

# **CHEMISTRY OF RESINOUS GUMS, DYES, ALKALOIDS, AND ACTIVE PRINCIPLES — CONTRIBUTIONS OF PELLETIER AND OTHERS IN THE NINETEENTH CENTURY**

**JAIME WISNIAK\***

(Received 09 May 2012; revised 10 January 2013)

The 19<sup>th</sup> century showed a concerted effort to try to analyze many of the active principles contained in vegetable and animal sources being brought to Europe from the Far East and the New World. These efforts set the basis of many substances of great importance used today in medical and industrial applications. Pioneering work was done in the identification and analysis of alkaloids, such as quinine, narceine, paramorphine, strychnine, emetine, brucine, and veratrine, animal materials such as cochineal and ambergris, as well as in their chemistry.

Many of the salifiable bases were found to contain nitrogen, chlorophyll was studied in detail, and the poisonous principles of many plants were isolated. Pierre Joseph Pelletier (1788-1842) was probably the chemist most associated with these discoveries.

**Key words:** Alkaloids, Ambergris, Brucine, Caffeine, Cochineal, Chlorophyll, Curare, Gums, Opium, Pelletier, Quinine, Resins, Strychnine, Toluene, Vegetable dyes, Veratrine

## **INTRODUCTION**

The discovery of the New World brought with it an intense chemical activity to identify, prepare, purify, and find the possible medical and industrial uses for the new raw materials, which were being brought to Europe from the colonies. During the end of the 18<sup>th</sup> century and particularly during the 19<sup>th</sup> one, the activity mainly centred on the vegetable and animal principles, alkaloids, gums, resins, and dyes, extracted from these imports. Pierre Joseph

---

\* Department of Chemical Engineering, Ben-Gurion University of the Negev, Beer-Sheva, Israel 84105. Email: wisniak@exchange.bgu.ac.il

Pelletier (1788-1842)<sup>1</sup> is probably one of the central chemists that contributed to the knowledge of these substances (Bussy 1842; 1843; Javillier 1951).

### 1. GUMS AND RESINS

Knowledge about these substances was scarce; Thomas Thomson (1773-1852)<sup>2</sup> considered them as composed of an extractive substance, a gum and a resin, probably located between resins and essential oils. He was unable to conciliate between their properties and the prevalent opinion about their composition and the name they had been assigned.

Pelletier's first publication dealt with the resin gum of opoponax, bdellium, and myrrh (Pelletier 1812c). Opoponax is a resin gum produced by the plant *Pastinaca opoponax*; it comes in round drops or irregular lumps, of a reddish yellow colour on the outside, with specks of white. According to Pelletier, it contains 33.40wt % gum, 42% resin, 4.10% starch, 1.00% extractive matter, 9.80% woody matter, 2.80% malic acid, and 30% wax. By distillation it yields brown oil, acetic acid, and bituminous oil. It has a peculiar nauseous bitter acrid taste and a strong odour, which it communicated by distillation both to alcohol and water.

Bdellium is an aromatic gum like myrrh, exuded from a non-identified tree growing in Africa and Asia. By analysis it was shown to contain 59.0% resin, 9.2% gum, 30.6% of a substance similar to the gum from Bassoara, and 2% of volatile oil. Again, myrrh was a reddish-brown resin produced from an unknown tree in Arabia (today we know it is the dry sap of a number of trees, particularly *Commiphora myrrha* and *Commiphora gileadensis*). Henri Braconnot (1780-1855) (Wisniak 2007) had found that it was mostly constituted by a resin a reddish gum, which on drying became insoluble; these results, opposing those found for other resin gums, stimulated Pelletier to make a more careful analysis. He found that the resin gum was composed of 34% resin and 66% of true gum. Nitric acid strongly attacked the gum, generating a large amount of oxalic acid. An aqueous solution was precipitated by alcohol and lead acetate. On heating it produced water, oil, and ammonium acetate. The latter result indicated that the gum contained nitrogen (Pelletier 1812c).

Galbanum is an aromatic resin produced from a plant belonging to the *Umbelliferae*, growing in Asia Minor. The resin exudes naturally but by

incisions made at the neck of the root it is produced in much large amounts (today we know it comes from certain Persian plant species, chiefly *Ferula gummosa*, syn. *galbaniflua* and *Ferula rubricaulis*). The resin has a yellowish milky colour, having bitter taste and strong and disagreeable smell. It contains a gum soluble in alcohol; addition of water to the alcoholic solutions precipitates a white powder completely soluble in nitric acid. The solution is also precipitated by lead acetate. Its analysis indicated that it contained 66.86% resin, 19.28% gum, 7.52% wooden material, 6.34% volatile oil, and traces of calcium malate (Pelletier 1812d).

Caranna resin gum originates from a tree growing in America. It appears as a greenish mass, which softens on chewing. It emulsifies with water and has all the properties of a resin. Pelletier analysis indicated that its composition was 96% resin, 0.4% calcium malate, and 0.9% foreign matter. Nitric acid converted it into a fatty material, little soluble in water; it easily dissolved in KOH, and could be precipitated in pure form by addition of a vegetable acid (Pelletier 1812e).

A following memoir, described the composition of four other resin gums, labdanum, olibanum (frankincense), euphorbium, and ivy, and gave a partial summary of the results accumulated so far on the composition of resin gums (Pelletier 1812f). All resin gums, excepting euphorbium and caranna, were composed of gum, resin, volatile oil, and a small amount of malic acid, free or as calcium malate. Most of them contained wax, and sometimes lignin and starch. Their properties originated from a simple mixture of the components; they were combined among themselves, a result indicating that the resin gums should be removed from the list of immediate principles of vegetables and placed as an appendix following gums, resins, or bassorin, depending on their main component.

Thomas Thomson had studied sarcocolla, classified it among the resin gums and reported that it was composed of four substances: a very abundant particular substance, to which sarcocolla owed its properties, a red alkaline earth substance, wood material, and a soft gelatinous substance. The second and third components, obviously foreign to sarcocolla, could be easily separated by mechanical means, the last one by dissolving the sarcocolla in water or alcohol. Evaporation of the latter solution yielded a sour sweet substance, soluble in water and alcohol. Upon heating it softened without

melting, releasing a piquant fume and leaving little residue after its combustion. Sarcocolla dissolved in nitric acid and the solution did not precipitate with gelatine, but it did with tin nitrate and lead acetate. Based on these properties Thomson recommended that sarcocolla (he named it sarcocollin) be classified as a principle between sugar and gum. Pelletier proceeded to analyse sarcocolla using the same procedures he had used with other resin gums and concluded that it contained 65.3% pure sarcocolla, 4.6% gum, 3.3% gelatinous matter, and 26.8% wood material (Pelletier 1813a). He separated pure sarcocolla and studied its properties. It dissolved in cold and hot water and in alcohol; by distillation it yielded water, brown oil, and acetic acid, without traces of ammonia. Concentrated sulphuric acid carbonized it and concentrated nitric acid dissolved it yielding a yellow bitter substance, little soluble in water and totally soluble in alcohol and ether. These, and other properties, confirmed Thomson's conclusion that sarcocolla should be included among the immediate principles of vegetables, in a position intermediate between gum and sugar (Pelletier 1813a).

The gum obtained from olive trees was also studied (Pelletier 1816). The olive tree growing in the hot regions of Italy and Minor Asia exudates a transparent substance shaped as tears, which the Greeks had used for the treatment of wounds. Pelletier found that the gum was composed of two substances, one very analogous to resinous substances and the other having a particular nature, and which he named *olivile* (olivil). The gum was also found to contain a very small amount of benzoic acid. Solution of the gum in alcohol, followed by filtering and natural evaporation, separated the two main components; the liquid phase retained the resin while impure olivil separated as white yellow needle-shaped crystals. The crystals were washed with ether and yielded a white brilliant powder formed by small needles. Heated, it decomposed into water, acetic acid, oil, and traces of ammonia. Olivil was more soluble in hot water than in cold one. It was not dissolved in ether but easily by acetic acid. It was promptly attacked by cold nitric acid producing a red solution that separated abundant oxalic acid (Pelletier 1816).

Pelletier summarized most of his results about resinous gums in the first doctoral thesis he presented to the Faculty of Sciences of the University of Paris (Pelletier 1812a). He indicated that the substances found in these

types of materials were gum, resin, volatile oil, wax, bassorin, malic acid, calcium and potassium malates, and a yellow brown bitter matter, which mixed or combined with malic acid and its salts, had been assumed to be the extractive matter. His thesis included information about all the resinous gums, which had been analysed by him and other researchers. The yellow bitter material that accompanied malic acid should not be considered a vegeto-animal substance because it was not precipitated by chlorine and gallnut but dissolved in water and in alcohol and was insoluble in ether and oils. It was mostly precipitated by lead acetate. Hence it was better to classify it as an analogue of soap principle (Pelletier 1812a).

It was found that pyrolysis of pine resin in the apparatus proposed by Mathieu to manufacture lightning gas resulted in the production of a series of highly hydrogenated substances (Pelletier and Walter 1837). The resin was first liquefied and then introduced in an incandescent tube where it decomposed, generating the gas, an oily product, and a carbon residue. Separation of the oil led to the identification of many different hydrocarbons, among them three new liquid ones, which they named *rétinaphthe*, *rétinyle*, and *rétinole*, as well as two solid ones, naphthalene (already known), and *methanaphthalene*, a new one. *Rétinaphthe* was a very volatile light liquid, having as formula  $C_{28}H_{16}$ , from which they prepared a large number of derivatives. *Rétinyle* corresponded to the formula  $C_{36}H_{24}$ , and could be transformed by the action of chlorine, bromine, and nitric acid into a series of new compounds representing a series of new combinations. *Rétinole* was an aromatic hydrocarbon having the formula  $C_{64}H_{32}$ , different from the one found by Michael Faraday (1791-1867) (Williams 1905),  $C_{24}H_{12}$ , by its formula, constitution, and properties. Likewise, methanaphthalene was a new compound, different from naphthalene in its properties, but isomeric with it (Pelletier and Walter 1837).

The Académie des Sciences appointed Louis-Jacques Thenard (1777-1857) (Wisniak 2002), Edmond Robiquet (1822-1860)<sup>3</sup>, and Jean-Baptiste André Dumas (1800-1884) (Dumas 1924) to report on and evaluate the above results (Thenard et al 1838). Dumas took the opportunity to analyse a sample of the naphthalene produced in a highly pure and crystalline form. An elementary analysis indicated that it contained 94.76% carbon and 6.16% hydrogen, that is, it had a higher larger percentage of carbon than the one

corresponding to the accepted formula  $C_{40}H_{16}$ . The discrepancy led Dumas to repeat the elemental analysis of naphthalene distilled from coal tar and to conclude that it was necessary to decrease the accepted atomic weight of carbon from 76.43 to 76.0 or 75.9 and that the methanaphthalene of Pelletier and Philippe Walter (1810-1847)<sup>4</sup> was not an isomer of naphthalene and that its correct formula was  $C_{64}H_{25}$ . For this reason Dumas recommended changing the name of the new substance to *réstisterène* (Thenard et al 1838).

Henry Sainte-Claire Deville (1818-1881) (Wisniak 2004) carried on extensive work on essential oils and resins, and their properties and chemical reactions. From the balsam of Tolu he obtained a hydrocarbon, which, because of its resemblance to benzene, he named *benzoene* (Deville 1841). He added that this compound had the same composition and properties as the hydrocarbon that Pelletier and Walter had isolated by distilling pine resin (*réinnaphthe*), and that it should be considered an isomer of the same. In 1850 Auguste Cahours (1813-1891)<sup>5</sup> distilled the liquid that separated when adding water to wood spirit and found that the product passing between 164-168° C had the same properties than the benzoene of Deville. He named this product *toluene* (Cahours 1850).

## 2. VEGETABLE COLOURS

In a paper about vegetable dyes of resinous nature (Pelletier 1814) these terms were defined as colouring substances insoluble in water so that their use in dyeing required the use of a non-aqueous solvent, or the addition to water of a foreign substance capable of reacting with the dye and solubilizing it. Although these characteristics were typical of true resins, they also described substances completely different from resins, for example, sandalwood dye. In this paper Pelletier reported his work on a type of sandalwood (*Pterocarpus santalinus*), a bush that grows in south India, on alkanet (*Alkanna tinctoria*), and their colouring matter. This material had been used as an astringent and as a colouring matter for pharmaceutical alcoholic liquors, or vinegar compositions, besides dyeing purposes. Very little was known about its chemical properties. Claude-Louis Berthollet (1748-1822) (Wisniak 2008), in his treatise about dyeing (Berthollet 1791), had described it as follows: "Sandalwood is a solid compact heavy wood that becomes brown in contact with air. It is used as a very fine powder, yielding

a brownish towards red solid hue. It is said that it hardens wool and becomes less soluble when mixed with other dyes." The known information suggested that to obtain the dye it was necessary to extract it with alcohol. Since it was probable that the wood contained other substances, which were also soluble in water and in alcohol, it was decided to study first the products of its maceration and brewing in water. It was found that cold water had not action on the wood. Hot water dissolved a small amount of a reddish substance, which was found to be composed of gallic acid and a brown colouring matter. The latter reacted with lead oxides, was soluble in water and in alcohol, insoluble in diluted sulphuric acid, it carbonized in concentrated acid, and easily reacted with vegetable acids. Oxygenated muriatic acid (chlorine) destroyed the red colour of the substance and nitric acid had no effect. Fixed alkali (NaOH and KOH) dissolved it very easily. Treatment with boiling distilled alcohol extracted about 17% of colouring matter. The pertinent solid dissolved completely in alcohol, ether, and diluted acetic acid. Although it was slightly soluble in heavy oils, the solute was powerful enough to impart a strong colour to the solution. Volatile oils such as turpentine, lavender, and rosemary produced solutions intensively coloured. On heating the solid became soft at about 100° C and then started to decompose yielding oils but no traces of ammonia (Pelletier 1814). From these results it was concluded that the colouring matter of sandalwood was formed by two main substances, one totally resinous and the other of special nature, containing the colouring principle. The latter had potential use as base for other dyes and for fabricating lacquers.

The second part of the paper was devoted to the study of orcanet, a dye known to be present in the roots of the plant, soluble in fats, alcohol, and ether, to which it communicated a red colour. Once again the colouring matter was extracted with boiling distilled alcohol, followed by evaporation. The resulting solid was of a dark red, almost black hue, which dissolved in ether and left a yellow brown bitter residue. Similarly to sandalwood, the colouring matter softened on heating and then decomposed into an aromatic oil, water, hydrocarbon, and gave no traces of ammonia. It was not attacked by dilute sulphuric acid but with concentrated acid it reacted vigorously with release of SO<sub>2</sub>. Nitric acid led to the formation of a large amount of oxalic acid and a small amount of a bitter substance. Oxygenated muriatic acid (chlorine) destroyed the red colour of the substance. Alkali combined actively

with the colouring matter changing its colour from red to a beautiful blue. An alcoholic solution was precipitated by all metallic solutions but not by aqueous solutions of the salts. It was believed that orcanet would find application in the arts as a blue oil colour (Pelletier 1814).

Another publication described the chemical analysis of the roots of curcuma (turmeric, terra-merita, safran des Indes); a plant growing in central Asia (Vogel and Pelletier 1815). Cold maceration of the powdered root with water produced a yellow brown slightly bitter solution that was not attacked by nitric and sulphuric acids. Alkali changed the colour to red while saturated potassium carbonate had no effect; these results proved that the extract did not contain albumin. Hot maceration extracted a larger amount of solutes, the solution became viscous because of the dissolved gum and starch; addition of iodine changed the colour to a beautiful blue. Distillation of a water suspension of powdered root produced a volatile yellow oil, having a penetrating odour; the water distilled had also a strong odour and was precipitated by lead acetate. The colouring matter of the root was separated by repeated alcoholic maceration. Evaporation of the solution yielded a mixture of two different substances, separable using ether. Ether removed the yellow colouring matter and left a brown substance soluble in water and alcohol and insoluble in oils. Addition of lead acetate precipitated a white salt. The compound soluble in ether was the true colouring principle of curcuma. On heating, it released first a large amount of a brown volatile oil, followed by acetic acid and a hydrocarbon, and leaving a carbon residue. No traces of ammonia were observed showing that nitrogen was not a component of the colouring matter. Alkali combined easily with the colouring matter and made it highly soluble in water. Diluted mineral acids did not attack the matter; addition of concentrated sulphuric acid or nitric acid caused the appearance of a brilliant crimson red colour; addition of water caused disappearance of the colour and precipitation of the colouring matter as yellow flakes. Acetic acid dissolved the colouring matter without changing its colour. An alcoholic solution of the dye was precipitated by an aqueous solution of lead acetate, silver nitrate, mercury nitrate or chloride, yielding a solid of different colour according to the salt employed (Vogel and Pelletier 1815).

It was concluded that the root of curcuma contained woody matter, starch, a yellow colouring matter, a brown colouring matter, gum, volatile

oil, and calcium nitrate. The yellow colouring matter was very similar to resins but should be looked upon as a particular substance to be classified among the highly hydrogenated ones, the same like the colouring matter of orcanet and other dyes of resinous nature (Vogel and Pelletier 1815).

According to Pelletier and Joseph Bienaimé Caventou (1795-1877)<sup>6</sup>, the substance that gave its green colour to the leaves of plants and trees had been hardly studied; no specific memoir about it had been published; in the analysis of vegetables it was designated as resin or green starch and it was not classified within the immediate materials of vegetables (Pelletier and Caventou 1817). In order to answer some of the questions they collected a certain amount of pure material by treating at room temperature a must of leaves of many herbaceous plants with distilled alcohol. The extract had a beautiful green colour and was evaporated in a controlled fashion, yielding a green resinous substance. The latter was pulverized and then treated with hot water, yielding a solution of highly pure material and a brown residue. The green material thus prepared offered all the known properties; it dissolved completely in alcohol, ether, and oils, and was bleached by chlorine. On heating it softened without melting; at a higher temperature it decomposed into water, oil, acetic acid, and methane. No traces of ammonia were found. Particularly interesting was the action of acids on it. Cold concentrated sulphuric acid dissolved it without alteration, even when in alcoholic solution. Addition of water to the solution caused turbidity. The behaviour with sulphuric acid was similar to that of indigo. Hydrogen chloride altered the green substance; the colour changed to yellow and remained as such. Nitric acid reacted vigorously, destroying immediately the green colour and replacing it by yellow grey, with simultaneous release of nitrogen dioxide. In the end the substance completely dissolved in the acid, and after evaporation it yielded a white odourless insipid salt, soluble in concentrated nitric acid, insoluble in alkali and water, without traces of oxalic or mucic acid. It was well known that alkali dissolved the green matter known without alteration. It was also dissolved by acetic acid. Result of treating it with many other reagents, was also reported. Pelletier and Caventou proposed that instead of the current names, resin or green starch, it be named chlorophyll, from the Greek *χλωρός* (chloros = colour) and *φύλλον* (phyllon = leaf, a name which indicated the role it played in nature) (Pelletier and Caventou 1817).

The most significant work on vegetable dyes was that on cochineal and its colouring matter (Pelletier and Caventou 1818a). Cochineal was first

extracted with ether and the solution evaporated in a water bath. The residue was a yellow-gold fatty material. The remaining cochineal was then extracted with alcohol, which eliminated only part of the remaining colour. The alcoholic extract was left to evaporate spontaneously yielding crystals of a beautiful red colour, which dissolved easily in water. The crystals dissolved in cold concentrated alcohol and left a brown substance of animal character. The first ethereal extract was evaporated to dryness leaving a fatty crystallizable substance (Pelletier and Caventou 1818a).

The colouring matter of cochineal dissolved (even traces of it) in water producing a crimson red tint. It did not dissolve in ether but did easily in weak acids. In the latter case the colour of the solution changed successively from crimson to live red, to yellow red, and finally to yellow. The colouring matter was carbonized by concentrated sulphuric acid; nitric acid did not carbonize it but change it into a bitter yellow material, unable to recover the original crimson colour. Chlorine and iodine destroyed the colour (Pelletier already uses the name chlorine instead of oxidized muriatic acid). The action of other chemicals, such as limewater, baryta water, alumina, different salts, etc., was also reported. From the many results it was concluded that the colouring matter of cochineal was formed of carbon, hydrogen (predominantly), oxygen, and did not contain nitrogen. It was suggested that the dye be named *carmine* (Pelletier and Caventou 1818a).

The following parts of this memoir reported the results of experiments done on the cochineal bug. The analysis indicated that it was formed of carmine, a particular animal matter, a fatty material composed of stearin, elaidine, an odorant acid, and inorganic salts such as calcium phosphate, calcium carbonate, potassium phosphate, and an organic salt of potassium. The memoir closed with a discussion of the uses of carmine in the arts and dyeing (Pelletier and Caventou 1818a).

### 3. VEGETABLE PRINCIPLES

In 1811 Pierre François Guillaume Boullay (1777-1869)<sup>7</sup> reported that the fruit of the tree *Menisperm cocculus*, growing in India, contained a crystalline substance, the first crystalline poison to be discovered (Boullay 1811). Boullay treated the ground seeds with cold water and obtained a red-brown bitter infusion smelling like cacao, which reddened litmus paper;

addition of alkali made the colour more intense, without precipitation, and galls, sulphuric, nitric, alcohol, and HCl deposited abundant flakes soluble in acetic acid. All the chemical tests indicated the presence of a free vegetal acid, of a substance of animal nature, calcium sulphate, and the absence of an astringent principle. After many additional tests Boullay concluded that these seeds contained a large percentage of a heavy oil, an albuminous vegeto-animal substance, a dye, a new bitter principle, crystallizable and poisonous, which he named picrotoxin (cocculin), fibres, malic acid probable in the state of acid malate of potassium and calcium, potassium sulphate, potassium chloride, calcium phosphate, and traces of iron and silica. Boullay was surprised to find that the seed did not contain mucilage or a starchy fecula, particularly since it was considered to be emulsive. Pelletier and J. P. Couerbe (1807-1867)<sup>8</sup> repeated part of the work of Boullay, studying in particular the properties of picrotoxin (Pelletier and Couerbe 1833). They reported its elemental analysis, its combinations and the fact that it behaved as an acid. They found that the hull of the almond did not contain picrotoxin but two other crystallizable materials, *menispermine* and *paramenispermine*; the first one an alkaline white tasteless powder, and the second a neutral volatile solid, insoluble in water and ether, and readily soluble in alcohol. Justus von Liebig (1803-1883) (Brock 1997) harshly criticized Pelletier and Couerbe's findings regarding the composition of picrotoxin, without providing an alternative analysis and pointing out an error in the calculations (Liebig 1834). Pelletier was highly hurt by having been attacked by "un chimiste allemand dont tout le monde reconnaît le haut savoir, mais dont l'urbanité est un peu contestable" (a German chemist, widely recognized by his knowledge, but having a somewhat questionable urbanity).

In 1813 were reported the results of a work on *Cytinus hypocistis*, a parasitic flowering plant that infects the roots of certain vegetables in Portugal, Spain, and southern France (today we do know that the species in this genus do not produce chlorophyll, but rely fully on its host plant) (Pelletier 1813b). The juice of this plant, although known to be one of the most astringent substances, had not been studied from a chemical point. The aqueous solution of hypocistis had a bitter stringent flavour and reddened litmus paper. Iron salts converted it in to strong ink, without formation of a sensible amount of precipitate, a fact indicating that the colour was due more to gallic acid than to tannin. Addition of a solution of gelatine produced a clear precipitate;

after filtration the liquid was less coloured, reddened litmus, and produced a blue-black precipitate with iron nitrate. The latter result indicated the possible presence of both gallic acid and tannin. Additional testing with concentrated sulphuric acid, potassium carbonate, limewater, alcohol, etc. indicated that hypocistis contained a substance, different from tannin, able to combine with animal matter (e.g. gelatine). As a result of all these tests, Pelletier concluded that in addition to gallic acid, hypocistis contained colouring matters, soluble in water and in alcohol, some of them able to precipitate gelatine, and others not. Gallic acid was combined with many vegetable substances and was able to precipitate gelatine and iron salts. In addition, Pelletier thought that contrary to the beliefs of many chemists, tannin was simply a combination of gallic acid with a colouring matter (Pelletier 1813b).

It was believed (François, Caventou and Pelletier 1830) that although diuretics were widely employed in the treatment of many serious illnesses, an examination of the different pharmacopeia's showed that many of them performed only by the large dose required, and others as a result of a more or less irritating action which led momentarily to a large emission of urine. Users of the latter had to stop their use because the stomach did not tolerate them or the resulting urinary inflammation. Physicians commonly believed that no substance was known which should really be considered a diuretic and could be used for long periods of time without straining the digestive organs. François, Caventou, and Pelletier believed they had found such a substance in the skin of the root of cahinca (snow berry, *Chiococca racemosa anguifuga flore luteo*), a bush of the Rubiaceae family, growing in the Minas de Geraes province of Brazil. According to a Dr. Cléménçon, the natives used the root, macerated or brewed, to treat dropsy, dyspepsia, and intermittent fever, all common illnesses along the river San Francisco. Caventou, and Pelletier isolated the active principle by their usual methods. They first made a large number of successive macerations to extract all the soluble matter present in the root. The alcoholic solution was then evaporated over a water bath to eliminate most the solvent and then left to cool naturally. By this procedure they were able to separate four distinct substances, a bitter crystallizable principle, a green nauseous fatty matter, a yellow colouring substance, and a viscous colouring material. The first was the most important one because it contained all the sapidity of the root. This principle was

crystallized as small white needles, almost odourless and flavourless when fresh; soon after it developed a strong non-permanent astringent effect. Heated above the boiling point of water it softened and eventually carbonized while releasing heavy white fumes and showing no signals of ammonia. It was little soluble in water and ether but dissolved easily in alcohol, and recrystallized on cooling. Its most important property was reddening litmus paper in the manner of acids, for this reason it was decided to name it *acide kaincique* (cahincic acid), a name related to its source. Experiments showed that this acid was a very effective diuretic. They recommended that the best method for obtaining it was to dissolve the alcoholic extract in water, followed by precipitation with limewater and decomposition of the resulting salt with oxalic acid dissolved in boiling alcohol. The acid was little soluble in water, hence for therapeutic purposes it was better to administer it in the state it was present in the plant, that is, as calcium acid cahincicate (François, Caventou and Pelletier 1830).

Little chemical information was available about ipecacuanha, it was not known if its emetic powers were due to a particular substance, which could be isolated, and if it was the same in the different species of the plant (brown, grey, and white) (Magendie and Pelletier 1817). The first part of a memoir was devoted to the chemical study of three species of ipecacuanha: brown (*Psychotria emetica*), grey (*Calococca-ipeacuanha*), and white (*Viola emetica*). The cortical part of the root of the brown species was finely ground, macerated with cold and warm ether, and the solution evaporated to dryness in a water bath. The residue was then treated with alcohol to separate all the material soluble in this solvent. On evaporation, the alcoholic solution deposited white flakes, which was identified as wax. Filtration of the latter and further evaporation yielded a bitter, almost odourless yellow red extract, soluble in cold water and having very strong emetic powers. Further analysis indicated that the root contained 2 wt. % fatty material, 16% emetic substance, 6% wax, 10% gum, 42% starch, and 20% woody material (the remaining 4% were analytical losses). The emetic substance crystallized as red brown scales; it was nauseating and had a bitter taste. By distillation it yielded water, acetic acid, CO<sub>2</sub>, oil, and left a carbonaceous porous residue. There were no traces of ammonia, indicating that the emetic principle did not contain nitrogen. Treated with nitric acid it changed its colour and eventually it released nitrous oxide and deposited oxalic acid (Magendie and Pelletier 1817).

The same emetic substance was found to be present in the three species of ipecacuanha studied, for this reason it was named *emetine*, from the Greek *Emeo, nomo*. The grey and white varieties contained 16% and 5% of emetine, respectively. Test of different doses of emetine on cats and dogs showed that administration of a few grains resulted in vomiting, drowsiness, and return to normal after a long period of time. The investigators tried it on themselves and felt the same effects as the animals. Stronger doses led the death of the animals; an autopsy revealed that the animal had developed a strong inflammation of the lung tissues and of the mucous intestinal membrane. It was concluded that emetine could be administered in very small doses during the treatment of diseases that required vomiting (Magendie and Pelletier 1817).

The observant reader will have noticed that the experimental technique of Pelletier was based on fractional (selective) extraction and not on distillation (destructive technique).

#### 4. ALKALOIDS

##### **Strychnine**

Carl Linnaeus (1707-1778) (Blunt and Stearns 1971) had stated that plants of the same family, with even more reason, those of the same gender, were very often endowed with analogous medical properties. This opinion was shared by the most famous botanists of the time. On this basis, Pelletier and Caventou (Pelletier and Caventou 1819) suggested that perhaps this took place because all these plants contained the same immediate principle, which acted on animals in the same manner with all the parts of the plant that contained it. In their words: "Plants owe their medical properties to the immediate materials of which they are composed; plants of the same family most often contain the same immediate principles; the characteristic medical property of each plant is principally due to one of these bodies; the intensity of this property is proportional to the quantity of the principle which determines it, and if this principle is missing from a species, the characteristic property is absent as well". To establish the truth of these statements unequivocally was the reason that led to research the most active plants from a medical viewpoint. Among these were selected several species of the *Strychnos* genre, particularly *nux vomica* (*Strychnos nux vomica*) and Saint

Ignatius beans (*Strychnos ignatia*). The analysis of the seeds of nux vomica had been reported in many publications but not so that of the Saint Ignatius bean (Pelletier and Caventou 1818bd; 1819).

In order to extract the active principle of the beans of Saint Ignatius, they were first cut finely and then macerated with ether. This produced a very thick, slightly green oily substance that remained transparent up to its fusion point. This substance already had a lethal effect on dogs. The remains of the ether extraction were treated exhaustively with alcohol until all the soluble substances had been dissolved. Evaporation of the alcoholic solution left a yellow brown bitter substance soluble in water and in alcohol, which had also a very strong lethal effect on animals. The latter substance was treated with alkali to separate the fatty substance it contained. This operation resulted in the precipitation of an abundant precipitate, which after washing with water offered a very bitter white crystalline substance. Further examination showed that it possessed strong alkaline properties. The same substance was found in the seed of nux vomica, although it was more difficult to separate in a pure form (Pelletier and Caventou 1818cd).

The presence of the same active substance in three plants of the same gender led to name it *strychnine*. It was explained that originally it had been named *vauqueline*, honouring the first scientist to have found an organic alkali, but the commissaries of the Académie had rejected this election on the basis that the name of such a respected chemist should not be associated with an evil principle (Pelletier and Caventou 1818bc) [J. Simon has given a detailed description of the controversy connected with the naming of the new principle (Simon 1999)].

The properties of *strychnine* were thoroughly studied. It crystallized as prisms, was odourless, and had an unbearable bitterness. It was highly insoluble in cold and hot water. On heating it swelled, blackened and generated an empyreumatic oil (tasting or smelling like burnt organic matter), a little of water and acetic acid, CO<sub>2</sub> and methane, and left a carbon residue. Distilled over cupric oxide it generated CO<sub>2</sub> and traces of nitrogen, which was assumed to come from the entrapped air. An elemental analysis indicated it was composed of carbon, hydrogen, and oxygen, and no nitrogen. The most outstanding characteristic of *strychnine* was its ability to combine with acids. It formed a neutral crystallizable salt with HCl and sulphuric, phosphoric,

and diluted nitric acids. It also formed salts with vegetable acids: acetic, tartaric, and oxalic. The reaction between strychnine and HCN, H<sub>2</sub>S, CO<sub>2</sub>, iodine, chlorine, metallic oxides and salts, etc., was also studied. Additional experiments demonstrated that in Saint Ignatius beans strychnine was combined with an acid, which Pelletier and Caventou were able to separate and study its properties. This substance was named *igasuric acid*, derived from the name given by the natives to the bean (Pelletier and Caventou 1818bc).

The last part of the memoir reported the physiological effects of pure strychnine, strychnine nitrate, hydrochloride, sulphate, hydrocyanide, etc. on rabbits. All died in a short period of time, showing all the symptoms of tetanus (Pelletier and Caventou 1818cd).

### **Brucine**

Within their search for active substances originating from vegetables, particular those having an analogy with the action exerted by strychnos genus, Caventou and Pelletier inspected the bark of false angostura (bark of *brucea anti-dysenterica*) and separated a new alkaline substance, different from strychnine (Caventou and Pelletier 1819). The bark was first treated with alcohol, the alcoholic solution evaporated, and the resulting solid washed with distilled water and then treated with lead acetate. This procedure allowed precipitating the largest part of the colouring matter. The remaining excess lead was precipitated with the aid of a stream of hydrogen sulphide. The colourless filtrated liquid turned yellow when treated with ammonia or with lead bicarbonate. Ammonia gave place to alkaline properties independent of the reagent itself. The same result was found when the solution was treated with calcined magnesia. The filtrated liquid was not only alkaline; it returned the primitive colour to litmus paper previously reddened by acid. The pure active substance was separated as its oxalate and then released from the salt by treatment with magnesia. It was further purified by recrystallization from alcohol. It was decided to name the new active principle *brucine*, because it remembered the mother vegetable and the name of the famous traveller James Bruce (Reid 1968) that had introduced the tree to them (Caventou and Pelletier 1819).

The same work reported the properties of brucine. It was very soluble in cold and hot water; it had a bitter taste and in small amounts was already

very poisonous. A little above 100°C it melted without decomposition. At much higher temperatures it decomposed yielding an empyreumatic oil, a little of water, acetic acid, hydrocarbon, and CO<sub>2</sub>. With acids it formed neutral or acid salts; it dissolved strongly in sulphuric acid yielding a neutral salt, crystallizing as long needles. The sulphate had a bitter taste, was very soluble in water and a little in alcohol, and was decomposed by KOH, NaOH, ammonia, baryta, strontia, and magnesia waters. It also decomposed under the action of morphine and strychnine (Caventou and Pelletier 1819).

Brucine hydrochloride, a neutral salt crystallizing as needles and very soluble in water, was also prepared. On heating it decomposed releasing its HCl. Phosphoric acid also combined with brucine forming a neutral salt, which could be crystallized when in the presence of an excess acid. The crystals were very soluble in water and little soluble in distilled alcohol. Brucine with nitric acid formed a neutral salt, which did not crystallize; by evaporation of its solution it yielded a mass resembling a gum. Prepared with an excess of acid it crystallized; when the crystals were exposed to heat they first reddened, then blackened, and finally caught fire. Brucine reacted with acetic and oxalic acids and the resulting salts crystallized in the form of long needles (Caventou and Pelletier 1819).

A study about the action of brucine on animals showed that its effects were similar to those of strychnine. It provoked an intense attack of tetanus and attacked the nerves without affecting the brain or the mental faculties. Brucine was a more intense poison than strychnine; four grains were enough to kill a rabbit. It was believed that brucine could replace the extract of nux vomica in therapeutic applications, and also, that the bark of false angostura contained brucine combined with gallic acid, gum, a yellow colouring matter, traces of sugar, and wood matter (Caventou and Pelletier 1819).

### **Curare**

Another work reported the separation of the poisonous material from the head of the arrows used by the natives, and its repeated maceration with warm alcohol until no more extraction was produced (Pelletier and Petroz 1829). The residue was extracted with warm water and dried to a syrupy state. Treated with alcohol it separated a green flocculent material. The remaining solution was mixed with the first alcoholic extract and the total

evaporated in a water bath to a brown bitter substance. This was treated with ether to separate the bitter matter from the accompanying fatty and resinous impurities. The ethereal extract was evaporated yielding a viscous residue, which proved to be composed of two different substances, one resinous and the other fatty. The fatty material was saponified and found to contain stearin and elaidine. The bitter substance, not soluble in ether, dissolved easily in alcohol and water and hardly reddened litmus paper. Treatment with dilute alkalis, alkaline bicarbonates, and potassium antimony tartrate did not give a precipitate. Surprisingly, it produced an abundant precipitate with tincture of gallnut. The bitter substance was obtained in a very pure state by treating the alcoholic extract with sulphuric acid and neutralizing the excess acid with baryta water. It was completely soluble in water and alcohol and insoluble in ether; diluted alkali, alkaline bicarbonates, and potassium antimony tartrate did not precipitate the solution. The most remarkable feature was the abundant white precipitate produced by a tincture of gallnut. It was concluded that all these properties indicated that the active principle should be classified among the vegetable alkalis (Pelletier and Petroz 1829).

### **Veratrine**

Another work studied the active principle present in several members of the colchicea family, among them sabadilla (*Veratrum sabadilla*), white hellebore (*Veratrum album*), and colchicum (*Colchicum autumnale*) (Pelletier and Caventou 1820b). Ether put in contact with seeds of sabadilla became coloured yellow and after some time it dissolved a large portion of the substance. The ethereal liquid was separated of the solvent by distillation leaving behind a yellow very smelly fatty unctuous matter, insoluble in water, soluble in alcohol and saponifiable, and strongly reddening litmus paper. The fatty material was separated by saponification with KOH, followed by decomposition with an excess of tartaric acid. The fatty material deposited as white flakes, which proved to be composed of oleic and tartaric acids. The residual filtered liquid was acrid, acid, and very smelly. By distillation it yielded an aqueous acid smelly phase. The residue contained a little of tartar cream, a sweet oily principle, colouring matter, and a substance which was subject to further analysis. The acid present in the liquid phase was separated by precipitation with baryta water. Pelletier and Caventou named it *cevadic acid* (Pelletier and Caventou 1820b).

The residue of the original treatment of seed with ether was now treated with boiling alcohol. The extracted alkaline matter was found to be present as a gallate. The same alkaline matter was found in the seeds of white hellebore and colchicum, and for this reason it was named *veratrine*. Inspection of the latter showed that it was an odourless extremely acrid white pulverulent solid, which introduced in the nose resulted in violent sneezing even in very small amounts; in larger amounts the irritation propagated to the intestine provoking vomit. Experiments with animals showed that small amounts of it led to death. Veratrine was very insoluble in cold water and slightly soluble in boiling water. It dissolved easily in alcohol and ether, turned blue litmus paper previously reddened, and reacted with acids, iodine and chlorine, forming non-crystallizable salts. Veratrine was insoluble in alkalis and soluble in vegetable acids.

Analysis of the seeds of *sabadilla* and the roots of white hellebore and colchicum indicated that they contained a fatty material composed of elaidine, stearin, and cevadic acid, wax, veratrine acid gallate, colouring matter, gum, wood material, and inorganic salts. In addition, the roots of colchicum also contained inulin (Pelletier and Caventou 1820b).

### **Caffeine**

In 1820 Pierre Jean Robiquet (1780-1840)<sup>9</sup> reported that coffee contained a volatile crystallizable matter (Robiquet 1820). About the same time Pelletier and Caventou had reached the same result without knowledge of Robiquet's work, while looking at the possibility that coffee contained quinine or a similar substance. Anyhow, little was known about caffeine, so Pelletier decided to find more about it (Pelletier 1826). Caffeine was separated by extracting non-roasted coffee beans with alcohol and then treating the alcohol extract with cold water to separate the fatty matter. The remaining extract was heated and treated with magnesium hydroxide and the resulting magnesium precipitate filtered, washed with water and then with alcohol. The caffeine dissolved in the alcohol was recovered by evaporation of the solvent. The latter operation was complicated by the fact that if the precipitate was not washed properly, then the caffeine extracted by the alcohol was accompanied by syrupy and coloured impurities, which were difficult to separate without much loss of caffeine; if the precipitate was well washed with water, most the caffeine was lost in the washes. For these reasons, the

operating procedure was modified as follows: the precipitate was first washed with water as long as necessary to completely eliminate the caffeine. All the washes were then evaporated to dryness in a water bath and then extracted with alcohol at 40°C. This dissolved all the caffeine leaving behind the gum and coloured impurities. The alcoholic extract was filtered through animal carbon, concentrated by distillation, and left to crystallize by cooling. The resulting caffeine was a crystalline neutral product. An elemental analysis indicated that it contained 46.51wt % carbon, 4.81% hydrogen, 27.14% oxygen, and 21.54% nitrogen. In spite of its high nitrogen content, caffeine did not undergo putrefaction, contrary to organic nitrogenous matter. This result indicated that the property of putrefaction did not depend on a large content of nitrogen but on the internal arrangement of the molecule. Crystallization forces were strong enough to maintain the stability of the elements both in vegetable and animal substances. Thus substances such as urea, uric acid, etc. did not putrefy in spite of their high nitrogen content (Pelletier 1826).

### **Quinine**

Bernardino Antonio Gomes (1768-1823)<sup>10</sup> had reported that the bark of grey quinquina from Loxa (Loja, Ecuador) contained a crystalline principle that he named cinchonine but did not notice its main property, alkalinity (Gomes 1812).

Pelletier and Caventou's initial method for separating the principle in a pure state consisted in washing the alcoholic extract of quinine with slightly alkaline water until the wash water stopped being coloured (Pelletier and Caventou 1820c). Alkaline treatment played here two roles, one, dissolving the colouring matter, two, separating the acid combined with the febrifuge principle, which made it soluble. Thus the principle remained combined with a little of fatty material, which could be easily eliminated by solution in diluted HCl. Afterwards, the principle was precipitated with the help of an alkali, dissolved in alcohol, and then recrystallized as pure cinchonine. A better alternative process was proposed where the cold alcoholic extract was treated with a dilute aqueous solution of HCl, and then cinchonine precipitated by adding an excess of magnesia. The precipitate was filtered, washed, and dried in a water bath and the active principle extracted with alcohol (Pelletier and Caventou 1820c).

This principle was white, crystalline, and bitter as quinquina, without being astringent, almost insoluble in water, very soluble in alcohol and ether, and forming with acids neutral salts, very soluble and crystallizable. A study was carried on about the reaction of the substance with different acids and the properties of the resulting salts. These salts were usually soluble and easy to crystallize, except the ones formed with oxalic, gallic, and carbonic acids (Pelletier and Caventou 1820c).

A search for the presence of cinchonine in many species of quinquina led to the surprising result that yellow quinquina contained an alkaline principle similar to that of grey quinquina, but differing from it in that it was non-crystallizable and was not saturated by the same amount of acid. Red quinquina simultaneously contained both alkaline species in very large amounts. They distinguished the second principle naming it *quinine* (Pelletier and Caventou 1820c).

The differences existing between cinchonine and quinine, be on their nature or on the relative amount present in the three species of quinquina, perhaps explained the slight variations on their effects noticed by physicians. It was believed that these two alkaline principles were the true febrifuges and antiperiodic components of quinquina (Pelletier and Caventou 1820c).

Grey quinquina (*Cinchona condaminea*) was examined first; Gomes had reported finding a particular principle that he named *cinchonine*. Initially Gomes's procedure was followed, consisting in preparing an alkaline extract of quinquina, then washing it several times with distilled water to separate the red insoluble substance that Gomes considered to be the extractive principle, and carrying on a final wash with water saturated with KOH to extract the remaining colorant. The water washes were then evaporated to dryness, and the resulting cinchonine purified by dissolving in alcohol and crystallization (Pelletier and Caventou 1820c).

Pelletier and Caventou described the method they had developed to obtain pure cinchonine: Grey quinquina was repeatedly macerated with alcohol, the extracts collected and distilled to eliminate all the alcohol, followed by addition of distilled water to avoid the principle being damaged by heat. The aqueous solution was filtered and the solid repeatedly washed with a dilute aqueous solution of KOH until the passing liquid was colourless, and then washed with distilled water. The remaining solid was white green,

very fusible, soluble in alcohol and crystallizable, and corresponded to Gomes' cinchonine. In this state it had several of the characters of resinous substances, but when dissolved in a diluted aqueous solution it separated a large amount of a fatty green material. The acid liquid was yellow gold and when evaporated it precipitated crystals soluble in water and in alcohol. It had a bitter taste and abundantly precipitated when treated with alkaline solutions, gallates, alkali oxalates, etc. After purification and recrystallization it yielded white brilliant crystals of highly pure cinchonine, in order to keep the harmony of the nomenclature, the product was named *cinchonine*. Its properties were then described, particularly the fact that it only contained carbon, hydrogen and oxygen, and *no nitrogen*. Cinchonine turned blue litmus paper that had been reddened by an acid, combined with all acids and could form neutral combinations so that it should be considered a salifiable organic base. Several of these salts were prepared (sulphate, nitrate, hydrochloride, phosphate, arsenate, acetate, oxalate, tartrate, and gallate) and their properties described (Pelletier and Caventou 1820c).

Crude cinchonine was subjected to a series of operations to separate all the materials soluble and insoluble in alcohol. The final conclusions were that grey quinquina was composed of nine fractions: (a) cinchonine combined with kinic (quinic) acid, (b) a green fatty matter, (c) a slightly soluble red colouring matter, (d) a soluble red colouring matter (tannin), (e) a yellow colouring matter, (f) calcium kinate, (g) gum, (h) starch, and (i) woody material. Determination of the properties of the green fatty material of all these fractions and the results led to the hypothesis that its colour was due to the presence of chlorophyll. Heating quinic acid it yielded pyroquinic acid, a substance very soluble in water and alcohol, crystallizing white, and differing from kinic acid in its ability to form a green precipitate with ferric sulfate (Pelletier and Caventou 1820c).

All these findings led to an improved method for preparing pure cinchonine. The alcoholic extract was now treated with hot diluted HCl, which dissolved the active principle and separated it from the red colouring material and the fatty matter. The resulting liquor was treated with an excess of magnesia, the precipitate washed, dried on a water bath, and the cinchonine redissolved in alcohol. The pure principle was obtained by evaporation of the solvent (Pelletier and Caventou 1820c).

The following sections of the memoir were devoted to the extraction of yellow quinquina (*Cinchona cordifolia*), red quinquina (*Cinchona oblongifolia*), quinquina of Carthagène (*Portlandia hexandra*), the bark of Kina-Nova, and quinquina of Sainte-Lucie (Kina-Piton, *Exostemma floribunda*), separation of the alkaline active principle, the different components, and synthesis of salts. During the last stage of purification of the product obtained from yellow quinquina, it was surprising to find that instead of cinchonine a yellow transparent and non-crystallizable substance was found, little soluble in ether and very soluble in alcohol. Initially it was assumed that the product was cinchonine mixed with a foreign matter characteristic of yellow quinquina. The foreign substance was found to dissolve in all acids, forming white salts easily crystallizable, a fact that forced the conclusion that it was a bitter salifiable base different from cinchonine, which was named quinine. Another surprising result was finding two different salifiable bases, having almost identical properties, in two closely related vegetable species. Quinine and cinchonine were easily separated by their different solubility in ether. A thorough study of quinine showed that it never crystallized; when dry it appeared as a porous white solid, slightly soluble in cold or hot water, easily soluble in alcohol, more soluble in ether than cinchonine, unalterable in air, decomposing under the action of heat yielding vegetable products, and not showing the presence of nitrogen. Pelletier and Caventou studied the salts formed with hydrogen chloride and sulphuric, nitric, phosphoric, arsenic, acetic, oxalic, gallic, and tartaric acids. It was concluded that yellow quinquina was composed of eight different substances: (a) quinine acid quinate (b) red cinchonine, (c) tannin, (d) fatty matter, (e) calcium quinate, (f) starch, (f) yellow colouring matter, and (g) woody material (Pelletier and Caventou 1820c).

The results for red quinquina indicated that it contained nine different materials: (a) quinine acid quinate (quinate), (b) cinchonine acid quinate, (c) calcium quinate, (d) red cinchonine, (e) tannin, (f) fatty material, (g) yellow colouring matter, (h) starch, and (i) woody material. In addition, grey quinquina contained only cinchonine, yellow quinquina only quinine, and red quinquina both salifiable bases. In addition, red quinquina had a much higher content of quinine than yellow quinquina.

The last section of the memoir contained the testimony of several physicians regarding the extreme success in treating different maladies with the help of quinine and its salts (Pelletier and Caventou 1820c).

Surprisingly, Pelletier did not request a patent for his process of making quinine sulphate and published all the details making it free for the public. Shortly thereafter, Pelletier alone, or in collaboration with others, began manufacturing quinine sulphate for medical purposes, in commercial quantities. In February 1827 Pelletier and Caventou wrote to the President and members of the Académie proposing their names as candidates to obtain one of the prizes instituted by the Baron de Montyon (Pelletier and Caventou 1827). In their letter they indicated that in 1820 when they had made quinine known, they were not so sure that it was the active principle of quinquina and that quinine sulphate would be found to be an outstanding medicine for the treatment of intermittent fevers. Other researchers had separated other principles present in quinquina and claimed that they were the main active principle. Eventually quinine sulphate was proven to be the most effective medicine for intermittent fevers and its manufacture had become a new French industrial activity for national uses and export to many countries in Europe, America, and the Indies. Just in 1826, Pelletier alone or in collaboration with others had treated about 160,000 kg of quinquina bark; Pelletier and Caventou estimated that the total French production for 1826 was about double that amount, representing a production of about 90,000 ounces of quinine sulphate. Since about 2.2 grams were enough to stop the fever, the 1826 production corresponded to the medical treatment of 1,444,000 persons. According to Pelletier and Caventou, the discovery of quinine had been heralded as a very important discovery. They believed that on the basis of present wide medical use it should be considered a great medical discovery and hoped that the members of the Académie would share this opinion. Pelletier and Caventou requested the Académie to submit their letter to the commission examining the award of the Monthyons (sic) prizes (Pelletier and Caventou 1827). In 1827 the Académie awarded Pelletier and Caventou the Montyon Prize of 10,000 francs in recognition of their discovery of quinine.

### **Opium**

In a first work about opium, Pelletier reported the preparation and properties of narcotine and morphine acetate (Pelletier 1823) and then he published an extensive memoir about the analysis of opium (Pelletier 1852). It begun with a short historical review about this substance, saying that in

1803 Jean-François Derosne (1774-1855)<sup>11</sup> had been the first to separate from opium a white crystalline substance that he named *narceine*, which he believed was the actual active principle, of opium, considered as a medicine or as a toxin (Derosne 1802). The following year, Armand Seguin (1767-1835)<sup>12</sup> reported the existence of the most energetic principle of opium (which he named morphine), the procedure for obtaining it, its outstanding properties, and the crystallization of several of its derivatives (Seguin 1814). Pelletier indicated that Friedrich Sertürner (1783-1841) (Göerig and Schulte 1991) had been the first to report that the active principle of opium was an alkali able to form neutral salts with acids, which was an unusual characteristic for a vegetable matter (Sertürner 1805).

Opium was macerated several times with cold distilled water and the product separated into opium marc (solid residue) and opium extracts (solution). The extract was evaporated to dryness and after treatment with distilled water it left a bright crystalline residue of narcotine, without morphine. The solution, partially free of narcotine, was heated to 100°C, treated with an excess of ammonia to decompose the morphine salt, and boiled again to eliminate the excess of alkali. Left to cool naturally it deposited the morphine in a crystalline state. The solid was separated by filtration and treated with ether. Evaporation of this extract led to the separation of an oily substance, narcotine crystals and meconin (Pelletier 1852).

Morphine was purified by repeated solution in boiling alcohol, recrystallization, and washing with ether to eliminate narcotine. Further purification was carried on by addition of sulphuric acid and crystallizing the resulting salt. Treatment of the salt with magnesia liberated morphine in a very pure state.

The ammonia solution mentioned above was treated with baryta water to yield a new precipitate of barium meconate. The final solution, free of narcotine, morphine, and meconic acid, was treated with ammonium bicarbonate, boiled to eliminate the remaining ammonia salt, and then evaporated. Treatment of the residue led to the separation of new crystalline substance, which was named *narceine* (Pelletier 1852).

The following section of the memoir reported the results of the examination of opium marc.

Successive extractions with water, ether, and alcohol showed the presence of gum, narcotine, resin, a brown acid, woody material, fatty oil, and bassorin. A summary of the first findings indicated that opium contained at least twelve components: narcotine, morphine, meconic acid, narceine, a brown acid, resin, fatty oil, gum, rubber, bassorin, and woody matter (Pelletier 1852).

The second section of the memoir was devoted to the particular study of narceine, narcotine, morphine, opium resin, oily matter, and rubber. It reported their main characteristics, elemental analysis (now, most of them known to contain nitrogen), the fact that four of them (morphine, narcotine, meconin, and narceine) functioned as bases, that only morphine was a salifiable base of first order (capable of forming neutral salts), and that meconic acid, brown acid, and fatty matter functioned as acids (Pelletier 1852).

The same year (1832), Couerbe published a short report of his discovery of a new component of opium, which he named *meconine* (Couerbe 1832a). Meconin crystallized as white needles, soluble in boiling water, ether, and alcohol. Burned with copper oxide it yielded only CO<sub>2</sub> and water, differently from narcotine and morphine. In a following publication Couerbe provided a detailed description of his procedure for extracting meconin, its elemental analysis of the substance, and its properties. It reacted with sulphuric acid yielding green meconin sulphate, and with nitric acid yielding meconic acid, a new substance containing carbon, hydrogen, oxygen, and nitrogen. Melted meconin reacted with chlorine gas forming a new crystalline substance containing 5.43wt % chlorine and 94.57% organic matter (Couerbe 1832b).

In a following publication Pelletier refined his procedure for fractioning opium and separated codeine, paramorphine (thebaine), and pseudo-morphine (oxydimorphine, dehydromorphine). The latter was found to be non-poisonous and to contain less carbon and more oxygen than morphine (Pelletier 1835). An interesting feature is that the Pelletier's report of having discovered the baine led to a bitter argument with Couerbe, who claimed that the discovery of the alkaloid should be attributed to Jean Blaise Auguste Thibouméry<sup>13</sup> (Couerbe 1836; Pelletier 1836a).

Pelletier formed a society with Thibouméry and Dubose (a student of his) for manufacturing quinine sulphate. Thibouméry took a patent of

invention in England for a process of purifying morphine and an importation patent in France for the same. Eventually the society was dissolved and a new one formed by Thibouméry and Dubose for the commerce of quinine sulphate. In their prospectus they advertised themselves as “ex directeur de la fabrique de M. le Professeur Pelletier” and “Elève de ce professeur”. The label of their products carried the arms of France and of England surrounded by the words “Brevet d’Invention» (patent of invention) and “Brevet d’Importation” (patent of importation). Pelletier took them to court feeling that these statements violated his property rights, and thence demanding that his name should not be mentioned in any publication of the industry and that the labels should also carry the words “for a particular process of manufacturing quinine sulphate”. On August 20, 1838, the Trade Tribunal of Paris ruled in favour of Pelletier stating that although it was true that Thibouméry and Dubose had worked for Pelletier, they had no right to use his name in their products without his authorization and that it was clear that their reason for doing so was to advance their sales alleging a patronage in detriment of Pelletier. In addition, the Tribunal fined Thibouméry and Dubose 500 francs. Thibouméry and Dubose appealed the decision to the Royal Court and on March 5, 1839, this court reversed the decision of the Trade Tribunal, stating that it was an undeniable fact that the plaintiffs had worked for Pelletier, as stated in their prospectus, and that Pelletier had made his process public, without taking a patent. Hence there was no legal reason why the label statement should be modified. Consequently, Pelletier’s demand was dismissed (Anonymous 1839).

Pelletier and Coriol studied the bark of a tree coming from Peru, which was used to adulterate quinquina, and found in it a new salifiable bases, which they named *aricine* (Pelletier and Coriol 1829).

For a long time Dumas had been involved in developing methods of analysis of vegetable and substances. His techniques were an extension of Joseph Louis Gay-Lussac’s (1778-1850) (Crosland 1978) volumetric method, based on the transformation of these types of substances into water, CO<sub>2</sub>, and nitrogen, collecting them, and measuring their respective volumes at the same pressure and temperature. This method was more precise than the traditional gravimetric one; measurement of volumes of the gases liberated (large values) was subject to a substantially smaller error than measuring small weights. The relative ratio of the volumes collected allowed an easy

way to determine the elementary composition of the substance. Dumas was also interested in the analysis of vegetable alkalis and for this reason he and Pelletier decided to join efforts in elucidating the correct composition of the new compounds discovered by Pelletier. Their initial activities were dedicated to developing the proper equipment to completely dry the initial materials and of assuring their total combustion. Once this was achieved, they carried on the elementary analysis of quinine, cinchonine, brucine, strychnine, veratrine, emetine, caffeine, morphine, and narcotine; with the following results in wt. % (the numbers in parenthesis are the modern values) (Pelletier and Dumas 1823):

	Carbon	Nitrogen	Hydrogen	Oxygen
Quinine	75.01 (74.04)	8.45 (8.64)	6.66 (7.46)	10.43 (9.86)
Cinchonine	76.97 (77.51)	9.02 (9.52)	6.22 (7.53)	7.79 (5.43)
Brucine	75.04 (70.03)	7.22 (7.10)	6.52 (6.64)	11.21 (16.22)
Strychnine	78.22 (75.42)	8.92 (8.38)	6.54 (6.63)	6.58 (9.57)
Veratrine*	66.75	5.04	8.54	19.60
Emetine	64.57 (72.47)	4.30 (5.83)	7.77 (8.39)	22.95 (13.32)
Morphine	72.02 (71.56)	5.53 (4.91)	7.01 (6.71)	14.84 (16.82)
Narcotine	68.88 (63.91)	7.21 (3.39)	5.91 (5.61)	18.00 (27.09)
Caffeine	46.51 (49.48)	21.54 (28.85)	4.81 (5.19)	27.14 (16.48)

\*veratrine is actually a mixture of alkaloids

#### Action of iodine and chlorine on salifiable bases

The action of halogenated compounds, particularly the halogens themselves, on salifiable organic bases was unknown (Pelletier 1836c). It was unknown if these compounds were able to combine with vegetable alkalis without alteration or if they exerted on them an elementary action that changed their composition. Did they generate iodates, iodides, bromates, bromides, chlorates and chlorides, or was the organic base destroyed and hydrogen substituted by halogen? Pelletier's experiments showed that iodine combined with most salifiable organic bases producing well-defined combinations. Thus strychnine yielded a crystallizable coloured iodide containing two atoms of iodine per mole of strychnine, brucine yielded two iodides, one containing two and four iodine atoms per mole of the base, respectively, and cinchonine and quinine each yielded compounds containing one atom of iodine per atom of base. Iodic acid ( $\text{HIO}_3$ ) combined with

salifiable organic bases forming neutral or acid salts and hydrogen iodide combined with all salifiable organic bases forming salts containing an excess of base; thus the hydroiodate of strychnine and brucine were sesquibasic salts without water of crystallization. These hydroiodates were decomposed by iodic acid, the hydroiodate changing into iodide. The reaction between iodine and morphine was an exception, part of it combined with hydrogen from the base forming HI while the rest combined with a substance originating from morphine. During the reaction of iodic acid and morphine the acid lost its oxygen, which reacted with part of the morphine producing a red substance like the one generated by nitric acid; the iodine liberated reacted on another part of the morphine in the same manner as by direct action (see above). Adding more iodic acid decomposed this derivative into iodine and red matter (Pelletier, 1836c).

A following publication related to the nature and classification of alkali bases (Pelletier 1836d). The discovery of organic bases was well documented and the question was if they should be classified within the basic oxides or as an ammonia congener. Yet, they could not be separated on the basis of their composition because if these bases contained oxygen the same as metallic oxides, they also contained nitrogen and hydrogen like ammonia. It was necessary to use other indicators. Metallic oxides combined with hydrogenated acids, for example HCl, to form water and a chloride, that is, it resulted in the reciprocal destruction of two bodies; on the other hand, ammonia and hydracids combined with chemical reaction. Subjecting organic alkali to this test, it was seen that they combined simply with HCl. The results proved that alkali united with HI without a reciprocal reaction, Hence vegetable alkali should be classified in the same group as ammonia, Nevertheless, their combination with oxygenated acids presented some characteristics worth of attention. Metallic oxides combined with oxygenated acids forming salts and without forming water, while ammonia combined with these acids with the help of water. In general, an ammonia salt generated by an oxygenated acid contained a mole of water. Organic alkalis combined with oxygenated acids forming salts and no water. Hence, with regard to oxygenated acids, organic alkalis should be classified with bases similar to metallic oxides. In other words, the accepted classification rules yielded contradictory results and it became necessary to put the organic bases in a third separate category. The general nature of organic alkalis could be

identified by other tests that had not been used before. It was known that chlorine, bromine, and iodine acted differently on oxygenated bases than on hydrogenated bases. For example, chlorine acted on oxygenated bases producing not only the metallic chloride but also hypochlorites or chlorates; its action on hydrogenated bases resulted in their destruction by taking their hydrogen. Organic bases behaved differently, as could be judged by the action of iodine. They combined without reaction, forming definite crystallizable compounds. In other words, these bases were not destroyed as ammonia was, they did not generate iodides or iodates as metallic oxides did. Thus strychnine formed neutral iodine, brucine a di-iodide, cinchonine a sub-iodide like quinine. Morphine gave place to complicated reactions. Treating the iodides of these bases with silver nitrate produced silver iodide, without release of oxygen (Pelletier 1836d).

A following memoir described the results of experiences on the action of chlorine on salifiable organic bases. In the opening statements it was said that chlorine acted on organic alkalis generating new compounds, product of very complicated reactions, which could not be explained on the basis of the chemistry knowledge available at the time. For this reason it had been necessary to interrupt the large number of experiences planned to perform, and to report only the partial results obtained (Pelletier 1836b).

When passing a stream of chlorine through a water suspension of finely divided strychnine, the temperature increased, strychnine was attacked, and a very white flaky substance was seen to float as froth on top of the liquid, while at the same time strychnine dissolved in the water as its chlorate. The formation of froth continued as long as strychnine was present in the liquid. Filtration of the liquid, followed by evaporation, showed it contained ammonium chloride, and no traces of organic matter. An interesting result was the red colour attained by the liquid, caused by the small amount of brucine present in the strychnine extracted from *nux vomica* or from the beans of Saint-Ignace. This reaction suggested using chlorine to detect the presence of brucine in strychnine (Pelletier 1836b). The white matter was washed first with cold water, followed by hot water washes to eliminate all the acidity dissolved, and finally dissolved in ether. Evaporation of the latter solution resulted in the crystallization of the solute in the form of flaky crystals. These crystals were white bright when wet and grey when dried.

They were hardly soluble in water, had a bitter taste, they dissolved well in alcohol, pure or diluted, and recrystallized in the form of extremely fine needles. Elemental analysis indicated that they contained 50.16% carbon, 4.74% hydrogen, 5.19% nitrogen, 24.50% chlorine, and 15.41% oxygen. These percentages indicated that this substance was the result of a reaction and not a strychnine chloride.

Similar results were obtained when treating a solution of brucine hydrochloride with chlorine gas. Initially the solution became yellow, then orange, clear red, and finally blood red. Afterwards it began to lose its colour. Treating a water suspension of powdery quinine resulted in dissolution of the base, and the liquid changing its colour from rose to deep red, and again disappearance of the colour. The results of experiments on cinchonine, morphine, and narcotine, indicated that (a) chlorine did not combine directly with salifiable organic bases; (b) it decomposed them by subtraction of hydrogen, forming HCl, (c) the result of this reaction was the formation of neutral substances, incapable of becoming saturated with acids, little soluble in water, and soluble in alcohol, (d) strychnine was the substance giving the most positive results; it produced a brilliant substance, soluble in alcohol and ether, composed of five elements in the proportion given before; and (e) the extreme sensitive of strychnine to chlorine could become a valuable mean for identifying it in toxicological investigations (Pelletier 1836b).

## 5. AMBERGRIS

All the chemists that had worked on ambergris agreed that it was a particular fatty material, although they had been unable to determine its nature in detail. Some regarded it as a bitumen, others as a vegetable product, a resin, or similar to the fatty substance present in dead bodies (adipocire). Pelletier and Caventou believed of interest to find if it was stearin, cetin, cholesterol, or a different substance (Pelletier and Caventou 1820a). Their first findings were that ambergris was very different from stearin and cetin but very similar, to cholesterol, to the point they could be mistaken. Nevertheless it differed from the latter in many properties so that it should be considered as next to cholesterol. For this reason they suggested naming it *ambrein* (actually *ambrein* is the chief constituent of ambergris). Ambrein could be easily obtained from ambergris by treating it with hot alcohol,

filtering the solution and leaving it to cool down. Ambrein deposited as more or less regular crystals, accumulating as a dome-shaped solid. The ambrein thus recovered was a brilliant white tasteless solid having a slight odour and not affecting litmus paper. It dissolved easily in alcohol and ether, it melted at about 30°C and above 100°C it first became brown and then decomposed releasing a white fume. According to Pelletier and Caventou the condensed fume seemed to be ambrein unaltered (Pelletier and Caventou 1820a).

Similarly to cholesterol, ambrein did not saponify but nitric acid acted completely different on both products. Addition of concentrated nitric acid to ambrein transformed it first into a paste followed by release of nitrous gas. The resulting substance was acid and looked like cholesteric acid; for this reason they named it *ambreic acid*. Pelletier and Caventou prepared a large amount of ambreic acid in order to study its properties and salts. It strongly reddened litmus paper; on heating it decomposed without releasing ammonia. It was slightly soluble in alcohol and ether; it reacted with potassium forming potassium ambreate. This salt formed a yellow precipitate when mixed with an aqueous solution of metallic salts, such as the chlorides of calcium, barium, mercury, tin and gold, and the sulphates of copper and iron, silver nitrate, lead acetate (Pelletier and Caventou 1820a).

This paper ended with a speculation about the possible origin of ambergris. It was known that it was produced by certain cachalots (sperm whales) but not in which organ and for what reason. Was it a natural excretion of a healthy animal or the result of an illness? On the basis of its strong similarity with human bile stones it was concluded that ambergris was probably formed by the agglomeration of a large number of similar matter formed by hardening of excremental matter in the body of the whale. This assumption was substantiated by the fact that ambergris was found in the inside and in the liquid excrements of sick whales (Pelletier and Caventou 1820a).

#### END NOTES

##### 1. Pierre Joseph Pelletier

There are several publications dealing with the life and work of Pierre Joseph Pelletier; the best one is the speech pronounced by Maurice Javillier (1875-1955), President of the Académie des Sciences of France, on the occasion of the inauguration of the rebuilt

statue of Pelletier and Caventou, which had been destroyed by the Germans during World War II (Bussy 1842; 1843). The material that follows has been taken mainly from this source.

Pierre Joseph Pelletier was born in Paris, on April 22, 1788, one of the two sons of Marguerite Sédillot and Bernard Pelletier (1761-1797). His father was a very famous master pharmacist and physician who occupied many important positions during his short life: professor of chemistry at the École Polytechnique, member of the Académie des Sciences Inspector of Military Hospitals, member of the Conseil de Santé des Armées, Commissary of gunpowder and saltpeter, member of the Bureau de Consultation des Arts et Métiers and of the Commission Temporaire des Arts. Pierre Joseph studied at the École located at the rue de l'Arbalète and then registered at the École de Pharmacie where he was an outstanding student: at the age of 19 he was awarded the First Prize in Chemistry and a year later, the First Prizes in Botany and Natural History (Javillier, 1951).

From the age 22 on he devoted all his time to scientific research and went on to receive in 1812 his degree of *docteur ès sciences* from the Faculté des Sciences de Paris, at the Université Impériale. His first publications were on the area of gums and resins, particularly those present in opoponax, bdellium, myrrh, galbanum, sarcocolla, caranna (caraña), and the exudations of olive tree. These were the subjects of his first doctoral thesis [which he dedicated to Nicolas Louis Nicolas Vauquelin (1763-1829)] where he demonstrated that resinous gums had a very complex composition and were very difficult to analyze (Pelletier 1812a). His second doctoral thesis (Pelletier 1812b), which he dedicated to his mentor René Just Haüy (1743-1822), was about the value of the physical properties employed in mineralogy. Haüy had shown that all crystalline substances have a primitive shape, which was constant in each species, and the mechanism by which secondary shapes formed by the addition of new molecules that group around the primitive nucleus. Haüy had also developed the laws that allowed discovering and calculating these secondary shapes. In his thesis Pelletier described the physical characteristics of minerals that allowed determining their species: specific gravity, hardness, elasticity, ductility, and tenacity, colour, refraction, phosphorescence, fusibility, magnetic and electrical properties, and their origin and ways of activating them. An important conclusion was that the electrical conductivity of minerals depended not so much on their composition but on the arrangement of their molecules. Thus certain sulfides were conductors of electricity while other were not, certain oxides in their natural state were conductors, while others, closer to the metallic state, were not. He finished his thesis with a classification of mineral substances into four large categories according to their conducting properties: (1) saline, (2) stones, (3) combustible non-metallic, and (4) metallic. For each category he gave a large number of examples and described the intensity of their conductivity.

From here on he went on to study other vegetable substances, among them chlorophyll, colouring matters (sandalwood, orcanet, curcuma, cochineal, etc.), active principles (picrotoxin, hypocystis, cahincic acid, emetine, etc.), alkaloids (strychnine, brucine,

curare, veratrine, caffeine, quinine, cinchonine, opium, morphine, etc.), the reaction of iodine with starch, the action of iodine and chlorine on salifiable organic bases, urinary calculi, ambergris, gases from pine resin, and gold compounds (particularly the chloride and chlorate). Several of them resulted in the discovery of many new principles, some with high medical and toxicological value. Pelletier and François Magendie (1783-1855) determined the chemical and physiological properties of the ipecacuanhas (*Psychotria ipecacuanha*), discovered in them the presence of emetine, another vegetable alkali, and proved that it was the active principle that possessed emetic properties. Pelletier and Caventou studied three species of strychnos (*Strychnos nux vomica*, *ignatia*, and *colubrina*) and discovered that the three contained the same active principle, strychnine.

An interesting fact is that the first reports of Pelletier and Caventou about alkaloids identified them as bases that did not contain nitrogen. Eventually, as the result of a joint effort with Dumas, they reported that alkaloids did contain nitrogen. For example, quinine contains between 8.4wt % and 8.8% nitrogen (the exact figure for dry quinine is 8.63%), and cinchonine 9% (the exact figure of 9.52%). This memoir also reported some interesting analytical results for seven other alkaloids (Pelletier and Dumas 1823).

His scientific achievements led him to occupy important positions in the academic and scientific circles. In 1815 he was appointed adjunct professor of natural history at the École de Pharmacie and remained there for the next 25 years. In 1825 he was promoted to the chair, succeeding Pierre Jean Robiquet (1780-1840), and in 1832 served as vice director of the school. In 1820 the King Louis XVIII created the Académie Royale de Médecine and appointed Pelletier member of the pharmacy section. Pelletier was also *Académicien Libre* of the Académie des Sciences (1840). In 1827 the Académie des Sciences awarded Pelletier and Caventou the Montyon Prize of 10,000 francs in recognition of their discovery of quinine, and in 1970 the French Postal Service issued a stamp honoring the 150 anniversary of the discovery of quinine (Fig. 1).



**Fig. 1** Stamp issued by the French Postal service in 1970 on the occasion of the 150 anniversary of the discovery of quinine by Pelletier and Caventou.

Pelletier passed away at Clichy-la-Garenne on July 19, 1842, after painfully suffering from intestinal cancer. He had married twice and was survived by his three children (Javillier 1951).

An interesting fact is that in 1783 Pelletier's father had bought the pharmacy belonging to the widow of Hilaire-Marin Rouelle (1718-1779) and changed its name from Pharmacie Rouelle to Pharmacie Pelletier. On the death of Bernard Pelletier his widow became the manager of the pharmacy and in 1836 it became the property of her son, Pierre-Joseph. In 1842, after the death of Pierre Joseph Pelletier, Guillaume Duclou bought the business. The pharmacy is still known by the name Pharmacie Pelletier.

2. A British physician turned chemist, fellow of the Royal Society and regius professor of chemistry at the University of Glasgow. He was assistant editor of the *Supplement to the Third Edition of Encyclopaedia Britannica*, and founder of the journal *Annals of Philosophy*. He authored *A System of Chemistry*; the most important English chemistry textbook of his time.
3. Edmond Robiquet carried on additional research on the sugar in aloes, the identity of picric and chrysoleptic acids, gallic fermentation, theory of etherification, and the therapeutic and optical properties of codeine.
4. Walter had a PhD in sciences: carried on research work on the essences of mint and cedar camphor and its chemical reactions, and the oil of moringa. Passed away at the early age of 37.
5. A French chemist, who discovered and synthesised a large number of chemicals, among them, amyl and allyl alcohol, toluene, xylene, cuminic and anisic acids, piperidine, organometallic compounds and radicals, and derivatives of phosphine and arsine. He also made as important contributions to the theories of valence, isomerization in the aromatic series, density of vapours, particularly the abnormal ones, the use of  $\text{PCl}_5$  as a chlorination agent, and the mechanism of respiration of fruits and flowers. He discovered meconin while working for Pelletier.
6. French pharmacist, professor at the École de Pharmacie de Paris, member of the Académie Nationale de Médecine, and correspondent member of the Académie des Sciences. In addition to the large number of papers published with Pelletier about alkaloids, he also did work on the extraction of natural principles from daffodil (*Narcissus pseudonarcissus*), golden rain (*Cytisus Laburnum*), pois d'iris, purging croton (*Croton tiglium*), great yellow gentian (*Gentiana Lutea*), and the roots of kainça, as well as the chemical behaviour of starch.
7. A French pharmacist who carried on important work on the preparation of ethyl ether and alkyl derivatives, the extraction of active vegetable principles, during which he discovered pyroxin, and violin, the synthesis of margaramide, and perfected the process of percolation to extract active substances and tinctures of the same.
8. Couerbe was a former student of Pelletier and *chef des travaux* at Pelletier's chemical plant. He refused to support Pelletier's claim to priority in the isolation of the baine,

another opium alkaloid. Instead, Couerbe gave credit for the discovery of the bain (called paramorphine by Pelletier) to Thibouméry, who had been employed by Pelletier as *directeur des travaux*. Besides his papers with Pelletier, he reported on a new principle derived from albumin, a short chemical history of meconin, the brain considered from a chemical and physiological viewpoint, the chemistry of carbon disulfide, the action of nitric and sulphuric acid on organic substances, the behaviour of CO<sub>2</sub> at high pressures, and procedures for measuring the density of vapours.

9. A French pharmacist who made important contributions in the areas of mineral chemistry, mineral and vegetable pigments, and extractive and analytical chemistry. Alone, or with his collaborators he discovered asparagine, alizarin and purpurin in madder, orcin, and orcein in lichens, glycyrrhizin in licorice, cantharidin in cantharides, amygdaline in bitter almonds, caffeine (independently of Pelletier, Caventou, Runge), and narcotine and codeine in opium.
10. A Portuguese a naval surgeon and botanist, who had served in Brazil between 1798-1801, and was the first to publish an approach to separate quinine from cinchona bark. His procedure yielded a crude crystalline mixture of the alkaloids present in the bark.
11. French pharmacist, member of the Académie de Médecine de Paris and at one time President of the Société de Pharmacie de Paris (1815 and 1822). Dedicated much of his time to the purify and determine the chemical properties of therapeutic and food products, particularly sugar beet. Studied in particular, the thermal decomposition of cupric acetate and proved that the composition of acetic acid was the same as the other acid called *acéteux*.
12. Armand Seguin published other papers about the properties of caloric, eudiometry, respiration, cinnabar, rosin, coffee, etc.
13. Thibouméry was the manager of Pelletier's factory for the production of alkaloids.

### BIBLIOGRAPHY

- Anonymous. *Journal du Palais*, Cour Royale de Paris, 5 Mars, 1839, volumes 111-112. First edition, Bureaux, Paris, 1839.
- Berthollet. C.L., *Éléments de l'Art de la Teinture*. 2 vols, Didot, Paris 1791.
- Blunt. W. and Stearn. W. *The Compleat Naturalist; a Life of Linnaeus*, Viking Press, New York, 1971.
- Boullay. PFG. "Nouveau Principe Immédiat Cristallisé auquel la Coque du Levant doit ses Qualités Vénéneuses". *Annales de Chimie*. 20. 1811. pp 209-214.
- Brock. WH. *Justus von Liebig: the Chemical Gatekeeper*. Cambridge University Press, New York, 1997.
- Bussy. A. "Discours Prononcé sur la Tombe de M. Pelletier". *Bulletin de l'Académie Royal de Médecine*. 7. 1842. pp 1011-1016.

- Bussy. A. "Discours Prononcé à la Distribution des Prix de l'École de Pharmacie pour l'Année 1842". *Journal de Pharmacie* [3]. 3. 1843. pp 48-58.
- Cahours. A. "Recherches sur les Huiles Légères Obtenues dans la Distillation du Bois". *Comptes Rendus*. 30. 1850. pp 319-323.
- Caventou. J-B. and Pelletier. PJ. "Sur un Nouvelle Base Salifiable Organique (la Brucine)". *Journal de Pharmacie*, 5. 1819. pp 529-545.
- Couerbe. JP. "Matière Nouvelle Retirée de l'Opium". *Annales de Chimie*. 49. 1832a. pp 44-45.
- Couerbe. JP. "Histoire Chimique de la Méconine". *Annales de Chimie*. 50. 1832b. pp 337-359.
- Couerbe. JP. "Réflexions sur le Dernière Mémoire de M. Pelletier". *Journal de Pharmacie*, 22. 1836. pp 22-29.
- Crosland. M. *Gay-Lussac, Scientist and Bourgeois*. Cambridge University Press, Cambridge, 1978.
- Derosne. JF. "Sur l'Opium". *Annales de Chimie*. 45. 1802. pp 257-285.
- Deville HSC. "Recherches sur les Résines. Étude du Baume de Tolu". *Comptes Rendus*. 13. 1841. pp 476-478.
- Dumas. J-B. *La Vie de J.-B. Dumas*. 1800-1884, Mimeograph edition, Paris, 1924.
- François. M. Caventou. J-B. and Pelletier, PJ. *Recherches sur les Propriétés Chimiques et Médicales de la Racine de Kahinça*. de Caprelet, Paris, 1830; *Journal de Pharmacie*. 16. 1830. pp 465-481.
- Göerig. M. and Schulte. Am. Esch. J. "Friedrich Wilhelm Adam Sertürner - On the 150th Anniversary of the Death of the Discoverer of Morphine". *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie*. 26. 1991. pp 492-498.
- Gomes. BA. "Ensaio Sobre o Cinchonino, e Sobre sua Influencia na Virtude da Quina e d'Outras Cascas". *Academia de Ciencia, Memorias, Lisboa*. 3. 1812. pp 202-217.
- Javillier. M. "Discours, Cérémonie de Remise a la Ville de Paris du Nouveau Monument a Pelletier et Caventou à Paris, 2 Mars, 1951". *Notices et Discours*, Institut de France, Académie des Sciences. 3. 1849-1856. pp 186-197.
- Liebig. J. "Bemerkungen zur Abhandlung von Pelletier und Couerbe über die Kockelkörner". *Liebig's Annalen*. 10. 1834. pp 203-210.
- Magendie. F. and Pelletier, PJ. *Recherches Chimiques et Physiologiques sur l'Ipécacuanha*. Colas, Paris, 1817; *Journal de Pharmacie*, 3. 1817. pp 145-164.
- Pelletier, PJ. *Essai sur la Nature des Substances Connues sous le Nom de Gommés Résines*. Première Thèse Présentée a la Faculté des Sciences de Paris, Université Impériale, Colas, Paris, 1812a.

- Pelletier. PJ. *Essai sur la Valeur des Caractères Physiques Employés en Minéralogie*. Deuxième Thèse Présentée a la Faculté des Sciences de Paris, Université Impériale Colas, Paris, 1812; published in *Journal de Physique*. 75. 1812b. pp 311-323.
- Pelletier. PJ. "De l'Opoponax, du Bdellium, et de la Myrrhe". *Bulletin de Pharmacie*. 4. 1812c. pp 49-56.
- Pelletier. PJ. "Analyse du Galbanum". *Bulletin de Pharmacie*. 4. 1812d. pp 97-102.
- Pelletier. PJ. "Examen Chimique de la Gomme Caragne". *Bulletin de Pharmacie*. 4. 1812e. pp 241-243.
- Pelletier. PJ. "D'un Mémoire sur l'Examen Général et Comparé des Gommés-Résines". *Bulletin de Pharmacie*. 4. 1812f. pp 502-505.
- Pelletier. PJ. "Analyse de la Sarcocolle". *Bulletin de Pharmacie*. 5. 1813a. pp 5-11.
- Pelletier. PJ. "Du Suc d'Hypocistis et de Quelques Combinaisons de l'Acide Gallique avec des Substances Végétales". *Bulletin de Pharmacie*. 5. 1813b. pp 289-294.
- Pelletier. PJ. "De Quelques Substances Colorantes de Nature Résineuse". *Bulletin de Pharmacie*. 6. 1814. pp 432-453.
- Pelletier. PJ. "Mémoire sur la Gomme de l'Olivier". *Journal de Pharmacie*. 2. 1816. pp 337-343.
- Pelletier. PJ. "Sur la Préparation de la Narcotine et de l'Acétate de Morphine". *Journal de Pharmacie*. 4. 1823. pp 530-533.
- Pelletier. PJ. "Note sur la Caféine". *Journal de Pharmacie*. 12. 1826. pp 229-233.
- Pelletier. PJ. "Nouvelles Recherches pour Servir à l'Histoire de l'Opium et ses Principes". *Journal de Pharmacie*. 21. 1835. pp 555-582.
- Pelletier. PJ. "Réponse à la Note de M. Couerbe". *Journal de Pharmacie*. 22. 1836a. pp 29-36.
- Pelletier. PJ. "De l'Action que l'Chlore Exerce sur les Bases Salifiables Organiques". *Journal de Pharmacie*. 24. 1836b. pp 153-166.
- Pelletier. PJ. "De l'Action de l'Iode sur les Bases Salifiables d'Origine Organique" *Comptes Rendus*. 2. 1836c. pp 231-232.
- Pelletier. PJ. "De l'Action de l'Iode sur les Bases Organiques". *Comptes Rendus*. 2. 1836d. pp 568-571.
- Pelletier. PJ. "Nouvelles Recherches sur l'Opium". *Journal de Pharmacie*. 18. 1852. pp 597-632.
- Pelletier PJ. and Caventou. J-B. *Notice sur la Matière Verte des Feuilles [Chlorophylle]*. Colas, Paris, 1817; published in *Journal de Pharmacie*. 3. 1817. pp 486-491, and *Annales de Chimie*. 9. 1818. pp 194-196.

- Pelletier. PJ. and Caventou, J-B. "Examen Chimique de la Cochenille et de sa Matière Colorante". *Annales de Chimie*. 8. 1818a. pp 250-286.
- Pelletier PJ. and Caventou J-B. "Note sur une Nouvel Alkali". *Annales de Chimie*. 8. 1818b. pp 323-324.
- Pelletier. PJ. and Caventou. J-B. "Expériences faites avec la Noix Vomique, la Fève de Saint Ignace, et la Vauqueline". *Journal de Médecine*. 2. 1818c. pp 359-360.
- Pelletier. PJ. and Caventou. J-B. and Magendie. F. *Mémoire sur une Nouvel Alkali Végétal (la Strychnine) Trouvé dans la Fève de Saint-Ignace, la Noix Vomique*, etc. Fain, Paris, 1818d.
- Pelletier. P.J. and Caventou J-B. "Sur un Nouvel Alkali Végétal (la Strychnine) Trouvé dans la Fève de Saint-Ignace, la Noix Vomique, etc". *Annales de Chimie*. 89. 1819. pp 142-177.
- Pelletier. PJ. and Caventou. J-B. "Note sur la Nature Adipocireuse de l'Ambre Gris et sur l'Origine de ce Produit". *Journal de Pharmacie*. 6. 1820a. pp 49-58.
- Pelletier. PJ. and Caventou. J-B. "Examen Chimique de Plusieurs Végétaux de la Famille des Colchicées, et du Principe Actif qu'ils Renferment [Cévadille (veratrum sabadilla)]; Hellébore blanc (veratrum album); Colchique commun (colchicum autumnale)]". *Journal de Pharmacie*, 6. 1820b. pp 353-365; *Annales de Chimie*. 90. 1820b. pp 69-89.
- Pelletier. PJ. and Caventou. J-B. "Recherches Chimiques sur les Quinquinas". *Annales de Chimie*. 15. 1820c. pp 289-318, 337-364.
- Pelletier. PJ. and Caventou. J-B. "Lettre de MM. Pelletier et Caventou à MM. les Membres de l'Académie Royale des Sciences, sur la Fabrication du Sulfate de Quinine". *Annales de Chimie*. 10. 1827. pp 331-365.
- Pelletier. PJ. and Coriol, "Notice sur une Nouvelle Base Salifiable Organique Venant du Pérou". *Journal de Pharmacie*. 15. 1829. pp 565-58.
- Pelletier. PJ. and Couerbe JP. "Nouvelle Analyse de la Coque du Levant". *Annales de Chimie*. 54. 1833. pp 178-208.
- Pelletier. PJ. and Dumas. J-B. "Recherches sur la Composition Elémentaire et sur Quelques Propriétés Caractéristiques des Bases Salifiables Organiques". *Annales de Chimie*. 24. 1823. pp 163-192.
- Pelletier. PJ. and Pétroz. H. "Examen Chimique du Curare". *Annales de Chimie*. 40. 1829. pp 213-219.
- Pelletier. PJ. and Walter. P. "Examen des Produits Provenant du Traitement de la Résine dans la Fabrication du Gaz pour l'Éclairage". *Comptes Rendus*. 4. 1837. pp 898-899.
- Reid. JM. *Traveller Extraordinary: the Life of James Bruce of Kinnaird*. Eyre & Spottiswoode, London, 1968.

- Robiquet. PJ. "Considérations sur l'Arôme". *Annales de Chimie*. 15. 1820. pp 27-37.
- Seguin. A. "Mémoire sur l'Opium (1804)". *Annales de Chimie*. 92. 1814. pp 121-140.
- Sertürmer. F. "Säure im Opium". *Trommsdorff Journal de Pharmacie*. 1805. pp 234-241.
- Simon. J. "Naming and Toxicity; A History of Strychnine". *Studies in History and Philosophy of Biology & Biomedical Science*. 30. 1999. pp 505-525.
- Thenard. LJ. Robiquet, E. and Dumas, J-B., "Rapport sur un Mémoire de MM. Pelletier et Ph. Walter Relatif aux Produits Pyrogénés de la Résine". *Comptes Rendus*. 6. 1838. pp 460-468.
- Vogel. HA. and Pelletier. PJ. "Examen Chimique de la Racine de Curcuma". *Journal de Pharmacie*. 50. 1815. pp 289-30.
- Williams. LP. "*Michael Faraday: a Biography*". Basic Books, New York, 1965.
- Wisniak. J. "Louis Jacques Thenard". *Rev. CENIC Ciencias Químicas*. 33. 2002. pp 141-149.
- Wisniak. J. "Henri Étienne Sainte-Claire Deville: A Physician Turned Metallurgist". *Journal of Materials Engineering and Performance*. 13. 2004 pp 117-128.
- Wisniak. J. "Henri Braconnot". *Revista CENIC Ciencias Químicas*. 38. 2007. pp 345-355.
- Wisniak. J. "Claude-Louis Berthollet". *Rev. CENIC Ciencias Químicas*. 39. 2008. pp 45-55.