Calc. for $CH_2O_2 = C_6H_3CH:C_4H_2O_2N_2S$: N, 12.07%; S, 13.79%. Found: N, 12.19; S, 13.71.

3,5-Dihydroxyphthalaldimalonylthiourea.—Resorcinoldialdehyde condensed with two molecules of thiobarbituric acid. The product was a reddish brown precipitate, soluble in alkalies, to a mahogany red solution.

Calc. for $(HO)_2C_6H_2(CH)_2(=C_4H_2O_2N_2S)_2$: N, 13.40%; S, 15.40%. Found: N, 13.90; S, 15.50.

Cinnamylidenemalonylthiourea. — Cinnamic aldehyde yielded with thiobarbituric acid a bright orange red precipitate, soluble only in alkalies.

Calc. for $C_6H_5CH:CHCH:C_4H_2O_2N_2S$: N, 10.85%; S, 12.40%. Found: N, 10.69; S, 12.15.

None of the substances described above could be melted without decomposition. The temperatures at which decomposition and charring began varied from 220° to 300°, but in no case was the decomposition temperature sufficiently sharp to serve as a means of identification. It is of interest to note that the condensation products of thiobarbituric acid with the three aldehydes which contain a hydroxyl group on the benzene nucleus gave a deep red coloration with caustic alkalies, while the others remained colorless under this treatment. In all cases the yield was practically quantitative.

The precipitation of aromatic aldehydes by thiobarbituric acid in the presence of 12% hydrochloric acid appears to be a general reaction. The products all have an intense yellow or yellowish red color. Three aliphatic aldehydes tried—formaldehyde, acetaldehyde and citral—failed to react under these conditions.

AMES, IOWA.

[CONTRIBUTION FROM THE SYNTHETIC PRODUCTS LABORATORY OF THE BUREAU OF CHEMISTRY.]

RESEARCHES ON ORGANIC PERIODIDES.

II. PERIODIDES OF ANTIPYRINE, IODOANTIPYRINE AND PYRAMIDONE.

BY W. O. EMERY AND S. PALKIN.

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Introduction.

The earliest available record of the action of iodine on antipyrine is that of Manseau,[1] who found that in aqueous solution and in the absence of free acid a relatively small but constant quantity of iodine was absorbed, which behavior he proposed to utilize as a basis for the proximate assay of antipyrine. Beyond noting the fact that apparent substitution took place until a point was reached when further addition of iodine produced a tarry precipitate, no attempt was made to ascertain the nature of the reaction or of the compounds formed. From a quantita-

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[1] *Bull. soc. pharm. Bordeaux*, 1889, 148.

tive standpoint, better results were obtained by Schuyten,[1] who titrated very small amounts of antipyrine in relatively large volumes of water with an aqueous solution of iodine. Clearer insight into the mechanism of reaction between iodine and antipyrine is afforded by the work of Bougault,[2] who caused these two substances to react in alcoholic solution and in the presence of mercuric chloride, thereby effecting an absorption of approximately 1 molecule of iodine for every molecule of antipyrine involved. It was further noted by this investigator that, when a neutral aqueous solution of antipyrine was treated with iodine and the liquid kept neutral or even slightly alkaline by an antiacid like sodium acetate, or better according to our own experience, sodium bicarbonate, reactions take place whereby primarily formed antipyrine diiodide splits off a molecule of hydriodic acid, with the result that an atom of hydrogen in antipyrine is replaced by an equivalent of iodine, thus yielding iodoantipyrine, $C_{11}H_{11}N_2IO$, identical with the substance first prepared by Dittmar[3] from antipyrine and iodinetrichloride. In fairly concentrated alcoholic or strongly mineral acid solutions, however, there is practically no substitution, hence it follows that in all operations looking to the formation of antipyrine periodides solely, careful attention must be paid to the nature and concentration of the solvent media employed.

In the course of an investigation designed to test the availability of Wagner's reagent (an aqueous solution of iodine and potassium iodide) in alkaloidal assay, Kippenberger[4] reported a method for estimating antipyrine based on the formation of a periodide. He found that when this reagent was added to a moderately concentrated solution of antipyrine in the presence of a mineral acid, a dark brown precipitate was formed, which, on shaking a few minutes, separated as a tarry uncrystallizable mass, leaving a clear supernatant liquid more or less colored with iodine. In the absence of any considerable excess of iodized potassium iodide, the separation proved to be quantitative, a fact we have made use of in the development of a recently published gravimetric method for the estimation of antipyrine.[5] According to Kippenberger's views, all the iodine of the tarry precipitate or periodide, to which he ascribed the composition, $C_{11}H_{12}N_2O.HI.I_2$, was derived solely from free iodine of the reagent, the hydriodic acid portion emanating from the interaction of free iodine with water, thus: $2I + 2H_2O = 2HI + H_2O_2$. This rather startling theory as viewed from the conditions of the experiment was very promptly attacked by Scholtz,[6] who, not satisfied with declaring the

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[1] *Chem. Ztg.*, **19**, 1786 (1895).

[2] *J. pharm. chim.*, [6] **7**, 161 (1898); [6] **11**, 98 (1900).

[3] *Ber.*, **18**, 1617 (1885).

[4] *Z. anal. Chem.*, **35**, 659 (1896).

[5] *J. Ind. Eng. Chem.*, **6**, 751 (1914).

[6] *Arch. Pharm.*, **237**, 71 (1899).

method worthless, pronounced the analytical results untrustworthy and the theory of the periodide formation untenable, whereupon a lengthy controversy ensued,[1] in the course of which Kippenberger, while admitting certain inaccuracies in his method, still insisted that the iodine of the hydriodic acid had its rise in free iodine itself. That Kippenberger obtained a tar of the above formula in certain definite concentrations of iodine, can hardly be questioned, but that a compound of the composition indicated always precipitates with only two "exterior" iodine atoms, irrespective of the quantity of iodine employed, was partly disproved by a number of experiments which he himself records, and we have ourselves obtained results fully substantiating the criticisms advanced by Scholtz and demonstrating beyond the possibility of doubt that Kippenberger's theory of periodide formation, in general, and his antipyrine method, in particular, are quite fallaceous. As will presently appear from a presentation of experimental data, the unsightly tars ordinarily obtained by the action of iodine on antipyrine may consist of one or several periodides, of which we finally succeeded, after no little trouble and experimentation, in isolating and characterizing the following in crystalline form:

$(C_{11}H_{12}N_2O)_2.HI.I_2$, $(C_{11}H_{12}N_2O)_3.(HI.I_2)_2$, $(C_{11}H_{11}N_2IO)_2.HI.I_2$,
$(C_{11}H_{11}N_2IO)_2.HI.I_4$, $(C_{11}H_{11}N_2IO)_2.HI.I_6$

All attempts to prepare a crystalline periodide of the composition favored by Kippenberger yielded negative results.

With a view to clearer presentation, the experimental portion of this paper has been subdivided into: I. Behavior of antipyrine toward iodized potassium iodide, and composition of the resulting tars; II. Crystalline periodides of antipyrine; III. Crystalline periodides of iodoantipyrine; IV. Crystalline periodides of pyramidone.

Experimental.

Behavior of Antipyrine toward Iodized Potassium Iodide, and Composition of the Resulting Tars.—In the following series of experiments, 10 cc. of a 1% solution of antipyrine were introduced into each of four 100 cc. volumetric flasks provided with glass stoppers, then treated with 40 cc. water and 30 cc. 0.965 $N/20$ iodine (equivalent to 28.95 cc. $N/20$ iodine). To the several flasks were thereupon added 2.5, 5, 10 and 12 cc. of concentrated hydrochloric acid (about 37%), respectively. After shaking for about five minutes, the liquid was diluted to 100 cc., again shaken to uniformity, then filtered through a funnel stoppered with glass wool overlaid with asbestos. A 50 cc. aliquot of the filtrate was titrated with sodium thiosulfate. Results of these experiments are set forth in tabulated form in Table I.

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[1] *Z. anal. Chem.*, **38**, 230, 278, 280 (1899); *Arch. Pharm.*, **238**, 135, 301 (1900).

TABLE I.

	Antipyrine. Gram.	N/20 iodine. Cc.	Concd. HCl. Cc.	N/20 $Na_2S_2O_3$ for unexpended iodine in 50 cc.	100 cc.	N/20 iodine consumed. Cc.
1	0.1000	28.95	2.5	1.75	3.5	25.45
2	0.1000	28.95	5.0	1.90	3.8	25.10
3	0.1000	28.95	10.0	2.50	5.0	23.95
4	0.1000	28.95	12.0	3.35	6.7	22.25

Examination of the foregoing data shows that iodine consumption varied with changing amounts of acid, gradually decreasing with increasing concentration of acid, and furthermore that, even with the minimum expenditure of iodine, there was no absorption equivalent to two atoms of iodine per molecule of antipyrine, although an approach to that relationship is indicated. Thus, it will be noted that as the acid increased from 2.5 cc. to 12 cc., the consumed iodine fell from 25.45 to 22.25 cc. N/20 iodine. Theoretically, 0.1000 g. antipyrine would require 21.3 cc. N/20 iodine for the formation of a tar or periodide corresponding in composition to Kippenberger's formula.

Such results quite naturally led us to consider what effect, if any, varying quantities of iodine would have on iodine absorption, all other factors remaining constant. To this end, 0.1000 g. portions antipyrine were introduced into 100 cc. volumetric flasks, as in the first series of experiments, along with 5 cc. concentrated hydrochloric acid, the mixture diluted somewhat, and from about 30 to 80 cc. standard iodine added. After shaking until the solution was clear and diluting to mark, 50 cc. aliquots were taken as before and titrated with thiosulfate. The results are shown in Table II.

TABLE II.

	Antipyrine. Gram.	N/20 iodine. Cc.	HCl. Cc.	N/20 $Na_2S_2O_3$ for unexpended iodine in 50 cc.	100 cc.	N/20 I. Cc.	Atoms I consumed per mol antipyrine.
1	0.1000	28.95	5	2.05	4.1	24.85	2.33
2	0.1000	33.75	5	2.70	5.4	28.35	2.66
3	0.1000	38.60	5	3.50	7.0	31.60	2.97
4	0.1000	48.25	5	5.95	11.9	36.35	3.42
5	0.1000	67.60	5	12.80	25.6	42.00	3.95
6	0.1000	77.20	5	15.50	31.0	46.20	4.30
7	0.1000	77.20	5	16.40	32.8	44.40	4.17

From these results it is evident that increase in iodine concentration causes a marked increase in the quantity of iodine absorbed, Experiments 1–6 showing a range of 2.33 to 4.3 atoms of iodine per molecule of antipyrine. In order to ascertain what affect heat might have on the reaction, Expt. 7 was carried out—identical in every way with Expt. 6 except that the liquid was heated to 60°—with the result that apparently less iodine was consumed than when the reaction took place in the cold. This is contrary to what might have been expected and is perhaps due to loss of iodine by volatilization rather than through difference in iodine absorbed or increased solubility of the tar in the reacting menstruum.

In the preceding experiments, conclusions relative to the nature of the tars produced were drawn solely from titrations of the unexpended iodine of the filtrates. In order to obtain a more direct index of the additive iodine content of the tar, estimations of halogen were made in the tarry residues themselves. The question naturally suggesting itself was whether all the iodine consumed in the operation was expended in the form of additive iodine for periodides and hence titratable, or whether some was used in other ways, notably in the formation of hydriodic acid or in direct substitution, whereby two atoms of iodine would be required for every atom substituted.

Accordingly, a series of experiments was run involving constant quantities of antipyrine in like concentrations of acid but varying volumes of $N/20$ iodine. The various operations of filtering and washing of the resultant tars were carried out in the manner already described, the aliquot portions of filtrates titrated with standard thiosulfate, while the tarry residue was dissolved in chloroform and titrated separately, being subjected to vigorous shaking in a glass-stoppered flask during titration to a complete discharge of color. The standard solutions were so adjusted that I = 0.0507 N = $Na_2S_2O_3$.. The results are set forth in Table III.

TABLE III.

	Antipyrine. Gram.	HCl Cc.	$N/20$ iodine. Cc.	$N/20$ thiosulfate. Cc.	Total I consumed. Cc.	Atoms I consumed per mol antip.	$Na_2S_2O_3$ required for tar. Cc.	Atoms I consumed per mol antip.	Iodine unaccounted for. Cc.
1	0.1	10	25	4.0	21.0	1.94	19.15	1.83	1.85
2	0.1	10	30	4.7	25.3	2.41	24.75	2.36	0.55
3	0.1	10	35	6.05	28.95	2.76	28.55	2.72	0.40
4	0.1	10	40	8.4	31.6	3.01	30.25	2.88	1.35
5	0.1	10	50	13.2	36.8	3.51	35.3	3.37	1.5
6	0.1	10	70	28.45	41.55	3.96	39.0	3.72	2.5
7	0.1	10	100	52.65	47.35	4.52	43.35	4.14	4.0
8[1]	0.1	10	50	48.6	48.6				1.4
9[2]	0.1	10	25	23.2	23.2				1.8

from which it appears that by far the greater portion of the expended iodine was present in titratable form, presumably in periodide combination, while a relatively smaller, yet variable, portion found application in other ways. Experiments 8 and 9 were carried out with a view of determining whether it would be possible under a somewhat modified treatment to realize a more nearly complete iodine recovery. To this end, chloroform was added to the flask after precipitation and the resulting mixture containing both the tar and unexpended iodine subjected to titration. Since the entire operation thus took place in the original closed

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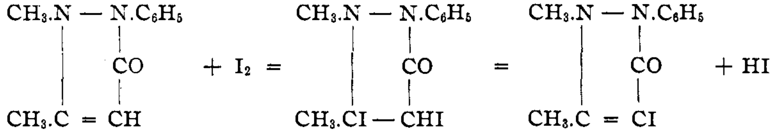
[1] Total supernatant liquid and tar titrated in original flask.

[2] As in the preceding, except that titration was effected after standing 2 1/2 hours.

system, mechanical loss of iodine was reduced to a minimum. Even under such conditions, practically the same discrepancy was found to exist between the quantity of iodine applied and recovered as in Expts. 1 and 5. It will be noted that the "unaccounted for" iodine ranges from 0.4 to 4.0 cc. $N/20$, an equivalent of about 0.04 to 0.4 atom per molecule of antipyrine, or an average of not more than 0.16 atom of iodine per molecule. This apparent loss—comparable in a way with that observed by Holmes[1] in somewhat similar work on the alkaloids: morphine, codeine and heroine—is in the case of antipyrine unquestionably due to a secondary reaction amounting in the end to substitution, the chief controlling factors of which are concentration of iodine and of mineral acid.

If one examines the constitution of antipyrine—as exemplified in its generally accepted formula—with respect to the possibilities or extent of iodation, it will be seen that, aside from additive tendencies centering about the nitrogen atoms, the pyrazolone ring is made up of two double bonded carbon atoms, which under certain conditions readily unite with iodine to yield antipyrine diiodide, the latter subsequently passing into iodoantipyrine and hydriodic acid, thus:



a reaction, which in reality forms the basis of procedures already mentioned in the introduction and developed by Manseau, Schuyten and Bougault. Examination of the data obtained in the foregoing series of experiments will show that the limit of iodine addition was approximately four atoms to the molecule of antipyrine, since by the use of 100 cc. $N/20$ iodine to 0.1 g. antipyrine (equivalent to nearly ten atoms iodine (Expt. 7.)) there was actually present in the tar only slightly over four atoms (4.14, to be exact) in titratable form, although the total consumption amounted to 4.5 atoms per molecule. This, taken in conjunction with the fact that antipyrine is a monoacid base, might justify the assumption that the above cited treatment with iodine and hydriodic acid would yield an addition product of the formula: $C_{11}H_{12}N_2O.HI.I_4$, which of course in no way accounts for the molecular distribution of the added components. It might be stated in this connection, however, that any iodine expended in the saturation of double bonded carbon atoms could hardly be so loosely held as to react with thiosulfate in the ordinary course of titration; furthermore, the behavior of iodine in the formation of addition products with organic bases is generally quite irregular and without regard to nitrogen valence; finally, since the periodides of anti-

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[1] *Phil. J. Sci.*, 6, 253 (1911).

pyrine as ordinarily obtained are noncrystalline tar-like masses, they may well, and doubtless do, act in the nature of solvents for iodine, beyond that required for addition products of definite composition. All such considerations, however, relative to the manner in which the iodine is actually consumed, would be of no great consequence from an analytical standpoint, provided a constant behavior could be assured, for the reason that the value of any method designed to secure quantitative results must necessarily depend on that feature.

Conclusions.

When an aqueous-acid solution of antipyrine is treated with a solution of iodized potassium iodide in excess:

(1) The quantity of iodine consumed varies inversely with the amount of mineral acid present.

(2) The quantity of iodine consumed varies directly with its concentration.

(3) Two atoms of iodine per molecule of antipyrine, as found by Kippenberger, is not the limit of possible iodine consumption. On the contrary, the quantity of additive iodine corresponds more nearly to four atoms.

(4) Some iodine is expended in substitution, controlling factors of which are concentration of iodine and of mineral acid.

Crystalline Periodides of Antipyrine.—In Kippenberger's investigations on the so-called periodides of antipyrine, special mention was made that all efforts to obtain definite crystalline compounds from the various tars examined were futile. Manseau likewise merely noted the formation of a tarry precipitate on treating an acid solution of antipyrine with iodine in excess. Bougault[1] reported that when an alcoholic solution of antipyrine was treated with iodine there is formed an addition product which first precipitated in the form of a black oil but, on long standing, yielded needle-like aggregates with greenish reflection. These he claimed decomposed easily, dissociated in almost all solvents with liberation of free iodine, and, as a consequence, were not susceptible of isolation in a pure state. Further than the above, no attempts apparently have been recorded with a view to the preparation of antipyrine periodides of definite composition. A systematic investigation of the possible ways of obtaining such compounds involved not only experimentation with a large number of solvents and solvent mixtures, but also application of various solvents to each of a large number of periodides which in themselves differed widely in iodine content. In a general way it may be stated that the following facts were observed, affecting the solubility of most of the periodides examined: They are, for example, practically insoluble in cold aqueous acids; only very slightly soluble in petroleum ether (b. p. 30–60°) and

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[1] *Loc. cit.*

carbon bisulfide; moderately soluble in cold, more so in hot ethyl acetate; very slightly soluble in cold ether, moderately soluble when warmed; quite soluble in all alcohols, more so in methyl than ethyl, and more in ethyl than amyl alcohol; chloroform is a very good solvent, while acetone is the best of all. From this it will be readily understood what an infinite field of possibilities opens up to the investigator who attempts an exhaustive study of all combinations of solvents, both pure and mixed, with the various periodide tars and under varying degrees of temperature. Nevertheless, a large number of experiments carried out in this field gradually forced the conviction that crystalline products could be best obtained by the use of organic solvents, of which alcohol, ether and ethyl acetate, yielded the most promising results. Thus, it was found possible, by the judicious application of the last mentioned solvent media—either singly or in admixture—to the tars themselves, to isolate three distinct periodides, derivatives of antipyrine.

For the sake of convenience and clearness it has been deemed expedient in a further presentation of the subject to divide the iodine addition products emanating from antipyrine itself into two general classes: (1) Periodides of antipyrine hydriodide, and (2) Periodides of iodoantipyrine hydriodide. Representatives of Class 1 were prepared in a more or less acid medium while those of Class 2 were isolated from media maintained quite neutral or slightly alkaline. Reference has already been made to certain principles underlying the conditions which inhibit or favor iodine substitution in the pyrazolone nucleus. Thus, the presence of a strong mineral acid or excess of an organic solvent such as alcohol, prevents substitution almost entirely, while carbonates, bicarbonates and even acetates of the alkali metals, as also diminution of the organic solvent (alcohol) by dilution with water, favor substitution to such a degree that with sufficient iodine available the reaction becomes complete as regards the eventual replacement of one hydrogen atom of the antipyrine by an equivalent of iodine. It should be noted, however, in this connection, that Class 1 differs further from Class 2 in that in the latter case an alkaline or neutral medium is maintained only until complete substitution has taken place, that is, until iodoantipyrine has been produced, the medium from there on being rendered acid, whereas in Class 1 the condition of the medium throughout the entire operation of periodide formation is one of acidity.

For the actual preparation of crystalline derivatives, two general methods naturally suggested themselves, either to prepare the indefinite tars by rapid precipitation in a medium in which they are quite insoluble (absence of organic solvent), followed by solution in a second medium more favorable to crystallization, or to bring together all the ingredients as antipyrine, hydriodic acid and iodine under conditions immediately favorable to crystallization (organic solvents), thus entirely eliminating all intermediate steps for preparing the tar. As a matter of fact, the former method is the one which first yielded crystalline derivatives, and for a time at least it was found impossible to obtain them by any other treatment. Later, however, better success was had with the second and more direct procedure, purer products being obtained and far more expeditiously than with the earlier method. The second method will therefore be described exclusively in the preparation of the several compounds presently to be enumerated.

Triantipyrine Dihydriodotetriodide, $(C_{11}H_{12}N_2O)_3.(HI.I_2)_2$.—This compound is readily obtained by dissolving its components: antipyrine, hydriodic acid and iodine in about equimolecular proportions in alcohol and allowing the resulting liquid to slowly deposit crystals. Thus, one sample was obtained in the following manner: 6.5 g. iodine were weighed out in a 50 cc. beaker and treated with a previously prepared solution of hydriodic acid[1] in alcohol in small portions, the mixture being stirred and subsequently decanted from any undissolved iodine into a 250 cc. beaker, until by this progressive treatment complete solution of iodine was effected. The iodized hydriodic acid was thereupon warmed to about 60° and slowly added with constant stirring to a warmed solution of 5 g. antipyrine in 20 cc. alcohol, the resulting liquid then diluted with a warmed mixture of 25 cc. alcohol and 25 cc. water, stirring the while, the beaker covered with a watch glass and set aside 24 hours. Slow crystallization favors the formation of large crystals, especially when the solution is seeded with one or more crystals. After standing the allotted time, the resulting product was filtered by suction through a small filter plate, the crystals thereupon returned to the beaker and washed several times by decantation with water, then subjected to renewed suction on the filter, dried in the air on filter paper, and finally in a desiccator until no odor of iodine could be detected. An additional crop of crystals can be obtained, either by chilling the alcoholic filtrate in a refrigerator or by slowly diluting same with a little warm water until the solution appears faintly turbid, then allowing to stand as before. This second treatment is not advocated, however, for the reason that the product resulting therefrom not infrequently shows an iodine content differing materially

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[1] 6.7 g. potassium iodide were dissolved in the least possible quantity of water contained in a 50 cc. lipped Erlenmeyer flask, 4 cc. concentrated hydrochloric acid added, followed more gradually and with constant agitation with 20 cc. absolute alcohol. The liquid was made to pass through a small folded filter, or better through a small suction plate and filter, the filtrate and washings (two 10 cc. portions absolute alcohol) being in the latter event collected in a test tube contained in the suction Erlenmeyer flask. In the case where the ordinary folded filter was used, both filtrate and washings were collected in a second 50 cc. Erlenmeyer flask. This method will be found most convenient for the rapid preparation of alcoholic hydriodic acid.

from that of crystals first separating. Attention might properly be called at this point to the proportions in which the essential ingredients are employed, namely: 1 molecule of antipyrine, 2 atoms of iodine and 1 molecule of hydriodic acid, the purpose being to produce a compound of the same composition as the tarry substance described by Kippenberger and alleged to have the formula $C_{11}H_{12}N_2O.HI.I_2$. No such compound resulted, however, as will presently be shown by the analytical data obtained. The above cited proportions are susceptible of considerable variation, with some consequent change in the yield, but little or none in the composition of the resultant periodide. Crystals from repeated experiments were small to large steely blue needle-like prisms with metallic luster, odorless when perfectly dry, quite stable in the air and having no water of crystallization. They are extremely soluble in acetone, less so in chloroform, moderately soluble in methyl and ethyl alcohol, sparingly so in iodized potassium iodide solution, and quite insoluble in water. The specific gravity of these crystals was found to be 1.91, the melting point 79–80°. In determining the composition of the periodide, recourse was had to elementary analysis with respect to carbon, hydrogen and nitrogen, to the estimation of total and of "exterior" or additive iodine, as also of antipyrine itself.

Aside from complications incident to the presence of nitrogen, considerable difficulty was experienced in the carbon and hydrogen determinations, owing to the relatively high iodine content and its resistance to fixation. Extraordinary precautions were therefore necessary to provide against possible passage of this element into the absorption train. In spite of all safeguards, however, as interposition of silvered copper between the lead chromate and reduced copper spirals, sufficient iodine escaped to materially affect the values for carbon and hydrogen.

In the otherwise comparatively simple operation of determining iodine by titration with thiosulfate, numerous difficulties presented themselves. As previously pointed out, when antipyrine and iodine are brought together in a neutral or alkaline medium, conditions favorable to substitution at once obtain, so that by dissolving the periodide in alcohol, or other organic solvent, and adding aqueous thiosulfate, the tendency to such reaction becomes more and more pronounced, progressively so in fact with increasing quantities of the aqueous reagent, hence treatment under the conditions mentioned invariably yielded low values for iodine. Since the total consumption of this element is in quantity twice that actually substituted, even slight substitution may involve a very material expenditure of iodine, in fact it is possible by continuous shaking and addition of water to divert practically all the "exterior" iodine to the formation of iodoantipyrine. If, on the other hand, titration is carried on in the presence of a strong mineral acid, little or no substitution takes place, but here again obstacles arise in the form of conditions favoring oxidation, so that even with moderate shaking the hydriodic acid liberated by the mineral acid is subjected to uninterrupted oxidation. Furthermore, since the sodium iodide formed in the course of the titration is continuously converted into hydriodic acid, the cycle becomes practically complete and iodine values are limited only by the willingness of the operator to persist in shaking and titrating. It will be readily appreciated from the above how extremely difficult it is to create and maintain conditions effectively excluding both substitution and oxidation. Nevertheless, it developed that the use of solid potassium or sodium bicarbonate in the alcoholic solution of the periodide, together with a few cubic centimeters of glacial acetic acid, yielded fairly concordant results. Titration also of the periodide in alcoholic solution with standard alcoholic thiosulfate gave equally satisfactory values for the "exterior" or additive iodine. Total iodine was determined by treating the sample either according to Carius or with sulfur dioxide[1] in aqueous-acetic acid solution, followed by precipitation with silver nitrate.

The estimation of antipyrine was effected in form of its iodo derivative by dissolving 0.5 g. of the periodide in about 10 cc. alcohol-free chloroform and shaking vigorously at intervals in a separatory funnel with a mixture of 10 cc. sodium bicarbonate solution, 25 cc. 0.1 *N* iodine and 50 cc. water. After standing a few minutes, excess of iodine is removed by the addition of a crystal of thiosulfate, and the resulting iodoantipyrine isolated by extraction with three 25 cc. portions chloroform, each portion being subsequently washed in a second separatory with 5 cc. water prior to withdrawal through cotton to a 100 cc. beaker, and later evaporated to apparent dryness on the steam bath. The residual iodoantipyrine is thereupon dried one-half hour at 110° in an air bath, then cooled and weighed. The conversion factor for antipyrine is 0.5990. The values resulting from the estimation of this substance as a whole were found to be more reliable than those obtained in determining the elemental constituents carbon and hydrogen, for reasons already pointed out.

Molecular-weight determinations made by the boiling point method, involving absolute alcohol and chemically pure acetone, yielded the values 344 and 346, respectively. These values, while concordant enough in themselves, are unquestionably low and indicate marked dissociation. The molecular weight of the simplest possible formula is, as will presently appear, 442.9. No determinations were attempted by the freezing point method owing to the lack of suitable solvents.

In view of the method of preparation, as also of the fact that antipyrine as such is recoverable from the crystalline periodide, any idea that iodoantipyrine may participate in its formation need not receive serious con-

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[1] Cf. Emery and Palkin, *J. Ind. Eng. Chem.*, 7, 519 (1915).

sideration. Accordingly, the choice of a suitable formula must be made solely from those involving antipyrine, hydriodic acid and iodine as component parts of the periodide molecule. Of the many possible combinations, only three perhaps deserve mention, namely: $C_{11}H_{12}N_2O.HI.I$, $(C_{11}H_{12}N_2O)_2.HI.I_3$ and $(C_{11}H_{12}N_2O)_3.(HI.I_2)_2$, the antipyrine and total iodine content of which are approximately the same. Comparison of the analytical findings, however, with the percentage composition of the remaining factors, particularly of "exterior" iodine, tends to confirm the third formula as being the most probable.

	Calc. for $C_{11}H_{12}N_2O$.-HI.I.	Calc. for $(C_{11}H_{12}N_2O)_2$.-HI.I_3.	Calc. for $(C_{11}H_{12}N_2O)_3$.-$(HI.I)_2$.	Found.					
C	24.4	24.4	29.8	....	....	....	....	....	31.2
H	2.9	2.8	2.8	....	....	....	....	....	3.1
N	6.3	6.3	6.3	....	....	....	....	....	6.8
I (total)	57.3	57.4	57.3	....	....	56.8	56.9	57.0	56.8
I ("exterior")	28.6	42.5	38.2	36.8	38.2	37.8	38.0	37.5	38.0
Antipyrine	42.5	42.5	42.4	....	....	....	42.6	42.9	43.2

Diantipyrine Hydriodo-diodide, $(C_{11}H_{12}N_2O)_2.HI.I_2$.—This compound was obtained substantially as follows: To a solution of 4.9 g. antipyrine in 25 cc. alcohol (95%) were added 3.37 g. iodine dissolved in 25 cc. alcohol (containing an amount of hydriodic acid equivalent to 4.45 g. potassium iodide and prepared in the manner previously described). The volume of the liquid was further increased by the addition of 50 cc. of alcohol, the whole then warmed on the steam bath to about 50° and thereupon diluted with 25 cc. of water with constant stirring. The solution was allowed to cool very gradually in the open until crystals began to appear, whereupon the cooling was continued in a refrigerator. The resulting product was filtered by suction on a small filter plate, washed several times with 60% alcohol previously saturated with iodine, then dried in the air by spreading over filter paper on a porous plate, and finally by placing in a desiccator for about 24 hours. The periodide appeared in the form of slender glistening ruby-red needles melting at 96–7°. Crystals obtained from the mother liquor were in nearly every instance found to be impure, the product being, as a rule, dull-lustered and lighter in color, and possessing a lower iodine content than the first crop. Recrystallization is inadvisable. On subjecting the crystals to analysis, difficulties developed very similar to those already described for the preceding periodide. By observing the necessary precautions, however, results were obtained satisfactorily confirming the composition as indicated in the caption, namely: $(C_{11}H_{12}N_2O)_2.HI.I_2$.

Calc. for $(C_{11}H_{12}N_2O)_2.HI.I_2$: 51.0% total I; 33.5% exterior I; 49.6% antipyrine. Found: I, 50.9, 50.4, 51.3; I, ext., 32.8, 33.0; antipyrine, 49.7.

Crystalline Periodides of Iodoantipyrine.—The isolation of these compounds was effected in two stages, *viz.:* (1) Preparation of iodoantipyrine, and (2) preparation of the periodides themselves. Iodoantipyrine, first reported by Dittmar[1] and prepared by the action of iodine trichloride on antipyrin, may be conveniently made as follows: 2 g. antipyrine and 1 g. sodium bicarbonate were dissolved in 100 cc. of water, the solution heated to 50° and a 0.1 N solution of iodine slowly added with constant stirring until a faint yellow coloration persisted. On cooling, colorless needles separated which were filtered by suction and washed several times with a little water. A second crop of crystals may be obtained by concentrating the filtrate on the steam bath and allowing the residual solution to stand for some time in the cold. The crystals as first obtained were recrystallized once from a hot 50% alcoholic solution. When thoroughly dried, the product melted at 160–1°.

Calc. for $C_{11}H_{11}N_2IO$: I, 40.4%. Found: I, 40.4, 40.5.

Di-iodoantipyrine Hydriodo-diiodide, $(C_{11}H_{11}N_2IO)_2.HI.I_2$. — This compound was prepared in the following manner: An alcoholic solution of hydriodic acid (obtained by treating 0.4 g. potassium iodide dissolved in 0.2 cc. water with 0.3 cc. conc. hydrochloric acid and 12 cc. absolute alcohol, and subsequent filtering from potassium chloride) and 0.51 g. iodine was poured into a 100 cc. beaker in which 1.24 g. iodoantipyrine had been previously dissolved in 12 cc. warm alcohol. Water was gradually added with constant stirring to the appearance of a brown amorphous precipitate, which became crystalline in the course of a few minutes. More water was then added until the total volume was about 55 cc. The ruby red needle-like crystals were thereupon filtered by suction, transferred to the original beaker and washed with several portions of water, stirring and decanting each portion as added, again filtered by suction on a perforated plate and finally dried in the air until odorless. The sample was then subjected to analysis, as also a second one obtained by recrystallizing the products from several other experiments, thus: 1.5 g. of the mixed samples were dissolved in 20 cc. warm alcohol, gradually diluted with water to the appearance of an amorphous precipitate, allowed to stand until crystallization set in, then water again very gradually added with constant stirring until the total volume amounted to 35 cc. The resulting ruby-red needles were thereupon filtered, washed and dried as above described. The titration of the iodine of addition by means of aqueous thiosulfate was effected without difficulty in alcoholic solution in the presence of sodium bicarbonate. Total iodine was determined both by the method of Carius and by the sulfur dioxide method.[1] The estimation of iodoantipyrine was made by extraction with chloroform, evaporation of the solvent and subsequent weighing.

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[1] *Loc. cit.*

Calc. for $(C_{11}H_{11}N_2IO)_2.HI.I_2$: 62.7% total I; 25.1% exterior I; 5.6% N; 62.2% iodoantipyrine.

Found: total I (I) 62.8, 62.5, (II) 62.9; ext. I (I) 25.2, 25.3, (II) 25.5; N, 5.6; iodoantip., 62.2.

This periodide melts at 124–5°, is readily soluble in acetone and chloroform, less so in alcohol and behaves toward other organic solvents very like the periodides of antipyrine itself.

Di-iodoantipyrine Hydriodo-tetriodide, $(C_{11}H_{11}N_2IO)_2.HI.I_4$.—An iodized alcoholic solution of hydriodic acid (prepared in the manner above described for the diiodide, from 0.2 g. potassium iodide, 0.1 cc. water, 0.15 cc. conc. hydrochloric acid, 12 cc. absolute alcohol and 0.41 g. iodine was added to a warm solution of 0.5 g. iodoantipyrine in 5 cc. alcohol. Water was then added with constant stirring to the formation of an amorphous or tarry precipitate, the mixture was allowed to stand 10 minutes, or until the precipitate became crystalline, then more water was cautiously added with stirring until the total volume amounted to about 30 cc., whereupon the product was allowed to stand one-half hour. The resulting crystals were filtered, washed and dried in much the same manner as specified for the preceding compound. The resulting chocolate-colored prisms melted at 94–5° and gave values for additive iodine about 2% below the theory (I). Two recrystallizations carried out in the same manner as indicated above yielded better results (II). The periodide forms chocolate-colored prisms, very soluble in chloroform amd acetone, quite so in alcohol, but insoluble in water. It is rather difficult to prepare in a pure condition.

Calc. for $(C_{11}H_{11}N_2IO)_2.HI.I_4$: 70.3 total I; 40.2 ext. I.

Found: (II) 69.7; ext. I (I) 37.9, (II) 40.2.

Di-iodoantipyrine Hydriodo-hexiodide, $(C_{11}H_{11}N_2IO)_2.HI.I_6$.—The alcoholic solution of hydriodic acid and iodine (prepared in the usual way from 0.2 g. potassium iodide, 0.1 cc. water, 0.15 cc. conc. hydrochloric acid and 12 cc. absolute alcohol) was added to 0.415 g. iodoantipyrine dissolved in 25 cc. warm alcohol, the resulting mixture gradually diluted with water until a tarry precipitate formed, set aside until crystallization took place (about 10 minutes), then more water added with constant stirring until the volume totalled 75 cc. The crystals, filtered, washed and dried as in the case of the preceding compound, formed dark green glistening needle-like prisms melting at 97–8°, amounting in weight to 0.81 g. The product was redissolved in 12 cc. alcohol and again brought to crystallization by the gradual addition of 25 cc. water. The resulting crystals, isolated as in the first instance, amounted to 0.57 g. and gave the same melting point as before.

Calc. for $(C_{11}H_{11}N_2IO)_2.HI.I_6$: 75.3 total I; 50.2 ext. I; 41.4 iodoantipyrine.

Found: total I, 75.3, 75.0; ext. I, 50.3; iodoantip., 41.4, 41.5.

Crystalline Periodides of Pyramidone (Dimethylamino-antipyrine).—In the preparation of these compounds, two essential operations were involved, namely: isolation (1) of the hydriodide of pyramidone, and (2) of the periodide of the latter product.

Pyramidone Hydriodide, $C_{13}H_{17}N_3O.HI$.—This salt was first reported by Nardelli and Paolini,[1] who employed it medicinally in aqueous solution with pyramidone. Later, Cousin[2] actually isolated the salt and at the same time the periodide, $C_{13}H_{17}N_3O.HI.I_2$, the former resulting from operations in aqueous, the latter in aqueous-alcoholic solution. The hydriodide was obtained by us in two ways: 1st. 2 g. pyramidone were dissolved in 10 cc. chloroform, to which was then added an alcoholic solution of hydriodic acid (from 1.66 g. potassium iodide, 1.5 cc. water, 1 cc. conc. hydrochloric acid and 20 cc. alcohol), the resulting liquid further diluted with alcohol to a final volume of about 50 cc. Ethyl ether was then added with constant stirring until the solution became slightly turbid and a white precipitate of the hydriodide began to form. After allowing the precipitate to settle for an hour, more ether was added to the turbidity point and the mixture again allowed to stand. The product was then filtered by suction and washed a few times with ether. For purposes of analysis, recrystallization was resorted to by dissolving in a small quantity of warm alcohol and reprecipitating with ether as above described. The crystalline product was again filtered by suction, washed several times with ether and dried for a day in the air. Thus prepared, pyramidone-hydriodide appeared as a fine white granular powder, darkening at 190° and melting at 196–7° (200° Cousin), and becoming yellow on long standing. 2nd. 5 g. pyramidone were dissolved in 10 cc. ethyl acetate and treated with gaseous hydriodic acid until the liquid ceased to yield a precipitate. The resulting needle-like prisms were filtered by suction, washed several times with ether and dried in the air. The melting point was the same as that observed for the granular preparation.

Calc. for $C_{13}H_{17}N_3O.HI$: 35.3% I. Found: 35.4, 35.7.

Pyramidone Hydriodo-diiodide, $C_{13}H_{17}N_3O.HI.I_2$.—To a solution of 1 g. of the hydriodide in hot glacial acetic acid (30 cc.) were added 0.7 g. iodine dissolved in 10 cc. acetic acid and the mixture allowed to stand one day in a shallow dish. The resulting crystals were filtered by suction, washed a few times with a small quantity of acetic acid (36%) and dried in the air until odorless. The compound had the form of fine ruby red needles, softening at about 180° and melting to a brownish oil at 190°. Titrations of this and the following periodide were carried out in a mixed solution of alcohol and acetic acid.

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[1] D. R. P. 180,120 (1905); Friedlaender, *Fortschritte der Teerfarben-Fabrikation*, p. 982 (1905–7).

[2] *J. pharm. chim.*, [6] **28,** 158; **29,** 49 (1908–9).

Calc. for $C_{13}H_{17}N_3O.HI.I_2$: 62.1% total I; 41.4 ext. I. Found: 62.2 total; 41.5 ext.

A periodide of like composition was obtained by Cousin[1] in the form of brown needle-like crystals from an aqueous alcoholic solution of the hydriodide and iodine. He reports also the formation of the same compound by the interaction of pyramidone (1 mol) and iodine (3 mol) in alcoholic solution. No melting point, however, is given.

Pyramidone Hydriodo-triiodide, $C_{13}H_{17}N_3O.HI.I_3$.—This compound was obtained by dissolving 1.2 g. of the hydriodide in about 50 cc. hot alcohol and treating the solution with 1.6 g. iodine likewise dissolved in warm alcohol (20 cc.). Water was then added to the liquid with constant stirring until a slight turbidity resulted, whereupon the mixture was allowed to stand several hours in the cold. Small, heavy, greenish glistening leaflets somewhat resembling herapathite gradually collected on the bottom of the container. The crystals were filtered by suction, washed several times with 50% alcohol and finally dried in the air until practically odorless. A second crop of crystals was obtained by diluting the filtrate with water and allowing it to stand for several hours. The melting point of this periodide was found to be at 155–6°.

Calc. for $C_{13}H_{17}N_3O.HI.I_3$: 51.4% ext. I. Found: 51.4.

It may not be amiss to mention that both periodides of pyramidone herein described can, with equal facility, be prepared directly from the base itself, without first isolating the hydriodide, by dissolving the components in alcohol and allowing the resulting addition product to slowly separate by crystallization.

Summary.

Conclusions have already been drawn relative to the behavior of antipyrine toward iodized potassium iodide in aqueous solution, and to the nature and composition of the tarry precipitates resulting therefrom. (Cf. p. 2172.)

The hitherto unreported periodides, $(C_{11}H_{12}N_2O)_3.(HI.I_2)_2$, $(C_{11}H_{12}N_2O)_2.HI.I_2$ and $(C_{11}H_{11}N_2IO)_2.HI.I_2$, derivative of antipyrine and iodoantipyrine, respectively, were isolated in crystalline form and characterized from tars obtained by the action of iodized potassium iodide on aqueous acid solutions of antipyrine and iodoantipyrine, respectively.

These same compounds, together with the crystalline periodides, $(C_{11}H_{11}N_2IO)_2.HI.I_4$ and $(C_{11}H_{11}N_2IO)_2.HI.I_6$, were more conveniently prepared and in purer form by dissolving their components in alcohol and allowing the resulting solution to slowly deposit crystals.

Two crystalline periodides of pyramidone, $C_{13}H_{17}N_3O.HI.I_2$ and $C_{13}H_{17}N_3O.HI.I_3$, were prepared and characterized, the latter having never before been described.

WASHINGTON, D. C.

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[1] *Loc. cit.*