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ÉTIENNE OSSIAN HENRY

Alkaloids and other vegetable principles

ÉTIENNE OSSIAN HENRY Alcaloides y otros principios vegetales

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ABSTRACT

Étienne Ossian Henry (1798-1873), a French pharmacist, carried extensive research on the chemistry, analysis, and extraction of alkaloids (quinine sulfate, quinidine, morphine, strychnine, and brucine) and active vegetable principles (among them, tanguin nut, white mustard, peanuts, New Zealand flax, asparagus, solanine, manioc, and rhubarb). Henry and Ollivier separated from the nuts of tanguin sweet oil and a viscous poisonous principle, which they named tanghinin, acting on the cerebrospinal system and causing death by syncope or asphyxia. With Garot they isolated from mustard oil a new acid (sulfosinapic acid) and prepared a large number of its salts. Henry and Pelouze were the first to isolate peanut oil, which eventually became a large major chemical commodity. Henry developed an efficient process for determining the amount of cinchonine sulfate present in quinine sulfate; together with Delondre they discovered the presence of a new alkaloid in the bark of yellow quinquina, which they named quinidine (a dextro rotatory stereoisomer of quinine) and prepared a large number of its salts, which were shown to be very similar to the corresponding salts of quinine, although much easier to crystallize. Henry and Plisson developed a new procedure for extracting morphine from opium that did not require alcohol and was based on the fact that morphine and narcotine could be easily separated with the help of diluted HCl

Keywords: alkaloids; cinchonine; mustard oil; opium; peanut oil; quinidine; rhubarb

RESUMEN

Étienne Ossian Henry (1798-1873), un farmacéutico francés que llevó a cabo un detallado estudio de la química, análisis y extracción de alcaloides (sulfato de quinina, quinidina, morfina, estricnina, y brucina) y principios vegetales activos, entre ellos, la nuez de tanguín, mostaza blanca, maníes, fibra de lino, espárrago, solanina, mandioca, y ruibarbo. Junto con Ollivier separaron de la nuez de tanguín un aceite dulce y un principio viscoso y venenoso, que llamaron tanghinin, que actuaba sobre el sistema cerebroespinal y causaba la muerte por síncope o asfixia. Con Garot aislaron del aceite de mostaza un ácido nuevo, el ácido sulfosinápico, y prepararon un gran número de sus sales; con Pelouze fueron los primeros en extraer el aceite de cacahuetes, que con el tiempo se convirtió en un producto de consumo mundial. Henry desarrolló un proceso eficiente para determinar la cantidad de sulfato de cinconina presente en el sulfato de quinina. Con Delondre descubrieron la presencia de un nuevo alcaloide en la corteza de la quinquina amarilla que nombraron quinidina (un estereo dextro rotatorio isómero de la quinina) y prepararon numerosas de sus sales, que resultaron ser muy similares a la correspondientes de quinina, aun cuando más fáciles de cristalizar. Henry y Plisson propusieron un procedimiento nuevo para extraer la morfina del opio que no requería el uso de alcohol y estaba basado en el hecho que la morfina y la narcotina eran fácilmente separables por medio de HCl diluido.

Palabras clave: alcaloides; cinconina; aceite de mostaza; opio; aceite de cacahuetes; ruibarbo

INTRODUCCIÓN

Life and career

There is very little information about the life and career of Étienne Ossian Henry. He was born in Paris in 1798, the son of the pharmacist Nöel Étienne (1769–1832), director of the Central Pharmacy of the Hospitals of Paris. Étienne received his degree of pharmacy from the École de Pharmacie in Paris, in 1821; during his studies he was awarded the prizes of chemistry and pharmacy. He joined the Central Pharmacy and there, for four years, taught a course of theoretical and practical chemistry to the young employees. For ten years he directed the pharmaceutical and chemical works of the institution, and eventually became its sub-Director. In 1824 he was elected adjunct member of the Académie Royale de Médicine (medical chemistry section). He was member of the societies of pharmacy, medical chemistry, and of the society of pharmacists of Northern Germany, and one of the editors of the Journal de Pharmacie. In 1846 he was elected to the Légion d'Honneur.

Henry carried research on a wide variety of subjects, including analytical chemistry, analysis of vegetable principles, analysis of potable and mineral waters, the determination and derivatives of alkaloids, etc. Among his many publications we can mention the analysis of the bark of paraguatan (Henry, 1833) and of illipe oil (Henry, 1835), the use of tannin for the quantitative determination of alkaloids in vegetables (Henry, 1834a, 1835a), some sulfo-derivatives of amyl alcohol (Henry, 1849b), the analysis of milk and its modifications, and medico-legal aspects of phosphorus (Chevallier and Henry, 1839, 1857), and analysis of mineral waters (Henry, 1843-1844; Henry and Henry, 1858; Plisson and Henry, 1831). He also collaborated with Pierre Hubert Nysten (1771-1818) in the publication of his medical, pharmaceutical, and veterinary dictionary (Nysten, Brichetau and Henry, 1839), and with Félix-Séverin Ratier (1797-1866) in the writing and publication of the Codex of Medicines for the French hospitals (Ratier and Henry, 1826). Most of the work done in collaboration with Antoine François Boutron-Charlard (1796-1879) (Boutron-Charlard and Henry, 1824, 1836, 1848, 1852; Henry and Boutron-Charlard, 1828) has been discussed previously and will not be repeated here (Wisniak, 2016). Both were awarded the 1850 Montyon Prize (2,000 francs) of the Académie des Sciences of their work on the chemical constitution of the waters of the Seine Department.

Scientific contribution

Henry published more than 170 papers and several books in the areas of vegetable principles, alkaloids, analysis of waters and hydrology, tannin as an analytical reagent, analytical chemistry, etc. etc. As customary for a candidate to the Académie des Sciences, he published a booklet detailing his main research achievements (Henry, 1840).

Vegetable principles

Tanguin (Tanghinia madagascariensis)

In 1824 Julien-Joseph Virey (1775-1846) reported that the natives of Madagascar used the seed of the tree Tanguin (*Tanghinia madagascariensis*) to ascertain the guilt of suspected persons, like those accused of witchery. These were forced drink the juice of tanguin; the ones who were able to withstand the ordeal were considered innocent; and, vice versa, those

who died were said to be guilty (Virey, 1822). The tree had been classified by the botanist Louis-Marie Aubert du Petit-Thouars (1758-1831) as belonging to the family of apocynaceae; its fruit, black on the outside, contained two extremely poisonous almonds, which the natives mixed with the juice of an aromatic plant to prepare the potion given the to accused, in different concentration according to the nature of the crime. Weak doses produced painful but not deadly effects; otherwise the accused passed away after suffering terrible convulsions and pain. According to Henry and the physician Charles Prosper Ollivier d'Angers (1796-1845), no research had been conducted to determine the nature and properties of the fruit. They were fortunate to obtain a sample of the seeds from the physician Mathieu Joseph Bonaventure Orfila (1787-1853), to carry on the necessary experiments (Henry and Ollivier, 1824).

The seeds were slightly larger than those of the common almond; its kernels were unctuous and had a bitter piquant taste. Pressed in between the fingers they released a colorless fixed oil; when ground in a mortar with a small amount of water they produced a white emulsion, and after calcination they a left a voluminous a carbon residue of coal while releasing a large amount of ammonium bicarbonate. They did not react with iodine or its tincture but treated with slightly warm mineral or vegetal acids they acquired a green blue color, more or less intense (this result was afterwards shown to be very important). Alkalis led to the formation of a red brown color. Treatment of the shells with ether, concentrated alcohol, and pure or acidulated water did not show the extraction of any substance of interest. Under pressure, the kernels released a thick white oil, solidifying at 8^0 to 10^0C, soluble in ether, insoluble in alcohol, and reacting with alkalis. The oil, washed with alcohol, became very liquid, colorless, tasting sweet, and having all the properties characterizing a fixed oil.

The residue of the alcohol wash was extracted repeatedly with ether and the solution left to evaporate spontaneously. The new residue was a white crystalline matter, which was purified by recrystallization from concentrated alcohol. Application of a very small quantity of this substance on the tongue produced a hot constriction in the back of the mouth, similar to the one caused by pyrethrum. Henry and Ollivier reported that this substance caused the prompt death of animals. All these results indicated that it was very poisonous and harmful to animal economy. Additional experiments indicated that this substance did not act on any of the color tinctures or alkalis and that some of the mineral acids communicated to it a yellow color. Under the influence of moderate heat it melted without vaporization and assumed the aspect of a resin. It did not contain nitrogen as seen during its decomposition by means of cupric oxide (Henry and Ollivier, 1824).

The results obtained indicated that the two principles isolated thus far did not produce with acids solutions colored green (indicated above), as did the almond. From them, Henry and Ollivier inferred that that parenchyma of the kernels had to contain a compound that originated this property. The parenchyma was first exhausted with ether and seen to take a green blue color, when contacted with a strong acid. In order to separate the third principle, Henry and Ollivier treated with alcohol the residue of the ethereal extraction and evaporated the solution until it became a viscous non-crystallizable material, insoluble in ether, very soluble in water, slightly bitter, and reddening litmus paper. This residue did not release ammonia when decomposed over fire and its aqueous solutions gave colored precipitates when treated with acids (sulfuric, nitric, phosphoric, arsenic, nitric, tartaric, citric, oxalic, and acetic). With alkalis the color of the precipitates varied between brown and red brown.

After some additional tests Henry and Ollivier concluded that the seeds from tanguin contained a fixed limpid sweet oil, solidifying at 10^0C; a particular poisonous neutral substance, crystallizable; a brown viscous principle, slightly acid and bitter, non-crystallizable, turning acids green and alkalis brown, and which they named *tanghuine*; traces of gum; a large amount of vegetable albumin; and traces of calcium carbonate and iron oxide (Henry and Ollivier, 1824).

In a following paper, read to the Académie de Médicine, Ollivier reported that the medical effects of the seeds corresponded to those of a bitter narcotic, with a frequency that varied according to the dose ingested. The deleterious principle was absorbed, transported in the blood, and acted on the cerebrospinal system causing death by syncope or asphyxia; 1.2 g were enough to kill a dog in about one hour, after experimenting convulsions and alternative opisthotonos symptoms and paralysis (Ollivier, 1824).

White mustard

In 1825 Henry and Garot (a student of Henry) reported to the Académie Royale de Médicine the results of their study on the state of sulfur in the seeds of mustard (Henry and Garot, 1825). In their review of the literature they indicated that L. Thibierge had analyzed the seeds of black mustard and found that they contained a soft, fixed oil, of a dark greenish color, soluble in alcohol and ether, which could be obtained by pressure; another oil, obtained by distillation, an albuminous vegetable principle, a large quantity of mucilage, sulfur, nitrogen, calcium phosphate and sulfate, and a little silica. According to Thibierge, the golden yellow oil fraction obtained by distillation was volatile, heavier than water, had a hot acrid taste, and was soluble in alcohol depositing sulfur. This was the oil that irritated the eyes and excited tears in mustard prepared for the table, and vesicated when mustard was applied to the skin. The sulfur was not present in a free state but in a particular state of combination (Thibierge, 1819). The latter result induced Henry and Garot to try to determine the nature of this combination.

Henry and Garot treated the oil with rectified alcohol and left the mixture to settle for about 15 days. The alcohol fraction was separated and left to evaporate spontaneously. A reddish granular substance was seen to crystallize on the walls of the vessel; it was very soluble in water, very acid, and having a piquant bitter taste, reminding that of sulfur. When recrystallized from alcohol, it precipitated as yellow or pink pearly needles. On calcination it produced carbon, CO_2, and ammonium sulfide. The alcoholic solution produced a white precipitate with lead sub-acetate and silver nitrate. These first results indicated that the sulfur was not present in a free state or as hydrogen sulfide and that the substance in question was a new acid containing carbon, hydrogen, sulfur, and nitrogen. Henry and Garot wrote that the next step was to determine if the compound contained oxygen and check the possibility that it was not an acid salt of ammonia. For these purposes they worked on yellow mustard, the variety that contained the most oil. Extraction with alcohol and concentration by distillation left a yellow extract that on cooling precipitated crystalline pearly plates, which appeared to be different from the ones obtained with black mustard. The precipitate was purified by recrystallization. The final product was small white yellow brilliant plaques having a slight piquant and bitter taste, and a tenuous sulfurous smell. They were completely soluble in water and alcohol, and a little in ether (Henry and Garot, 1825).

The crystals were treated with over 23 reagents, including litmus paper, lime water, alkalis, acids, ferrous sulfate, lead sub-acetate, silver nitrate, and chlorine. The results indicated that the new substance was a true acid, which formed true crystallizable salts and contained an appreciable amount of sulfur. For this reason Henry and Garot decided to name it *sulfosinapic acid*.

In the following section of their paper they described in detail the preparation, properties, and composition of the sulfo-sinapates of calcium, barium strontium, potassium, sodium, and ammonium. All these salts reddened to the maximum a solution of ferric chloride. Henry and Garot carried on an elemental analysis of the acid and reported that it contained, by weight, 49.5% carbon, 8.3% hydrogen, 17.33% sulfur, 12.96% nitrogen, and 11.91% oxygen (Henry and Garot, 1825).

In 1830, Théophile-Jules Pelouze (1807-1867, a student of Joseph-Louis Gay-Lussac (1778-1850), published a paper claiming that sulfosinapic acid was actually calcium sulfocyanate (Pelouze, 1830). Henry and Garot were outraged by this paper, which they believed "was written curtly and with a surprising casualness"; consequently, they decided to carry on additional experiences, while recognizing that their original paper contained some mistakes easy to explain. In their following paper they first gave a detailed description of the method for isolating their sulfo-sinapic acid, the properties of sulfo-sinapisine (the new name they proposed for the acid), its elemental analysis, its reactions with acids and alkalis, and a variety of salts (Henry and Garot, 1831). The seeds of white mustard (*Sinapis alba*) or black mustard or of tower mustard (*Turritis glabra*) were first crushed, then boiled with distilled water and the resulting product filtrated and extracted with alcohol. The alcoholic liquid reddened strongly ferric salts and did not show the presence of any amount of calcium. The fraction insoluble in alcohol was shown to contain gum, a coloring substance, and calcium phosphate, citrate, and malate, as reported by Pelouze. Concentration of the alcoholic extract yielded a white precipitate having the reported properties of sulfo-sinapic acid. Purification of the latter with ether, eliminated a very volatile red substance, and left a residue soluble in hot water or alcohol, which Henry and Garot named now *sulfo-sinapisine*, recognizing that it was not an acid.

Sulfo-sinapisine was a white odorless and slightly bitter substance, more soluble in hot water and hot alcohol, and crystallizing as pearly needles. On heating it first transformed into a yellow liquid and then decomposed into very fetid pyrogenic materials containing ammonium carbonate and bisulfate, brown oil, and voluminous carbon, and leaving no traces of calcium, sodium, or potassium. The gaseous compounds were found to contain a large amount of sulfur. The aqueous solution did not act on test papers and other reagents. An elemental analysis of sulfo-sinapisine indicated that it contained, per weight, 50.504% carbon, 7.795% hydrogen, 4.940% nitrogen, 9.657% sulfur, and 27.104% oxygen. These results indicated that sulfo-sinapisine contained all the elements to develop hydrosulfocyanic acid (thiocyanic acid), if treated by the proper reagents (Henry and Garot, 1831).

Acids acted on sulfo-sinapisine as follows: nitric acid speedily, producing a bright color, red vapors, and sulfuric acid. It dissolved in HCl, producing a green solution, which on heating disengaged a strong smell of prussic acid; chlorine produced a similar result. Distillation of a solution in sulfuric or phosphoric acid generated a large amount of thiocyanic acid. The alkalis produce singular phenomena: ammonia dissolved it and rendered it either yellow or orange-yellow; by evaporation small brilliant crystals were produced, which contained no

alkali, and appeared to consist of the substance scarcely altered. A solution of KOH or NaOH rendered the color yellow, which changed to orange and green; the solution evaporated to dryness, released an abundant odor of the volatile oil of mustard. The influence of salts was variable: barite transformed it partially into thiocyanic acid; it was not affected by the salts of calcium, zinc, and manganese, and lead acetate and sub-acetate; the ferric salts reddened it strongly; and cupric sulfate, the mercurous nitrate and silver nitrate, all gave white precipitates. Henry and Garot concluded now that that limewater, barite, and KOH dissolved sulfo-sinapisine, which afterwards crystallized retaining variable amounts of alkalis; these crystals they had wrongly recognized before as salts. These mixtures, when distilled, contained hydrogen cyanide and thiocyanic acid, In other words, under the influence of barite, for example, the sinapic substance was modified and thiocyanic acid was a byproduct of the reaction (Henry and Garot, 1831).

Based on the results of their additional experiments, Henry and Garot concluded that (1) the seeds of white mustard contained a particular crystallizable substance (sulfo-sinapisine), composed of the same elements as thiocyanate, accompanied by an organic material which provided the volatile oil of mustard; (2) sinapisine was a neutral compound, which under the influence of certain acids, oxides, or salts, was able to transform into thiocyanic acid, free or combined; and (3) contrary to Pelouze's claims, calcium thiocyanate was not present in the seeds (Henry and Garot, 1831).

Peanuts (Arachis hypogea)

In a paper published in 1825, Anselme Payen (1795-1871) and Henry reported that a farmer by the name of Vallet had succeeded in obtained substantial crops of peanuts and was interested in knowing what benefits could be obtained from them (Payen and Henry, 1825). Payen and Henry wrote that the Italian botanist G. Biroli had reported that peanuts contained about 50% of an oil that differed from olive oil only in its solidification temperature and a slight smell of radish, which was eliminated by heating. Peanut oil could easily substitute olive oil in domestic uses; the juice retained a large amount of white starchy material, very similar to that of wheat, and which could be used to replace cacao in the manufacture of chocolate. In addition, many customers attested that the seeds contained substantial amounts of sugar material (Biroli, 1810).

As a first task, Payen and Henry decided to verify Biroli's assertions. From 1950 grams of peanuts they obtained 1495 g of seeds and 455 g of shells. The seeds were covered by a brown skin, were internally white, and had a slight taste recalling that of beans. Cold pressing released green white oil; the oil remaining in the marc could be removed by heating and further pressing, and by extraction with ether. The total oil extracted amounted to 47% of the weight of the full fruit. The following series of experiments was devoted to separate and identify the different components of the seed. For this purpose, Payen and Henry subjected the marc to different treatments, including extraction with water and alcohol, calcination, evaporation of the different fractions, treatment with HCl, ammonia, lead sub-acetate, iodine, steam distillation, etc., From the results they concluded that peanuts contained oil, casein (instead of albumin), water, crystallizable sugar, calcium phosphate, coloring matter, sulfur, starch, potassium chloride, and probably gum, calcium malate, free malic acid, and essential oil. Peanut oil seemed to be the most important component, and for this reason was investigated further. Its density was 0.9163, was insoluble in alcohol and completely soluble in ether. Cooled to 3^0C deposited a large quantity of stearin; further cooling to -3^0 to -4^0C

turned it into a soft mass. Treated with NaOH produced soap; with oxygen it led to slow rancidity. The overall set of properties indicated that peanut oil could be used as a substitute of almond oil in pharmaceutical preparations and fine perfumery (Payen and Henry, 1825). This is an interesting paper because it shows the infancy of an industry which today produces more that 35 million tons of fruit per year. The largest growers are India and China and the main use is as oil.

New Zealand flax (Phormium tenax)

According to Henry, this flax originated from New Zealand where the natives used it for making materials, ropes, etc. It grew successfully in light soils and wet places and had been well acclimatized in several European countries, among them England and France. The French Society of Agriculture was interested in more knowledge about this plant, which would help find better ways for separating the threads and their working. It was already known that an easy way of achieving these objectives was to boil the plant in water containing a small amount of soap. Before testing producing the threads mechanically, as was done with common flax and hemp, it was necessary to have more information about the components of the fiber (Henry, 1826).

Henry took a certain quantity of well-powdered flax and digested it with water in an autoclave. The resulting brown viscous liquid was nauseous, had a very bitter disagreeable bitterness, which did not persist for a long time. Concentrated alcohol extracted a resinous material mixed with the bitter portion. The resin was found to redden litmus paper. After drying, the large gray residue was insipid, friable, very soluble in water, and produced a slightly salty solution. The gray coloration was deepened by alkalis. The bitterness present in the original viscous liquid was easily eliminated by partial evaporation, followed by addition of water. The material remaining from the first water cooking was then treated with alcohol and ether; the first solvent showed the presence of a small amount of wax, while ether removed the chlorophyll present. The final product was the insoluble fibers, which did not react with alkalis and acids. Heating the plant did not result in the release of nitrogen.

Henry wrote that the plant growing in the meadow exuded a white gelatinous insipid substance, which on drying turned into yellow transparent plates. The raw plant, when cut by a sharp instrument, exuded a similar gummy material. The natural exudation was soluble in water, and insoluble in alcohol and acids, Nitric acid converted it into white pulverulent mucic acid, accompanied by a small amount of oxalic acid (Henry, 1826).

Henry went on to examine the different principles present in the flax. Treatment of the powdered material with boiling ether resulted in the extraction of the chlorophyll and a waxy material. The residue was extracted further with hot concentrated alcohol; the alcoholic yellow brown solution was slightly acid and very bitter. Addition of water precipitated a brown insipid resin while the liquid retained its disagreeable taste; the liquid did not react with acids and alkalis. Further treatment indicated that the flax also contained a large amount of a colored gum, potassium and sodium chloride, sodium sulfate, potassium bimalate, calcium phosphate and sulfate, iron oxide, silica, and a large amount of fibrous material. All these facts explained the action of many agents upon the flax. Acids dried, wrinkled, and packed the fibers while alkalis dissolved the gum and resin that filled the interstices between the fibers and facilitated their division (Henry, 1826).

Asparagine

In his first his paper about asparagus (Robiquet, 1805), Pierre Jean Robiquet (1780-1840) wrote that Antoine Augustin Parmentier (1737-1813) had requested from the apothecaries of the Military Hospital to repeat the experiments that M. Antoine had performed on this vegetable. After many experiments Robiquet concluded that the green feculent juice of asparagus was composed of three substances: one insoluble in alcohol and of nature similar to animal matter, the other two soluble in alcohol, but separating on cooling. The filtered juice contained (a) albumen, which coagulated on the first ebullition, (b) potassium phosphate, (c) asparagus acid combined with lime, (d) foliated earth, (e) a vegeto-animal substance, (f) an extractive matter obtained after precipitating with gall nuts the portion of the extract insoluble in alcohol, (g) a triple salt of ammonia and lime, and (h) a coloring principle susceptible of becoming red by acids and yellow by alkali (Robiquet, 1805).

In a following publication, Louis Nicolas Vauquelin (1763-1829) and Robiquet wrote that having left in the laboratory a certain quantity of juice of asparagus, concentrated by evaporation, Vauquelin observed in it a considerable number of crystals, of which two seemed to belong to a new substance, and were easily separated because they differed from the others in form, transparency, and taste. Repeated recrystallization yielded perfectly white and hard, brittle clear rhomboidal crystals having a cool taste, somewhat nauseous, which provoked the flow of saliva. Analytical examination led Vauquelin and Robiquet to conclude that it was an immediate principle of asparagus (asparagine), which contained mainly carbon, hydrogen, and carbon, and a small amount of nitrogen (Vauquelin and Robiquet, 1806). Further work by Auguste-Arthur Plisson (-1832) (Plisson 1829) showed that asparagine, under the action of several agents, transformed into aspartic acid, capable of forming salts with the bases.

In 1830 Plisson and Henry published a monograph about asparagine describing the knowledge available about this amino acid and adding experimental data and new an easy way of obtaining it from the roots of marshmallow (*Althaea officinalis* L.) (Plisson and Henry, 1830). The dry and skinned roots were extracted repeatedly with warm water and the collected extracts evaporated and clarified by ebullition. Left to cool the concentrate precipitated bulky octahedral crystals, which were purified by recrystallization. One kilo of marshmallow yielded about 20 g of pure colorless asparagine. Asparagine crystals were transparent, odorless and colorless, and tasting like aspartic salts. They were soluble in water and insoluble in absolute alcohol and ether. Calcined it disappeared completely, yielding all the pyrogenic products of organic materials. Elemental analysis indicated that asparagine contained ammonia, cyanogen, ethylene, and CO_2 in the proportion 2:1:3:4. The reactions of asparagine with warm water, acids, and alkalis were singular. With water it generated ammonia and ammonium aspartate; with potassium carbonate and bicarbonate, ammonium carbonate and potassium aspartate; and with HCl and HNO_3, the ammonium salt and ammonium aspartate. From these results Plisson and Henry inferred that the practice of covering corpses with lime to avoid exhalation of foul gases, could be explained by lime generating nonvolatile materials, quite different form those formed during natural putrefaction (Plisson and Henry, 1830).

Delphin and solanine

In a research note published in 1831 Henry wrote that among the alkaloids found in the organic kingdom, delphin and solanine had not been investigated in detail because of the small amounts prepared by their discoverers (Lassaigne and Feneulle, 1819; Desfosses, 1821). Having developed a method for preparing large amounts of vegetable alkaloids Henry felt that he could add important information about these two compounds, including their elemental analysis (Henry, 1832).

For extracting delphin, he powdered a certain amount of the seeds of lice grass (*Delphinium staphysagria*) and extracted it with warm concentrated alcohol mixed with a little of sulfuric acid. After settling, the alcoholic extract was separated and treated with an excess of calcium carbonate. The solution became green and deposited a strong yellow green flocculent precipitate. On distilling the filtrated alcoholic solution, it deposited a fatty green matter, insoluble in water, which was then washed with dilute sulfuric acid. The filtrate was evaporated to dryness leaving a resinous residue of delphin. Solanine was obtained by a similar procedure from the seeds of nightshade (*Solanum dulcamara*) (Henry, 1832).

Henry described delphin as a white pulverulent substance, gelatinous when in a fresh humid state, having a very acrid taste and irritating the nose without causing sneezing. It was sparingly soluble in water and very soluble in alcohol and ether. The alcoholic solution turned blue a reddened litmus paper. Under moderate heat it melted into a yellow resin, which in contact with water, hydrated and turned opaque white. It reacted with acids without producing crystallizable salts; the latter were decomposed by ammonia, precipitating the alkaloid as a jelly or white flakes. Elemental analysis of delphin indicated that it contained, by weight, 74.24% carbon, 8.87 hydrogen, 3.328% nitrogen, and 13.562% oxygen. Solanine was a white slightly green pulverulent material, gelatinous when humid, having an irritant acrid bitter taste. It was insoluble in water and little soluble in ether. The last property allowed eliminating any possible chlorophyll present. It was soluble in alcohol at 35^0C; the alcoholic solution turned blue a reddened litmus paper. It reacted with acids without producing crystallizable salts. Elemental analysis of delphin indicated that it contained, by weight, 74.000% carbon, 9.142% hydrogen, 3.080% nitrogen, and 12.778% oxygen. The gallnut tincture precipitated the alcoholic solutions of delphin or solanine (Henry, 1832).

Manioc (Jatrapha manihot)

According to Henry (Henry, 1834b) manioc (*Jatraphra manihot*) is a shrub belonging to the euphorbiaceae, originating from America, and producing a root used as a food source. There are two varieties, sweet manioc and bitter manioc. The latter variety is the one that is cultivated the most, in spite of containing a very poisonous principle. The toxic substance is rapidly destroyed by heat and the remaining material can be used for the nutrition of men and animals, in the form of cassava or tapioca. In order to prepare cassava, the roots are grated and the pulp pressed between sacks. The expressed pulp is cooked and left to dry on the roof of the houses. The roots provide a substantial amount of starch, which is prepared in the standard manner. The portion of the pulp that does not pass the sieve is dried, slightly toasted, and crushed to prepare a rough flour named tapioca, which is used to prepare an excellent food by boiling it with milk (Henry, 1834b).

The poisonous material was contained in the juice of the roots and seemed to be a very volatile compound, thermally labile, having a penetrating smell reminding that of HCN. Eugène Soubeiran (1797-1859) had already investigated it, examined the roots and reported

that the volatile compound had an odor very similar to the water distilled from bitter almonds, although it did not seem to contain HCN (Soubeiran, 1828). According to Henry, this apparent contradiction with his results was due to the very small amount of roots examined by Souberain.

Henry carried out a detailed analysis of the juice of bitter manioc, which he obtained by pressing fresh roots. This juice was yellow green and contained a small amount of starch particles, separable by filtration. Evaporated in free air it deposited small crystalline grains. It was found to contain a small amount of calcium carbonate and a very strong acid. Exposed to heat, it developed a distinct smell of HCN, followed by another one very piquant. Henry observed that passing these volatile compounds through a solution of silver nitrate resulted in the precipitation of white flakes. These flakes, treated with HCl, released HCN, clearly identified by its odor. These results proved that the juice of manioc contained HCN or a principle able of releasing it. Decomposition of the acid in the presence of cupric oxide proved that it was not formic acid or a formiate. Further testing with a variety of reagents led Henry to conclude that the juice of manioc also contained acetic acid; an organic magnesium salt of the acid; a bitter and acrid substance, very soluble in water and alcohol, and irritating the throat; starchy substances, and a very small amount of calcium phosphate (Henry, 1834b).

Two years latter, Henry in collaboration with Antoine François Boutron-Charlard (1796-1879) published a very detailed analysis of the composition of the root of manioc (Henry and Boutron-Charlard, 1836). This work has been discussed in another publication and will not be repeated here (Wisniak, 2016).

Rhubarb

According to Henry, there was much confusion and contradiction regarding the origin and analysis of the many varieties of rhubarb available in the commerce. There was particular interest in the variety Rheum australe as a possible cultivar for the Paris area and Henry had been requested to make an analysis of its roots (Henry, 1836).

The samples received by Henry were brown colored in the exterior and marble yellow in the inside; they were surrounded by a thin cortical portion easily separated; they possessed a sensibly aromatic smell and a taste, mucilagous at first, and then bitter, nauseous, and astringent. The saliva was tinted yellow after being chewed a few minutes. As a first step, Henry grated the roots, and then dried and powdered them. A known weight was then extracted by alcohol, followed by extraction with warm water, and the extracts evaporated to dryness. The brown residue was partly soluble in water; the solution was acid, produced a deep black color with ferric salts, formed a precipitate with gelatin, and was found to contain a large amount of calcium malate. The insoluble part was found to contain calcium oxalate, sulfate, and phosphate, a little iron, lignin, and pectin. The original powder was subjected to moderate heat in a crucible and seen to emit a yellow aromatic vapor, which collected in the mouth of a funnel in the form of a yellow powder, fusing at high temperature into a brown oily liquid, which Henry assumed to the coloring matter of rhubarb (Henry, 1836).

One hundred grams of the original powder was extracted with ether and the resulting solution evaporated until its volume had been by three-fourths. The remaining deep brown yellowish liquid was evaporated under vacuum to a crystalline looking solid, weighing 7.3 g,

and constituting the yellow matter or yellow resin of rhubarb (*rheine*). This product dissolved in boiling water and when cooled precipitated a yellow astringent powder, from which a small amount of non-volatile oil could be separated. Rheine was found to be slightly soluble in sulfuric acid, acetic acid, and HCl. Nitric acid transformed it into a brownish yellow substance, which did not contain oxalic acid, and was partially soluble in water. Strong bases such as KOH, NaOH, and ammonia, produced solutions having a beautiful reddish color, suggesting their possible use in dyeing. The aqueous solution of rheine produced different colors with a variety of reagents: yellow with barium chloride, rose with lead acetate, black with ferric chloride, yellow white with tin dichloride, and yellow with alum. Henry added that he unable to determine if the coloring matter contained a volatile oil, which gave it an aromatic odor, or whether the odor belonged to rheine itself (Henry, 1836).

The residue of the ethereal extraction was treated with alcohol and with pure cold water. The resulting solutions were joined and evaporated; during this operation a brown pulverulent substance separated, which was sparingly soluble in water and found to contain tannin (apothema of tannin). The results of further treatments led Henry to conclude that *Rheum australe* contained (weight percent) 7.30% rheine (yellow matter), 14.0% fixed oil, 5% apothema of tannin 60% pectin, and 20.30% of ligneous fiber, moisture, and vegetable albumen, in addition to small amounts of sugar, gum, starch, calcium oxalate, and inorganic salts (Henry, 1836).

Monesia

In 1841 François Bernard Derosne (1776-1856), Henry, and J. F. Payen, published a paper describing the chemical analysis of the bark of monesia, a tree growing in South America, used for the treatment of dysentery and other affections of the alimentary canal. In spite of all their efforts they had been unable to determine the family, genus, and true name of the tree, (probably *Chrysophyllum glycyphloeum*) (Derosne, Henry, and Payen, 1841). Inspection of the bark suggested that it had to come from a large-sized tree because it was in pieces 6 to 8 mm thick, very compact, heavy, hard, and gorged with extract, colored deep brown, and tasting initially sweet and then acrid and irritative to the throat.

The extract of Monesia received for inspection by Derosne, Henry and Payen, came in cakes of about 500 g, 20 to 25 mm thick, deep brown, almost black, breaking easily, and entirely soluble in water. Its initial taste was sugary and then became astringent, leaving in the throat a marked and persistent acridity. A previous examination indicated that the bark contained chlorophyll, vegetable wax, a fatty crystallizable fatty matter, a small quantity of tannin, an acrid slightly bitter matter, glycyrrhizin, a red coloring material closely resembling cinchona, and a calcium salt of an organic acid. The pharmacist Heydenreich had extracted the ligneous residue successively with cold water, hot water, and ether and found that it contained about 52% of tannin (becoming blue with iron), 10% of gum or mucilage, and 36% of sweet matter.

Derosne, Henry, and Payen reduced the bark to powder and extracted it exhaustedly with water. The resulting red brown solution was acid; having an initial sugary sweet taste, which then turned styptic, bitter and very acrid. It gave a yellow precipitate with potassium antimony tartrate, a grayish one with lead acetate, a blush black with ferric sulfate, and formed abundant yellow floccules with gelatin. Treatment of the bark with ether showed the presence of wax, chlorophyll, and fatty matter. The latter was soluble in alcohol and

crystallized by spontaneous evaporation in pearly laminae; fusing at 32^0 to 34^0C, and saponified easily with KOH. All these properties indicated that it was probably stearin. The sugary material presented all the properties of glycyrrhizin and the red coloring matter seemed to be a kind cinchona red (Derosne, Henry, and Payen, 1841).

The residue of the ether extraction was further extracted with alcohol at 34^0C; the deep brown alcoholic tincture was acid, initially astringent, and then bitter and very acrid to the throat. Evaporated to dryness it left a deep brown residue, very friable, and completely soluble in water. The aqueous solution produced an abundant precipitate with gelatin, a flocculent one with potassium antimony tartrate, a gelatinous precipitate with lime, baryta, lead acetate, KOH, and ammonia, and a bluish black precipitate with ferric sulfate.

The acrid matter, which Derosne, Henry, and Payen named *monesine*, was examined in more detail. Dried at 20^0C it appeared as slightly yellow transparent plates, easily reduced to a white powder, very soluble in alcohol and water, hardly soluble in ether, and communicating to water the property of frothing considerably. The aqueous solution was initially tasteless, and then little bitter; it did not react with acids. Derosne, Henry, and Payen wrote that the different physical and chemical properties of the acrid principle were very similar to those of saponin and pyrogallic acid.

Additional testing led Derosne, Henry, and Payen to conclude that the dry monesia bark contained, per weight, 1.4% glycyrrhizin, 4.7% monesine, 7.5% of tannin or tannic acid, 9.2% red coloring matter, 1.3% malic acid and calcium malate, and about 71.7% of pectin and lignin, in addition to small amounts of calcium and magnesium phosphates, potassium chloride and sulfate, and the oxides of iron, manganese, and silicon (Derosne, Henry, and Payen, 1841). The memoir ended with a description of the pharmaceutical preparations of monesia, appropriate for the treatment of hæmoptysis, menorrhagia, debility of stomach, dysentery, scorbutic disease, diarrhea, skin diseases, etc. etc. (Derosne, Henry, and Payen, 1841).

Alkaloids

Henry and Plisson carried out extensive work on the preparation, properties, and derivatives of the most important alkaloids. A summary of some of their initial findings was published already in 1827 (Henry and Plisson, 1827).

Quinine sulfate

In 1820 Pierre-Joseph Pelletier (1788-1842) and Joseph Bienaimé Caventou (1795-1877) described a procedure for extracting quinine and cinchonine based on mixing an alcoholic extract of quinine with water acidulated with HCl, followed by boiling the liqueur with an excess of magnesia, separating the solid that precipitated, and digesting it with concentrated alcohol. Evaporation of the alcoholic extract to dryness left a residue composed of both alkaloids, which were then separated with the help of acid (Pelletier and Caventou, 1820).

Henry wrote that during his work at the Central Pharmacy of the hospitals he had had the opportunity of using Pelletier and Caventou's procedure and found it unsatisfactory and inefficient. For this reason he decided to look for a faster and less expensive procedure based on the facts that quinine and cinchonine existed in the bark of quinquina surrounded by a

resinous fatty material and an insoluble red coloring substance, and that both alkaloids were easily dissolved by acids. This information suggested an extraction method based on heating the bark in the presence of acetic acid and using quicklime as a cheap replacement of the expensive magnesia (Henry, 1821).

Experiments proved the method appropriate except for the inconvenience that the quicklime reacted with acetic acid, forming calcium acetate, very soluble in water and alcohol, and hence requiring large amounts of water for its separation. The increase in the water requirement meant a significant loss of the alkaloid. In order to eliminate this loss Henry replaced the acetic acid by sulfuric acid; the resulting calcium sulfate was sparingly soluble in water and insoluble in alcohol. The basic procedure consisted in treating one kg of bark of yellow quinquina with a solution containing 50 to 60 g of sulfuric acid dissolved in 8 kg of distilled water and using quicklime to bleach and neutralize the resulting liquor. The deposit was washed with a small amount of water, treated several times with concentrated alcohol, and the alcoholic extract distilled until it became a viscous brown residue. This residue was washed with warm water acidulated with sulfuric acid. On cooling, the mixture precipitated about 32 g of white pearly crystals, completely soluble in alcohol, little soluble in cold water, and much more soluble in hot water. These crystals reacted with barium nitrate producing a precipitate insoluble in nitric acid. The strong alkalis (KOH, NaOH, and ammonia) also produced an abundant precipitate. All these information indicated that the crystals were quinine sulfate in a very pure state (Henry, 1821). Henry wrote that he had tried unsuccessfully to use his procedure to extract cinchonine sulfate from the bark of gray quinquina (*Cinchona condaminea*). He assumed that the failure was due to the presence of only a very small amount of cinchonine in gray quinquina, or that this salt crystallized with difficult (Henry, 1821).

It was known that quinine was always accompanied by cinchonine; in gray quinquina it was the predominant alkaloid, in yellow quinquina it was present in very small amounts. Hence, it was very easy for quinine sulfate to contain variable amounts of cinchonine sulfate. In two following papers Henry described a procedure for determining the presence and proportion of cinchonine sulfate in quinine sulfate (Henry, 1848, 1849a). The initial procedure developed was based on the different solubility in cold water of the acetates of both alkaloids (Henry 1848); in the second, improved process, the supposed mixture was ground with a mixture of barium acetate and acetic acid. The liquor was filtrated, treated with an excess of diluted sulfuric acid, and then boiled with an excess of ammonia, which resulted in the precipitation of pure cinchonine (Henry, 1849b).

Years later Auguste Pierre Delondre (1790-1865) and Henry published a paper about the falsification and test of quinine sulfate; this compound had become an important item of commerce and led its adulteration and falsification (Delondre and Henry, 1852). In this paper they did not provide a unique method for proving that quinine sulfate was pure, but a list of examinations that had to be carried on, among them, the salt had to be very white, well crystallized and showing an homogeneous structure; 10 g of salt, exposed to 100^0 to 105^0C during two hours had to lose 12% water; two g of salt should dissolve completely in 120 g of alcohol of density 0.9753, at room temperature; quinine sulfate pure should dissolve completely in acidulated water, leaving intact acids, fatty materials, as well as crystallized resins; the powdered salt treated with a small amount of sulfuric acid became poppy red if it contained salicin or phlorizin, etc. etc. To recognize the presence of cinchonine or its sulfate it was enough to mix 5 g of the sample in 120 g of warm alcohol sparingly acidulated

followed by addition of an excess of ammonia and boiling. On cooling, cinchonine or its sulfate would precipitate as long bright needles (Delondre and Henry, 1852).

Quinidine

In 1829 the pharmacist Friedrich Sertürner (1783-1841), the discoverer of morphine, published a paper in which he announced that the precipitates generated by treating with alkalis the diluted acid extracts of the bark of red and yellow quinquinas, contained an additional alkaloid, which he named *quinioïdia*. This fact was similar to the finding that narcotine accompanied morphine in opium. This new alkaloid was present in the alkaline precipitate combined intimately with an acid resin. He had been able to separate the resin by treating the mixture with carbon obtained from croconic acid. The new alkali was sparingly soluble in water, had more alkaline power and saturation capacity than any other vegeto-alkali separated from quinquina, and its febrifuge ability was far superior to that of quinine and cinchonine (Sertürner, 1829).

In a comment to Sertürner's publication, Henry and Delondre expressed their surprise at his conclusions, noting that Henry's procedure for preparing quinine sulfate had shown only and only the presence of quinine and cinchonine. Nevertheless, they decided to repeat Sertürner's procedure to verify his findings. For this purpose they carried out a series of five experiments on the mother liquor, under different conditions, and using carbon black of the best quality (since they did not have available carbon produced from croconic acid). In every case the results confirmed their previous results and not those of Sertürner (Henry and Delondre, 1830a).

Henry and Delondre concluded that they did not have any doubts regarding the non-existence of quinoïdine and this material was actually a modification of quinine and cinchonine, joined together and made non-crystallizable by a particular yellow substance. The yellow resinous substance that accompanied quinine (much more than cinchonine), seemed to change substantially the properties of the alkaloid, and was different from the yellow coloring material present in quinquina, which was fixed by alumina and the oxides of lead and tin. In addition, the best way to discharge the mother liquor was to add to it turpentine (Henry and Delondre, 1830a).

In 1833 Henry and Delondre announced the discovery of a new alkaloid in the bark of yellow quinquina, which they named *quinidine*. Quinidine was found in the yellowish waters, which floated on quinine and cinchonine after the distillation of the alcoholic tinctures during the preparation of quinine, and was accompanied by a yellow substance supposed to be an acid (Henry and Delondre, 1833). Quinidine was white and crystallizable in prismatic needles, in the state of a hydrate. It was extremely bitter, especially when dissolved in alcohol or an acid. It dissolved in alcohol of specific gravity of 0.949, or even 0.963; from where it precipitated either in crystals, or at first in a sort of resin, which, when moistened by alcoholic water on exposure to the air, into beautiful crystalline needles, which effloresced in dry air. The crystals speedily turned the syrup of violets green, and restored to its blue color litmus paper reddened by an acid.

Crystallized quinidine combined perfectly with sulfuric, hydrochloric, nitric and acetic acids, to form white pearly salts, very crystallizable like those of quinine and precipitable by sodium carbonate. It decomposed at high temperatures, diffusing at first an aromatic, then an

empyreumatic animal odor, while partly subliming in the midst of its volatile products. An elemental analysis indicated the presence of a substantial amount of nitrogen. Henry and Delondre believed that it was possible that quinidine was present in the mother liquor of the preparation of quinine sulfate and in Sertüner's quinoïdine (Henry and Delondre, 1833).

In a following paper Henry and Delondre reported the preparation of large amounts of quinidine and the results of its reaction with a variety of acids (HI, HCl, HNO_3, phosphoric, iodic, acetic, citric, tartaric, oxalic, succinic, picric, quinic, acid, etc.). In every case the resulting salts were similar to the corresponding salts of quinine, although much easier to crystallize. An elemental analysis indicated that the composition of quinidine was identical with that of quinine (quinidine is actually a dextro-rotary stereoisomer of quinine) (Henry and Delondre, 1834).

Quinic acid

In 1803, Deschamps, a pharmacist from Lyon, separated from quinquina a particular calcium salt, which he named calcium quinquinate; he also described its principal properties (Deschamps, 1803). A few years later, Vauquelin separated quinquinic (quinic) acid and described some of its properties (Vauquelin, 1806) and Pelletier and Caventou discussed in detail the chemical analysis of quinquinas (Pelletier and Caventou, 1820). Henry and Plisson believed that the information available was far from providing a complete description of the acid and its properties. For this reason, they first prepared it in large quantity using the original and a modified form of Vauquelin's procedure (Henry and Plisson, 1829). Quinic acid appeared as neat voluminous transparent crystals, having a very acid but not bitter taste, a specific gravity of 1.637 at 8.5^0C, not affected by air, melting into a colorless liquid, and then decomposing into a brown residue and gases smelling like burning tartrates. Sulfuric acid converted it first into a green substance and then carbonized it. Nitric acid converted it into oxalic acid. Quinic acid reacted with organic and inorganic bases forming with most of them crystallizable, soluble neutral salts, known as quinates. An elemental analysis indicated that quinic acid contained, by weight, 34.4320% carbon, 5.5602% hydrogen, and 60.0078% hydrogen. Henry and Plisson prepared and determined the properties of fifteen inorganic quinates (e.g. magnesium, calcium, sodium, potassium, ammonia, barium, iron, manganese, silver, mercury, etc.), as well as the quinates of quinine, cinchonine, and morphine (Henry and Plisson, 1829).

Morphine

According to Henry and Plisson, the procedures available for extracting morphine from opium were expensive because they used large amounts of alcohol, and morphine appeared mixed with variable amounts of narcotine (noscapine), which could be only eliminated with ether. For this reason, they went on to develop a new method, which did not require alcohol and was based on the fact that morphine and narcotine could be separated with the help of diluted HCl (Henry and Plisson, 1828).

In their procedure, well-divided opium was treated with tepid water acidulated with HCl. After filtration, the filtrate was treated with an aqueous solution of ammonia or NaOH and the resulting precipitate separated and washed carefully. The morphine hydrochloride was easily decomposed by washing with and excess of aqueous ammonia. The overall procedure yielded 26 to 27 g of morphine per 400 g of commercial opium (Henry and Plisson, 1828).

Strychnine and brucine

According to Henry, the available processes for extracting strychnine and brucine were complicated and for this reason he went on to develop a more efficient one: The seeds of nux vomica were first softened with the help of steam, then finely ground, and the powder extracted twice with alcohol acidulated with sulfuric acid. The resulting liquor was neutralized with an excess of quicklime. The filtrate was then distilled to a green brown fatty substance, containing the alkaloids. This residue was washed with water slightly acidulated with acetic or sulfuric acid. The filtrate was treated with an excess of ammonia, washed, and then contacted with warm alcohol of 18^0, to dissolve the brucine. The residual strychnine was dissolved in boiling alcohol of 36^0, bleached with animal carbon, and recrystallized by cooling. The brucine solution was evaporated in a water bath, treated with highly diluted sulfuric acid, and then precipitated with the help of ammonia (Henry, 1830). According to Henry, his method produced highly pure strychnine and brucine, exempt of coloring matter, fat, and resin. He thought that it also provided a very useful procedure for determining their content in gray or yellow quinquina, much shorter and economical than the ones currently in use (Henry, 1830).

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