trouble of filtering and aliquoting saved, and recovery of the chloroform. Also, the method of titration is itself capable of great exactness. The method would appear to be well adapted to the needs of the manufacturer, for after the extent of the blank had been well established on a given stock, the results should be quite satisfactory.

As a qualitative test, the method is both quick and reliable. It is only necessary to shake the chloroform, after titration, with a small amount of water, separate and filter the aqueous solution to remove emulsion, and test with ferric chloride or apply Mohler's test. The used chloroform may be recovered by shaking several times with water made alkaline with sodium or potassium hydroxide. It should be tested by shaking 100 cc. with dilute hydrochloric acid, separating and titrating with the 0.1 *N* sodium alcoholate. Not more than 0.02 cc. should be required to give the end point with phenolphthalein.

THE CRYSTALLIN ALKALOID OF CALYCANTHUS GLAUCUS.

[FOURTH PAPER.]

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

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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 determin, owing to the extreme slowness with which this water is given off. When the alkaloid is kept *in vacuo* over a drying agent, the loss of the water of crystallization is at first fast, but very soon slackens down to such an extent that it can be observed only when working upon considerable quantities and weighing every few weeks. I have been keeping 1.9862 grams of the alkaloid in a vacuum desiccator over sulfuric acid for nearly twenty months. So far the loss amounts to 0.0894 gram, 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 of water. Calculated for $C_{11}H_{14}N_2.{}^1/_2H_2O$, 4.92 per cent. H_2O.

It was also shown in that paper that the alkaloid contains an NH group, since when treated with nitrous acid, it gives an insoluble nitrosoamine. It was therefore expected that it would react with one molecule of methyl iodide to form a tertiary methyl isocalycanthine of the formula $C_{11}H_{13}(CH_3)N_2$, and with two molecules of methyl iodide to form a neutral

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[1] This Journal, 31, 1305.

quaternary iodide having 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 at ordinary temperature or at 100° under pressure, in no case is either of the expected substances formed. Under all conditions so far tried the products of the reaction 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 isocalycanthine is converted into its hydriodide, while the rest is transformed into a new quaternary iodide having the entirely unexpected formula $C_{24}H_{28}N_3IO.H_2O$. The relative quantities of these substances were determined by the following procedure: The whole of the reaction product, obtained by evaporating the methyl alcohol and the excess of methyl iodide to dryness, as described below, was taken up with dilute acetic acid (about 6 per cent.). The acid easily dissolves the unchanged isocalycanthine, but takes up only a small amount of its hydriodide produced in the reaction, and still less of the new quaternary iodide, which is very difficultly soluble in water even in presence of weak acids. From the acid solution the unchanged isocalycanthine is obtained by precipitation with ammonia. From 10 grams isocalycanthine taken, 3.5 grams were recovered unchanged. The residue left after treatment with the acetic acid was rubbed up with concentrated ammonia, which liberates the isocalycanthine from its hydriodide formed in the reaction, but does not affect the new quaternary compound, except to make it less soluble in water. After standing over night, the ammoniacal liquid was sucked off, the residue washed with water till the washings were free from ammonia, and then again treated with dilute acetic acid. In the new filtrate the free isocalycanthine was again precipitated with ammonia. This operation yielded 3.5 grams isocalycanthine coming from its hydriodide produced in the reaction. The residue left after the second treatment with the acid consists of the new quaternary iodide. From 10 grams isocalycanthine about 4 grams quaternary iodide were obtained.

It is difficult to explain how from an oxygen-free base containing two atoms of nitrogen in the molecule an oxygen-containing iodide is produced having three atoms of nitrogen in the molecule. It may be that the reaction consists not in a simple methylation, as is usually the case when methyl iodide acts on an organic base, 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 excess of the fixed base drives out the volatil ammonia from the ammonium iodide, giving isocalycanthine hydriodide. The reaction would then be as follows:

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

An indication of formation of ammonia was obtained by placing a strip of moistened red litmus paper under the stopper of the flask in which the reaction took place. After 24 hours' standing the paper was decidedly blue. On the other hand, aside from the not very plausible supposition that methyl iodide would react in such a peculiar way with an organic base,[1] 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 these two substances from each other. The quaternary iodide being considerably less soluble in presence of ammonia than in that of weak acids, undoubtedly dissolves to an appreciable extent in the dilute acetic acid, and is then precipitated by the ammonia together with the free isocalycanthine. The amount of quaternary iodide found is therefore less, while that of free isocalycanthine more than is actually formed in the reaction. As a matter of fact, both the isocalycanthine which remained unchanged, as well as that coming from the hydriodide, contains some of the quaternary iodide. This is easily proved by the presence of iodine in the recovered isocalycanthine and by the yellow color of its solutions in strong acids (see below).

The identity of the 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 nitrosoamine.

That none of the expected methylisocalycanthine is formed in the reaction is shown by the fact that in the acetic acid solution of the free base isolated from the reaction products, nitrous acid quantitatively precipitates the base as a nitrosoamine. In the filtrate from the nitrosoamine no appreciable amounts of base can be detected by the usual alkaloidal reagents.

That the new reaction product is really a quaternary ammonium salt, not a hydriodide of a secondary or tertiary 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 somewhat difficultly soluble crystallin nitrite, while in acid solution no insoluble nitrosoamine is formed.

The new quaternary iodide is both a neutral ammonium salt and a very weak monoacid tertiary base. Itself perfectly colorless and very difficultly soluble in water, it is capable of combining with strong acids to

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[1] I have not been able to find an analogous reaction in the literature on alkaloids.

form readily soluble salts of a fine yellow color. From the yellow solutions of such salts ammonia, fixed alkalies and alkaline carbonates reprecipitate the colorless quaternary iodide. With weak acids no such salts are produced. 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 taking up strong acids to form readily soluble salts of a fine yellow color. With weak acids they do not combine. The amount of strong acid taken up by these quaternary salts can be exactly and conveniently 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, are only very slightly colored by 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, *o*-xylylene dibromide and benzenesulfochloride were fruitless. In all these cases the free isocalycanthine was quantitatively recovered unchanged.

The quaternary iodide or chloride can be changed by means of silver oxide to the corresponding free quaternary hydroxide. The hydroxide has a strong alkaline reaction and eagerly absorbs carbon dioxide from the air. It could not therefore be prepared in pure condition. On heating the impure hydroxide to about 200–20° in a current of carbon dioxide, it breaks up into two amorphous 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 a slight modification of the procedure described.

Ten grams crystallized isocalycanthine are boiled under reflux condenser with a mixture of 20 grams 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 commences 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 separate 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 small 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 crystallin mass washed with water till the washings are free from ammonia. The mass is digested for a few hours with dilute acetic acid (about 6 per cent.), and the acid liquid again sucked off, washing the crystals till the washings are neutral. In the acid filtrate the free isocalycanthine is precipitated with ammonia yielding about 6 grams free alkaloid. The new quaternary iodide left after the treatment with acid and amounting to about 4 grams 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 ether, chloroform and benzene, very difficultly soluble in water, and a little more soluble in alcohol. Of hot methyl alcohol it requires about 30 parts for solution. It turns yellowish on prolonged exposure to the air. It also becomes yellow upon addition of strong acids, but the color is discharged by ammonia, fixed alkali or alkaline carbonates. It contains one molecule of water of crystallization, which it gives off *in vacuo* over drying agents. Hydrated it turns brown at 213–14°, assuming a pasty consistence, 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:

Calculated for $C_{24}H_{28}N_3IO$: I, 25.32; N, 8.39; C, 57.46; H, 5.63
Found: I, 25.52; N, 8.49; C, 57.21; H, 5.96

0.1632 gram of the anhydrous salt dissolved in 100 cc. methyl alcohol (Merck's *pro analysi* and redistilled) gave in 200 mm. tube at 23.5° a rotation of 0.62°. Hence $[\alpha]_D^{23.5} = 189.95°$.

Hydriodide of the Quaternary Iodide, $C_{24}H_{28}N_3IO.HI.H_2O$.—Three grams quaternary iodide and 4 grams 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 per cent.). After standing in a cool place for 24 hours the crystals which separated out are washed with a little water and dried at about 40°. Bright yellow, flat silky needles, difficultly soluble in cold solvents, easily soluble in hot water or hot alcohol and insoluble in ether, chloroform or benzene. It gradually turns brown when heated, but does not melt even at 325°.

The water of crystallization is given off *in vacuo* over sulfuric 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. total I.

Quaternary Chloride, $C_{24}H_{28}N_3ClO.3H_2O$.—Fifteen grams of the quaternary iodide are shaken with an excess of freshly prepared silver chloride and about 300 cc. of very dilute hydrochloric acid (about 1.5 per cent.) 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 crystallin 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 are dried at about 35°. Snow-white, glittering flat needles, easily soluble in methyl alcohol or hot water. Of cold water about 50 parts are required for solution. It turns brown when heated to 214° and melts to a dark liquid at 220°. With gold chloride in presence of sodium carbonate it gives the same intense color reaction as isocalycanthine and calycanthine,[1] but the violet color is not so prompt to make its appearance. The water of crystallization is given off *in vacuo* over drying agents. 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 gram of the anhydrous salt dissolved in 50 cc. water gave in 200 mm. tube at 24° a rotation of 2.67°. Hence $[\alpha]_D^{24} = 246.76$.

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, insoluble in ether or chloroform. Dried in the air it turns greenish at 155°. On further heating it becomes pasty but does not melt at 250°. For the determination of hydrochloric acid and total chlorine it was dried *in vacuo* over sulfuric acid.

0.1523 gram 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 $C_{24}H_{23}N_3ClO.HCl$, 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 chloroaurates of the quaternary base underlying the quaternary iodide were not successful. Neither in acid nor in neutral solution could these salts be obtained. The precipitates produced by adding platinum tetrachloride or gold chloride to

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[1] This Journal, 27, 153.

solutions of the quaternary chloride had a strong tendency to pass through the filter, and their color varied with the slightest change in the conditions of preparation. The platinum salt examined under the microscope consisted of a mixture of crystals and amorphous masses.

Quaternary Nitrate, $C_{24}H_{28}N_3O.NO_3$.—The salt is prepared by dissolving the quaternary chloride in hot water and adding a strong solution of potassium nitrate in water. It is recrystallized from boiling water and dried *in vacuo* over sulfuric 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.

Calculated for $C_{24}H_{28}N_3O.NO_3$:	C, 66.02; H, 6.47.
Analysis gave:	C, 65.60; H, 6.22.

Quaternary Picrate, $C_{24}H_{28}N_3O.C_6H_2N_3O_7$.—The picrate is prepared by dissolving 2 grams 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 hot water containing some sodium carbonate and dried *in vacuo.* Soft, orange-yellow, oblong plates, difficultly soluble in all solvents tried. It turns reddish at 145° and melts at 155°. The salt contained 13.96 per cent. N. Calculated for above formula, 13.96.

Quaternary Picrolonate, $C_{24}H_{28}N_3O.C_{10}H_7N_4O_5$.—This salt is prepared as follows: Sodium carbonate and picrolonic acid, 1 gram 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 1 gram of quaternary chloride in 200 cc. hot water. On cooling, most of the picrolonate crystallizes out. It is recrystallized from boiling water, of which it requires about 2000 cc. Bright, orange colored microscopic needles, very difficultly soluble in the usual solvents. Air-dried, it melts at 164–66° to a thick liquid. For the estimation of N it was dried *in vacuo* over sulfuric acid. The salt contained 15.86 per cent. N. Calculated for above formula, 15.38.

The investigation is to be continued.

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NOTE.

Prevention of Bumping.—It is sometimes necessary to boil alcohol out of an aqueous solution which is covered by a layer of specifically lighter oil, as in soap and oil analyses. This is quite difficult to accomplish without loss and is always very tedious on account of the great liability to explosive ebullition.

By introducing a piece of glass tubing open at both ends, the difficulty