Educación Química

Reflexión

Louis Alphonse Adrian

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Resumen

Louis Alphonse Adrian (1832-1911) fue un farmacéutico francés que junto con Auguste Trillat estudió la síntesis y química de los fosfogliceratos, neutros y ácidos, sus derivados, propiedades y dosificación, en particular, los fosfogliceratos orgánicos y cálcicos, y también la reacción entre la glicerina y el ácido fosfórico. Aislaron varios primeros principios nuevos presentes en ***Artemisa absinthium***, en ***Digitalis lutea*** y en el ácido agárico. Con Bardet y Blondel llevaron a cabo un estudio botánico, químico y fisiológico detallado del Piligan, un musgo originario de Brasil, y demostraron que el componente activo era el alcaloide piliganin. Adrian desarrolló nuevos procedimientos de dosificación para determinar la cantidad de guayacol presente en productos comerciales.

Palabras clave

Absintio; ácido agárico; ajenjo; digitalis; guayacol; fosfogliceratos .

Abstract

Louis Alphonse Adrian (1832-1911) was a French pharmacist who with Auguste Trillat studied the synthesis and chemistry of phosphoglycerates, neutral and acid, their derivatives, properties, and dosage, particularly, organic and calcium phosphoglycerates, as well as the reaction between glycerin and phosphoric acid. They isolated several new first principles present in ***Artemisia absinthium,*** in ***Digitalis lutea,*** and in agaric acid. With Bardet and Blondel they carried a detailed botanical, chemical, and physiological study of Piligan, a moss originating from Brazil, and proved that the active component was the alkaloid piliganin. Adrian developed new dosage procedures for determining the amount of guaiacol present in commercial products.

Keywords

Absinthe; agaric acid; digitalis; guaiacol; phosphoglycerates; wormwood.

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Life and career (Anonymous, 2023)

Louis Alphonse Adrian was born on February 13, 1832, in Oise (commune Guiscard), the son of Louis Stanislas Adrian, a blacksmith, and Marie Laudivine Boucher. After finishing his basic education and obtaining his diploma of bachelier ès-lettres et ès-sciences (1852) he decided to study pharmacy and within this framework he won by competition a pharmacy internship in the hospitals of Paris and served as préparateur at the École Supérieure de Pharmacie in Paris. In 1859, he obtained his diploma of Pharmacist of 1st Class after successfully defending two theses, one about milk, from the viewpoint of its composition, analysis, and falsification, and the other, about synthesis in pharmacy and chemistry (Adrian, 1859ab). He installed and managed his own factory for producing fine pharmaceuticals, which at one time employed more than 300 workers. Adrian served in many scientific societies and public offices: among them, he was member of the Société de Pharmacie and its Vice-President; founding member of the Société de Thérapeutique and its Secretary and President, and founding member of the Société Française de Produits Pharmaceutiques; member of the Chambre Syndicate des Produits Chimiques, and three time its Vice-President; member of the Commission Permanente des Valeurs en Douane, etc. He also served as organizer and jury of several international expositions of chemical products (Paris, Moscow, London, and Chicago). In 1894, he was appointed Chevalier de la Légion d'Honneur.

Adrian passed away on January 1, 1911.

Scientific contribution

Adrian wrote more than 30 papers and books (i.e., Adrian, 1864, 1869, 1887abc; 1890, 1891a, 1892. 1894, 1897c, 1903, 1905, 1907; Adrian, Bardet, & Blondel, 1886; Regnauld, & Adrian, 1864) about his research activities in organic, inorganic, and analytical chemistry, chemical synthesis, plant principles, etc. In addition to the few subjects described below, Adrian studied the influence of weather and vegetation on the amount of hydrogen cyanide contained in the water distilled from cherry laurel (Adrian, 1862); the preparation bismuth sub-nitrate (Adrian, 1880); he identified a new form of saffron falsification (Adrian, 1889a), studied the possibility of distinguishing tannin in water from tannin in alcohol (Adrian, 1889b); demonstrated the significant differences in the morphine and narcotine contained in commercial opium (Adrian, 1891b); described the different procedures used to provide the anesthetics chloroform, ethyl ether, and ethyl bromide in a sufficiently pure and safe state for medicinal purposes (Adrian, 1894); studied methyl salicylate (Adrian, 1898); with J. A. Regnault they developed a new method for dosing diethyl ether (Regnauld & Adrian, 1864); with Bougarel they developed a new industrial process for separating directly the barium from any strontium salt (Adrian & Bougarel, 1892); with Trillat they determined the composition of the herbicide disodium methyl arsonate (Arrhenal) (Adrian & Trillat, 1902); with F. Gallois they proposed a better procedure for the dosage of opium (Adrian & Gallois, 1887); etc.

Phosphoglycerates

Adrian and Auguste Trillat (1861-1944) wrote that the value of calcium phosphoglycerate had increased significantly in the last years due to its importance in the understanding of biological processes, as well as in therapy (Adrian & Trillat, 1897). This compound had been discovered in 1845 by Théophile-Jules Pelouze (1807-1867), during his study about glycerin and its reactions (Pelouze, 1845). In his first experiments, Pelouze had confirmed his previous results about the composition of glycerin. He took a certain amount of glycerin, totally colorless and leaving practically no cinders, and dried in a stove at 120º to 130 ºC, followed by oxidation by means of cupric oxide. Analysis of the combustion products indicated that glycerin contained, by weight, 38.95% carbon, 8.72% hydrogen, and 52.33% oxygen, corresponding to the formula C_6H_8O6 (C =75, H=12.5, and O =100). Similarly, he determined that the formula of calcium sulfoglycerate was $CaO,(SO_3)_2,C_6H_7O_5$. The synthesis of this compound was very difficult and took a long time and for this reason Pelouze decided to repeat the process, replacing by phosphoric acid the sulfuric acid. He remarked that the reaction between glycerin and phosphoric acid solid, anhydrous, or hydrated, was very exothermic, and the resulting mixture contained a new compound, which he named *phosphoglyceric acid*. This acid combined with several bases forming salts, which were soluble in cold water and sparingly soluble in alcohol. The calcium salt was precipitated by alcohol in a very pure state. Calcium phosphoglycerate was a white substance that did not decompose when heated from 160^0 to 170 ºC. Its elemental composition corresponded to the formula $C_6H_7O_5,PO_5,2CaO$. What made this new acid particularly interesting was that Theodore Nicolas Gobley (1811-1876) had found almost simultaneously that it was present abundantly in egg yolk, with the corresponding physiological significance (Gobley, 1845).

The Pelouze synthesis process was difficult, of low yield, and expensive. It took various years until Ludovic Portes, and Georges Prunier developed an improved version in which 3 kilos of liquid phosphoric acid of 60% weight, were heated with 3.60 kilos of pure glycerin of 28º, for six consecutive days at a temperature of 100° to 110 °C. After cooling, the product was neutralized with calcium carbonate milk, afterwards precipitated with alcohol, and purified by recrystallization from water. The final product was white, slightly crystalline, soluble in cold water, and insoluble in boiling water and alcohol (Portes & Prunier, 1894).

The same year, Etienne Arthur Petit and Max Polonovski (1861-1939) examined several commercial phosphoglycerates and found that they left much to be desired from the viewpoint of purity; one of the samples examined was simply a mixture of glycerin and crystalline sodium phosphate (Petit & Polonovski, 1894). The medical importance of these compounds led Petit and Polonovski to describe their prominent properties, which allowed their proper evaluation. Among them, they mentioned the following: (1) phosphoglycerates were not precipitated by the reagents normally employed for phosphates, such as the ammonia-magnesium mixture, ammoniacal silver nitrate, uranium acetate, and ammonium molybdate; (2) all the phosphoglycerates were precipitated by lead acetate; the resulting precipitate was insoluble in acetic acid, soluble in nitric acid, and ammonium acetate; (3) most of them contained water originating from the humidity of the air or from the water of crystallization; and (4) calcination of alkaline or alkaline terreous phosphoglycerates turned them pyrophosphates. Petite and Polonovski also gave general methods for the analysis of phosphoglycerates, based on the determination of the weight of their calcination residues

and on the determination of phosphoric acid. They also provided the general properties and chemical reactions of many phosphoglycerates, among them, those of iron, calcium, strontium, lithium, sodium, and potassium (Petit & Polonovski, 1894).

According to Adrian and Trillat, the available knowledge made it possible easily to produce calcium phosphoglycerate, nevertheless, the chemical information concerning glycerophosphates in general, phosphoglyceric acid and their reactions, as well as the methods of assaying them, was very incomplete. For these reasons they decided to study the subject in detail (Adrian & Trillat, 1897, 1898abcd).

As mentioned above, in 1894 Petit and Polonovski had reported that the products sold under the name calcium phosphoglycerates were very impure. It was interesting to check if three years later, after the process for making a pure compound had been made available, the product available commercially was now pure enough, and how it satisfied the criteria established by Petit and Polonovski. Adrian and Trillat inspected seven samples from various origins; before analysis they crushed and dried them for several days at a temperature of 100 ^{0}C, and then analyzed each several times. They also put each powdered sample in contact with distilled water and 25 ^{o}C, for 12 hours, to determine their solubility, their acidity, and composition of the undissolved residue. The average content of calcium and phosphoric acid was found to vary between 20 and 24.5% and 26 and 30.80%, respectively. Some samples were found to be acid, others basic, and the rest neutral. The solubility in distilled water at 25 ^{o}C varied in the range 4.05 to 7.60 grams per 100 grams of water. An interesting finding was that the highest solubility corresponded to the samples, which were acidic in litmus paper. The solid residue was found to be composed of calcium phosphate and calcium sulfate. According to Adrian and Trillat, the presence of these salts was partly due to the use of calcium in the neutralization stage, Anyhow, all these results indicated that most of the samples could not be considered free of impurities, without passing judgement in their relative importance and significant (Adrian & Trillat, 1897).

Adrian and Trillat also examined the action of boiling alcohol and heat on the commercial samples. For this purpose, the pulverized samples were boiled repeatedly with ten parts of absolute alcohol for four hours. The residue was found to be formed sometimes by glycerin, sometimes by a mixture of this product with free phosphoric acid. Adrian and Trillat speculated that since this acidity came from the presence of free phosphoglyceric acid in the salt, it meant that absolute alcohol had split this acid into glycerin and free phosphoric acid. The content of glycerin and of free phosphoric acid varied between 1.3 to 3.4% and 0 to 1.5%, respectively (Adrian & Trillat, 1897).

It was known that calcium phosphoglycerate was almost insoluble in boiling water. Adrian and Trillat found that this effect started to be appreciable at temperatures below 100 ^{o}C. It began at about 32 ^{o}C and became almost complete at the boiling point. This property provided a means of purifying the product; it made it possible, in fact, to eliminate the free glycerin, the phosphoglyceric acid as well as the free phosphoric acid. An additional finding was that the precipitated calcium phosphoglycerate was crystalline, and not amorphous as the standard form (Adrian & Trillat, 1897).

Adrian and Trillat used the new information to present an improved procedure for preparing calcium phosphoglycerate. Basically, it consisted of heating a mixture of equal weights of liquid phosphoric acid and glycerin in an enameled container, at a temperature varying from 130^o to 150 °C, for twenty-four hours. At the end of this period, the reaction

was terminated, the product had become blackish and viscous; and began to release vapors with an irritating odor. The blackish tint disappeared later by a treatment with animal black. The neutralization of the product was done with calcium triphosphate instead of calcium carbonate. The second part of the neutralization was done with a lime milk, which transformed the phosphoglyceric acid into the calcium derivative, while the dibasic calcium phosphate was transformed into tribasic phosphate. The desired product was then separated with boiling alcohol (Adrian & Trillat, 1897).

The next publication described several analytical procedures for the dosage of phosphoglycerates based on the use of helianthin (methyl orange) and phenolphthalein as indicators (Adrian & Trillat, 1898a). These methods included a volumetric determination of phosphoglycerates, the determination of phosphoric acid in the presence of a phosphoglycerate and glycerin, and the determination of phosphoric acid in the presence of glycerin, a neutral phosphoglycerate, and an acid phosphoglycerate, or vice versa. The volumetric procedure was based on the observation that when sulfuric acid of known strength was added to a cold aqueous solution of a neutral alkaline earth phosphoglycerate, using helianthin as an indicator, the change of the indicator took place as soon as a half a molecule of acid had been added for one molecule of neutral salt. This observation indicated that the sulfuric acid converted the neutral phosphoglycerate into an acid salt and that the latter was no longer decomposed by sulfuric acid, at least in the cold. In addition, Adrian and Trillat verified that the glycerin did not interfere with the titration by the indicators. The last procedure was based on the known fact that phosphoric acid required one molecule of KOH to be neutral to helianthin and a new molecule of KOH to be neutral to phenolphthalein (Adrian & Trillat, 1898a).

Adrian and Trillat remarked that the above dosage methods had the additional advantage that they allowed a better study of the action of phosphoric acid on glycerin. Initially, they believed that the pertinent reactions were simple and would allow isolating phosphoglyceric acid. The results proved them wrong, they were unable to isolate the acid in the pure state (Adrian & Trillat, 1898b). According to Pelouze, phosphoglyceric acid could be prepared by reacting glycerin with vitreous phosphoric acid (Pelouze, 1845). Adrian and Trillat carried the reaction exactly as described by Pelouze and instead of phosphoglyceric acid obtained a product like white wax, having partly the composition of barium acid glycerophosphate. They also tried to decompose potassium phosphoglycerate with tartaric acid. Once again, they obtained a viscous mass, constituted, mostly, by potassium acid glycerophosphate. They also tested the possibility of regenerating phosphoglyceric acid by decomposing lead and copper glycerophosphate with hydrogen sulfide; the actual product was phosphoric acid. Adrian and Trillat tried to prepare phosphoglyceric acid directly as the crude product of the reaction of phosphoglyceric acid on glycerin, to avoid dissolution of a mineral matter. The product turned out to be a material whose composition was closer to that of a diether formed of a molecule of phosphoric acid and two of glycerin, and very slowly decomposable in the cold by alkaline carbonates into phosphoglyceric acid. Finally, the acid could not be prepared from commercial phosphoglyceric acid because they had already found that this substance was a mixture, in aqueous solution, of phosphoric acid, glycerin, acid phosphoglycerate and a variable amount of phosphoglyceric acid. Based on these results, they concluded that phosphoglyceric acid could not be obtained in a chemically pure state because its own concentration led to its decomposition, and all

the synthesis processes led to the formation of acid salts, which remained dissolved in phosphoglyceric acid (Adrian & Trillat, 1898b).

Another publication of Adrian and Trillat referred to acid phosphoglycerates, their preparation, and properties (Adrian & Trillat, 1898c). It was based on the idea that like phosphoric acid, phosphoglyceric acid could also give a series of acid salts, which could be obtained by two methods: (1) by the decomposition of a neutral glycerophosphate by sulfuric acid, and (2) by the double decomposition between an acid phosphoglycerate and a soluble sulfate. The first case was applicable for the preparation of acid salts of barium, strontium, etc., that is, of metals whose sulfates were insoluble; the second case could be used for metals whose sulfates were soluble (Adrian & Trillat, 1898c).

Adrian and Trillat illustrated how these methods were used to prepare the acid salt of barium, zinc, and magnesium. For example, 15 to 20 g of a neutral barium salt were dissolved in one liter of cold water and mixed with a few drops of a solution of the indicator helianthin (methyl orange). Diluted sulfuric acid was now added slowly until the indicator turned slightly red. At this point, a small amount of freshly precipitated alumina was added and the whole boiled for five to ten minutes to agglomerate the barium sulfate. The filtrate was cooled with a large volume of alcohol of 95°. This resulted in the precipitation of barium acid phosphoglycerate as a gelatinous mass, which was separated by filtration and redissolved in a very small quantity of water, and again precipitated by the alcohol. The product was finally dried at 120º to 130 °C. The salt appeared as a white mass, which could be pulverized, although it was highly hygroscopic and assumed a vitreous appearance of a consistency analogous to that of wax. It was very soluble in water and in diluted alcohol (Adrian & Trillat, 1898c).

Adrian and Trillat indicated that contrary to the neutral salts, the acid ones were very soluble in cold water as well as highly diluted alcohol, Acidic glycerophosphates were distinguished from neutral and acidic phosphates by the same reactions as neutral glycerophosphates, for example, ammonia molybdate and uranium acetate only gave a precipitate with prolonged boiling; lead acetate gave a white precipitate soluble in acetic acid, and silver nitrate and ferric chloride did not give a precipitate. Acid glycerophosphates could be used to prepare organic glycerophosphates and could be dosed by titration with KOH, using helianthin or phenolphthalein. This possibility was presented in the following publication (Adrian & Trillat, 1898c).

Adrian and Trillat reiterated that their experiments showed that phosphoglyceric acid broke down easily by simple concentration and regenerated free phosphoric acid. When trying to react this acid with a base, they always observed the formation of the corresponding phosphate. For these reasons, they elected to use acid salts instead of phosphoglyceric acid for the preparation of organic phosphoglycerates (Adrian & Trillat, 1898d). Basically, their method involved reacting calcium phosphoglycerate with an organic base such as cocaine, quinine, phenylhydrazine, etc. The results indicated that the strong bases quinine and cocaine were the only ones capable of completely displacing the calcium from the acid phosphoglycerate. Weaker bases like aniline, phenylhydrazine, and pyridine did precipitate a certain quantity of neutral calcium phosphoglycerate, but the residue of the filtered solution always contained a considerable portion of the product, insoluble or poorly soluble in alcohol, which corresponded to the double salt of calcium. The cocaine and quinine salts were prepared by neutralizing a calcium acid phosphoglycerate solution

with cocaine in ethereal solution; the neutral calcium phosphoglycerate formed was then precipitated by alcohol. Purification produced a vitreous amorphous mass, very soluble in alcohol and water, and almost insoluble in ether. Heated in the presence of water, it decomposes quickly. For example, heating an aqueous solution of quinine phosphoglycerate for a few minutes in a water bath, and then left to cool, resulted in a notable precipitate of crystalline needles. Analysis of these needles indicated that they were identical with the quinine phosphate prepared by the direct reaction between phosphoric acid and quinine (Adrian & Trillat, 1898d).

Adrian and Trillat reported some properties of several organic phosphoglycerates. For example, the cocaine salt assumed a reddish-brown coloration with iodated potassium iodide; with hot concentrated sulfuric acid, it released benzoic ether recognizable by the smell. The quinine salt produced a yellowish-white precipitate with bromine water, which turned purple on addition of a drop of dilute ammonia, then dark green with excess ammonia. The pyridine salt produced a yellowish precipitate with picric acid and a brown one with iodated potassium iodide. The quinoline salt produced a green precipitate with potassium ferrocyanide acidulated with HCl (Adrian & Trillat, 1898d).

Plant principles

Adrian and Trillat also collaborated in the isolation of several plant principles (Adrian & Trillat, 1898e, 1899, 1901).

1. Wormwood (Artemisia absinthium)

The first work related to the separation of a new crystalline principle from the residues left by the alcoholic extract of *Artemisia absinthium*, after elimination of the absinthin. The resulting material was a pasty yellowish extract, which treated with amyl alcohol gave up a substance, which crystallized after two to three days in the form of beautiful prismatic needles, straw yellow. Adrian and Trillat remarked that the new substance had no physiological action and differed from absinthin by its color, its crystalline form, and above all, its non-bitter flavor (Adrian & Trillat, 1898e).

Chemical analysis by combustion indicated that the new substance contained, by weight, 62.90% carbon, 5.12% hydrogen, and 31.98% oxygen. Cryoscopy measurement in bromoform indicated a molecular weight of 1002. All this information suggested two possibilities for the global formula, $C_{52}H_{51}O_{20}$ (molecular mass 995) and $C_{52}H_{51}O_{20}$ (molecular mass 1007). The high molecular mass did not allow making a finer guess. Adrian and Trillat found that the new substance was a solid melting at 165 °C, insoluble in water, ether, and diluted acids, and very soluble in hot amyl alcohol, chloroform, acetone, and benzene. Concentrated acids dissolved it in the cold; addition of water to the solution precipitated a white material in the form of crystalline tufts. Diluted alkalis had no action even when boiling, while concentrated alkalis resinify it. It was not attacked by oxidants like potassium dichromate or lead dioxide in acetic solution, and was unaffected by nascent hydrogen and Fehling's liquor. According to Adrian and Trillat, these and other measurements suggested that the new substance had a neutral character, contained one aromatic nucleus, and was susceptible to condensation (Adrian & Trillat, 1898e).

The next paper was related to absinthine, one of the active principles present in *Artemisia absinthium,* discovered by Henri Braconnot (1780-1855) in 1813 (Braconnot,

1813), isolated by Henri Paul Duquesnel (Duquesnel, 1886), and analyzed in detail by Paul Bourget, who reported that its global formula and melting point were $C_{15}H_{20}O_4$ and 68 °C, respectively (Bourcet, 1898). In 1899 Adrian and Trillat informed that they had followed an extraction method different from the ones used by other chemists and had succeeded in obtaining a new principle, of different composition, melting point, and properties. They named this substance *anabsinthin*, to differentiate it from other active principles, which went under names such as absinthin, absinthein, absinthinine, absinthol, and artemisinin (Adrian & Trillat, 1899).

In their procedure, the plant was pulverized, extracted with alcohol, and the extract evaporated to dryness. The residue was extracted with chloroform, evaporated to dryness, and extracted again with boiling alcohol. The liquor was precipitated with lead acetate and the excess of acetate eliminated with tartaric acid. The resulting filtrate was evaporated to dryness, and purified to yield anabsinthin, as yellow needles. Elemental analysis indicated that anabsinthin contained by weight, 71.78% carbon, 8.61% hydrogen, 19.61% oxygen, and 0% nitrogen, corresponding to the formula $C_{18}H_{24}O_4$ (Adrian & Trillat, 1899).

Anabsinthin was described as a solid matter, crystallized as long white prismatic needles; very bitter, not having other physiological properties, and melting at 258º-259 °C, which after exposure to air dropped to 236º-238 °C. It was slightly soluble in water, and more soluble in alcohol, benzene, and chloroform. Dissolved in concentrated sulfuric acid produced a red violet solution that afterwards turned blue; with 20% HCl acid it gave a brown colored solution. Anabsinthin showed no reaction with oxidants, reductors, alkalis, diluted acids, and Fehling's liquor (Adrian & Trillat, 1899)

2. Straw foxglove (Digitalis lutea)

Adrian and Trillat decided to treat straw foxglove similarly, to try to remove the yellow matter present in the residue left after extraction of the digitalis (Adrian & Trillat, 1899). Their procedure involved evaporating the mother liquor to a syrupy consistency and then mixing the cold residue with benzene. The filtrate was evaporated to eliminate the benzene, and then treated with gas oil to separate the yellow matter from the accompanying oily liquid. The suspended solid was left to decant and then separated by filtration. This solid was extracted with hot amyl alcohol, which allowed it to crystallize after cooling. The crude material was purified by repeated recrystallization from alcohol of 90^0. The pure material appeared as yellow needles melting at 217º-218 °C, was insoluble in water, in diluted mineral acids and in petroleum ether; it dissolved easily in alkaline solutions and in hot alcohol, chloroform, and amyl alcohol. It did not react with boiling HCl, acetic acid, and phenylhydrazine. Chemical analysis by combustion indicated that it contained, by weight, 71.86% carbon, 4.655% hydrogen, and 23.475% oxygen, corresponding to the formula $(C_4H_3O)_n$. Its low solubility did not allow determining its molecular mass by cryoscopy; Adrian and Trillat used instead ebullioscopy and obtained the value 253, corresponding approximately to $C_{16}H_{12}O_4$ (Adrian & Trillat, 1899)

Adrian and Trillat remarked that their formula was substantially different from that of the digitoflavone that Franz Fleischer had recently isolated from *Digitalis pupurea* (Fleischer, 1899).

3. Pseudo agaricic acid

Adrian and Trillat commented that there were notable differences regarding the composition and properties of the product removed from white agaric and referred to as agaricic acid. For example, the reported boiling temperature varied from 69.5° to 141 °C, and the global formula from $C_{13}H_{30}O_2$ to $C_{16}H_{28}O_5$. These divergences led them to do more experiments, using the extraction procedure they had developed for other first principles (Adrian & Trillat, 1901). Their basic procedure consisted in treating one part of coarse powdered agaric with10 parts of alcohol boiling at 95 °C. The resulting alcoholic extract was distilled and again exhausted with hot benzene. The crystalline matter obtained after cooling was separated by filtration and recrystallized repeated from boiling alcohol as needles melting at 258 °C; after exposure to humidity for several days, this melting point dropped to 240 °C. This substance was insoluble in cold water and sparingly soluble in HCl and hot NaOH. It dissolved in most boiling organic solvents. Elemental analysis indicated that the crystals contained, by weight, 74.77% carbon, 9.83% hydrogen, and 15.40% oxygen. The molecular mass, determined by ebullioscopy, was 630. These set of data fitted well to the global formula $C_{39}H_{60}O_6$ (Adrian & Trillat, 1901).

Adrian and Trillat tried to establish the constitution of the body $C_{39}H_{60}O_6$ by fusing and distilling it with KOH. The acid part of the did not indicate the presence or absence of benzoic acid, phthalic acid, phenol, resorcinol, pyrocatechin, and phloroglucin. Nevertheless, the distillation indicated the presence of two very distinct products. One was a liquid having the character of an unsaturated fatty acid and boiling point at 180°-190 °C; the second was a neutral liquid belonging to the aromatic series and endowed with a peppery odor. Reacted with fuming nitric acid generated a nitro derivative insoluble in water and decomposing slowly at 50 °C. These and other results indicated that the alcoholic extract from agaric was not an acid and did not have any specific physiological property (Adrian & Trillat, 1901).

4. Piligan

Adrian, Georges Bardet, and Raoul Blondel (1864-1944) carried a detailed botanical, chemical, and physiological test of Piligan, a moss originating from Brazil. A sample of this plant was sent from Brazil to the physicians George Octave Dujardin-Beaumetz and Raoul Blondet at the Cochin hospital in Paris, stating that its infusion produced violent vomit and was employed for the treatment of gastric dyspepsia. A first chemical test, carried out by Bardet, head of the Therapeutics laboratory at the Cochin hospital, detected the presence of a resinoid product and an active alkaloid to which Bardet gave the name of *piliganin* (Adrian, 1886; Adrian, Bardet, & Blondel, 1886).

In the first stage, the plant was extracted with boiling water, yielding a slightly yellow colored liquid, which concentrated by evaporation turned into a soft brown paste having a nauseous odor and sweet taste. Extraction of this material with concentrated alcohol produced a yellow tincture, from which water precipitated a pale green resin. The aqueous solution contained the alkaloid, and small amounts of resin and glucose. According to Adrian, Bardet, and Blondel, one kilo of Piligan yielded 257 g of aqueous extract and 43 g of resin. The resin was a green granular material, without odor, having purgative properties, and burning with a sooty flame (Adrian, 1886; Adrian, Bardet, & Blondel, 1886).

To separate the alkaloid, Adrian treated the pulverized Piligan with boiling water, concentrated the extract by evaporation, and the residue with strong alcohol. The alcoholic

extract was precipitated with lead acetate, filtered, and mixed with lime milk, which precipitated the excess lead. It was filtered again, and the clear solution was neutralized with tartaric acid added in slight excess, then filtered. The filtrate was distilled, and the residue dissolved with water, which separated a little resin. The new filtrate was treated with sodium carbonate, followed by extraction with chloroform. The chloroform solution was distilled to eliminate the solvent, leaving a residue of sticky matter of dark yellow color. Purification was carried out by dissolving in HCl and, after further precipitation with sodium carbonate, further stirring with chloroform. The piliganin was purified by additional extractions with chloroform, until it remained as a soft, slightly yellow, and transparent mass, of alkaline reaction, which was then dried under vacuum. This material was found to emit white vapors when approached by a stirrer wet with non-smoking HCl (Adrian, 1886).

Adrian reported that piliganin hydrochloride was deliquescent and crystallized easily when dried, not in contact with air or water vapors. It was soluble in water, alcohol, chloroform, and sparingly soluble in ether. Treated with ordinary chemicals it produced colored precipitates: sodium phosphomolybdate, yellow white; iodated potassium iodide, light brown; tannin, white; double iodide of mercury and potassium, very abundant curdled white precipitate; picric acid, yellowish, etc. Mercuric chloride and platinum dichloride showed no action (Adrian, 1886).

The report from Adrian, Bardet, and Blondel contained a detailed report about the physiological effects of the resin al alkaloid upon humans and animals. The resin presented purgative effects which were not present with the alkaloid. The alkaloid provoked intense vomiting, accompanied by strong gastric pains, shivering, and headaches (Adrian, Bardet, & Blondel, 1886).

Creosote and guaiacol

Auguste Béhal (1859-1941) and Eugène Choay (1861-1942) carried extensive research of creosote, guaiacol, and their derivatives (i.e., Béhal, 1893-1894; Béhal and Choay, 1893abc; 1894ab, etc.). One important result was finding that guaiacol was really a solid and not a liquid, as commonly believed. According to Béhal and Choay, creosote and guaiacol were becoming increasingly significant in medical uses. Creosotes were defined in the French Codex and foreign pharmacopoeias only by their physical properties or color reactions, without indication about their exact composition. In other words, the same name represented a variety of different products made of a complex mixture of phenols and phenol ethers. Guaiacol had been considerably studied but continued to be an ill-defined compound; it was described as a liquid body boiling sometimes at 200 °C, sometimes at 205 °C, sometimes at 207 °C; its relative density had been also reported as 1.046 and 1.1171 at 13 °C (Béhal & Choay, 1893a).

These errors were understandable because no one had yet been able to isolate pure guaiacol; its properties were unknown and there was no rigorous means of dosing it in creosotes, except determination of distillation points and observation of certain color reactions. For these reasons, Béhal and Choay decided to prepare pure guaiacol by synthetic means to be used as standard to determine its content in commercial samples. The method they developed was based on the following series of events: (1) guaiacol was completely demethylated by a stream of gaseous hydrobromic acid and transformed into pyrocatechin;

(2) the resulting pyrocatechin and the homopyrocatechin were not entrained by water vapor (steam distillation), while the other constituent parts of commercial guaiacol were easily entrained; (3) ether was used to separate pyrocatechin and homopyrocatechin from an aqueous solution, together with monophenols; and (4) pure benzene largely separated pyrocatechin from homopyrocatechin by crystallization (Béhal & Choay, 1893a).

Béhal and Choay mixed a solution composed of 58 g of sodium and 600 g of methanol with another containing 270 g of pyrocatechin in methanol. The resulting solid was mixed with an excess of methyl iodide and heated to 120°-130 °C. After cooling, it was distilled to eliminate the alcohol and then steam distilled to separate the guaiacol. The crude guaiacol was mixed with aqueous NaOH to remove the veratrole. The guaiacol was released with HCl and separated again by steam distillation. Fractional distillation purified the final product. The fraction passing at 205° to 207 °C was collected and cooled with methyl chloride; the product crystallized as pure guaiacol. Pure guaiacol was a white solid body, composed of hard crystals built of twelve-sided prisms belonging to the rhombohedral system, melting at 28.5 °C and boiling at 205 °C. Its density, at 0° and 15 °C, was 1.1534; and 1.143, respectively. It was soluble in most organic solvents, such as anhydrous glycerin and petroleum ether. Guaiacol had a sweet flavor; deposited on the tongue, it melted, then caused an intense sensation of astriction, without altering the mucous membrane (Béhal & Choay, 1893a).

Béhal and Choay analyzed six commercial samples and found that most of them contained less than 50% of chemically defined guaiacol, the rest being formed mainly of creosol and cresylic acid (Béhal & Choay, 1893a):

Sample number	Sold as (%)	Actual content (%)
I	40	25
II	45	28
III	60	45
IV	80	54
V	90	60
Pure liquid guaiacol	90	70

Table I. Analysis of commercial guaiacol.

According to Adrian, although Béhal and Choay's analytical method, based on the demethylation by hydrobromic acid, was the best process available, it was little used because it required an experienced operator, a lot of time, and a large quantity of expensive reagents. For these reasons, he decided to search for an alternative procedure, which would overcome these shortcomings (Adrian, 1897ac).

His study of the chemical reactions of guaiacol led him to notice that nitrous acid (as sodium nitrite) could serve as a reagent for the qualitative and even quantitative analysis of guaiacol, as shown by the following experiments: (1) a drop of pure guaiacol was added to a test tube containing water up to two-thirds of its height and the whole mixed well. Two drops of sodium nitrite solution were added, followed by a drop of nitric acid. The mixture turned immediately orange, slightly tending to red; (2) the same experiment was carried with creosote totally demethylated with hydrobromic acid. Now, the mixture assumed a yellowish and cloudy coloration, quite different from the previous one; and (3) the procedure was applied to a guaiacol containing 50 or 90% pure guaiacol. The intensity

of the orange-red color was more vivid and clearer as the guaiacol content was higher. Adrian took care to verify that these colorations effects took place with commercial nitric, that they were not due to the action of nitric acid alone, but to the nitrous acid contained in commercial nitric acid, and that it was not a result of the additional chemicals present in medicinal creosote (Adrian, 1897abc).

This test could be used for determining the relative amount of guaiacol present in a commercial solution, through a quick comparison with the color presented by synthetic mixtures of guaiacol, as shown in the following table:

Table 2. Relative amounts of guaiacol, according to the coloration.

Synthetic mixture (guaiacol %)	Color observed
90	Light orange red.
80	Light orange red (less intense).
75	A little more yellow than the previous one.
60	A little more yellow, begins to disturb.
55	Yellowish-red, cloudy.
20	Red, more yellowish, cloudy.

Adrian tested Béhal and Choay's demethylation method for the determination of guaiacol, and found it correct, except for a few modifications. The experimental device consisted of a bottle with a capacity of 500 cm^3 used to release hydrobromic acid; a device to prevent absorption; a bottle with a capacity of 250 cm^3, intended to receive the guaiacol to be analyzed; an ascending refrigerant; and a washing bottle containing a little water. 250 g of phosphorus tribromide were placed in the first flask and water added dropwise. This resulted in the instantaneous production of hydrobromic, which was directed into the flask containing 100 g of guaiacol to be analyzed and 10 cm^3 of water. A glass balloon of 200 cm^3 capacity was located between both balloons to avoid the absorption of guaiacol. This inconvenience was also avoided by placing an ascending condenser after the flask containing the guaiacol. The reaction product was poured into a flask with a capacity of about 1.5 liters and diluted with 500 to 600 cm^3 of water. The balloon was connected to a steam source capable of entraining only the volatile phenols. The pyrocatechin and homopyrocatechin were eliminated by extraction with ether and then separated one from the other by means of benzene, which extracted only pyrocatechin (Adrian, 1897abc).

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