XI.—*The Identity of Caffèine and Theïne, and the Reactions of Caffèine with Auric Chloride.*

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CAFFEÏNE was isolated from coffee, and its chief properties were described in the year 1821 by Runge, by Pelletier and Caventou, and by Robiquet, working independently of each other. Six years later, in 1827, Oudry described a crystalline substance he had obtained from tea, which he called theïne. In reviewing Oudry's work, Berzelius drew attention to the similarity in properties of caffèine and theïne, and he suggested that the two substances were identical. In 1832, caffèine was analysed for the first time by Liebig and Pfaff, their results being published in the first volume of the *Annalen* (p. 17); these results were corroborated by independent analyses made by Wöhler. Six years later, at the suggestion of Liebig, Jobst (*Annalen*, 25, 63) analysed theïne, and showed that its composition was the same as that of caffèine.

The analyses of caffèine and theïne subsequently made by Mulder (*Annalen*, 36, 93) confirmed this identity of composition, and since no differences were detected in the properties and principal chemical reactions of the two compounds, their identity has never been questioned on chemical grounds.

The circumstance that the physiological effects of tea differ from

those of coffee led Dr. T. J. Mays, in 1866, to examine the physiological action of caffeine and theine. His experiments (*J. Physiol.*, **7**, 458; *Therapeutic Gaz.*, 1886, 587) were made, for the most part, with frogs, and disclosed several marked differences in the action of the two substances. The most important of these were, that theine paralyses sensation, whilst caffeine does not; unlike caffeine, theine causes convulsive spasms and tetanus; theine produces local anaesthesia, but caffeine does not; the toxic dose of theine is greater than that of caffeine.

There is no evidence that the caffeine and theine used in these experiments were chemically pure, and it is a significant fact that the theine is found to produce physiological effects of which caffeine is incapable. It is now well established that tea contains other bases besides theine, and it is not improbable that theine which has been isolated from tea by the ordinary processes would be contaminated with small quantities of foreign bases, and that the observed differences in the physiological action of theine and caffeine may be due to impurities in the theine.

Lauder Brunton and Cash (*Proc. Roy. Soc.*, **42**, 238; *J. Physiol.*, **9**, 112) have recently compared the physiological action of caffeine and theine, and, although they are unable to confirm all the conclusions arrived at by Mays, their results seem to indicate that the physiological effects of the two substances are not identical. They state that theine is a more active muscular poison than caffeine, whilst it leads to rhythmical contractions in muscle which are not observed when caffeine is administered. The substances used by these observers were believed to be pure, but no comparison of their chemical and physical properties appears to have been made; it is, therefore, possible that the theine may have been contaminated with traces of foreign bases.

In face of these assertions, it seemed desirable to review the evidence for the identity of caffeine and theine, and, if necessary, to institute fresh experiments, for the purpose of confirming or disproving it.

On referring to the original papers of Jobst and Mulder, it appears that identity of composition, as evidenced by the results of combustions, is all that is really proved. The substances have also been shown, qualitatively, to exhibit the same chemical reactions, but no experiments have been recorded which would disprove an isomerism of these compounds, similar to that which subsists between hyoscyamine and atropine.

Schmidt (*Annalen*, **217**, 270), however, has shown that artificial caffeine, prepared from theobromine, is identical in every respect with theine, and, it seems most probable that any chemical or physical

differences between caffeïne and theïne would have been disclosed before now, had they existed. It has been pointed out, however, that caffeïne prepared from coffee rarely, if ever, comes into the market, and that the caffeïne of commerce is obtained from tea; the opportunities for a comparison of the properties of the two substances have, therefore, not been as numerous as might seem to be the case.

Since the possibility of isomerism cannot be negated by an appeal to existing experimental data, Dr. Lauder Brunton suggested to one of us that, as the subject was of interest to the physiologist and the physician, it was desirable that the chemical question should be settled. We, therefore, undertook to search for evidence of isomerism between caffeïne and theïne. With this end in view, we have isolated caffeïne from coffee, and theïne from tea, and we have examined the physical and chemical properties of both these bases, as well as those of some of their well characterised compounds, notably the aurochlorides, which, in other cases, have proved of such service in revealing isomeric differences. In carrying out this work, we incidentally prepared some new compounds, which we believe are unique and of considerable chemical interest, and, indeed, the investigation has turned out to be profitable for other reasons than that for which it was originally undertaken.

Caffeïne and Theïne.

The caffeïne was extracted from 1 lb. of unroasted coffee berries. The berries, very finely powdered, were repeatedly boiled with water until nothing further was removed. The aqueous extract was evaporated to a small volume, and about 100 grams of lime was then intimately incorporated with it, and the mixture thoroughly dried over the water-bath. The finely-powdered mass was repeatedly boiled with alcohol until caffeïne was no longer removed, the alcohol distilled off, and the residue dissolved, as far as possible, in dilute sulphuric acid (1 per cent.); the solution, after filtration, was made alkaline with ammonia, and the caffeïne extracted by repeatedly shaking the solution with chloroform. The impure base remaining after the distillation of the chloroform was purified by recrystallisation from water, this operation being repeated until the melting point of the crystals did not change. By this means fine, silky needles were obtained which melted constantly at 234.5° (corr.). According to Strecker (*Annalen*, 118, 151), caffeïne melts at $234-235^{\circ}$; other observers have recorded $230-231^{\circ}$, which is certainly too low.

The theïne was extracted from 1 lb. of tea by boiling it for several

hours with water (2 litres). This process was then repeated with the residue until nothing further was removed. The aqueous extract was concentrated to a small volume, and 90 grams of lime were incorporated with it. The dried and finely-powdered mass was then mixed with alcohol, and the mixture boiled for several hours, the extraction with alcohol being continued until no more base was dissolved.

The alcohol was then distilled from the mixed solutions, and the residue acidified with dilute sulphuric acid. The filtered acid liquid was made alkaline with ammonia, and the theine extracted by shaking with chloroform.

The impure base obtained from the solution in chloroform was then repeatedly crystallised from water. Fine, silky needles were thus obtained corresponding in their appearance with caffeine. These melted constantly at 234.5° (corr.), that is, at exactly the same temperature as caffeine.

It is, therefore, almost certain that the two compounds are identical and not isomeric. To confirm this conclusion, the properties of the aurochlorides and of the mercuriochloride compounds formed by the two specimens were examined.

Caffeine and Theine Aurochlorides, $C_8H_{15}N_4O_2, HAuCl_4$.

The aurochloride of caffeine was first obtained by Nicholson in 1847, in the course of the experiments he made in the Royal College of Chemistry at the suggestion of Professor Hofmann, to confirm the formula Liebig proposed for caffeine, which had been called in question by Payen (*Reports Roy. Coll. Chemistry*, **1**, 106). The salt has since been described by several chemists (Schmidt, *Annalen*, **217**, 282; Biedermann, *Arch. Pharm.* [3], **21**, 175); but its melting point does not appear to have been determined. When warm solutions of caffeine hydrochloride and auric chloride are mixed together, the aurochloride separates, as the solution cools, in orange needles.

The theine was dissolved in water, the liquid strongly acidified with hydrochloric acid, and the warm solution mixed with aqueous auric chloride. The crystalline needles, which soon separated, were removed, and an attempt made to recrystallise them from hot water. This, however, did not succeed, for the hot solution deposited a copious, yellow precipitate, evidently not the aurochloride, which did not dissolve even on boiling the liquid.

The salt was therefore crystallised from aqueous alcohol, recrystallisation being repeated until a salt, having a constant melting point, was obtained. The pure salt air dried, melted at 242.5° (corr.). This hydrated salt lost the equivalent of $2H_2O$ when dried for several

hours at 100°, and the anhydrous compound melted at 248·5° (corr.). On analysis, this substance furnished the following data:—

0·1642 gram of salt gave 13·9 c.c. of nitrogen at 0° and 760 mm.
= 10·5 per cent.

0·1458 gram of salt on ignition left 0·0544 gram of gold = 37·3 per cent.

	Found.	Calculated for $C_8H_{10}N_4O_2, HCl, AuCl_3$.
Nitrogen.....	10·5 p. c.	10·49 p. c.
Gold	37·3 „	36·77 „

Similar experiments were now made with caffeïne. The aurochloride was formed as above described, and presented an exactly similar crystalline appearance. Like theïne aurochloride, the aqueous solution gradually deposited a yellow precipitate when it was heated. The salt was purified by recrystallisation from aqueous alcohol until its melting point was constant. The pure air-dried substance melted at 243° (corr.), that is, at virtually the same temperature as the hydrated theïne aurochloride. The amount of water in the salt was determined with the following result:—

0·1658 gram of salt lost 0·0106 gram of water = 6·3 per cent.

Calculated for $C_8H_{10}N_4O_2, HCl, AuCl_3, 2H_2O$ = 6·3 per cent.

Several hours' exposure at 100° was necessary to expel all the water. The anhydrous salt melted at 248·5° (corr.). Like theïne aurochloride, the salt did not melt quite sharply, and the melting was evidently attended with some decomposition. No better evidence could be obtained as to the identity of caffeïne and theïne than that furnished by the exactly similar properties of the hydrated and anhydrous aurochlorides prepared from the two bases, for chemically isomeric bases have been shown to furnish aurochlorides of different melting point.

Caffeïne and Theïne Mercuric Chlorides, $C_8H_{10}N_4O_2, HgCl_2$.

Nicholson (*loc. cit.*) observed that caffeïne combines with mercuric chloride to form a crystalline double salt of the formula

This compound is best named *caffeïne mercuric chloride*. As it crystallises well and is very stable, we selected it for the purpose of confirming the conclusion that caffeïne and theïne are not isomerides. We have prepared this substance both from theïne and from caffeïne.

A warm concentrated aqueous solution of theïne was mixed with an equivalent quantity of mercuric chloride also dissolved in water.

As the mixed solutions cooled, silky needles separated in abundance. It was found that these readily dissolved in hot water, and that the aqueous solution could be boiled without any appreciable decomposition of the compound taking place. This is remarkable, since compounds of bases with mercuric chloride usually dissociate when they are heated with water. After two recrystallisations from water, the substance was dried at 100° .

The mass of long, silky needles bears an extraordinary resemblance to the parent base. The pure salt melted at 246° (corr.). Precisely the same compound was prepared from caffeine. The pure, dry crystals melted at 246° (corr.), and corresponded in every respect with the theine compound.

The compound was analysed by dissolving it in water and adding aqueous hydrogen sulphide, drop by drop, until the whole of the mercury had been precipitated as sulphide, only just a perceptible excess of hydrogen sulphide being used. The mercuric sulphide was collected, dried, and weighed. The filtrate was then warmed to expel any hydrogen sulphide, and repeatedly extracted with chloroform to remove the caffeine. The solution of chloroform was evaporated, and the residue of caffeine dried at 100° and weighed. The following data were obtained:—

0.4864 gram of compound furnished 0.1998 gram of caffeine and 0.2410 gram of mercuric sulphide.

	Found.	Calculated for $C_8H_{10}N_4O_2, HgCl_2$.
Mercury	42.67 p. c.	43.0 p. c.
Caffeine	41.07 „	41.72 „

It has thus been shown that caffeine and theine, as well as their aurochlorides and mercuric chloride compounds, exhibit identical properties, and there is, therefore, no chemical ground for supposing them to be structurally isomeric.

The observed differences in their physiological action must be due either to the presence of small quantities of impurity or to differences in the animals used in the experiments. We have already referred to the likelihood of the first error having been introduced, and, with reference to the second, we need only draw attention to extraordinary discrepancies in the accounts given by various pharmacologists of the physiological action of caffeine, which such distinguished authorities as Schmiedeberg and Filehne have already ascribed to the above-mentioned cause.

We now proceed to describe some new gold compounds of caffeine which we obtained in the course of this investigation.

Aurochlorcaffëine, $C_8H_8(AuCl_2)N_4O_2$.

When an aqueous solution of caffëine aurochloride is heated, a yellow, amorphous precipitate is gradually formed. This substance may also be prepared by heating together aqueous solutions of auric chloride and caffëine.

The decomposition of the aurochloride by hot water was noticed by Nicholson (*loc. cit.*), but he does not appear to have examined the product.

The substance has none of the properties of an aurochloride, being nearly, if not quite, insoluble in water, alcohol, ether, and chloroform. Hydrochloric acid dissolves it, reproducing the aurochloride. It is not very easily obtained in a pure state. The first specimens we examined were made by quickly heating the aqueous solution of the aurochloride at 100° . Prolonged heating leads to the separation of metallic gold. As soon as the precipitate has ceased to form, the liquid is filtered and the filtrate heated with more water, when a further quantity of precipitate is obtained. This operation may be repeated several times, and a series of fractions of precipitate obtained. The first and last fractions melted at about 220° , and contained aurochloride, whilst the intermediate fractions melted near 207° (corr.), and, on heating these with water again, the pure substance melting at 207° (corr.) was obtained; its melting point was not changed by repeating the process of heating with water. The substance dried at 100° is of a paler yellow than when moist. It was analysed in the following manner, which made it possible to determine the gold, caffëine, and chlorine in one and the same quantity of material. To the substance suspended in water, aqueous hydrogen sulphide was added in slight excess, and the gold sulphide collected on a filter, washed, ignited, and the residue of gold weighed. A current of air was passed through the mixed washings and filtrate until the slight excess of hydrogen sulphide was removed. The chloride was then precipitated as silver chloride in the usual manner, whilst the caffëine was extracted from the filtrate, after the addition of excess of ammonia, by agitation with chloroform; the solution in chloroform was evaporated and the residue of caffëine dried at 100° .

The following results were obtained with two different specimens of material:—

- I. Weight of substance taken, 0.2714 gram; weight of gold obtained, 0.1162 gram; weight of silver chloride, 0.1656 gram.
- II. Weight of substance, 0.2910 gram; weight of gold obtained, 0.1224 gram; weight of silver chloride, 0.1744 gram; weight of caffëine, 0.1204 gram.

	Found.		Calculated for	
	I.	II.	$C_8H_9(AuCl_2)N_4O_2$	$C_8H_{10}N_4O_2, AuCl_3$
Gold.....	42·8	42·06 p. c.	42·60	39·47 p. c.
Chlorine ..	15·07	14·8 „	15·43	21·45 „
Caffeine...	—	41·3 „	42·0	39·07 „

For some time we were at a loss to know what the formula of this compound could be, the only form of combination of organic bases with auric chloride known to us, besides the ordinary aurochloride, being the comparatively rare form in which the base unites directly with auric chloride without the intervention of hydrogen chloride; one of us has already described such a compound of aconitine with auric chloride (Dunstan and Ince, Trans., 1891). The percentages calculated for caffeine auric chloride, which are given above, show, however, that the substance is not this compound. Nevertheless, we were aware that the substance is formed from the aurochloride by the splitting off of hydrogen chloride, and that it could be reconverted into the aurochloride by dissolution in hydrochloric acid. Eventually we were able to prove beyond question that the substance is derived from the aurochloride by the splitting off of two mol. proportions of hydrogen chloride, one being derived from the separation of 1 atom of hydrogen from the caffeine molecule with 1 atom of chlorine from the auric chloride, thus: $C_8H_{10}N_4O_2, HCl, AuCl_3 = C_8H_9(AuCl_2)N_4O_2 + 2HCl$. The analytical data are in agreement with this formula, and the compound is, therefore, derived from caffeine by the replacement of one atom of hydrogen by the group or residue of gold chloride, $AuCl_2$, and may be named *aurochlorcaffeine*. We are unable to find that such a reaction between auric chloride and an organic base has been described before; no similar derivative of any of the vegetable alkaloids seems to have been obtained.

An attempt was made to confirm this view of the formation of the compound expressed by the above equation by estimating the quantity of hydrogen chloride which is formed when a known weight of the aurochloride is heated with water. This, however, proved to be impossible, owing to the occurrence of reverse chemical change; the liberated hydrogen chloride dissolves some of the derivative, reforming the aurochloride—

The aurochloride, prepared from the aurochlorcaffeine by dissolving it in hydrochloric acid, was analysed, after recrystallisation from dilute alcohol, with the following results:—

Weight of dried salt taken, 0·0864 gram; weight of gold obtained,

0.0321 gram; weight of silver chloride obtained, 0.0895 gram; weight of caffeine obtained, 0.0304 gram.

	Found.	Calculated for $C_8H_{10}N_4O_2, HAuCl_4$.
Gold	37.1 p. c.	36.77 p. c.
Chlorine	25.58 „	26.64 „
Caffeine	35.1 „	36.39 „

The ease with which aurochlorcaffeine is produced from the aurochloride may possibly throw some light on the constitution of caffeine. Caffeine, being trimethylxanthone, contains only one "labile" atom of hydrogen, that contained in the CH group. It must, therefore, be this atom of hydrogen which is eliminated as hydrogen chloride, so that the formula of aurochlorcaffeine may be written $C_8(CH_3)_3(AuCl_2)N_4O_2$. Two constitutional formulæ have been assigned to caffeine, one by Medicus and the other by E. Fischer. So far, it has not been possible to determine with any certainty which of these formulæ is the more probable, since both are in harmony with the principal reactions of caffeine.

It may be safely assumed that in the aurochloride both the hydrogen chloride and the auric chloride are attached to the doubly linked nitrogen atom of either of these formulæ. Now in Fischer's formula the atom of hydrogen in the CH group is represented as separated from the auric chloride with which it so readily reacts, whilst in the formula of Medicus the two reacting groups are contiguous to each other. The ease with which aurochlorcaffeine is formed from the aurochloride would therefore seem to be better represented by the formula suggested by Medicus than by that proposed by Fischer.

Caffeine Auric Chloride, $C_8H_{10}N_4O_2, AuCl_3$.

Several unsuccessful attempts were made to prepare a compound of caffeine with auric chloride. This compound would be intermediate between caffeine aurochloride and aurochlorcaffeine,

Alcoholic solutions of caffeine and auric chloride were mixed, and the liquid slowly evaporated. The several fractions separated in this way were found by repeated recrystallisation to be mixtures of caffeine aurochloride and aurochlorcaffeine. Other experiments were made in which auric chloride, purchased as pure, was dissolved in absolute alcohol and the liquid mixed with a solution of caffeine in chloroform. The crystals deposited from the mixed solutions melted at 242° , and exactly resembled caffeine aurochloride in appearance. On analysis, they furnished the following results:—

Weight of substance taken, 0.4335 gram; weight of gold obtained, 0.1595 gram; weight of silver chloride, 0.4535 gram; weight of caffeine, 0.1560 gram.

	Found.	Calculated for $C_8H_{10}N_4O_2.HCl.AuCl_3$.
Gold	36.79 p. c.	36.77 p. c.
Caffeine	35.9 „	36.29 „
Chlorine	25.8 „	26.64 „

An examination of the “pure” auric chloride showed that it was really the hydrochloride of auric chloride, the so-called chlorauric acid ($HAuCl_4.3H_2O$). All the commercial specimens of “auric chloride” examined by us were found to be either this substance or its potassium salt.

For the purpose of further experiments, pure auric chloride was prepared by Kruss' method of decomposing aurous chloride with water. When an alcoholic solution of pure auric chloride is mixed with a solution of caffeine in chloroform, yellow crystals are deposited. When these are collected and washed with anhydrous alcohol, they become almost white; they are in fact resolved by washing into auric chloride and caffeine. If the crystals are merely drained from the liquid in which they were deposited and placed on filter paper, auric chloride is absorbed by the paper, whilst white crystals of caffeine remain. It may, therefore, be concluded that caffeine auric chloride, even if it exists at all, is so unstable as to be incapable of preparation by the usual methods.

Caffeine Potassium Aurochloride, $C_8H_{10}N_4O_2.KCl.AuCl_3$.

In one series of the experiments in which we attempted to produce caffeine auric chloride, a strong alcoholic solution of a substance purchased as “pure” auric chloride was mixed with a solution of caffeine in chloroform. Almost immediately the yellow liquid deposited a number of small, dark-red, needle-shaped crystals. After recrystallisation from a mixture of alcohol and chloroform, these melted

constantly at 208° (corr.). A number of different specimens, on analysis, furnished the following data:—

- I. Weight of salt taken, 0.2412 gram; weight of gold obtained, 0.0828 gram; weight of silver chloride obtained, 0.2348 gram.
- II. Weight of salt taken, 0.2882 gram; weight of gold obtained, 0.1 gram; weight of silver chloride obtained, 0.2885 gram.
- III. Weight of salt taken, 0.087 gram; weight of gold obtained, 0.0299 gram; weight of silver chloride obtained, 0.0721 gram.
- IV. Weight of salt taken, 0.3574 gram; weight of caffeine obtained, 0.1178 gram; weight of salt taken, 0.4402 gram; weight of potassium chloride obtained, 0.0585 gram.

	Found.					Calculated for $C_8H_{10}N_4O_2, KCl, AuCl_3$.
	I.	II.	III.	IV.		
Gold	34.3	34.7	34.3	—	p. c.	34.32 p. c.
Chlorine . .	24.04	24.7	24.6	—	„	24.86 „
Caffeine . .	—	—	—	32.96	„	33.97 „
Potassium .	—	—	—	6.95	„	6.83 „

It was not at first suspected that the “auric chloride” contained potassium, and a number of different specimens of this red salt were prepared and analysed with the view of obtaining numbers corresponding with some compound or derivative of caffeine and auric chloride. Since no such formula could be found to agree with the analytical numbers, and as three concordant analyses of various specimens proved that we were dealing with a definite compound in a pure state, the “auric chloride” which had been used was examined, and found to be potassium chloraurate, $AuCl_3, KCl$. The red crystals were then tested and also found to contain potassium, the amount of which was estimated in the usual way. It will be seen that the results agree well with the formula of *caffeine potassium aurochloride*, $C_8H_{10}N_4O_2, KCl, AuCl_3$; this compound may be regarded as *caffeine aurochloride*, $C_8H_{10}N_4O_2, HCl, AuCl_3$, in which the hydrogen of the hydrogen chloride is replaced by potassium. Consistently with this view of its constitution, we find the salt can be formed by mixing an alcoholic solution of caffeine aurochloride with exactly the proper quantity of potash dissolved in alcohol; on evaporation, the red crystals separate. It may also be produced by acting on caffeine aurochloride with an alcoholic solution of normal potassium tartrate, and by mixing caffeine aurochloride with the proper quantity of potassium carbonate; the red salt is formed when the mixture is

rubbed in a mortar or moistened with alcohol or water, or, again, if it is gently heated.

This remarkable compound, which is quite stable when dry, dissolves in alcohol and water, forming yellow solutions which appear to contain, not the salt as such, but its constituents, the double chloride of gold and potassium and caffeïne in the free state. The aqueous solution deposits a yellow precipitate of aurochlorocaffeïne when it is heated. The salt is nearly insoluble in chloroform and ether, which, however, slowly remove auric chloride from it. When either of these liquids is added to the yellow solution in alcohol, the red salt is precipitated. It is doubtful whether this salt can exist at all in solution. In this respect the action of acetone is noteworthy. Immediately this liquid touches the substance, it loses its red colour and becomes nearly white, whilst the acetone acquires a yellow colour from the presence of auric chloride which it has removed from the compound, leaving the caffeïne as a white residue. Gradually the caffeïne dissolves in the acetone, which, however, still remains yellow. When the yellow solution is evaporated, its colour does not alter, but as soon as the solvent has almost entirely volatilised, the red salt again makes its appearance.

We are not aware that any compound of this type has been prepared before; similar compounds of the vegetable alkaloids with the double potassium and auric chloride do not appear to have been described.

We find that a *caffeïne sodium aurochloride*, $C_8H_{10}N_4O_2 \cdot NaCl, AuCl_3$, may be prepared by methods similar to those which yield the potassium compound. This salt also forms red needles, and closely resembles its potassium analogue.

We are indebted to Mr. Francis H. Carr for the assistance he has rendered us in making some of the later experiments described in this paper.

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