filtrate the free isocalycanthine was again precipitated with ammonia, yielding about 3.5 gm. isocalycanthine coming from its hydriodide. The residue left after the second treatment with acetic acid consisted of the new quaternary iodide. From 10 gm. isocalycanthine about 4 gm. quaternary iodide were obtained.

It is difficult to explain how from an oxygen-free base containing two atoms of nitrogen in the molecule, a quaternary oxygen-containing iodide is produced with three atoms of nitrogen in the molecule. It may be that the reaction consists not in a simple methylation, but that the methylation is accompanied by an elimination of an atom of nitrogen as ammonium iodide from two molecules of isocalycanthine under the combined action of the methyl iodide and the oxygen of the air, and that the large excess of free isocalycanthine drives out ammonia from the ammonium iodide, giving isocalycanthine hydriodide. The reaction could then be represented by the following two equations:

$$2C_{11}H_{14}N_2 + 2CH_3I + O_2 = C_{24}H_{28}N_3IO.H_2O + NH_4I$$
$$C_{11}H_{14}N_2 + NH_4I = C_{11}H_{14}N_2.HI + NH_3$$

An indication of formation of ammonia in the reaction was obtained by placing under the stopper of the flask in which the reaction took place a strip of moistened red litmus paper. After 24 hours' standing the paper turned decidedly blue. On the other hand, the amount of isocalycanthine hydriodide produced seems to be in excess of what might be expected considering the amount of quaternary iodide formed. But this discrepancy may be due to the difficulty of quantitatively separating the two substances from each other. The quaternary iodide being considerably less soluble in presence of ammonia than in neutral or acid liquids, undoubtedly dissolves to an appreciable extent together with the free isocalycanthine in the dilute acetic acid, and is then precipitated by the ammonia together with the free base. The amount found of quaternary iodide is therefore less, while that of isocalycanthine hydrodide, is more than is actually formed in the reaction.

The identity of isocalycanthine recovered from the reaction products, after purification by solution in acidified water, precipitation with ammonia and recrystallization from a mixture of acetone and water, was established by the melting point, optical rotation and the formation of an insoluble nitrosamine.

That none of the expected tertiary methylisocalycanthine is produced in the reaction is shown by the fact that from the acetic acid solution of the free base isolated from the reaction products, nitrous acid quantitatively precipitates the base as a nitrosamine. In the filtrate from the nitrosamine no basic substance could be detected by the usual alkalodal reagents.

That the new reaction product is really a quaternary iodide, not a salt of a tertiary or secondary base, is shown by the fact that ammonia, fixed alkalies and alkaline carbonates simply diminish its solubility in water, but do not precipitate any free base with the removal of hydriodic acid, and that nitrites in neutral solution give a rather difficulty soluble crystalline nitrite, while in acid solution no insoluble nitrosamine is formed.

The new quaternary iodide is both a neutral ammonium salt and a very weak monoacid tertiary base. Itself perfectly colorless and extremely difficultly soluble in water, it is capable of combining with strong acids to form much more easily soluble salts of a fine yellow color. From the solutions of such salts ammonia, fixed alkalies and alkaline carbonates reprecipitate the colorless quaternary iodide. By means of silver chloride the quaternary iodide can be changed to the corresponding quaternary chloride. The latter is quite soluble in water, and can be used for the preparation of other salts of the quaternary hydroxide underlying the quaternary iodide. All of these salts are colorless, except those with colored acids, like picric and picrolonic. They are all capable of combining with strong acids to form much more easily soluble salts of a fine yellow color. The amount of acid taken up by these quaternary salts can be exactly determined by titration with standard alkali, using as end point the disappearance of the yellow color. Further addition of alkali has no effect upon them. They all have a neutral reaction towards indicators, do not combine with weak acids, like acetic, do not react with nitrous acid and do not combine with methyl iodide, though they undoubtedly contain a tertiary nitrogen atom.

Attempts to corroborate the secondary nature of isocalycanthine by acting upon it with ethyl iodide, amyl iodide, benzyl iodide, orthoxylylene dibromide and benzenesulphochloride, were fruitless. In all cases the free base was quantitatively recovered unchanged.

The quaternary iodide or cloride can be changed by means of silver oxide to the corresponding free ammonium hydroxide. The hydroxide has a strong alkaline reaction and absorbs carbon dioxide eagerly. It could not therefore be prepared in pure condition. On heating the hydroxide to about 200°-220° in a current of carbon dioxide, it decomposes into two new substances, one of which is soluble, the other insoluble in dilute hydrochloric acid. These will be investigated later.

EXPERIMENTAL.

Having determined the exact nature of the reaction between isocalycanthine and methyl iodide, as described above, the best method for making the new quaternary iodide was found to be as follows:

Ten gm. crystallized isocalycanthine are boiled under reflux condenser with a mixture of 20 gm. methyl iodide and 30 cc. methyl alcohol for about 20 minutes.

The alkaloid quickly dissolves in the warm liquid, but very soon heavy crystals begin to separate out, and the boiling mixture begins to bump so violently that it is liable to be thrown out through the condenser. The flask is then detached from the condenser, cooled, stoppered and set aside for four or five days. A large amount of a mixture of white and yellowish heavy crystals separates out, firmly adhering to the sides and bottom of the flask. The supernatant liquid is poured off into a shallow evaporating dish, and evaporated to dryness at ordinary temperature in a good current of air. The crystals in the flask are now added to the residue in the evaporating dish, and the whole rubbed up with about 20 cc. of concentrated ammonia. The solid material is now almost perfectly white. After standing under cover for 24 hours, the ammoniacal liquid is sucked off, and the crystalline mass washed with water till the washings are free of ammonia. The mass is digested for a few hours with about 70 cc. dilute acetic acid (6%), and the acid liquid again sucked off, washing the crystals till the washings are neutral. In the acid filtrate the isocalycanthine is precipitated with ammonia, yielding about 6 gm. of free alkaloid. The new quaternary iodide left after the treatment with acid and amounting to about 4 gm. is recrystallized twice from methyl alcohol and dried at 30° for about 6 hours. Thus obtained the quaternary iodide forms snow white, light soft, glittering flat needles, insoluble in benzine, ether or chloroform, very difficultly soluble in water, a little more soluble in alcohol. Of hot methyl alcohol it requires about 30 parts for solution. It turns yellow on prolonged exposure to the air. It also becomes deep yellow upon addition of strong acids, but the color disappears again upon addition of ammonia, fixed alkali or alkaline carbonates. It contains one molecule of water of crystallization which it gives off in vacuo over sulphuric acid. Hydrated it turns brown at 213-14°, assuming a pasty consistence, but does not melt even at 265°. Anhydrous it turns darker and darker when heated, but does not melt even at 325° (on Bloc Maquenne).

The hydrated salt contained 4 per cent H_2O.

Calculated for $C_{24}H_{28}N_3IO.H_2O$, 3.47 per cent H_2O.

The analysis of the anhydrous salt gave: I, 25.52 per cent; N, 8.49 per cent; C, 57.21 per cent; H, 5.96 per cent.

Calculated for $C_{24}H_{28}N_3IO$: I, 25.32; N, 8.39; C, 57.46; H, 5.63.

0.1632 gm. of the anhydrous salt dissolved in 100 cc. methyl alcohol (Merck's pro analysis and redistilled) gave in 200 mm. tube at 23.5° a rotation of 0.62°. Hence $[d]_{D}^{23.5°} = 189.95$.

HYDRIODIDE OF THE QUATERNARY IODIDE, $C_{24}H_{28}N_3IO.HI.H_2O$.

Three gm. quaternary iodide and 4 gm. potassium iodide are dissolved with the aid of heat in a mixture of 10 cc. methyl alcohol and 10 cc. dilute hydrochloric acid about 10%). After standing for 24 hours the crystals which separate out are washed with a little water and dried at about 40°. Flat, bright yellow, silky needles, difficultly soluble in cold solvents, easily soluble in hot water or hot alcohol, insoluble in ether or chloroform. It gradually turns brown when heated, but does not melt even at 325°. The water of crystallization is given off in vacuo over sulphuric acid.

The hydrated salt contained 3.32 per cent H_2O.
Calculated for $C_{24}H_{28}N_3IO.HI.H_2O$, 2.8 per cent H_2O.
The anhydrous salt contained 40.30 per cent, total I.
Calculated for $C_{24}H_{28}N_3IO.HI$, 40.35 per cent I.

QUATERNARY CHLORIDE, $C_{24}H_{28}N_3ClO.3H_2O$.

Fifteen gm. quaternary iodide are shaken with an excess of freshly prepared silver chloride and about 300 cc. very dilute hydrochloric acid (about 1.5%) for half an hour and the liquid filtered. The clear deep yellow filtrate is made strongly alkaline with ammonia, which discharges the color immediately, and evaporated to a small bulk. On cooling the whole mass solidifies to a crystalline cake. After washing with a little water, the quaternary chloride is dissolved in methyl alcohol and the solution covered with ether. The crystals which separate out after 24 hours are dried at about 35°. Snow white, glittering, flat needles, easily soluble in methyl alcohol or hot water. Of cold water the salt requires about 50 parts for solution. It turns brown at 214° and melts to dark liquid at 220°. With gold chloride in presence of sodium carbonate it gives the same intense color reaction as calycanthaine[2], but the violet color is not so prompt to make its appearance. The water of crystallization is given off in vacuo over sulphuric acid. The anhydrous salt is very hygroscopic.

The hydrated salt contained 10.75 per cent, H_2O.
Calculated for $C_{24}H_{28}N_3ClO.3H_2O$, 11.01 per cent, H_2O.
The anhydrous salt contained 8.82 per cent, Cl.
Calculated for $C_{24}H_{28}N_3ClO$, 8.65 per cent, Cl.

0.2705 gm. of the anhydrous salt dissolved in 50 cc. water gave in 200 mm. tube at 24° a rotation of 2.67°. Hence $[d]^{24^\circ}_{D} = 246.76$.

HYDROCHLORIDE OF THE QUATERNARY CHLORIDE, $C_{24}H_{28}N_3ClO.HCl$.

This salt is obtained by dissolving the neutral quaternary chloride in a mixture of methyl alcohol and a little concentrated hydrochloric acid, and covering the solution with ether. It is recrystallized from methyl alcohol covered with ether. Yellow microscopic needles, extremely easily soluble in methyl alcohol, quite soluble in water, but insoluble in ether or chloroform. Dried in the air it turns greenish at 155°. On further heating it becomes pasty, but does not melt to a liquid even at 250°. For the determination of HCl and total Cl it was dried in vacuo over sulphuric acid.

0.1523 gm. dissolved in 75 cc. water and titrated with 0.1 N KOH to disappearance of yellow color required 3.4 cc. for neutralization.

Calculated for $C_{24}H_{28}N_3ClO.HCl$, 3.4 cc. 0.1 N KOH.
The salt contained 16.17 per cent, total Cl.
Calculated for $C_{24}H_{28}N_3ClO.HCl$, 15.89 per cent, total Cl.

Attempts to prepare chloroplatinates and chloraurates of the quaternary chloride were not successful. Neither in acid nor in neutral solutions could salts of definite composition be obtained. The precipitates obtained by adding platinum tetrachloride or gold chloride to solutions of the quaternary chloride had a tendency to pass through the filter, and their color varied with the slightest change in

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[2] J. Am. Chem. Soc., 27, 153.

the conditions of preparation. The platinum salt examined under the microscope consisted of a mixture of crystals and amorphous masses.

QUATENARY NITRATE, $C_{24}H_{28}N_3O.NO_3$.

The salt is prepared by dissolving the quaternary chloride in hot water and adding a saturated solution of potassium nitrate in water. It is recrystallized from boiling water and dried in vacuo over sulphuric acid. Snow white rectangular prisms, difficultly soluble in cold water, quite soluble in methyl alcohol and hot water. It turns yellowish at 190° and melts at 192-94° to a reddish liquid.

Analysis gave: C, 65.60 per cent; H, 6.22 per cent.

Calculated for $C_{24}H_{28}N_3O.NO_3$; C, 66.02; H, 6.47.

QUATENARY PICRATE, $C_{24}H_{28}N_3O.C_6H_2N_3O$.

The salt is prepared by dissolving 2 gm. of quaternary chloride in 500 cc. hot water and adding an excess of a hot solution of sodium picrate containing some free sodium carbonate. It is recrystallized from boiling water containing a little sodium carbonate and dried in vacuo. Soft, orange-yellow, oblong plates, difficultly soluble in all solvents. It turns reddish at 145° and melts at 155°.

It contained 13.96 per cent N.

Calculated for $C_{24}H_{28}N_3O.C_6H_2N_3O$, 13.96.

QUATENARY PICROLONATE, $C_{24}H_{28}N_3O.C_{10}H_7N_4O_5$.

The salt is prepared as follows: Sodium carbonate and picrolonic acid, one gm. each, are dissolved in 800 cc. warm water, and the solution set aside over night in a cool place. The liquid is filtered, and to the filtrate, heated nearly to boiling, is added a solution of one gm. quaternary chloride in 200 cc. hot water. The salt is recrystallized from boiling water, of which it requires about 2000 cc. for solution. Bright orange colored microscopic needles, very difficultly soluble in all solvents. Air dried it melts at 164-66° to thick liquid. For the estimation of N it was dried in vacuo.

The salt contained 15.86 per cent N.

Calculated for above formula, 15.38.

The investigation is to be continued.

NORTHWESTERN UNIVERSITY SCHOOL OF PHARMACY.

CALCIUM HYDROXIDE.

A Plea For Its Introduction Into the U. S. P.

PHILIP ASHER, PH. G.

The official method of making lime water is simple enough; and the principal question of interest is its only constituent, the lime, and which has caused an endless amount of unnecessary worry to those who have to make this solution.

The first difficulty the retailer meets is in obtaining lime of good quality.

Often lime is obtained which is difficult to slake, or, after having had it for a short time, one finds it has become air slaked and naturally it is thrown out.

The city druggist often experiences trouble in getting lime of good quality, and this difficulty is still greater in the country.