

**The chemical character of so-called iodo-tannin compounds / by Frederick B. Power and Frank Shedden.**

**Contributors**

Power, Frederick B. 1853-1927.

Shedden, Frank.

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THE CHEMICAL CHARACTER  
OF SO-CALLED  
IODO-TANNIN COMPOUNDS

BY  
FREDERICK B. POWER, PH.D.  
AND  
FRANK SHEDDEN, B.Sc., A.I.C.



THE WELLCOME CHEMICAL RESEARCH LABORATORIES  
FREDERICK B. POWER, PH.D., *Director*  
6, King Street, Snow Hill  
LONDON, E.C.



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Chemical Character of So-called  
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A number of preparations made by the action of iodine upon tannic acid, or upon drugs containing considerable amounts of tannin, such as krameria, cinchona, etc., have been used medicinally for many years, especially in France, where they appear to have originated. These preparations are usually in the form of a syrup or wine, and various working formulæ for them have been published (see, for example, *Rép. de Pharm.*, 1896, pp. 145-150; Hager's 'Handbuch,' Bd. i., p. 138, Bd. ii., p. 141; also the "Sirup de Raifort Iodé" of the French Codex). Since they contain no free iodine it is usually assumed, or even definitely stated, that the iodine is in organic combination with the tannin, and that they are therefore more readily assimilated than the alkali iodides, whilst not producing the unpleasant effects which sometimes attend the use of the latter.

The behaviour of iodine towards a solution of tannic acid is referred to in several works on pharmaceutical chemistry, but usually without any definite statement as to the character of the product formed. Thus, in Schmidt's 'Pharm. Chemie,' 3rd

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edit., Bd. ii., p. 1,017, it is stated:—"A solution of tannic acid takes up iodine in considerable amounts, forming a reddish-brown liquid, in which free iodine can no longer be detected by starch paste." Practically the same statement occurs in Hager's 'Handbuch,' Bd. i., p. 134, with the additional conclusion that the liquid contains *organically combined iodine*, from the fact that the presence of this "element cannot be detected by starch." Flückiger, 'Pharm. Chemie,' 2nd edit., pt. ii., p. 356, has recorded the following observation:—"1 part of powdered iodine affords with a solution of 7 parts of tannic acid in 50 parts of water, a turbid, reddish-brown liquid, which can be diluted without the separation of iodine, and produces no blue precipitate in solutions of starch."

The first study of the chemical changes which take place by the action of iodine on tannin appears to have been made by Socquet and Guilliermond, in a paper entitled "Sur une nouvelle combinaison de l'iode" (*Journ. de Pharm. et de Chemie*, 3 série, t. xxvi., 1854, pp. 280-285). The notice given in Gmelin-Kraut's 'Handbuch der Chemie,' Bd. vii., 1862, p. 884, or in the Cavendish edition, 1862, vol. xv., p. 459, is apparently a brief abstract of the preceding paper.

With reference to the observations of Socquet and Guilliermond (*loc. cit.*) the following points may be noted. They observed that the action of iodine upon tannin only takes place in the presence of water, and that in alcoholic solution no reaction ensues, however prolonged may be the contact. They then further state that "tannin, in aqueous solution, can thus dissolve considerable quantities of iodine—as much as half its own weight. What is remarkable in this absorption of iodine by tannin is that if it is arrested when a certain proportion exists between the two substances one will see that a *true chemical combination is effected*."

They observed that from the iodo-tannin solution a sparingly soluble substance was separated, which was estimated to amount to about one-sixth of the weight of tannin employed. When washed with water and dried it did not retain any trace of iodine, which remained entirely in the solution from which it was deposited, but, as it had an acid character and retained some of the properties of tannin, it was regarded as an *altered tannin*. The iodo-tannin solution was found to be more strongly acid than a solution containing simply the same amount of tannin, but to show the same deportment as the latter towards various reagents. It does not stain the skin, and the taste and odour do not permit of the recognition of iodine. It is capable of absorb-

ing an additional quantity of iodine, and the highly coloured solution then possesses the odour of iodine.

In order to ascertain the nature of the combination formed by the tannin and iodine, Socquet and Guilliermond conducted the following simple experiments:—

(1) With a solution of lime a precipitate of calcium tannate was obtained, whilst the iodine remained in solution as calcium iodide.

(2) With gelatin a precipitate was obtained which, when thoroughly washed with water, was found to contain no iodine, the latter remaining entirely in the solution in a state of combination, although accompanied by some tannate of gelatin, which was difficult to separate.

(3) With lead acetate a precipitate of lead iodide was first obtained, and subsequently lead tannate was precipitated.

(4) On evaporating the iodo-tannin solution no free iodine was developed until it approached the point of dryness. A similar result was obtained on distilling a large volume of the solution, when a purely aqueous distillate was obtained, and a strongly acid solution, containing no free iodine, was left in the retort.

From these results they arrived at the following conclusions:—  
“That during the contact of the water, iodine, and tannin, a portion of the water becomes decomposed; that hydriodic acid is formed, and that a portion of the tannin is transformed by oxidation into a particular tannin which is less soluble than ordinary tannin, and that *the unaltered tannin forms, with hydriodic acid, a soluble and stable combination which even distillation is not able to change.*”

The same authors finally proposed a formula for an iodo-tannin syrup, and recommended extract of rhatany to be used for this purpose in place of gallo-tannic acid, on account of the disagreeable astringency of the latter.

Barnouvin (*Rep. de Pharm.*, 1892, p. 350, and *Proc. Amer. Pharm. Assoc.*, 1893, vol. 41, pp. 578, 775), in a paper entitled “Composés iodo-tanniques,” has described a so-called “iodo-tannin compound” which he prepared by adding iodine to tannin in such a proportion that after standing for an hour or two it no longer gave a reaction for free iodine with starch. It was then evaporated to a syrupy consistence, spread on glass, and thus obtained in yellowish-brown scales, which were soluble in water and in alcohol. No statement is made in the paper respecting the amount of iodine contained in this preparation, nor does it appear to have been ascertained that it actually contained iodine;

but the opinion was expressed that the study of the subject with reference to the compounds of iodine with organic bodies might be of some interest. It was also incidentally noted that a large number of other organic bodies besides tannin, such as those contained in extracts, syrups, etc., have the property of effecting this so-called dissimulation of iodine.

In a later paper by Barnouvin, entitled "Sur l'iode dissimulé" (*Rép. de Pharm.*, 1898, 3 sér., 10, p. 337), the action of iodine upon gallic acid is considered. In this paper the author refers to the action of iodine upon tannin, and states that gallic acid possesses the same property, being capable of absorbing as much as a third of its weight of iodine. The iodine thus combined is only made manifest by the action of nitrous acid or an alkali hypochlorite. The so-called iodo-gallic solution left on evaporation a yellowish, amorphous residue, sparingly soluble in water, which only reacted with starch after the addition of the above-mentioned reagents. On treating this residue with ether, and evaporating the latter, crystals consisting of fine needles were obtained, which were sparingly soluble in water. Since these crystals afforded a reaction for iodine under the conditions previously mentioned, they were regarded as a definite compound (an iodo-gallic acid), comparable to bromo-gallic acid, and it was noted that from this point of view the fact was of sufficient interest to call for further research. We have considered this question in connection with our experimental work.

The latest study of so-called iodo-tannin preparations, which, however, were considered more especially with regard to their pharmaceutical character than their chemical composition, was embodied in a paper by Professor Gay, entitled: "Sur les sirops iodo-tanniques et la dissimulation de l'iode par le sucre inverti" (*Rép. de Pharm.*, 1896, pp. 145-150).

The author, referring to the observations of Guilliermond, states that the absorption of iodine by tannin indicates a true combination between the two bodies. He considers that a portion of the iodine is introduced into the tannin molecule, while another portion forms hydriodic acid, the tannin at the same time suffering a partial decomposition with the formation of gallic acid and even ellagic acid. He noted, furthermore, that the reaction deserves to be examined more closely than it has been possible for him as yet to do.

Professor Gay then describes the various methods for the preparation of iodo-tannin syrups, and records a number of experiments as evidence of the so-called absorption or dissimulation of iodine by invert sugar or by glucose. He

especially calls attention to the difference in character of the iodo-tannin syrup when prepared by the method of Guilliermond, in which the iodine, dissolved in a little alcohol, is first allowed to act upon extract of rhatany dissolved in water, and the solution subsequently converted into a syrup by the addition of sugar, or when prepared by the method adopted by the Paris School of Pharmacy, in which the iodine, dissolved in a little alcohol, is added to a syrup of rhatany, and allowed to stand until it no longer gives a reaction for free iodine with starch. By the first method the iodine is considered to be dissimulated by the tannin of the extract of rhatany, whereas by the second method it acts upon the cane sugar, and, to a greater or less extent, is dissimulated by the invert sugar thus produced. A similar difference exists between the formula of Berthet, as adopted by the formulary of the Civil Hospital of Paris, and the formula of Perrens (*Journ. de Pharm. et de Chim.* [4], xvi., p. 48).

With regard to the practical conclusions to be drawn from these facts, Professor Gay considers that from a therapeutic point of view it matters but little whether the iodine is dissimulated by the tannin or by the sugar, although the latter is more readily assimilated, and, furthermore, the question is raised whether medical men who prescribe these compounds pretend to utilise the physiological properties of tannin, or whether they only regard it as an agent for the dissimulation of the iodine. In the latter case it is suggested that preference should be given to such preparations as the iodised syrup of horseradish of the Codex, or to an iodised syrup of citric acid.

Our purpose in this investigation was to ascertain the chemical character of the preparations produced by the action of iodine upon tannic and gallic acids, with consideration of the various statements that have been made respecting them, to which we have referred. Such a study of the subject seemed the more desirable in view of the fact that no definite compound of iodine with either tannic or gallic acid has as yet been described, although the well-known bromo- and dibromo-gallic acids,  $C_6HBr(OH)_3COOH$  and  $C_6Br_2(OH)_3COOH$ , are very easily prepared.

#### EXPERIMENTAL.

In the first place the amount of iodine reacting with, or taken up by, tannic and gallic acids in aqueous solution was determined, under different conditions of time and temperature.

For these experiments the following solutions were employed :—(a) A 1 per cent. solution of tannin; (b) a 0.5 per

cent. solution of gallic acid; (c) a standard solution of iodine in potassium iodide, which was approximately decinormal.

To a convenient quantity of the solution of tannic or gallic acid, contained in a glass-stoppered bottle, an excess of solution of iodine was added, and the mixture allowed to stand, either at the ordinary temperature or in a water-bath, for the time specified. The contents of the bottle were then transferred to a beaker, diluted with a little water, starch added, and subsequently a decinormal solution of sodium thiosulphate run in until the green coloration changed to light brown, the colour of the oxidation product. The following results were obtained, from which it will be seen that gallic acid is more readily acted upon than tannic acid:—

| No.   | Amount of Tannin. | Amount of Iodine Absorbed. | Time in Hours. | Condition of Experiment. |
|-------|-------------------|----------------------------|----------------|--------------------------|
| 1.... | 0.10 gramme.      | 0.036 gramme.              | 1.             | Cold.                    |
| 2.... | 0.10 "            | 0.037 "                    | 4.             | "                        |
| 3.... | 0.10 "            | 0.051 "                    | 24.            | "                        |
| 1.... | 0.10 gramme.      | 0.162 gramme.              | 1.             | Heated in water-bath.    |
| 2.... | 0.10 "            | 0.196 "                    | 4.             | " "                      |
| 3.... | 0.10 "            | 0.225 "                    | 8.             | " "                      |

| No.   | Amount of Gallic Acid. | Amount of Iodine Absorbed. | Time in Hours. | Condition of Experiment. |
|-------|------------------------|----------------------------|----------------|--------------------------|
| 1.... | 0.10 gramme.           | 0.088 gramme.              | 1.             | Cold.                    |
| 2.... | 0.10 "                 | 0.092 "                    | 4.             | "                        |
| 3.... | 0.10 "                 | 0.178 "                    | 24.            | "                        |
| 1.... | 0.10 gramme.           | 0.367 gramme.              | 1.             | Heated in water-bath.    |
| 2.... | 0.10 "                 | 0.414 "                    | 4.             | " "                      |
| 3.... | 0.10 "                 | 0.474 "                    | 8.             | " "                      |

The amount of iodine necessary to react with 0.10 gramme of tannic acid to form a mono-substitution product would be 0.078 gramme; to form a di-substitution product 0.157 gramme.

The amount of iodine necessary to react with 0.10 gramme of gallic acid to form a mono-substitution product would be 0.135 gramme; to form a di-substitution product 0.270 gramme.

It will be seen, however, that the amounts of iodine taken up are very variable, and are not in any definite molecular proportion to the tannic or gallic acid employed. Even where

an approximation to such a proportion may exist, it is evidently to be regarded as a mere coincidence.

#### ACTION OF IODINE UPON TANNIC ACID.

(1) 5.0 grammes of tannin, 1.275 grammes of iodine, and about 60 C.c. of water were heated together in a glass-stoppered bottle until the free iodine had disappeared. After standing for twenty-four hours the liquid deposited about 0.5 gramme of a dark brown powder, which gave the ellagic acid reaction (that is, a blood-red colour with fuming nitric acid and water). The formation of ellagic acid,  $C_{14}H_8O_9$ , by the action of iodine on tannic and gallic acids in the presence of water, as also the colour reaction referred to, was first observed by Griessmayer (Liebig's 'Annalen,' 160, p. 51). The filtered liquid was diluted with water to the measure of 250 C.c.

(a) 50 C.c. of this liquid were digested with 2 grammes of hide powder for several days, then filtered, the powder well washed, and the combined liquids titrated with N/10 NaOH, using methyl orange as an indicator. This required 7.7 C.c. N/10 NaOH. The powder was then mixed with 10 C.c. N/10 NaOH solution, filtered, and the excess of the latter titrated with N/10  $H_2SO_4$ , for which 2 C.c. were required. The total amount of acid present was, therefore, equivalent to 15.7 C.c. N/10 NaOH, corresponding to 0.997 gramme of iodine as hydriodic acid in 250 C.c. of liquid.

In order to confirm this result, both the liquids after titration were mixed, acidified with nitric acid, filtered, and precipitated with silver nitrate. 0.384 gramme of silver iodide was obtained, corresponding to 0.207 gramme of iodine or 1.035 gramme iodine in 250 C.c. of the original liquid. A large proportion of the iodine used had therefore been converted into hydriodic acid. The hide powder remaining from this experiment, after treating with fuming nitric acid, diluting and shaking with chloroform, was found to contain no iodine.

(b) Another portion of the original liquid was shaken out with ether, when a small amount of a varnish-like substance was obtained which resembled tannin in its properties and contained no iodine.

(2) In another experiment 8.0 grammes of tannin and 1.1188 grammes of iodine were digested with water in a glass-stoppered bottle until the free iodine had completely disappeared. The liquid, when cold, was filtered from the small amount of ellagic acid formed, and diluted with water to the measure of 250 C.c.

(a) 50 C.c. of this solution were diluted with water, and heated on a water-bath with a little dilute sulphuric acid and an excess of silver nitrate. 0.4112 gramme of silver iodide was obtained, corresponding to 0.2222 gramme of iodine, or to 1.1110 gramme of iodine in 250 C.c. of liquid. The filtrate from the above was heated with a little fuming nitric acid, when an additional 0.0028 gramme of silver iodide was obtained, corresponding to 0.0015 gramme of iodine, or to 0.0075 gramme in 250 C.c. The total amount of iodine found was thus:  $1.1110 + 0.0075 = 1.1185$  gramme, as compared with 1.1185 gramme, the amount originally taken.

(b) Another portion of 50 C.c. of the liquid was treated with hide powder, and the filtrate therefrom acidulated with nitric acid and precipitated by silver nitrate. 0.2586 gramme of silver iodide was obtained, corresponding to 0.1397 gramme of iodine. The hide powder was then treated with a dilute solution of sodium carbonate, filtered, and the filtrate acidulated with nitric acid, when a precipitate was produced which was filtered off, but neither this precipitate nor the remaining hide powder then gave any reaction for iodine. The filtrate, however, gave with silver nitrate an additional 0.1526 gramme of silver iodide, corresponding to 0.0825 gramme of iodine. The total amount of iodine found was thus:  $0.1397 + 0.0825 = 0.2222$  gramme, as compared with 0.2238 gramme originally contained in the 50 C.c. of solution employed.

(c) Another portion of 50 C.c. of the liquid was first concentrated to a small bulk on a water-bath, and then kept in a vacuum desiccator over lime and sulphuric acid for two or three days. The dry residue was in the form of light brown scales, which were slowly soluble in water, and which would correspond to the so-called iodo-tannin compound obtained by Barnouvin (*loc. cit.*). The solution of this substance gave a slight purple colour to chloroform, showing the presence of a little free iodine, but it also afforded an intense blue-black colour with ferric chloride. On the addition of sodium chloride a precipitate was obtained similar to that produced in a solution of tannin, but which contained no iodine. From the solution, acidulated with nitric acid, the whole of the halogen was precipitated by silver nitrate. A little of the substance was boiled with acetic anhydride. A part of this liquid was diluted with hot water and another part with alcohol, but in both cases the precipitated products contained no iodine. 1.0488 grammes of the above-described scales, in the form of powder, were heated

in a flask provided with a ground glass condenser with an excess of silver nitrate and a little fuming nitric acid. The contents of the flask, after dilution, gave 0.2098 gramme of silver iodide, corresponding to 0.1134 gramme of iodine, or 10.8 per cent.

(d) A portion of the original solution was extracted with ether, the latter washed twice, and the ether distilled off. The residue was a pale brown varnish, containing no halogen.

(e) A portion of the original solution was evaporated on a water-bath to complete dryness, and kept in a water-oven for a day. The product was a black powder, which gave a slight reaction for free iodine when shaken with chloroform.

#### ACTION OF IODINE UPON GALLIC ACID.

(1) 5 grammes of gallic acid, 1.2615 grammes of iodine, and about 50 C.c. of water were heated together in a glass-stoppered bottle on a water-bath for several hours until the free iodine had disappeared. The liquid, while hot, was filtered from a small amount of a black powder, which gave the reaction for ellagic acid. From the cold filtrate gallic acid separated out. This, when filtered off, washed and dried, weighed 3.6 grammes, and contained no iodine. The combined filtrate and washings from this gallic acid were diluted with water to the measure of 250 C.c.

(a) 25 C.c. of this solution were boiled with dilute sulphuric acid and excess of ferric chloride, and the liberated iodine absorbed by a solution of potassium iodide. The liquid required 8.9 C.c. N/10 sodium thiosulphate, corresponding to 1.13 grammes of iodine in 250 C.c.

(b) Two portions of 25 C.c. each were extracted three times with ether to remove any free gallic acid, boiled with animal charcoal, and titrated with N/10 sodium hydrate solution, using methyl orange as an indicator. One portion required 9.0 C.c. N/10 NaOH, and another portion 8.8 C.c. N/10 NaOH, the mean being 8.9 C.c., which corresponds to 1.13 gramme of iodine in 250 C.c. of liquid. These two concordant results not only represent approximately the amount of iodine originally taken, but indicate that all of the iodine contained in the solution is in the form of hydriodic acid.

(2) As a confirmative experiment 1.0 gramme of gallic acid and 1.964 gramme of iodine, with some water, were heated together in a glass-stoppered bottle in a water-bath for two hours, and the solution diluted with water to the measure of 250 C.c.

(a) 25 C.c. of the solution were largely diluted and titrated with N/10 sodium thiosulphate, using starch as an indicator. 3.1 C.c. N/10 thiosulphate were required to remove the dark coloration. After acidulating with sulphuric acid an excess of silver nitrate was added, when 0.3776 gramme of silver iodide was obtained, corresponding to 0.204 gramme of iodine, as compared with 0.196 gramme originally taken.

(b) Another 25 C.c. of the solution required 3.2 C.c. N/10 thiosulphate, and gave 0.3790 gramme of silver iodide, corresponding to 0.205 gramme of iodine.

(3) 4.0 grammes of gallic acid and 1 gramme of iodine, with some water, were heated together in a glass-stoppered bottle until all the free iodine had disappeared. The liquid was filtered, while hot, from a small amount of a black powder, which gave the ellagic acid reaction.

(a) A portion of the solution when evaporated on a water-bath gave off fumes of hydriodic acid as it became concentrated. When thoroughly dry it gave no reaction for halogen when heated with silver nitrate and fuming nitric acid.

(b) Another portion of the solution was first concentrated to a small bulk on a water-bath, and then kept in a vacuum desiccator over lime and sulphuric acid for two or three days. The product was found to be free from halogen.

(c) Another portion of the solution was extracted with ether, the latter washed twice with water, and the ether then distilled off. The residue was a light brown crystalline powder, containing no halogen, and consisted of unchanged gallic acid.

From these results there can be little doubt that the crystalline product obtained by Barnouvin (*loc. cit.*) under similar conditions, and which he assumed to be an iodo-gallic acid, although apparently without having further examined it, consisted simply of gallic acid with a little adhering hydriodic acid.

In this connection it may be noted that some preparations designed for medicinal use have recently been patented by German manufacturers under the designations of "Tanninhaltiger Jodleimverbindungen" (Iodo-gelatin compounds with tannin), "Bromtannineiweiss-Verbindungen" (Bromo-tannin albumen compounds), etc. Compare *Chemiker Zeitung*, 1901, No. 9, p. 91, and No. 41, p. 449. These are stated to be prepared by precipitating respectively a solution containing iodine and tannin with gelatin, or a solution of bromine and tannin with albumen. It is obvious, however, that these preparations are of a very different character from those which have formed the subject of our consideration.

The preceding experiments would thus appear to have established the fact that true or definite compounds of iodine with either tannic or gallic acid cannot be formed by the simple interaction of these bodies in the presence of water, for, as might be expected, under these circumstances the iodine acts simply as an oxidising agent. The resulting products, therefore, contain the iodine in the form of hydriodic acid, associated with more or less unaltered tannic or gallic acid, and the oxidation products of the latter.

In accordance with these facts, and with the opinion previously expressed by Professor Gay (*loc. cit.*), it follows that unless the physiological action of tannin is desired conjointly with that of the iodine there is no necessity for its use as a means of effecting the chemical change resulting in the so-called dissimulation of the iodine. In place, however, of the various other expedients that have been proposed for attaining this result, it would be more rational, from the standpoint of accuracy in medicine, to employ a preparation containing a definite amount of hydriodic acid, for which a syrup is probably best adapted, the strength and dosage of which can so easily be controlled.

As a further result of this investigation, and in the attempt to obtain a definite compound of iodine with tannic or gallic acid, we have been led to undertake a more extended chemical study of these acids and some derivatives of them, and this is still engaging our attention.

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