Judging from the above observations, it seems likely that nature makes use of comparatively few basal coloring substances with which to produce many different colors by means of slight chemical changes. These substances are generally acid, sometimes neutral in character, and generally change color in acids and alkalies, alternately, acting as indicators. It is noticeable also that many of them are very sensitive to the action of light and air. The faintly colored alcoholic solutions of the Rose or the Perennial Pea, when evaporated to dryness, leave the bright red colored substance. The pink blossoms of the Perennial Pea, when picked and allowed to wilt, change to a violet color. The whole subject of natural coloring matters deserves a careful study from the chemical standpoint.

MANHATTAN, KANSAS.

THE PERIODIDES OF ACID AMIDES AND THEIR ADDITION PRODUCTS WITH METALLIC SALTS. SUBSTANCES OF EXCEPTIONALLY HIGH MOLECULAR WEIGHT.

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It is well known that many organic bases form periodides usually containing more or less hydriodic acid, and that these substances, in their turn, form double compounds with metallic salts. The literature of such substances is extensive and widely scattered, and no complete review of it will be attempted here. It will be sufficient to call attention to the work of Geuther[1] who reviewed most of the work of others done up to this time; and that of François,[2] who devoted his attention chiefly to the periodides of the alkaloids. Little seems to have been done in the direction of preparing periodides of substances of the amide type, though Hoogewerff and van Dorp[3] studied the action of alkali and bromine upon the amide of benzene-*m*-disulfonic acid and observed the formation of a perbromide, $2C_6H_4(SO_2NBr_2)_2 + KBr + HBr$. Hofmann[4] noticed that acetamide formed a compound,

$$CH_3CONBr_2 + NaBr + H_2O.$$

Titherley[5] observed the formation of double salts of acetamide such as $2CH_3CONH_2$, NaBr and $2CH_3.CONH_2$, NaI; and André[6] fused acetamide with various metallic salts and obtained different products, such as

$$2CH_3CONH_2.CoCl_2.H_2O;$$

and Wheeler[7] also prepared some colored perhalides of acid anilides of

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[1] *Ann.*, **240**, 66 (1887).

[2] *J. pharm. et chim.*, [6] **30**, 193 (1909).

[3] *Rec. trav. chim.*, **8**, 173 (1889).

[4] *Ber.*, **15**, 415 (1882).

[5] *J. Chem. Soc.*, **79**, 413 (1901).

[6] *Jahresb. Chem.*, **1886**, p. 1303; *Compt. rend.*. **102**, 115 (1886).

[7] *Am. Chem. J.*, **18**, 85 (1896); **19**, 672 (1897).

the general type $An.HI.I_2$ and $An_2.HI.I_4$. Periodides of succinimide and its phenyl derivatives have also been prepared by Piutti.[1] These compounds had the general formula $S_4.KI.3I$ and $S_2.KI.2I$. Finally there remain to be mentioned some derivatives of benzamide prepared by Curtius,[2] which will be discussed further on.

With the exception of the compounds mentioned by Curtius, Piutti, and Wheeler, substances of the properties described in the present paper seem not to have been prepared, which is rather remarkable in view of the ease with which they are formed and their rather striking physical properties. Their preparation in this laboratory was in a certain sense accidental. In the course of an investigation upon the behavior of benzbromoamide, which has been going on here for several years, it seemed desirable for purposes of comparison to prepare benziodoamide. The method chosen was analogous to that hitherto in use for the preparation of the bromine compound.[3]

Iodine was dissolved in cold alkali and benzamide was dissolved in the freshly prepared solution. On acidification with dilute acetic acid, there was precipitated, not the colorless iodoamide which had been expected, but a dark green compound which preceded the precipitation of free iodine. It was found on experimentation that this substance could be best purified by solution in ether and subsequent dilution of this solution with benzene. In this way the material was obtained in long, green, hairlike needles of coppery luster. Later on, it was found that the use of alkali in the preparation was not necessary, and that, inasmuch as the product consisted only of benzamide, alkali iodide, and free iodine, the compounds could be readily prepared by heating together these ingredients in water.

Substances of this type were prepared in considerable number and showed many properties in common. They were for the most part immediately decolorized when shaken with metals such as silver or mercury, or upon the addition of alkali or sodium thiosulfate. The products formed were the amide and metallic salts.

The simplest compounds were obtained either as addition products of amide, sodium or potassium iodide, and iodine, or else of amide, hydriodic acid and iodine, and the analysis showed that a few simple types, such as $(C_6H_5CONH_2)_2HI.I_2$, $(C_6H_5CONH_2)_3NaI.I_2$, and $(C_6H_5CONH_2)_3KI.I_2$ were formed.

Solutions of the above compounds were treated with solutions of inorganic salts of other metals, in the expectation that the less soluble derivatives of the latter might be precipitated by metathesis. This was

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[1] *Gazz. chim. ital.*, **25**, II, 524 (1895).

[2] *Ber.*, **23**, 3040 (1890).

[3] Moore and Cederholm, THIS JOURNAL, **28**, 1190 (1906).

not the case, but analogous compounds of barium and copper, for example, could be formed by warming the corresponding iodide with benzamide and iodine in water.

Substances of still a different type were formed when iodides of lead or mercury were warmed with benzamide, iodine, and potassium iodide. In these cases a product crystallized out which exactly resembled in appearance the simple potassium compound, but which also contained the heavy metal. This could not be removed by recrystallization, and analysis leaves little reason to doubt that the substances concerned are really "double" or "complex" salts, of the composition

$$((C_6H_5CONH_2)_3KI.I_2)_6PbI_2$$

and

$$((C_6H_5CONH_2)_3KI.I_2)_6HgI_2.$$

From similar indications, it was at first thought that analogous compounds, in which hydriodic acid replaced the potassium iodide, might be capable of existence. Since these products, however, on further purification showed a constant decrease in amount of heavy metal present, it is evident that such compounds, if they exist, are hardly stable enough for analysis.

The striking thing about the compounds mentioned is their high molecular weight. It will be seen that, for the lead compound, this reaches the value 5160, while the mercuric salt has a molecular weight of not less than 5152. In a series of synthetic experiments on the tannin group Emil Fischer[1] has recently prepared a complex derivative of maltose, which has a molecular weight of 4021, and which he describes as the compound having the highest molecular weight of any hitherto prepared by organic synthesis. The compounds here described are not, of course, "products of synthesis" in the same sense as those described by Fischer, all of which have been built up step by step, and to which there can be assigned definite constitutional formulae. They are, on the other hand, loose addition products of the "complex" variety, and are more or less dissociated in solution. Most of them, indeed, lose iodine in solution or in vacuum, and some frequently lose hydriodic acid; and it is doubtless a fact that their various components are held together by subordinate valences, in a sense analogous to the compounds which have been so extensively studied by Werner. Nevertheless, it is interesting that chemical complexes of such magnitude of any kind should be capable of isolation and stable enough to be recrystallized and analyzed.

The reactions above indicated yield analogous products with some other amides, both simple and substituted, but in the case of the simple amides the reaction does not seem to be as general as was at first supposed.

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[1] *Ber.*, **46**, 3288 (1913).

Most of the anilides prepared, however, show the reaction well. The capacity of forming these compounds seems to be exceptionally highly developed in the case of benzamide, and it is here that it has received most study. Many tests, however, have been made with a variety of compounds, but it has not proved practicable up to the present time to lay down any rule which might connect the capacity for the formation of these periodides with the constitution of the amide employed. It is possible that some such regularity may be developed later.

Analysis.—When these compounds were to be analyzed the substances determined were usually total iodine, active iodine, and the metal, when present. Total iodine was almost universally determined by the Carius method, except when the presence of some other component suggested a difficulty. Active iodine was usually determined by adding water and benzene to the sample and then titrating with sodium thiosulfate until the pink color of iodine disappeared from the benzene layer. Here it was found that the addition of potassium iodide in considerable excess at the outset made it possible to titrate more rapidly, but did not change the numerical result, except in one or two cases, which are not even yet clearly understood. They will be mentioned in the experimental part. Metals were usually determined by the methods customary in such cases. When the methods of determination call for special consideration, they will be discussed under the individual compounds.

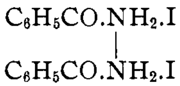
Experimental Part.

Periodides of Benzamide.

Benzamide, Sodium Iodide, and Iodine.—As indicated above, this substance was first prepared by dissolving iodine in sodium hydroxide, adding finely ground benzamide and acidifying with acetic acid in ice-cold solution. It was soon found, however, that warming was advantageous, as it brought more iodine and benzamide into solution, and no decomposition was to be feared. A typical preparation is the following: 1.5 g. of benzamide were warmed with 10 cc. of 10% sodium hydroxide solution and 3 g. of iodine. On precipitation with dilute acetic acid 2.6 g. of crude product separated. This was purified by solution in ether and careful dilution with benzene, whereupon the product crystallized in long coppery green hairs. Yield, 2.15 g. The second crystallization yielded 1.30 g. of good product. The product was dried over sulfuric acid and had no odor of iodine when analyzed.

Calc. for $(C_6H_5CONH_2)_3NaI.I_2$: Na = 3.00%; active I = 33.11; total I_2 = 49.67. Found: 2.92, 3.05, 2.75, 3.12; 32.25, 31.85, 33.73; and 48.91, 48.77.

There seems to be little doubt but that this substance was once in the hands of Curtius. He prepared it by suspending the sodium salt of benzamide in chloroform and adding iodine. He apparently overlooked the sodium content, and he arbitrarily assigned the formula



$$\begin{array}{c} C_6H_5CO.NH_2.I \\ | \\ C_6H_5CO.NH_2.I \end{array}$$

to the product, stating that he was unable to get concordant results on analysis. In order to test this assumption we prepared the same compound by treating sodium benzamide with iodine in ether. The product had the same appearance as the substance previously obtained and a sodium determination gave 2.44% sodium. Curtius had already observed that the product lost iodine when it was shaken with metallic mercury. We verified this fact, and found that molecular silver produced the same result. It was also decolorized by the action of aniline. When treated with trimethylphenylammonium iodide, the periodide,

$$(CH_3)_3C_6H_5.NI.I_2$$

was formed and benzamide could be isolated. All these reactions show an easy removal of the iodine from the rest of the molecule, indicating that it is held simply as in a loose addition product. It will be seen later that these periodides show varying degrees of stability in this respect. Sodium thiosulfate also removes the iodine rapidly, and this reaction was made use of in the determination of active iodine in these compounds.

Benzamide, Potassium Iodide and Iodine.—Most of the product was obtained by a method analogous to that first described for the sodium compound, but later it was observed that it was necessary only to warm the three substances together in water until they became entirely liquid. In one preparation 3 g. of benzamide were warmed with 1 g. of potassium iodide and 2.4 g. of iodine in 25 cc. water. On cooling, a pulpy mass of greenish crystals filled the liquid. These were collected on a filter, dried, washed with carbon tetrachloride to remove any excess of iodine, and finally purified by solution in ether and crystallization by the careful addition of benzene. The product consisted of fine green hairs, which melted at 128°–130°.

Calc. for $(C_6H_5CONH_2)_3KI.I_2$: K = 4.98, active I = 32.44; total I = 48.66. Found: 5.57, 5.61, 5.50; 30.01, 29.90, 30.74, 30.80; and 49.97, 49.60.

These results speak for a slight loss of active iodine during drying. No other rational formula corresponded quite so well with the results of the analysis.

It was found that the formation of the periodides was not limited to aqueous solvents. Thus 2 g. of benzamide, 1.3 g. of potassium iodide, and 3.1 g. of iodine, when warmed together in 10 cc. nitrobenzene, yielded 3.9 g. of an addition product which was apparently identical with that described.

Benzamide, Potassium Bromide and Bromine.—Two grams of bromine were added to a mixture of 1 g. of potassium bromide, 4 g. of benzamide, and 15 cc. of water. The solid benzamide was instantly coated with a reddish substance. When warmed on the steam bath the solid dissolved. Rapid cooling resulted in the separation of beautiful green crystals which filled the tube. When dried these crystals were brick-red with a purple luster, but in the air they lost bromine too rapidly to permit of analysis.

Benzamide, Potassium Bromide and Iodine.—These substances, when heated together, gave a product which formed gray greenish hairs like the iodide derivative, with some unchanged benzamide. Carbon tetrachloride removed scarcely any iodine. The compound was not analyzed, but was evidently a double compound of the type suggested.

Dibenzamide, Potassium Iodide and Iodine.—These substances reacted smoothly when warmed with water on the steam bath. The product was a green solid which appeared to be like the benzamide compound. It was probably the potassium compound analogous to the one described by Curtius (*Loc. cit.*) and which probably contained sodium, although he overlooked that fact in his analysis, as already suggested. The substance was not analyzed.

Tribenzamide could not be made to react with iodine, either in the presence of potassium iodide or hydriodic acid.

Benzamide, Hydriodic Acid and Iodine.—Five grams of benzamide were treated with 10 cc. of aqueous hydriodic acid (sp. gr. 1.90), which was already black with iodine. 5 cc. of water and 1 g. of iodine were also added. On warming, a black oil was formed which solidified when the solution cooled. Washing with carbon tetrachloride removed some iodine, but left a crystalline product, which was dissolved in ether, and precipitated by carbon tetrachloride in tiny flakes, showing a green-black iridescence. Yield of purified product, 8.5 g.

Calc. for $(C_6H_5CONH_2)_2HI.I_2$: Active I = 40.70; total I = 61.05. Found: 37.92, 38.88, 38.93; and 61.45, 61.32.

It is interesting to note that the color of this compound differs from that of the corresponding sodium and potassium compounds, and also that this substance contains two benzamides instead of three, as in previous cases.

Benzamide, Barium Iodide and Iodine.—The best proportions were 1 molecule of benzamide, 6 molecules of barium iodide and 4 atoms of iodine. These were warmed together in the presence of water. The solid product when treated with ether formed a black oil, and this, when treated with benzene, yielded a precipitate consisting of chocolate-brown flakes and needles which were steely blue by reflected light. The substance belongs to the less stable members of this class and dissociates somewhat in solution. On crystallizing it, if too much free iodine is present in the solution, the product comes out oily, and, on the other hand, the presence of too little iodine results in the separation of barium iodide. Crystallization from pure solvent causes loss of iodine, so that in this, as well as in several other cases, it is advisable to add iodine judiciously to the solvent.

Barium was determined directly by smoking off with sulfuric acid and also, as a check, by precipitation from the filtrates from the silver iodide in the Carius determination of total iodine.

Calc. for $(C_6H_5CONH_2)_6BaI_2.I_4$: Ba = 8.43; active I = 31.26; total I = 46.89. Found: 8.49, 8.53, 8.52; 31.20, 31.49; and 44.96, 44.80.

It should be added that numerous other determinations of active iodine from different samples gave results as much as 2% lower than those here quoted. The tendency to dissociation above mentioned seems to account for this.

Benzamide, Cuprous Iodide and Iodine.—1.5 g. of slightly moist cuprous iodide, 1.5 g. of benzamide, and 3 g. of iodine were warmed with water on a steam bath. The iodine melted to a lower layer, and most of the solid dissolved. The aqueous layer was filtered hot. In the filtrate coppery needles were formed, while upon the surface of the liquid there appeared a fine film of cuprous iodide. This could be removed mechanically. The copper-colored needles were collected by filtration. They were sometimes mixed with benzamide, from which they could be separated mechanically. They melted at about 90° to a black liquid. This substance lost weight very rapidly when an attempt was made to dry over phosphorus pentoxide, and over alkali the loss was also rapid, so that a sample which had stood six weeks contained only 4.5% active iodine. The material used for analysis was therefore dried rapidly in the air. Numerous determinations were made, and particular pains taken with the analysis, but the results were not very satisfactory. Difficulty was experienced in the determination of active iodine, in that the end point of the titration was changed by the addition of potassium iodide. No thoroughly adequate explanation has been found for this. Copper was determined first by smoking off directly with nitric acid and weighing as oxide; second, according to Bray,[1] by conversion to sulfate, and titration against sodium thiosulfate after addition of potassium iodide; and third, by Jörgensen's[2] method, of treatment with sulfurous acid and weighing as cuprous iodide. The iodine in the filtrate from the cuprous iodide was precipitated with silver nitrate.

On account of the beautiful appearance of this compound numerous analyses were made. As stated above, the results were not entirely satisfactory, those quoted being some of the best.

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[1] THIS JOURNAL, **32**, 1208 (1910).

[2] *J. prakt. Chem.*, [2] **2**, 353 (1870).

Calc. for $(C_6H_5CONH_2)_8CuI.I_6$: Cu = 3.31; Cu_2I_2 = 9.32; active I = 39.66; total I = 46.26. Found: 3.27, 3.13, 3.16, 3.81, 3.47, 3.43; 10.28, 9.75, 10.28; 37.99, 36.18, 36.80, 37.10; and 45.43, 46.01, 47.55, 47.30.

It may be stated, in general, that the determinations for active iodine which differed most widely varied between 35.66 and 40.06.

Benzamide, Cobalt Iodide and Iodine.—Two grams of cobalt iodide were warmed with 1.6 g. of benzamide, 2.6 g. of iodine and 10 cc. of water on the steam bath. On cooling, a green precipitate settled out, which could be purified by dissolving in ether and precipitating with carbon tetrachloride. It was not analyzed.

Nickel iodide also yields a similar product. Attempts to prepare corresponding compounds, using silver iodide, lead iodide, mercuric and mercurous iodide, all resulted without success.

Benzamide, Potassium Iodide, Mercuric Iodide and Iodine.—Ten grams each of benzamide and iodine were warmed with 100 cc. of 10% potassium iodide solution, to which mercuric chloride had been added until mercuric iodide began to precipitate. The resulting crude product weighed 23 g. The filtrate contained little free iodine. The precipitate was dissolved in 150 cc. of ether containing 5 g. of iodine. A dirty gray residue of benzamide was removed which weighed about 2 g. The filtrate was then treated with 250 cc. of benzene and later, as precipitation took place slowly, with 100 cc. more. The solution at this point was purple and very full of crystals. The solution was filtered by suction and the crystals were washed with benzene. Four crops in all were obtained, of which about 9 g. made up the first, which was very pure. Repeated crystallization of the entire product made little or no difference in the mercury content. A sample for analysis was dried over caustic alkali, and melted in the air at about 50°. Mercury was determined as sulfide, following the method described in Treadwell's "Analytical Chemistry."[1]

Calc. for (1) $((C_6H_5CONH_2)_3KI.I_2)_7HgI_2$, (2) $((C_6H_5CONH_2)_3KI.I_2)_6HgI_2$: (1) K = 4.62; Hg = 3.37; active I = 29.96, total I = 49.20; (2) K = 4.56; Hg = 3.88; active I = 29.57; total I = 49.30. Found: 4.49, 4.48; 3.34, 3.30, 3.56; 30.36, 30.42; and 48.52, 48.42.

The analysis hardly gives sufficient data to decide between the two formulas quoted.

Benzamide, Potassium Iodide, Lead Iodide and Iodine.—One and five-tenths grams of lead iodide and 5 g. of potassium iodide mixed in 15 cc. water gave a fine pale yellow precipitate of a double compound. To this were added 10 g. each of benzamide and iodine. The product melted entirely on the steam bath and solidified on cooling. It was dried as thoroughly as possible, the process being difficult on account of the lumping of the material. The product was dissolved in ether containing considerable iodine and crystallized on addition of benzene in gray-green

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[1] (Hall) 3rd Ed., Vol. II, 169.

hairs. The first crop of 6 g. gave a strong test for lead; the later crops, not so strong. When the first crops were recrystallized, however, a perceptible decrease in lead content was not noted. In analyzing the product, lead and potassium were changed together to sulfate by smoking off with sulfuric acid and subsequent ignition. The precipitate was then digested thoroughly with dilute sulfuric acid (1 : 20), cooled completely, filtered and washed with 1 : 20 acid, followed by 1 : 1 alcohol, the precipitate being weighed as lead sulfate. The solution was evaporated and the residue ignited and weighed as potassium sulfate. The iodine here was not determined by the Carius method as it was feared that the silver iodide formed might be contaminated with lead iodide, and instead the sample was digested with sodium carbonate solution, filtered, and washed. The filtrate was treated with sulfurous acid to reduce any iodate to iodide, and finally precipitated with silver nitrate.

Calc. for $((C_6H_5CONH_2)_3KI.I_2)_6PbI_2$: K = 4.55; Pb = 4.01; active I = 29.54; total I = 49.22. Found: 4.30; 3.96; 30.14; and 49.26.

The above results were obtained from one recrystallized sample, representing the purest product available.

Benzamide, Mercuric Iodide, Hydriodic Acid and Iodine.—An attempt was made to prepare a compound which combined all the above four components, and as a matter of fact crystals were obtained. These, however, did not prove sufficiently stable to permit of analysis, and in the course of crystallization the mercury content steadily decreased.

Experiments with Other Amides and with Anilides.

p-Toluamide, Potassium Iodide and Iodine.—Five-tenths gram of *p*-toluamide (2 mols), 0.3 g. of potassium iodide (1 mol), and 0.5 g. of iodine (2 at.) were rubbed together with 2 cc. of water. They formed a thick pulp in a few minutes. The yield was 1.2 g. The color was not removed by carbon tetrachloride. The product was purified by adding carbon tetrachloride to the ethereal solution; and it too formed coppery green hairs. The analytical results on the different samples were not concordant and it is probable that the small quantity prepared did not permit of adequate purification. The substance contained about 5% of potassium. *p*-Toluamide, when warmed with hydriodic acid and iodine, gave a fine grayish black crystalline precipitate, which was practically insoluble in boiling carbon tetrachloride. This has not yet been analyzed. *o*-Toluamide gave no addition product with potassium iodide and iodine. With hydriodic acid and iodine it gave a black tar which would not crystallize.

p-Bromobenzamide gave a greenish precipitate with potassium iodide and iodine. *m*-Bromobenzamide, on the other hand, did not react.

The three nitrobenzamides were next tested, and in this case the *m*- and *p*-compounds gave crystalline products, but the *o*-compound did not.

Experiments were then made with several other amides, including some belonging to the aliphatic series. No addition products were obtained with acetamide, salicylamide, oxamide, or succcinamide. Succinimide, on the other hand, gave, with potassium iodide and iodine, the addition product $(C_4H_5O_2N)_4.KI.I_3$. This substance had already been prepared and described by Piutti (*Loc. cit*). Phthalimide also gave an addition product with potassium iodide and iodine which has not yet been analyzed. Benzene sulfonamide gave a fine greenish brown precipitate. Experiments with urea, thiourea and benzoylphenylurea all gave negative results.

Anilides.—Attention was next turned to the anilides, and here it was found that the reaction was fairly general, although substances which gave addition products with potassium iodide and iodine frequently did not do so with hydriodic acid, whereas in certain other cases this relationship was reversed. Among the compounds tested are acetanilide, benzanilide, phenylacetanilide, diphenylbenzanilide, aceto-*o*-toluidide, aceto-*p*-toluidide, benz-*o*-toluidide, and methylacetanilide. In the case of a few of the products formed, analyses have already been made, but it seems best to postpone the discussion of these addition products until some more work has been done. They will, accordingly, be reserved for some subsequent paper.

Summary.

1. Benzamide and some other amides form complex periodides containing iodine and hydriodic acid, or else some metallic iodide. The general composition of most of these compounds is $Am_3.MeI.I_2$ and $Am_2.HI.I_2$, though other combinations are observed.
2. Similar reactions seem to be very general in case of substituted anilides.
3. The compounds described in (1) can exist in combination with iodides of heavy metals, like lead and mercury, forming complex molecular aggregates of exceptionally high molecular weight.

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STUDIES IN BACTERIAL METABOLISM.

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XXXI. The Metabolism of the Typhoid-Dysentery-Alcaligenes Group in Milk.

One of the great problems in modern civilization is that of safeguarding that great river of milk which flows daily into practically every city and town. This problem in the last analysis is a bacterial problem, for those