CERTAIN ALKALOIDAL PERIODIDES, AND THE VOLUMETRIC ESTIMATION OF ALKALOIDS AS HIGHER PERIODIDES.[1]

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THE PERIODIDES IN RESPECT TO COMPLETENESS OF PRECIPITATION.

IN aqueous solutions of salts of the alkaloids, one of the most delicate of qualitative reagents is iodopotassium iodide. Wormley gives the limit of this precipitation, for the chief medicinal alkaloids, as from $\frac{1}{50000}$ to $\frac{1}{100000}$ of a grain of the alkaloid in one grain of water; that is, from 0.0000013 to 0.0000007 gram in one cc. of water.[3] The precipitate is not appreciably soluble in excess of the reagent, an advantage over several other qualitative precipitations of alkaloids in general. In some cases the precipitate is appreciably soluble in excess of the alkaloidal salt, and this condition is one most easy to avoid. The potassium iodide solution of iodine was recommended as a reagent for alkaloids by Bouchardat, a medical writer in Paris, in 1839.[4]

As a volumetric solution, the decinormal solution of iodine with potassium iodide was first proposed by Wagner, in 1861,[5] and the decinormal strength is generally the most suitable for volumetric use.

HISTORICAL AS TO THE FORMATION OF PERHALIDES IN GENERAL.

The formation of the alkaloidal periodides was first made a subject of systematic observation by Jörgensen, at Copenhagen,

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[1] The portion of this article which concerns atropine was given in substance in this Journal, 20, 329, under the title "Atropine Periodides and Iodomercurates," by H. M. Gordin and A. B. Prescott (reprints). Also that concerning morphine and opium, except the "Results of Opium Assay," appeared in Kremers' *Pharmaceutical Archives*, June, 1898, 1, 121, under the title "A Volumetric Assay of Opium," by H. M. Gordin and A. B. Prescott (reprints).

[2] In the work of Research Committee D, Section 2, Committee on Revision of the Pharmacopeia of the United States.

[3] Microchemistry of Poisons, 1885, Tabular View.

[4] Bouchardat, 1839: *Compt. rend.*, **9**, 475; *L'Institut*, 7, 358. This precipitation, however, was proposed as an antidote for strychnine, in cases of poisoning of dogs. Further, see Donné: *Ann. chim. phys.* (2), **38**, 82.

[5] R. Wagner: Dingler's *poly. J.*, **161**, 40; *Ztschr. anal. Chem.*, 1, 102.

in 1869,[1] and the masterly researches of this Danish chemist, extending over nine years, afford a model of logical inquiry into chemical structure. A still wider study of all periodides and some other perhalides of organic bases was commenced in 1887 by Prof. Geuther[2] of Jena, but was cut short by his death in 1889. Among various periodides reported of later years have been picoline periodides by Wm. Ramsay in 1878;[3] cesium and rubidium periodides by Wells, and others, in 1893;[4] iodonium periodides by Victor Meyer in 1894;[5] sulphon periodides by Kastle in 1894;[6] periodides of diazo bodies by Hantsch in 1895;[7] halogen addition-products of the anilides by Wheeler and others in 1896-97;[8] perhalides of aliphatic amines by Norris in 1898;[9] mixed perhalides of alkyl anilines by Samtleben in 1898.[10]

In this laboratory since 1895 the perhalides and various double halides of pyridine have been obtained,[11] also the perhalides of caffeine,[12] and work on picoline perhalides is in hand. In the course of work upon an entirely different inquiry, a new order of perhalides has just been obtained, a periodide of bromtriphenylmethane.[13]

It is of interest to inquire what classes of compounds are liable to the formation of perhalides, and this inquiry has a special interest when it is proposed to estimate a single class of compounds, in vegetable drugs or their extracts, by formation of periodide. In general terms the reply is easily given, that

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[1] Jörgensen, 1869-1878: *J. prakt. Chem.* (2). **2**, 347, 433; **3**, 145, 328; **14**, 213, 356; **15**, 65, 418; **16**, 352: *Ber. d. chem. Ges.*, **2**, 460.

[2] A. Geuther: *Ann. Chem. Pharm.* (Liebig). **240**, 66-91, with lists of the organic periodides previously obtained.

[3] *Phil. Mag.* (5). **2**, 269; **4**, 241; **6**, 19.

[4] *Am. J. Sci.* (3), **44**, 42; **43**. 17.

[5] *Ber. d. chem. Ges.*, **27**, 1594.

[6] *Am. Chem. J.*, **16**, 116.

[7] *Ber. d. chem. Ges.*, **28**, 2754.

[8] *Am. Chem. J.*, **18**, 85; **19**, 672.

[9] *Am. Chem. J.*, **20**, 51.

[10] A. Samtleben: *Ber. d. chem. Ges.*, **31**, 1141.

[11] Prescott, the Periodides: This Journal, 17, 775; *Pharm. Rnndschau*, **13**, 233. Prescott and Trowbridge, Periodides of Pyridine: This Journal. 17, 859. Flinterman and Prescott, Dipyridine Methylene Dibromide: *Ibid.* **18**, 28. Prescott, Pyridine Alkyl Iodides: *Ibid*, **18**, 91. Trowbridge, Periodides of Pyridine: *Ibid*, **19**, 322. Trowbridge and Diehl, Halides and Perhalides of Pyridine: *Ibid*, **19**, 558.

[12] Gomberg, Perhalides of Caffeine: This Journal, **18**, 347-378.

[13] See paper by Gomberg read at Boston meeting of the American Chemical Society, August, 1898, and to be published in a subsequent number of this Journal.

periodides are limited to the organic basis, that is the more or less basal compounds of the nitrogen family of elements, and the inorganic alkalies. It is remarkable that the iodonium compounds yield periodides, which is quite in accord with the claim of Victor Meyer that in these bodies iodine itself strangely serves (with the benzene ring) as a base-forming element like a member of the nitrogen family. This view is supported further by Gomberg's production at this time of a periodide of a triphenylmethane derivative, as cited just above.

At present it seems highly improbable that any plant constituent other than the alkaloids, in the larger sense of organic bases, are of the sort of bodies which can form periodides in precipitation. Moreover, Wagner's reagent is used in a qualitative way along with plant analysis to an extent likely to call attention to any interference with its use for alkaloids. From the work of Wheeler it is evident that periodides may be formed by acid amides, but probably not by precipitation in dilute solutions. The formation of iodonium periodides, and a sulphone periodide, indicate that the limits of formation of perhalides cannot yet be declared, and it will be well for analysts to be watchful of new developments.

HISTORICAL AS TO ANALYTICAL USE OF PERIODIDES.

The volumetric use of a potassium iodide aqueous solution of iodine dates from Wagner in 1861,[1] and the solution in decinormal strength of iodine is named Wagner's reagent.

This iodine solution was tried briefly by Schweissinger in 1885,[2] and at length by Kippenberger in 1895,[3] but both seem

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[1] R. Wagner, 1861: Ding. *poly. J.*, **161**, 40; *Ztschr. anal. Chem.*, 1, 102. Wagner wisely avoided washing the precipitate, but he failed to add the solution of alkaloid to that of iodine: "Man versetzt die Losung der Basen, deren Menge man bestimmen will, mit überschüssiger Iod lösung, filtrirt und bestimmt in einem gemessenen Theil des Filtrats mit unterschwefligsaurem Natron das überschüssige Iod." As periodides had not then been prepared and analyzed, the iodine factors of Wagner were empirical, and, as the higher periodides are not invariably the sole products when iodine solution *is added to* the alkaloid solution, the factors adopted proved unsatisfactory. It is noteworthy that "Mayer's reagent" was so nearly contemporaneous with Wagner's, in publication. The potassium mercuric iodide method of volumetric estimation dates from 1862: *Proc. Am. Pharm. Assoc.*, 230; *Am. J. Pharm.*, 35, 20; *Chem. News*, 7, 159; **8**, 177, 189. Of special American interest is Dr. F. Hoffmann's biography of Ferdinand F. Mayer as a New York chemist (*Pharm. Rundschau*, 1894, **12**, 125), and of more general interest, Prof. Schaer's history of Mayer's alkaloid reagent (*Pharm. Rundschau*, **12**, 142).

[2] *Arch. Pharm.*, *1885*, 611.

[3] K. Kippenberger, 1895: *Ztschr. anal. Chem.*, **34**, 317; **35**, 407, 422.

to have obtained the lower periodides, at least in part, in their methods of estimation. The last-named author proceeded upon a volumetric deduction of a general formation of triiodides, and sought to so vary the conditions as to support the factor of a triiodide. In 1896, Gomberg,[1] along with his production of caffeine perhalides above referred to, established the volumetric estimation of caffeine in acidulated solutions as a pentaiodide, and this was used, with a method of extraction from Kola, throughout the work of Mr. Knox and one of us[2] upon the caffeine compound of kola, with complete satisfaction.

THE HIGHER PERIODIDES IN RESPECT TO CONSTANCY OF COMPOSITION.

The number of the periodides ot pyridine is representative of the fact that most of the alkaloids of pyridine-derived constitution will form each more than one periodide, according to conditions. We find it is more expedient to secure the exclusive formation of the higher periodide, by needful conditions, than that of any other periodide obtainable. The higher periodides are not surpassed in completeness of precipitation, and they are sufficiently stable. At least this is true of those alkaloids included in this report. In future reports we desire to be able to give analyses of all the readily obtained periodides of each of the alkaloids reported upon in this article.

If we add the iodopotassium iodide solution to the solution of an alkaloidal salt, keeping from the beginning to the end the alkaloid in excess, it is generally the lowest periodide (in most cases a triiodide) that is formed, but if the order be reversed and the alkaloidal solutions added to the iodopotassium iodide solution, keeping all the time a large excess of iodine, it is generally the highest periodide that is formed. We have found this rule to hold good with atropine, strychnine, brucine, aconitine, and several other alkaloids. It was mainly the lower periodides of alkaloids that were made and described by Jörgensen; they are generally very stable and can be easily obtained in crystalline form by crystallization from some suitable solvent. As to the higher periodides, some of them are stable enough to be

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[1] This Journal, 18, 331.

[2] Knox and Prescott: *Proc. Am. Pharm. Assoc.*, 44, 128; 45, 131: This Journal, 19, 63; 20, 34.

recrystallizable; many others are easily decomposed in solution into free iodine and lower periodides. Atropine enneaiodide belongs to the first class; strychnine heptaiodide and brucine heptaiodide belong to the second.

Following the above-mentioned rule, we have succeeded in obtaining an enneaiodide of atropine, $C_{17}H_{23}NO_3HI.I_8$; a heptaiodide of strychnine, $C_{21}H_{22}N_2O_2HI.I_6$; a heptaiodide of brucine, $C_{23}H_{26}N_2O_4HI.I_6$, and, as it is probable, a triiodide and a heptaiodide of aconitine. The tetraiodide of morphine, obtained by Jörgensen, is the only periodide of morphine that we have been able to make by precipitation.

These compounds are of the common order of alkaloidal hydriodide periodides. The single atom of iodine in the normal hydriodide is transposed by silver nitrate solution with precipitation, but does not respond to reducing agents. The rest of the iodine, being additive to the first atom of this element, is very easily taken up by reducing agents, such as sulphur dioxide, a thiosulphate, or powdered zinc.

PREPARATION OF THE HIGHER PERIODIDES IN PURITY FOR ANALYSIS.

The periodides, of which analysis is given in this paper, were all made according to the following method: One gram of the alkaloid was dissolved in about 200 cc. of water acidulated with sulphuric or hydrochloric acid, and the solution poured, in small quantities at a time, into 500 cc. of water containing one per cent. free iodine and one and a half per cent. potassium iodide. After shaking until the liquid became perfectly clear, the mother-liquor was removed in filtration by means of a pump, the precipitate well washed with cold water and dried first on porous plates and then in a vacuum over sulphuric acid. For the aconitine triiodide the order of mixing was reversed, and an excess of aconitine kept during the whole operation. After drying, the precipitate was recrystallized from alcohol. These periodides, so prepared, were subjected to analysis by the method given under atropine below, and as stated further under the several alkaloids, and from the results of the analysis, the volumetric factor of free iodine for each alkaloid was determined.

ATROPINE ENNEAIODIDE AND ITS ANALYSIS.

The enneaiodide, obtained as above described, is a very dark brown, almost black powder, quite permanent in dry air, and has only a slight odor of iodine. It is very difficultly soluble in ether, chloroform, benzene, or carbon disulphide, but is soluble in alcohol, very freely when hot. In cold water it is insoluble; hot water decomposes it quickly; it is also decomposed by concentrated solutions of potassium iodide. At 90° C. it commences to give up iodine vapors, and at 140° C. melts to a dark liquid. To obtain it in crystalline form it is first washed with a little cold alcohol to remove traces of free iodine, and then dissolved in warm alcohol. On cooling it crystallizes out in dark-green prisms and leaflets, having the same properties as the non-crystallized body. In analysis we estimated the additive iodine volumetrically, and the total iodine both gravimetrically and volumetrically.

To estimate the additive iodine a small quantity of the enneaiodide is dissolved in very little alcohol, an excess of a standardized solution of sodium thiosulphate added, and the excess titrated back with a standard solution of iodine, using starch as the indicator.

For total iodine the substance is covered with an excess of powdered metallic zinc and some water, and then boiled gently for ten or fifteen minutes, taking care to prevent loss by spurting; the mixture is then thrown upon a filter, and the containing flask and the filter are thoroughly washed with hot water. The iodine in the zinc iodide thus formed can either be estimated by precipitation with silver nitrate and nitric acid and weighing as silver iodide, or it is precipitated with an excess of a standardized solution of silver nitrate and the excess titrated back with a standard solution of ammonium thiocyanate, using ferric nitrate as indicator.

In the following analyses the standard silver nitrate solution was made to correspond with one per cent. of iodine, and the ammonium thiocyanate solution to correspond, cc. per cc., with the silver nitrate solution. The standard solution of iodine contained one per cent. of iodine, and the sodium thiosulphate solution corresponded, cc. per cc., with the iodine solution.

Analysis of the atrophine enneaiodine not recrystallized: In the volumetric estimation for total iodine, 0.15225 gram required 12.2 cc. of the silver nitrate solution. For the iodine removed by reduction, 0.19255 gram required 13.7 cc. of the thiosulphate solution.

	Calculated for $C_{17}H_{23}NO_3.HI.I_8$.	Found.
Iodine by reduction	70.88	71.15
Total iodine	79.74	80.13

In the gravimetric estimation from 0.218 gram 0.3207 gram silver iodide was obtained.

	Calculated for $C_{17}H_{23}NO_3HI.I_8$.	Found.
Total iodine	79.74	79.48

Analysis of the atropine enneaiodide recrystallized from alcohol.—The methods employed were the same as with the non-recrystallized compound, and the standard solutions of the same strength.

In the volumetric estimation of total iodine, 0.12685 gram required 10.1 cc. of the silver nitrate solution. For the iodine removed by reducing agents, 0.23105 gram required 16.4 cc. of the thiosulphate solution.

	Calculated for $C_{17}H_{23}NO_3.HI.I_8$.	Found.
Total iodine	79.74	79.62
Iodine by reduction	70.88	70.98

In the gravimetric estimation of total iodine, 0.2031 gram gave 0.30035 gram silver iodide.

	Calculated for $C_{17}H_{23}NO_3.HI.I_8$.	Found.
Total iodine	79.74	79.90

The constitution of the compound is that of atropine hydriodide octaiodide. The alkaloidal hydriodide is formed, in the (acidulated) solution, by transposition of the alkaloidal salt taken with potassium iodide. Thus: $C_{17}H_{23}NO_3.HCl + KI + I_8 = C_{17}H_{23}NO_3.HI.I_8 + KCl$.[1] Therefore the ratio of the free iodine consumed, to the absolute atropine, is the ratio of I_8 to $C_{17}H_{23}NO_3$, equal to ratio 1012.24 to 288.38, or of 1 of iodine to 0.2849 of atropine.[2] And 1 cc. of decinormal iodine solution consumed is equivalent to 0.0036048 gram of the atropine. *This decinormal*

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[1] For experimental verification of this equation, see a later paragraph in this paper.

[2] The atomic weights taken were those of L. Meyer and K. Seubert, H = 1.

factor was found to hold good under the control estimations reported further on.

OTHER ATROPINE PERIODIDES, AND ATROPINE MERCURIC IODIDES.

Having obtained the enneaiodide of atropine, it was natural to suppose the existence of a heptaiodide, with probability of a complete series from the triiodide to the enneaiodide. And in fact in the course of our work we once obtained this heptaiodide. But our efforts to determine the exact conditions necessary for the formation of this body have so far not been successful. Whether additional quantities of atropine will make the precipitate take up more atropine and become a lower periodide we shall try to determine by later experiments. On the other hand, when the order is reversed and the iodine solution is added to the atropine solution, it is always a lower periodide that is formed; but whether on continued addition of the iodine the precipitate will take up more of it and become a higher periodide, we cannot say as yet.

The easiest way to obtain the periodides of atropine is to use chloroform as a solvent. On adding twenty grams atropine to a warm solution of thirty grams iodine in chloroform (500 cc.) the enneaiodide crystallizes out very soon in the shape of small, shining, dark green crystals. If these be removed by filtration, the mother-liquor will give several successive crops of the dark blue pentaiodide, and at last a crop of the brownish-red triiodide.

Atropine mercuric iodides are best known as products of precipitation of atropine salts by Mayer's reagent, the solution of potassium mercuric iodide.[1] We find that they can be obtained by shaking the alcoholic solution of a periodide with metallic mercury and warming the mixture. Double iodides of atropine and mercury can also be made by mixing theoretical quantities of atropine and iodine, adding a little alcohol and an excess of mercury, slightly warming, and shaking till the color of iodine disappears. If the higher periodides of atropine be used in the preparation of this double iodide of atropine and mercury there

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[1] Groves, 1859: *Quar. J. Chem. Soc.*, **11**, 97, 188. F. F. Mayer, 1862: *Am. J. Pharm.*, **35**, 20; *Chem. News*, 7, 159; **8**, 177. 189. Prescott, 1880.: *Am. Chem. J.*, **2**, 294; **14**, 606.

is always separation of mercurous iodide; but if theoretical quantities of atropine and iodine be used there is no separation of mercurous iodide. The formula of this double iodide of mercury and atropine, as shown by our analysis, seems to be $C_{17}H_{23}NO_3.HI.HgI_2$. It resembles in composition several other double iodides of alkaloids and mercury obtained by Groves by a different method, and agrees in proportion with the strychnine compound, not with the morphine or quinine compound obtained by one of us in 1880.[1] But besides this double iodide we also obtained another having the composition $(Atrop. HI)_2.HgI_2$. It was made by treating a solution of the $(Atrop. HI).HgI_2$ in diluted alcohol with an excess of potassium iodide. From the liquid obtained by shaking an alcoholic solution of atropine and iodine with mercury the monoatropine hydriodide mercuric iodide crystallizes out in shining, yellow crystals, melting at 80° to 90° C., difficultly soluble in ether or chloroform, partly soluble in hot water, and very soluble in warm alcohol. The diatropine hydriodide mercuric iodide obtained, as said above, by the action of potassium iodide on the mono compound, crystallizes in perfectly white, silky needles, which, on being dried, assume a yellowish tint. They melt at 98° to 99° C., are very easily soluble in warm alcohol, and quite soluble in hot water.

The analysis for mercury and for iodine in these bodies can be made in different ways, but the best results are obtained by a modification of the method of Risse.[2] The mercury and the iodine are determined in two separate portions. For mercury the substance is dissolved in a little warm alcohol and a little water added; the solution is then acidulated with a few drops of dilute hydrochloric acid and saturated with hydrogen sulphide. The mercuric sulphide is then dried and weighed in the usual way. For the determination of iodine the substance is treated with a hot solution of potassium hydroxide (1 : 10), diluted with water, filtered, and when completely cold, neutralized with acetic acid. The iodine is now precipitated with silver nitrate and nitric acid, and determined as silver iodide in the usual way.

In the following analyses the standard silver nitrate solution

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[1] Prescott: *Am. Chem. J.*, 2, 297.

[2] *Ann. Chem.* (Liebig), 107, 223.

was made to correspond with one per cent. of iodine, and the ammonium thiocyanate solution to correspond, cc. per cc., with the silver nitrate solution. The standard solution of iodine contained one per cent. of iodine, and the sodium thiosulphate solution corresponded, cc. per cc., with the iodine solution.

Analyses of the Double Salts of Atropine Hydriodide and Mercuric Iodide : 0.2632 gram of the monoatropine hydriodide mercuric iodide gave 0.0699 gram mercuric sulphide, and 0.30445 gram of the substance gave 0.24785 gram silver iodide.

	Calculated for $C_{17}H_{23}NO_3.HI.HgI_2$.	Found.
Mercury	23.03	22.89
Iodine	43.74	43.98

Of the diatropinehydriodide mercuric iodide, 0.1798 gram gave 0.032 gram mercuric sulphide, and 0.257 gram of the substance gave 0.18885 gram silver iodide.

	Calculated for $(C_{17}H_{23}NO_3.HI)_2HgI_2$.	Found.
Mercury	15.58	15.34
Iodine	39.46	39.70

STRYCHNINE HEPTAIODIDE AND ITS ANALYSIS.

The heptaiodide of strychnine is a dark brown powder, hardly soluble in ether, chloroform or benzol, and requires considerable alcohol for solution. It cannot be recrystallized, as it is easily decomposed into free iodine and the triiodide.[1]

The total iodine was determined by silver nitrate after reduction with zinc and ammonia. The additive iodine was estimated after dissolving the periodide in alcohol, by titrating with thiosulphate.

For total iodine :

1. 0.3816 gram of the periodide gave 0.51345 gram silver iodide.
2. 0.30625 gram gave 0.4112 gram silver iodide.

	Calculated for $C_{21}H_{22}N_2O_2.HI.I_6$.	Found.
1	72.66	72.70
2	....	72.54

For additive iodine :

1. 0.1754 gram of the substance was found to contain 0.109 gram free iodine.
2. 0.17805 gram contained 0.111 gram free iodine.

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[1] A triiodide was reported by Tilden in 1865 (see Geuther's lists, *loc. cit.*).

	Calculated for $C_{21}H_{22}N_2O_2.HI.I_6$.	Found
1	62.28	62.14
2	....	62.34

Six atoms iodine coming from the free iodine of the iodo-potassium iodide solution, we get the ratio: I_6 to $C_{21}H_{22}N_2O_2$, or 1 of iodine to 0.439 of strychnine absolute. This gives the *decinormal factor* (the value of one cc. of decinormal iodine solution) as 0.0055547 for strychnine.

BRUCINE HEPTAIODIDE AND ITS ANALYSIS.

This was made according to the general method already given, by pouring a half per cent. solution of brucine acidulated with hydrochloric acid into a large excess of a one per cent. solution of iodine. In appearance and solubility it closely resembles the heptaiodide of strychnine, but it exercises a strong reducing action on silver salts, so that its analysis for total iodine is best accomplished by the aid of nitrous acid and bisulphide of carbon as described under the head of morphine tetraiodide and its analysis.

For total iodine:

1. 0.1916 gram of the periodide was found to contain 0.13229 gram total iodine.

2. 0.2395 gram of the periodide contained 0.16536 gram total iodine.

	Calculated for $C_{23}H_{26}N_2O_4.HI.I_6$.	Found.
1	69.21	69.04
2	....	69.04

For additive iodine:

1. 0.1622 gram of the substance contained 0.096006 gram free iodine.

2. 0.192 gram contained 0.114 gram free iodine.

	Calculated for $C_{23}H_{26}N_2O_4.HI.I_6$.	Found.
1	59.32	59.19
2	....	59.37

For brucine, therefore, the ratio is I_6 to $C_{23}H_{26}N_2O_4$, or 1 of iodine to 0.5179 of anhydrous brucine. And 1 cc. of strictly decinormal solution of iodine indicates 0.0065530 of brucine, *the decinormal factor*, subjected to trial as stated later.

MORPHINE TETRAIODIDE AND ITS ANALYSIS.

Two samples were made. In the first, one gram of morphine dissolved in 200 cc. acidulated water was added to a solution of five grams iodine and seven and one-half grams potassium iodide in 500 cc. water, the mixture shaken till the supernatant liquid was perfectly clear, and the precipitate washed and dried in vacuum. In the second, two grams iodine and three grams potassium iodide were dissolved in 200 cc. water and the solution poured slowly into a solution of morphine containing three grams morphine in 600 cc. acidulated water. The analysis, as given below, showed that the precipitate in both cases was the same; namely, $C_{17}H_{19}NO_3HI.I_3$. This compound, morphine tetraiodide, was made known by Jörgensen in 1870.[1] We find it to be the only periodide formed by morphine under any of the conditions of this precipitation from aqueous solutions.[2] It is notable that in this periodide the base as a monamine holds an even number of atoms of total iodine. The periodide precipitate of morphine is practically insoluble when the iodine is in excess, though appreciably soluble when the morphine is in excess, as it is in pure water, the more so if strongly acidulated.

In the analysis of the morphine periodide, the precipitate is to be collected and quickly washed with water by the aid of the pump, and then dried in vacuum over sulphuric acid to a constant weight. The additive iodine is readily determined, in a weighed portion, by dissolving in alcohol and titrating with a standard solution of sodium thiosulphate as stated in previous paragraphs. The total iodine determination in this compound gives special difficulty, as neither the sulphur dioxide nor the powdered zinc, previously used in this laboratory for analytical reduction of periodides, works well with morphine periodide, but the following procedure suffices. The periodide is covered with powdered zinc and stronger water of ammonia and set aside half an hour, the mixture is then heated on the water-bath till all the ammonia is driven off, avoiding loss by spurting. A little water is now added and the mixture boiled about ten minutes. The whole is filtered into a separator of about 500 cc.

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[1] *J. prakt. Chem.* (2), **2**, 437.

[2] The present hypothesis of structure of periodides would imply, therefore, that the compound is a dimorphine octaiodide (This Journal, 17, 780; **19**, 331). A lower periodide of morphine was obtained by evaporation of an alcoholic solution containing excess of morphine, by H. R. Bauer (*Arch. Pharm.* [3], 5, 289-309).

capacity, the excess of zinc well washed with hot water, and water added to make 200 or 300 cc. When perfectly cold, the mixture is acidified slightly with very dilute sulphuric acid, then twenty cc. of carbon disulphide are poured into the separator, and ten to twelve drops of concentrated sulphuric acid *saturated with nitrous acid* are added. The separator is closed and shaken, and the solution of iodine in carbon disulphide carefully run out upon a wetted filter. Fresh carbon disulphide is added in the separator and the separation repeated till all the iodine is removed. The iodine is now washed on the filter, first with water, then with a very weak solution of sodium bicarbonate. It is then run into a flask, and thirty cc. of a solution of sodium bicarbonate, five grams to the liter, are added. Finally the iodine is titrated with the standard solution of sodium thiosulphate. The results were as follows :

I. Iodine in excess :

0.2692 gram gave 0.13 gram additive iodine and 0.2732 gram gave 0.174311 gram total iodine.

	Calculated for $C_{17}H_{19}NO_3.HI.I_3$.	Found.
Additive iodine	48.02	48.29
Total iodine	64.03	63.80

II. Morphine in excess.

0.3155 gram were found to contain 0.152832 gram additive iodine and 0.2708 gram contained 0.172076 gram total iodine.

	Calculated for $C_{17}H_{19}NO_3.HI.I_3$.	Found.
Additive iodine	48.02	48.44
Total iodine	64.03	63.54

For morphine the ratio is I_3 to $C_{17}H_{19}NO_3$, or ratio of 379.59 to 284.38, that is 1 of free iodine consumed to 0.74918 of morphine, anhydrous. And one cc. of strictly decinormol solution of iodine corresponds to 0.0094794 gram of morphine.

ACONITINE HEPTAIODIDE (?) AND ITS ANALYSIS.

The alkaloid we used was obtained from Merck and marked "From Acontum Napellus, crystallized, pure." This periodide was made according to the general plan of obtaining the highest periodide of an alkaloid.

For additive iodine 0.2588 gram contained 0.126886 gram free iodine and 0.1471 gram contained (by nitrous acid method) 0.082271 gram total iodine.

	Calculated for $C_{33}H_{45}NO_{12}.HI.I_6$.	Found.
Additive	49.58	49.03
Total	57.85	55.93

We make our calculations upon the aconitine formula of Dunstan.[1] The formula of Freund[2] though distinctly different in constitution, gives but slightly different molecular weight. Other proposed formulas approach the same molecular weight. $C_{34}H_{47}NO_{11} = 643.55$ (Freund). $C_{33}H_{45}NO_{12} = 645.54$ (Dunstan). $C_{33}H_{47}NO_{12} = 647.54$ (Jürgens). $C_{33}H_{43}NO_{12} = 643.54$ (Wright and Luff).

An insufficiency of the aconitine in our hands prevented our making duplicate estimations. With both the higher and the lower periodide, it is to be seen that the total iodine found is somewhat too low for the calculated quantity of this element, calculating for heptaiodide and triiodide, respectively. The additive iodine in both cases falls below calculation, but not enough below to discredit the formulas. When we return to these estimations with a larger supply of the alkaloid we shall find whether the instability of aconitine will prevent constant results in analysis of the higher periodide or not.

ACONITINE TRIIODIDE (?).

This was made by adding a one per cent. solution of iodine to an acidulated solution of aconitine, leaving the latter in excess, and recrystallizing the precipitate from alcohol. Thus obtained it forms beautiful brown-red crystals, very soluble in alcohol, insoluble in water and hardly soluble in ether, benzol, or chloroform. Melting-point 211°–212° C.

For additive iodine:

0.01773 gram of the substance contained 0.042352 gram free iodine.

Calculated for $C_{33}H_{45}NO_{12}.HI.I_2$.	Found.
24.69	23.89

For total iodine by the aid of nitrous acid and bisulphide of carbon, as given under the head of morphine.

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[1] *J. Chem. Soc.*, 67, 459.

[2] *Ber. d. chem. Ges.*, 27, 722.

0.2111 gram contained 0.07505 gram total iodine.

Calculated for $C_{33}H_{45}NO_{12}.HI\ I_2$.	Found.
37.03	35.56

VERIFICATION OF THE EQUATION FOR THE IODINE FACTOR.

Partly from the fact that Kippenberger[1] has proposed a different reaction in the formation of periodide precipitates, and for other reasons, we thought it advisable to prove irrefutably that the iodide of potassium of the iodine solution takes an active part in the reaction by which the atropine enneaiodide, as an example, is formed and gives off an amount of iodine which is just equal to the amount of the normal iodine of the enneaiodide.

We proceeded in the following manner: We first determined the strength of our iodine solution with regard to free iodine; this was done by means of a sodium thiosulphate solution of known strength. We then took ten cc. of this iodine solution and determined the total amount of iodine, free as well as bound to potassium, by shaking them in a flask with an excess of powdered metallic zinc till the color of iodine disappeared, filtering the solution of zinc iodide and potassium iodide thus obtained, washing the flask and the excess of zinc with hot water and precipitating the iodides in the filtrate with silver nitrate and nitric acid. From the weight of silver iodide washed and dried in the usual way, we calculated the amount of total iodine present in our iodine solution. By subtracting the amount of free iodine from that of the total iodine we obtained the amount of iodine present in our solution as potassium iodide. We thus found that the iodine solution contained one per cent. free iodine and 1.2312 per cent. combined iodine.

We then put forty cc. of this iodine solution in a 100 cc. measuring flask, added twenty cc. of a three-tenths per cent. solution of atropine alkaloid, and after shaking well, diluted the liquid in the flask to 100 cc. We now took two vials and in each filtered off twenty-five cc. from the flask. In the first vial, the amount of free iodine titrated back with sodium thiosulphate was found to be 0.0465. From this it is easy to deduce that the twenty cc. of the three-tenths per cent. atropine solution consumed 0.214

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[1] *Ztschr. anal. Chem.*, 35, 10; **34**, 317. On this question also see Gomberg, 1896: This Journal, **18**, 332.

gram of the free iodine. In the second vial the total iodine was determined in the same way as described above, and the quantity of silver iodide was found to be 0.3023 gram, which shows that after the treatment with atropine the liquid contained 1.633 per cent. total iodine. From these data we deduce that the twenty cc. of the atropine solution have taken up 0.02528 gram iodine from the bound iodine. As the twenty cc. of atropine solution contained 0.06 gram atropine we find for 100 parts of precipitated enneaiodide

	Found. Per cent.	Calculated. Per cent.
Atropine	20.05	20.26
Iodine taken from the free iodine of the iodine solution	71.50	70.88
Iodine from the iodine bound as KI	8.45	8.86

We see that in aqueous acidulous solutions the potassium iodide takes an active part in the reaction by joining in a yield of hydriodic acid for the normal hydriodide of the alkaloid, necessary to hold the additive iodine of the periodide. When carbon disulphide or carbon tetrachloride is used as a solvent for the atropine and the iodine, no periodide seems to be formed, possibly for the reason of there being no generation of hydriodic acid for the making of hydriodide. As to the formation of the periodides in chloroformic solution of atropine and iodine, it might possibly be explained by the substituting action of iodine either upon the chloroform or upon a side-chain of the atropine.

The direct substitution of iodine for some of the hydrogen in these bodies might, in this case, be made possible by the presence of the natural base, which combines with the hydriodic acid when formed by such a substitution. Part of the atropine would then act in a manner similar to that of mercuric oxide, which is usually employed in the iodizing of hydrocarbons. An analogous case we have in the easy substitution of iodine for some of the hydrogen in aniline, a part of which combines with the hydriodic acid, which is set free through the substitution of iodine for hydrogen in another part. At any rate we shall endeavor to determine the by-products formed when atropine enneaiodide is produced in chloroformic solutions.

PROCEDURE IN THE VOLUMETRIC METHOD.

The general mode of procedure in the estimation of the strength of an aqueous solution of an alkaloidal salt is as follows: To about ten cc. of decinormal iodine solution diluted with a little water, one cc. of the acidulated alkaloidal solution is added, and the mixture well shaken for a few minutes. Should the precipitate separate out very quickly, and the clear supernatant liquid have only a light yellow or greenish color, or be altogether colorless, the alkaloidal solution is too strong and must be diluted, till after a few trials the clear supernatant liquid retains a very dark red color after the separation of the precipitate. The acidulated alkaloidal solution is then made up to a given volume, and ten or fifteen cc. of it are run from a burette into a graduated vessel, into which has been previously put twenty-five or thirty cc. decinormal iodine solution diluted with a little water. The mixture is then made up to a given volume and shaken till the supernatant liquid is perfectly transparent, and is of a very dark red iodine color. This point is very important, and should the clear liquid not have this dark red color, the experiment with most alkaloids (except morphine and possibly some others) should be repeated, putting more decinormal iodine into the graduated vessel, or decreasing the number of cc. of the alkaloidal solution. It would not do to add more decinormal iodine to the same mixture, as the iodine must be in large excess during the whole operation, in order to prevent the formation of lower periodides, which once formed, might not take up fresh iodine and form higher periodides. Only with morphine, which in such solutions forms but one periodide, these precautions are unnecessary. When the liquid has become perfectly clear, an aliquot portion of it is filtered off, and the excess of iodine determined by standard sodium thiosulphate. From these data are obtained the quantity of iodine consumed. This quantity of iodine, multiplied by the "ratio of alkaloid to 1 of iodine," gives the quantity of alkaloid sought. If preferred, but generally with less convenience to the chemist, the number of cubic centimeters of decinormal solution of iodine consumed may be multiplied by the "alkaloidal factor of 1 cc. $\frac{N}{10}$ I sol."

VERIFICATION OF THE IODINE FACTORS BY VOLUMETRIC CONTROL.

For Atropine.—In the following estimations of the strength of atropine solutions, both the iodine solution and the sodium thiosulphate solution were strictly decinormal. Of the iodine solution twenty or twenty-five cc. were put into a 100 cc. measuring flask and atropine solutions of known strength run in from a burette, and the operation continued as described above. When the supernatant liquid was perfectly transparent the flask was filled up to 100 cc. and fifty cc. were filtered off. In these fifty cc. the excess was determined by means of the tenth-normal thiosulphate solution, and the strength of the atropine solutions calculated by using the factor 0.0036048 for every cubic centimeter of decinormal iodine used up.

	Actual strength. Per cent.	Number of cc. of the atropine solution taken.	Number of cc. of the tenth-normal iodine used up.	Results in strength. Per cent.
1	0.50	12	15.6	0.47
2	0.40	15	14.9	0.36
3	0.30	17	13.2	0.28
4	0.25	12	10.0	0.28

For Strychnine.—To test the correctness of the ratio of 1 of free iodine to 0.4390 of strychnine, two solutions were prepared, one of one per cent., the other of 0.612 per cent. of the alkaloid. The estimations, by the volumetric method, gave results as follows:

	Actual strength. Per cent.	Strychnine solution taken. cc.	Iodine consumed.	Results obtained. Per cent.
1	1.0	3	0.07	1.026
2	0.612	7	0.191	0.633

For Brucine.—Two solutions of the alkaloid were made, and estimated volumetrically, calculating by the ratio 1 part of iodine to 0.5179 part of anhydrous brucine, with these results:

	Actual strength. Per cent.	Brucine solution taken. cc.	Iodine consumed.	Results obtained. Per cent.
1	1.0	10	0.193	0.999
2	0.5	10	0.096	0.497

For Morphine.—Three standard solutions were made of strengths in anhydrous alkaloid as below tabulated. This was done by weighing a good article of well-crystallized morphine, free alkaloid, as $C_{17}H_{19}NO_3.H_2O$. The results were calculated by the ratio 1 of iodine to 0.74918 of morphine, absolute.

	Strength in per cent.	Morphine solution. cc.	Iodine solution. cc.	Iodine consumed.	Result in per cent.
1	0.518	10	20	0.070116	0.525
2	0.259	10	20	0.034272	0.257
3	0.100	10	20	0.014020	0.105

THE IODINE FACTORS OF THE ALKALOIDS SO FAR DETERMINED.

Higher periodide formed.	Ratio of alkaloid to one of iodine.	Alkaloid factor of one cc. tenth-normal iodine solution.
Atropine, $C_{17}H_{23}NO_3.HI.I_8$	0.2849	0.0036048
Strychnine, $C_{21}H_{22}N_2O_2.HI.I_6$	0.4390	0.00555467
Brucine. $C_{23}H_{26}N_2O_4.HI.I_6$	0.5179	0.00655299
Morphine, $C_{17}H_{19}NO_3.HI.I_3$	0.74918	0.00947937
Aconitine, $C_{33}H_{45}NO_{12}.HI.I_6$	......	......
By Gomberg in 1896 :[1]		
Caffeine, $C_8H_{10}N_4O_2.HI.I_4$	0.3834	0.00485

APPLICATION IN ASSAY OF CRUDE MEDICINAL DRUGS.

We have made estimations of total alkaloids in nux vomica, and in belladonna, by the periodide volumetric method, after extraction of the alkaloid in several ways, and have obtained satisfactory results. We have work in hand by which we hope to reach more expeditious methods of extraction. Among the menstrua under experimentation, are a saturated solution of gaseous ammonia in ether, a chloroformic solution of ammonia,[2] and similar agents.

A VOLUMETRIC ASSAY OF OPIUM.

The morphine was estimated as periodide, after successive treatment with benzol, amyl alcohol or acetone, and lime-water.

This method proceeds upon the following plan : The opium alkaloids are set free by action of ammonia with certain solvents. The free narcotine, papaverine, codeine, and thebaine are then removed by percolation with benzene, after which the morphine is taken out by percolation with acetone,[3] in which the morphine

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[1] This Journal, **18**, 339.

[2] Suggested by Siedler and Thoms : *Ber. d. pharm. Ges.*, *1898*, 28.

[3] Instead of acetone there may be used pure amyl alcohol, boiling between 128° and 132° C., and leaving no residue upon evaporation below the boiling-point.

is sufficiently soluble. The acetone is then evaporated off, and the residue taken up with lime-water, which completely dissolves and purifies the morphine. It remains to filter the lime solution, acidulate it with hydrochloric acid, and estimate the morphine as periodide by titration as already detailed in this paper.

In the percolation of the opium with different solvents to separate the morphine, we depend upon two things, (1) the preparing of the opium powder by digestion with the ammonia and the solvents and then drying, and (2) an admixture with dried common salt in transferring to the percolator.

The Materials for the Assay.—Opium in fine powder (No. 60 or finer), one gram; stronger ammonia water; alcohol, ether, chloroform, pure benzene (crystallized); acetone, boiling between 54° and 58° C., about 200 cc.; some good lime-water; ordinary common table salt, about twenty grams; some diluted hydrochloric acid (ten per cent.); decinormal solution of iodine with potassium iodide (Wagner's reagent), and sodium thiosulphate solution standardized with the solution of iodine.

Directions for the Assay.—Of the opium in fine powder one gram is weighed into a small mortar or deep dish, such as can be well covered with admission of a small pestle.[1] A mixture is made of five cc. of stronger ammonia water, five cc. of alcohol, twenty cc. of ether, and ten cc. of chloroform. The opium is rubbed up with two or three cc. of this mixture, to make a uniform paste, using a pestle that can be left in the dish when it is covered. The covered dish is now put aside for about three hours, from time to time moving the dish gently; about fifteen grams of well dried and finely powdered common salt are now added and carefully mixed into the mass. Then the dish is left open in a warm place, of 30° to 35° C., for two or three hours, when it is placed in a desiccator containing sulphuric acid and a dish of paraffin, a vacuum desiccator being preferable, until the mixture is perfectly dry as shown by the looseness of the powder under the motion of the pestle. If left over night it is sufficient. The entire contents of the dish are now transferred to a little glass percolator of about one and three-tenths centimeters

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[1] A screw-top ointment jar of mortar-shaped bottom and four or six ounces capacity serves very well.

(one-half inch) inner diameter and twenty-two centimeters (nine inches) length,[1] rubbing out the dish twice with a little more of the dried common salt. The mass is now percolated with the benzene, until the percolate is colorless, and until upon evaporating one or two drops of the percolate in a watch-glass, taking up the residue with four or five drops of acidulated water and adding a drop or two of Wagner's reagent, no turbidity appears (removal of alkaloids other than morphine). A shallow dish is now set under the percolator, and pure acetone used to continue the percolation to complete exhaustion, as found by evaporating ten drops of the percolate on a watch-glass, taking up the residue with two or three drops of acidulated water, and adding a drop or two of Wagner's reagent, when no turbidity at all should appear. Usually as much as 200 cc. of acetone are required. The acetone is now evaporated, at a temperature not exceeding 45° C., to complete dryness. The residue when cool is rubbed up with good fresh lime-water, the solution poured without filtering into a graduated stoppered cylinder of 100 cc., the dish washed four or five times with portions of lime-water, to fully clean the dish, when lime-water is added to make the volume 100 cc. The cylinder is now securely stoppered and well shaken for half an hour. Of the mixture enough is now filtered into another graduated cylinder, with glass stopper, to make up a filtrate exactly fifty cc. To this liquid is added diluted hydrochloric acid (ten per cent.) to just perceptible acidulation, and the tenth-normal iodine solution is slowly run in from the burette while gently shaking the cylinder until precisely twenty-five cc. have been added. Water is added to any convenient mark of the cylinder, which is then stoppered securely and shaken vigorously and continuously (for about twenty minutes) until, on standing a minute or two, the supernatant liquid (of a pronounced iodine-red color)[2] is perfectly clear and transparent. The liquid is now filtered off so as to take just one-half the volume of the filtrate. In this half of the liquid the excess of iodine is titrated back with the tenth-normal sodium thiosulphate solution, using starch as an indicator. The number of cubic centimeters of the thiosulphate solution multiplied by two,

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[1] The tube of a one-ounce syringe does very well.

[2] If the liquid does not have this red color, it must be because of a lack of the indispensable excess of the iodine, of which an additional quantity should be added.

is subtracted from twenty-five, the number of cubic centimeters of iodine solution used. The remainder is now multiplied by the factor 1.89586 (0.0094793 × 2 × 100), the product being the percentage of morphine in the powdered opium as weighed.

The precautions most essential are (1) that the opium residue before percolation be thoroughly dried, (2) that the acetone should not contain anything distilling below 54° C., or above 58° C., and (3) that after the added excess of iodine the container be continuously shaken until the precipitate is so fully separated that the solution above it is clear. An automatic shaker is an aid in this assay. A second estimation can be made with the remaining part of the lime solution.

Without the use of lime-water in purification of the morphine of the residue, we find the color of the resulting acidulous solution to be inconvenient in the titration, and find the percentage figure to be uniformly higher than when obtained after lime solution. The vessel is easily cleaned from adhering morphine periodide by the use of acetone.

RESULTS OF THE OPIUM ASSAY BY THE PERIODIDE METHOD.

We can give here the results of assays of but three samples of powdered opium, these coming from three different reputable houses. They were all marked, sample A to contain fourteen per cent., samples B and C to contain the quantity required by the U. S. P. Three analyses of each sample were made, and to sample A the U. S. P. method was also applied, and was found to contain 14.4 per cent. morphine by that method. The volumetric method was carried out exactly as described above.

SAMPLE A.

	Opium taken in grams.	Iodine consumed by one-half.	Percentage morphine found.
1	1.0036	0.116644	17.41
2	1.008	0.116732	17.37
3	1.0022	0.116642	17.44

SAMPLE B.

	Opium taken in grams.	Iodine consumed by one-half.	Percentage morphine found.
1	1.0033	0.08872	13.25
2	1.0023	0.08872	13.20
3	1.0026	0.08872	13.21

SAMPLE C.

	Opium taken in grams.	Iodine consumed by one-half.	Percentage morphine found.
1	0.9969	0.096319	14.48
2	1.0016	0.097219	14.55
3	0.9988	0.094552	14.19

AS A VALUATION OF THE MORPHINE OF ANY PHARMACOPOEIAL ASSAY.

If it should be desired to estimate the alkaloid in the crystals obtained in assay by the pharmacopoeia of this or any other country, the periodide volumetric analysis could be well applied as follows :

Let the crude morphine obtained by the pharmacopoeial method be taken up with lime-water, the latter made up to a given volume, and a measured portion of the filtered solution, placed in a graduated vessel and acidulated with hydrochloric acid; let a definite excess of the decinormal iodine be added, in small portions at a time, and shaken after each addition, till the periodide separates out, and the clear liquid retains a dark red color, making up the mixture to a given volume, filtering off half and then titrating the excess of iodine in this half by standard sodium thiosulphate, the amount of iodine consumed can be easily found. Working on ten grams opium, a tenth portion of the lime-water solution would represent one gram of opium, and the percentage of morphine would be equal to the weight of iodine consumed, multiplied by 74.918, or to the number of cubic centimeters of the tenth-normal iodine consumed, multiplied by 0.94793. Several analyses could be made with the remaining part of the lime-water solution.

CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.
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NEW BOOKS.

A LABORATORY GUIDE IN QUALITATIVE CHEMICAL ANALYSIS. BY H. L. WELLS, YALE UNIVERSITY. New York: John Wiley and Sons. pp. 189. Price $1.50.

In the first nine chapters the author endeavors to get the student to learn, by direct experiment and by numerous questions, how to distinguish and divide what are usually termed bases