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Reflexiones

Edouard Charles Ernest Duvillier: the chemistry of oxoacids

Edouard Charles Ernest Duvillier: la química de los oxoácidos

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Resumen

Edouard Duvillier (1851-1904) fue un químico francés que estudió en particular la química de los oxoácidos y sus derivados. Este trabajo llevó a la síntesis de numerosos compuestos nuevos y determinación de sus propiedades físicas y químicas, entre ellos, los ácidos metiloxobutírico, *n*-etiloxobutírico, isooxovalérico, tioisovalérico, y tiooxobutírico, sus derivados, metil-, etil-, y fenilamido, and la etiloxobutiramida. Duvillier reportó la síntesis, composición y propiedades de una variedad de derivados de productos químicos pertenecientes a los grupos de la creatina y creatinina, entre ellos, *a*-oxobutirocyamina y cyamidina. También desarrolló un método eficiente para separar las tres aminas pertenecientes al mismo radical alcohólico.

Palabras clave

Aminas; creatine; creatinine; oxoácidos; síntesis química.

Abstract

Edouard Duvillier (1851-1904) was a French chemist who studied the chemistry of oxoacids and their derivatives. This work led to the synthesis of many new chemical compounds and the determination of their physical and chemical properties, among them methyloxobutyric, *n*-ethyloxobutyric, isooxyvaleric, thioisovaleric, and thiooxybutyric acids, their, methyl-, ethyl-, and phenylamido derivatives, and ethyloxobutyramide. Duvillier reported the synthesis, composition, and properties of a variety of derivatives of chemicals pertaining to the groups of creatine and creatinine, among them *a*-oxobutyrocyamine and cyamidine. In addition, he developed an efficient method for separating the three amines pertaining to the same alcohol radical.

Keywords

Amines; chemical synthesis; creatine; creatinine; oxoacids

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Life and career (Perdrix, 1905)

Figure 1. Edouard Duvillier (1851-1904).

Little information is available in the literature regarding the life and career of Edouard Charles Ernest Duvillier (Figure 1) (Perdrix, 1905). He was born on May 2, 1851, in Cambrai (Nord department, Hauts de France). After finishing his basic education at a local lyceum in Douai he begun working as temporary teacher at the Lycée de Lille (1870) and shortly thereafter he was hired as préparateur délégué by Charles Viollette (1823-1897), dean of the Faculty of Sciences of Lille. Viollette introduced him into the proper laboratory practice and analytical procedures. Duvillier stayed in this position for nine years, a period during which he worked as préparateur de chimie, obtained his degree of licencié ès-sciences physiques and of docteur ès-sciences physiques, after successfully defending a thesis about the derivatives of *a*-oxobutyric and isooxovaleric acids (Duvillier, 1879f). The examiners of this work were Viollette, Camille-Pierre-Guillaume Forthomme, and Paul Augustin Terquem (1821-1906). Shortly thereafter (1880), Duvillier was appointed maître de conferences de chimie at Lille and full professor of chemistry at the l'Ecole Supérieure de Sciences et Lettres d'Alger. In 1884 he was appointed professor of industrial chemistry at the Faculty of Sciences of the University of Marseille. Duvillier passed away on September 20, 1904, after a serious illness.

Duvillier received several awards for his scientific achievements : a medal from the local committee of the Congrès de l'Association Française pour l'Avancement des Sciences, gold and silver medals of the Sociétés Savants (1878 and 1879), was elected corresponding member of the Société des Sciences of Lille (1881), non-resident member of the Société Chimique de Paris, and staff representative of the Faculty of Sciences at the Conseil Général des Facultés (Perdrix, 1905).

Scientific contribution

Duvillier wrote more than 60 papers and booklets about his research activities regarding the chromates, phosphates, and arseniates of barium and lead, the monobasic alcohols of the fatty series, procedure for the synthesis of fatty amines, and of several compounds pertaining to the creatine and creatinine series. In addition to the subjects described below, Duvillier also developed a method for preparing chromic acid (Duvillier, 1872, 1873a),

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for determining the amount of lead sulfate present in lead chromates (Duvillier, 1873b), and for recovering the platinum present in chloroplatinates (Duvillier, 1877); he studied the preparation of chloroform from chloral and of formic acid by dehydration of oxalic acid (Duvillier and Buisine, 1880e); developed an efficient method for the preparation of ethylene chloride (Duvillier, 1880g) and for the synthesis of some new betaines (Duvillier, 1887b, 1890); etc.

Oxoacids

Most of Duvillier's research activity was devoted to the synthesis of oxoacids, their derivatives, and properties (Duvillier, 1878a-d, 1879a-f, 1880a-j, 1883). His first paper described the synthesis of *n*-ethyloxobutyric acid by the reaction between *n*-ethyl bromobutyrate and sodium ethoxide in alcoholic solution (Duvillier, 1878a). The product was distilled to eliminate the alcohol and then mixed with water. The phase insoluble in water was dried and purified by rectification. The ethyl ethyloxobutyrate, CH_3-CH_2-CH(OC_2H_5)-COO-C_2H_5, contained in the fraction passing between 168º and 174 ºC, was easily saponified by a concentrated alcoholic solution of KOH and then purified by evaporation, neutralization with diluted sulfuric acid, and drying with concentrated alcohol. The potassium salt, CH_3-CH_2-CH(OC_2H_5)-COOK, was converted into its zinc salt and then hydrolyzed with hydrogen sulfide. The resulting acid, CH_2-CH(OC_2H_5)-COOH, was completely soluble in water, alcohol, and ether. Duvillier also reported the preparation of the corresponding salts of zinc, barium, and silver, of ethyl ethyloxovalerate and its salts, and of thiooxobutyric and thiooxovaleric acid by the reaction between bromobutyric and bromovaleric acids with a concentrated solution of potassium sulfide. The two sulfurized acids had a repugnant odor; thiooxobutyric acid was completely soluble in water, alcohol, and ether, while thiooxovaleric acid was slightly soluble in cold and hot water (Duvillier, 1878a, 1880ij).

In a following paper Duvillier extended his procedure to the synthesis of methyl ethyloxobutyrate and ethyloxobutyramide (Duvillier, 1878b). The butyrate was obtained by heating at 100 ºC in a closed tube and for several days, a mixture of sodium ethyloxobutyrate and a solution of methyl iodide in dry methanol. The purified methyl ethyloxobutyrate was a colorless liquid having an agreeable odor and a burning taste, boiling between 156º and 158 ºC, little soluble in water, and completely soluble in methanol, ethanol, and ether. The amide was prepared by heating at 100 ºC in closed tube, a mixture of ethyl ethyloxobutyrate with a concentrated alcoholic solution of ammonia. This substance was a crystalline solid, melting between 68º and 69 ºC, soluble in water, alcohol, and ether. Heated to higher temperatures it boiled and sublimed with decomposition (Duvillier, 1878b).

Duvillier wrote that it was expected that the synthesis of *n*-methyloxobutyric acid would take place under the same conditions as for ethyloxobutyric acid (Duvillier, 1878c), e.g.

$$CH_3\text{-}CH_2\text{-}CH(Br)\text{-}COO\text{-}C_2H_5 + C_2H_5ONa = CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}COO\text{-}C_2H_5 + NaBr$$

In practice, boiling ethyl bromobutyrate with a methanol solution of sodium methoxide resulted in the separation of a liquid lighter than water and distilling between 150º and 155 ºC, and another liquid, slightly soluble in water, completely soluble in methanol, methanol, and ether, and containing, by weight, 55.36% carbon and 9.75% hydrogen, indicating that the composition of the product of the reaction was actually intermediate between that of ethyl methyloxobutyrate and of methyl methyloxobutyrate. The latter originated from the action of methanol on ethyl methyloxobutyrate. Duvillier reported the synthesis of several

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salts of methyloxobutyric acid and that all of them were non-crystallizable and very soluble in water and alcohol (Duvillier, 1878c).

A following paper described the synthesis of several derivatives of isooxovaleric and *n*-oxobutyric acids (Duvillier, 1878d). Isooxovaleric acid was usually prepared by the procedure of John Clark and Rudolph Fittig (1835-1910) based on the transformation of crude isooxovaleric acid (obtained by the reaction between silver oxide and bromovaleric acid) first into calcium isooxovalerate, then into zinc isooxovalerate, and finally, liberation of the acid by means of sulfuric acid (Clark and Fittig, 1866). According to Duvillier, a faster procedure was to directly form the zinc salt, without passing through the calcium one. For this purpose it was enough to add zinc chloride to a hot crude solution of potassium isooxovalerate. The resulting zinc salt was filtered, washed with a little of water, then evaporated to dryness, and finally, separated from the residue by means of boiling alcohol (Duvillier, 1878d). Ethyl isooxovalerate was prepared by heating from 150^0 to 160 °C, for four days, a solution of crystalline isooxovaleric acid in alcohol. Ethyl isooxovalerate was a liquid of disagreeable odor, lighter than water, partially soluble in water, and completely soluble in alcohol and ether. Duvillier also reported the synthesis and properties of ethyl ethylisooxovalerate, methyl methyl isooxovalerate, methyl bromoisooxovalerate, and the acids thioisooxovaleric, thiodiisooxovaleric, thiooxobutyric, thiodioxobutyric, and ethyloxobutyramide, CH_3-CH_2-$CH(OC_2H_5)$-$CONH_2$. The latter was prepared by heating at 100 °C a mixture of ethyl ethyloxobuyrate with three times its volume of a concentrated alcoholic solution of ammonia. Thioisooxovaleric acid was obtained by the reaction between bromoisovaleric acid with potassium sulfide. Thioisooxovaleric acid had a repugnant odor, was almost insoluble in hot water and very soluble in ether, ethanol, and methanol (Duvillier, 1878d).

Duvillier described the synthesis of several organic derivatives of methyloxobutyric acid: ethyl methyloxobutyrate, CH_3-CH_2-$CH(OCH_3)$-COO-C_2H_5, demethyl methyloxobutyrate, CH_3-CH_2-$CH(OCH_3)$-COO-CH_3, and methyloxobutyramide, CH_3-CH_2-$CH(CH_3)$-$CONH_2$ (Duvillier, 1879b). The demethyl derivative was prepared by treating methyl bromobutyrate with a methanol solution of sodium methoxide, and the amide, by heating for several days to 100 °C in a closed vessel and for several days, a mixture of methyloxobutyrate with a saturated solution of ammonia in absolute ethanol. The amide crystallized as fine needles, soluble in water, alcohol, and ether, and melting between 77^0 and 78 ^{0}C. At higher temperatures it boiled and sublimated with decomposition (Duvillier, 1879b).

Duvillier also prepared the methylamido, ethylamido, and phenylamido derivatives of *a*-butyric, isovaleric, caproic, and propionic acids (Duvillier, 1879a, 1880bcd, 1883c, 1884, 1885a, 1886a, 1891). Methylamido *a*-butyric acid, CH_3-CH_2-$CH(NH$-$CH_3)$-$COOH$, was prepared by slowly adding one mole of *a*-bromobutyric acid to a concentrated aqueous solution (2 to 3 moles) of methylamine. This step was a highly exothermic reaction that resulted in the formation of methylamido *a*-butyric acid and methylamine bromohydrate. The product was kept boiling for several hours in a reflux apparatus, followed by addition of an excess of barium hydrate to decompose the bromohydrate. The barium hydroxide was then precipitated by addition of the stoichiometric amount of sulfuric acid, followed by the successive addition of silver carbonate and hydrogen sulfide. The filtrate was then evaporated to dryness under vacuum, in the presence of sulfuric acid. The residue was extracted by boiling ethanol and then left to cool alone. The precipitated methylamido

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a-butyric acid was purified by successive recrystallization from absolute ethanol. The purified product appeared as a bright white powdered, tasting slightly sweet, very soluble in water, little soluble in cold alcohol, very soluble in boiling alcohol, and insoluble in ether. It could be heated to 120 °C without decomposition; heated more it sublimed without blackening and without decomposition. At higher temperatures it decomposed partially while releasing ammoniacal vapors. Phenylamido *a*-butyric acid, CH_3-CH_2-CH(NH-C_6H5)-COOH, was prepared by treating one mole of aniline dissolved in ether, with one mole *a*-bromobutyric acid, CH_3-CH_2-CH(Br)-COOH. The ether was then eliminated, and the residue kept for several hours at 100 °C to complete the reaction. Addition of water dissolved the aniline bromohydrate and the phenylamido *a*-butyric acid, which precipitated upon cooling. It was then purified by successive recrystallization from water. Phenylamido *a*-butyric acid appeared as crystalline grains, little soluble in cold water, a little more in boiling water, very soluble in methanol, ethanol, and ether, and presenting a faint acid reaction. It could be heated to 100 °C without melting. Heated stronger it became a yellow liquid, which turned into viscous matter upon cooling (Duvillier, 1879a).

Diethylamidocaproic acid was prepared by heating in a sealed tube at 100 °C one mole of *n*-*a*-bromocaproic acid with excess of diethylamine (3 moles) in concentrated aqueous solution (Duvillier, 1891). The base was recovered by boiling with barium hydroxide, followed by precipitation of the barium hydroxide with the exact amount of sulfuric acid and treatment of the product with silver oxide, followed by hydrogen sulfide. The filtrate was evaporated to syrup, and the pure amido acid recovered by conversion into its copper salt (colored violet), purified by crystallization from an aqueous solution over sulfuric acid, and decomposition by hydrogen sulfide. The free acid, CH_3-CH_2-CH_2-CH_2-CH(N[C_2H_5]$_2$)-COOH, was very soluble in water and alcohol and insoluble in ether. Its solutions, when strongly concentrated, gave a crystalline mass, which decomposed on distillation. The hydrochloride was a syrupy substance, soluble in all proportions in water and alcohol. The chloroplatinate was deposited from very concentrated aqueous solutions in orange-red, monoclinic prisms; it was very soluble in water, and soluble in alcohol, but insoluble in pure, dry ether. The corresponding chloraurate was sparingly soluble in water (Duvillier, 1891).

A more extensive and detailed paper described the preparation of the acids ethyloxobutyric and *n*-methyloxobutyric, and their derivatives, composition, and properties; adding more particulars to those reported in other specific publications (see above) (Duvillier, 1879c). This publication was also an enlarged summary of the doctoral thesis of Duvillier, a work divided in two large sections: (a) derivatives of oxobutyric acid and (b) derivatives of isooxovaleric acid (Duvillier, 1879f). In the opening paragraphs Duvillier wrote that the ether derivatives of glycolic and lactic acids had been extensively studied by many scientists, among them, Charles-Adolph Würtz (1817-1884), Charles Friedel (1832-1899), and Wilhelm Heintz (1817-1880), but not so the derivatives of oxobutyric and isooxovaleric acids. It was his intention to carry on similar research on these two acids, particularly their ethers, amides, and sulfur derivatives (Duvillier, 1879f).

Friedel and V. Machuca had prepared *n*-oxobutyric acid by treating *n*-bromobutyric acid with wet silver oxide (Friedel and Machuca, 1861), while A. Naumann had done it by treating the same acid with a solution of barium hydroxide (Naumann, 1861). This acid was diatomic and monobasic hence it could generate three series of ethers with the same alcohol, depending on if the alcohol radical replaced acid hydrogen or the alcoholic hydrogen,

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or substituted simultaneously one or another of these two hydrogen atoms. Thus, for example, with ethanol it was possible to obtain ethyl oxobutyrate, CH_3-CH_2-CHOH-$COOC_2H_5$, ethyloxobutyric acid, CH_3-CH_2-CH(OC_2H_5)-COOH, or ethyl ethyloxobutyrate, CH_3-CH_2-CH(OC_2H_5)-$COOC_2H_5$, the first two derivatives being clearly isomers. After this introduction, Duvillier went on to describe the preparation and properties of some derivatives of *n*-ethyloxobutyric acid (potassium, sodium, barium, zinc, copper, silver, ethyl, and methyl ethyloxobutyrates; and ethyloxobutyramide), and of *n*-methyloxobutyric acid (ethyl and methyloxobutyrates, potassium, sodium, barium, zinc, and silver methyloxobutyrate; and methyloxobutyramide) (Duvillier, 1879c). For example, ethyl ethyloxobutyrate was prepared by a method like that of Würtz for synthesizing ethyl ethyl-lactate (Würtz, 1861), that is, reacting *n*-ethyl bromobutyrate with an alcoholic solution of sodium ethoxide. Potassium ethyloxobutyrate was prepared saponifying a boiling solution of ethyl ethyloxobutyrate with KOH, for about six hours, in an apparatus provided with reflux. Afterwards, the excess alcohol was eliminated by evaporation and the residue diluted with water and neutralized with the exact amount of diluted sulfuric acid. The mixture was then evaporated to dryness. Extraction with alcohol separated the potassium ethyloxobutyrate from the potassium sulfate. This product was purified by repeated recrystallization from alcohol. Potassium ethyloxobutyrate crystallized as fine needles, highly deliquescent, very soluble in water and alcohol, which could be heated to 150 °C without alteration and melting (Duvillier, 1879c). Ethyloxobutyramide, CH_3-CH_2-CH(OC_2H_5)-$CONH_2$, was prepared by heating at 100 °C in a closed tube for three days, a mixture of ethyl ethyloxobutyrate with three times its volume of a concentrated alcoholic solution of ammonia. The product was left to cool under vacuum and in the presence of sulfuric acid. Treatment with water resulted in the separation of a small amount of an oily liquid. The aqueous residue was left again alone under vacuum and in the presence of sulfuric acid, after some time the amide precipitated as thin crystalline plates, which were purified by repeated recrystallization by the same process. Ethyloxobutyramide was soluble in water, alcohol, and ether. Its crystals could only be purified under vacuum because heated to 100 °C it volatilized releasing heavy vapors. Sodium methyloxobutyrate, CH_3-CH_2-CH (CH_3)-COONa, was prepared by precipitating an aqueous solution of barium methyloxobutyrate with a slight excess of a solution of sodium sulfate. The filtrate was evaporated to dryness and the sodium methyloxobutyrate extracted with absolute alcohol. The purified salt was deliquescent and non crystallizable; it could be heated to 150 °C without alteration; at higher temperatures it blackened and decomposed leaving an abundant carbon residue. Methyloxobutyramide, CH_3-CH_2-CH(OCH_3)-$CONH_2$, was prepared by the same procedure as ethyloxobutyramide (Duvillier, 1789c).

Duvillier wrote that the reaction between ethyl bromoisovalerate and alcoholic sodium ethoxide produced ethyl ethylisoxovalerate, ethyl isoangelate CH_3-C(CH3)=CH-$COOC_2H_5$, ethanol, and sodium bromide, according to (Duvillier, 1879de, 1880fh):

$$CH_3\text{-}CH(CH_3)\text{-}CH(Br)\text{-}COOC_2H_5 + C_2H_5ONa = CH_3\text{-}CH(CH_3)\text{-}CH(OC_2H_5)H\text{-}COOC_2H_5 + NaBr$$

$$CH_3\text{-}CH(CH_3)\text{-}CH(OC_2H_5)\text{-}COOC_2H_5 + C_2H_5ONa = CH_3\text{-}C(CH3)=CH\text{-}COOC_2H_5 + C_2H_5OH + NaBr$$

The excess alcohol was separated by distillation and the residue diluted with water. The ethers were concentrated in the upper liquid layer and the sodium bromide in the lower aqueous one. The oily phase was dried and then distilled. The fraction passing between 155^0 and 190 ^{0}C was saponified with alcoholic KOH, the alcohol eliminated by distillation and the released KOH neutralized with sulfuric acid. The residue was mixed with zinc

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chloride and then evaporated to dryness. Treatment with alcohol dissolved the zinc salts of isoangelic and ethylisoxovaleric acids. The solution was dried again, and the residue treated with ether, which dissolved the isoangelic acid. Cooling this solution resulted in the precipitation of the solute as colorless transparent crystals, little soluble in water and very soluble in alcohol and ether (Duvillier, 1879de).

In a paper published in 1878 Duvillier mentioned that he had been unable to prepare pure ethyl isooxovaleric acid by treating ethyl bromoisovalerate with a solution of sodium ethoxide in absolute alcohol, due to the occurrence of a secondary reaction (Duvillier, 1878d). Two years later he reported that he had found that the product of the secondary reaction was dimethyl acrylic acid, CH_3-C(CH3)=CH-COOH, an isomer of angelic acid (Duvillier, 1880a):

$$CH_3\text{-}CH(CH_3)\text{-}CH(Br)\text{-}COOC_2H_5 + C_2H_5ONa = CH_3\text{-}CH(CH_3)\text{-}CH(OC_2H_5)\text{-}COOC_2H_5 + NaBr$$

$$CH_3\text{-}CH(CH_3)\text{-}CH(OC_2H_5)\text{-}COOC_2H_5 + C_2H_5ONa = CH_3\text{-}C(CH3)=CH\text{-}COOC_2H_5 + C_2H_5OH + NaBr$$

The reagents were heated for several hours in a flask provided with reflux and then the alcohol eliminated by distillation. Addition of water produced two liquid layers; the lower aqueous one contained the sodium bromide and the upper one, the ether. The upper layer was dried, and distilled, and the ethyl dimethyl acrylate collected in the fraction passing between 155º and 190 ºC. This liquid was saponified with an alcoholic solution of KOH and then neutralized with the exact amount of sulfuric acid. Zinc sulfate was added to decompose the potassium salt and the filtrate evaporated to dryness. The purified dimethyl acrylic acid appeared as colorless and transparent crystals, little soluble in water and very soluble in alcohol and ether (Duvillier, 1880a).

Creatine and creatinine

Duvillier reported the synthesis, composition, and properties of a variety of derivatives of chemicals pertaining to the groups of creatine and creatinine (Duvillier, 1880e, 1882, 1883ab, 1885b, 1886b, 1887ab).

a-Oxobutyrocyamine

This compound, a homologue of glycocyamine and alacreatine, was prepared by adding to a cold aqueous solution of one mole of amido-*a*-butyric acid, one mole of cyanamide and a few drops of aqueous ammonia and leaving the mixture alone at room temperature for several days (Duvillier, 1880e). The crystallization process continued for about one month. The crystals were separated and purified by washes of boiling alcohol and then recrystallized from aqueous ammonia. The crystals of *a*-oxobutyrocyamine were shaped as fine needles, little soluble in cold water and slightly more in hot water, insoluble in ethanol and ether and soluble in cold diluted inorganic acid. They did not contain crystallization water, and their elemental composition corresponded to the formula $C_5H_{11}N_3O_2$.

a-Oxobutyrocyamidine

This compound, a homologue of glycocyamidine, was prepared by boiling for several hours a solution of one mole of *a*-oxobutyrocyamine in an excess of diluted sulfuric acid

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(Duvillier, 1880e). The resulting solution was neutralized with barium carbonate and the filtrate evaporated to dryness. The residue contained *a*-oxobutyrocyamidine mixed with unconverted *a*-oxobutyrocyamine. It was extracted with ordinary alcohol, which did not dissolve *a*-oxobutyrocyamine. The purified product was found to contain one mole of crystallization water, $C_5H_9N_3O$ + H2O, which it lost by heating to 150 °C. The hydrate was soluble in cold water and very much in hot water, and in alcohol.

Isooxovalerocyamine

The preparation of this compound, $C_6H_{13}N_3O_2$, was by a process very similar to that for *a*-oxobutyramide (Duvillier, 1880e). It appeared as small cubic crystals, little soluble in cold water and more in hot water, little soluble in alcohol, insoluble in ether, and soluble in diluted mineral acids.

Methylamido-*a*-butyrocyamidine (*a*-butyric creatinine)

This compound was prepared by leaving to react for several months, a mixture of one mole of cyanamide dissolved in an aqueous ammonia solution, with one mole of methylamido-*a*-butyric acid (Duvillier, 1882). The crystals formed were separated, dissolved in boiling alcohol, and left to recrystallize at room temperature. According to Duvillier, this synthesis was the first example of a creatinine obtained directly, without passing through the corresponding creatine. A similar process was used to prepare methylamido-isovalerocyamidine (isovaleric creatinine).

Methylamido-*a*-caprocyamidine

This compound was prepared by letting to react for several weeks a cold solution containing one mole of methylamido-a-caproic acid, one mole of cyanamide, and a few drops of ammonia (Duvillier, 1883a). At the end of this period, the mixture had acquired a solid milky state that a microscopic examination showed to be formed by a multitude of fine needles. The substance was pressed and then purified by crystallization from water. Elemental analysis indicated that it contained, by weight, 56.41% carbon, 9.34% hydrogen, 24.73% nitrogen, and 9.52% oxygen, corresponding to the formula $C_8H_{15}N_3O$. This caproic creatinine was little soluble in cold water, much more in hot water, very soluble in cold and hot alcohol. A similar process was used to prepare ethylamido-*a*-caprocyamidine, $C_9H_{17}N_3O$. All the above synthesis demonstrated that the action of cyanamide on the acids methylamido-*a*-butyric, -*a*-isovaleric, -*a*-caproic, and ethylamido-*a*-caproic yielded creatinines directly and not creatines.

Ethylamido-*a*-butyrocyamidine

Duvillier also reported the synthesis of this new compound by the reaction between one mole of cyanamide and a cold aqueous solution of one mole of ethylamido-*a*-butyric acid mixed with a few drops of aqueous ammonia (Duvillier, 1883b). Again, after several months of contact, the solution deposited flat voluminous rhombic crystals, of elemental weight composition 53.69% carbon, 8.83% hydrogen, 26.65% nitrogen, and 10.83% oxygen,

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corresponding to the formula $C_7H_{13}N_3O$. These did not contain crystallization water and were very soluble in water and alcohol.

a-Ethylamido-propionocyamidine

Duvillier reported that the addition of one mole of cyanamide and a few drops of aqueous ammonia to a cold and saturated aqueous solution of one mole of *a*-ethylamidopropionic acid led to the slowly precipitation of crystals of dicyandiamide (Duvillier, 1885b). Concentration of the mother liquor resulted in the precipitation of rhomboidal crystals and of rhomboidal crystals of *a*-ethylamido-propionic acid. One or two recrystallizations from water allowed precipitation of prismatic crystals of *a*-ethylamido-propionocyamidine that did not contain crystallization water. Elemental analysis indicated that these crystals contained by weight, 50.83% carbon, 8.09% hydrogen, 29.45% nitrogen, and 11.63% oxygen, corresponding to the formula $C_6H_{11}N_3O$. This creatinine was soluble in alcohol (one part in 18 of alcohol at 16 °C) and much more soluble in water (one part in 3.7 of alcohol at 17 °C). According to Duvillier, these results indicated that the reaction of cyanamide with amido acids resulted in the formation of a creatine with the amido acids of ordinary ammonia, and the formation of a creatinine with compound amido acids with ammonia (Duvillier, 1885b).

Ethylamido-acetocyamidine (ethylglycocyamidine)

Duvillier wrote that an aqueous concentrated solution of ethyl glycocoll (ethyl glycine) and cyanamide left alone, resulted in the precipitation of crystals, shaped as long needles, mixed with a small number of crystals of dicyandiamide. Concentration of the filtrate produces new crystals that after purification by recrystallization from water, proved to be the creatinine ethylglycocyamidine, $C_5H_9N_3O$ (Duvillier, 1886b).

Additional papers on the subject reported the synthesis of the creatinines *a*-amidocaprocyamine and *a*-amidocaprocyamidine (Duvillier, 1887a).

Amines and their separation

Duvillier and Alphonse Jean Baptiste Aimable Buisine (1856-1918), also a student and préparateur de chimie at the Faculté des Sciences de Lille, published a series of papers about the chemistry of alkyl amines (Duvillier and Buisine, 1879abc, 1880a-d, 1881). They wrote that the different procedures for preparing ammonia compounds, very seldom-yielded one base only; generally, they resulted in the formation of the three derivatives of a given alcoholic radical, in a variable proportion. Sometimes they also produced the quaternary derivative (Duvillier and Buisine, 1881). According to August Wilhelm Hofmann (1818-1892), the reaction of ethyl chloride and ammonia produced monoethylamine, diethylamine, and triethylamine, in the same proportion. The action of ethyl bromide on ammonia provided mainly monoethylamine accompanied by near a fifth of diethylamine and traces of triethylamine (Hofmann, 1870). The action of iodides on ammonia generated the three bases (Hofmann, 1860). Charles Würtz's (1817-1884) procedure for preparing primary bases by reacting isocyanate and cyanate esters with KOH yielded a small quantity of

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tertiary bases (Würtz, 1850) and Wilhelm Heintz (1817-1880) had shown that reacting KOH with ethyl cyanate always produced a small amount of triethylamine (Heintz, 1864). Hence, Duvillier and Buisine believed that the preparation of pure bases required the development of a precise process for separating the primary, secondary, and ternary bases. No special procedure was needed for separating the quaternary ones, distillation transformed them into triamines, or they were not separated from their salts by potassium (Duvillier and Buisine, 1881). Hofmann had found that the three ethylamines could not be separated by distillation despite the large difference between their boiling points: monomethylamine, 18 °C, diethyl amine, 57 °C, and triethylamine, 91 °C. Instead, he proposed isolating them by means of an excess of diethyl oxalate. Under these conditions, monoethylamine yielded diethyloxamide, an insoluble substance, diethylamine, and the ester ethyl diethyloxamate, insoluble in water: $COOC_2H_5\text{-}COOC_2H_5 + 2(NH_2C_2H_5) = CONHC_2H_5\text{-}CONHC_2H_5 + 2(C_2H_5OH)$

$$COOC_2H_5\text{-}COOC_2H_5 + NH(C_2H_5)_2 = CON(C_2H_5)_2\text{-}COOC_2H_5 + C_2H_5OH$$

The triethylamine did not react and, hence, could be separated by distillation. The residue deposited the diethyloxamide, which could be separated by pressure filtration. Afterwards, Otto Wallach (1847-1931; 1910 Nobel Prize in Chemistry) and A. Boerhinger, and P. Weist proved that operating under the conditions described by Hofmann (excess of diethyl oxalate) resulted also in the formation of large amounts of ethyl monoethyloxamate, $CONHC_2H_5\text{-}COOC_2H_5$, invalidating Hofmann's procedure. In addition, the boiling points of the esters ethyl monoethyloxamate and diethyloxamide were very close making their separation extremely difficult. They recommended that the best method for obtaining the diethyloxamide was to operate with a concentrated aqueous solution of the ethyl bases (Wallach and Boerhinger, 1874; Wallach and Weist, 1876).

Duvillier and Buisine followed Wallach and Boerhinger's suggestion. The mixture of the bases was prepared by reacting ethyl bromide with an alcoholic solution of ammonia. The excess of ammonia was eliminated, and the amine mixture transformed into their hydrochlorides, followed by addition of alcohol to eliminate the ammonium chloride. The resulting solution was found to contain mostly monoethylamine, accompanied by about 20% of diethylamine, and traces of triethylamine (Duvillier and Buisine, 1879a, 1880d, 1881). To carry on the separation, the solution, kept in an ice bath, was slowly mixed with a known amount of diethyl oxalate (in slight excess above the stoichiometric quantity). After 24 hours, the deposited diethyloxamide was separated by pressure filtration and the very alkaline filtrate distilled over a water bath to eliminate the alcohol formed by the reaction (see above equations), and the non-reacted bases. Cooling led to precipitation of the remaining diethyloxamide, which was separated again as the previous batch. The residue was concentrated to syrup state containing diethyloxamate ester, diethyloxamic acid, $COOH\text{-}CON(C_2H_5)_2$ (originating from the hydrolysis of the ester), and diethyloxamate acid oxalate, $COOH\text{-}COOHNH(C_2H_5)_2$:

$$COOC_2H_5\text{-}CON(C_2H_5)_2 + H_2O = COOH\text{-}CON(C_2H_5)_2 + C_2H_5OH$$

$$COOH\text{-}CON(C_2H_5)_2 + H_2O = COOH\text{-}COOHNH(C_2H_5)_2$$

Duvillier and Buisine had the brilliant idea of transforming these three products into one, diethyloxamate acid oxalate, which had the advantage of being easily crystallizable. For doing so, they added to the syrup 8 to 10 times its volume of water, followed by strong boiling during 10 to 12 hours and evaporation to a very small volume. Cooling led to abundant crystallization. The filtrate was subjected several times to the same process.

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The accumulated crystals were found to contain, by weight, 44.02% carbon, 8.11% hydrogen, 8.77% nitrogen, and 39.1% oxygen, corresponding to $C_6H_{13}NO_4$, the formula and composition of diethyloxamate acid oxalate. Duvillier and Buisine believed that their procedure was very advantageous for separating diethylamine because it provided a substance perfectly crystallizable. They added that subjecting the methylamines to the same procedure provided syrup of similar behavior (Duvillier and Buisine, 1879a, 1880d).

A particular problem was the so-called "commercial trimethylamine" (Duvillier and Buisine, 1879bc, 1881). This product was far from being pure trimethylamine. Duvillier and Buisine first verified that this material did not contain ammonia; treatment with diethyl oxalic yielded a variety of bases and an abundant white precipitate, which was separated by filtration. The filtrate was distilled to a allow completion of the precipitation, and the new solid formed added to the previous batch. Duvillier and Buisine found that this deposit was formed by the oxamide of the primary bases. Additional treatment allowed separating it into three portions, (1) a waxy material, (2) a granulose one more soluble in water, and (3) a deposit soluble in cold water and more in hot water. The first fraction was purified by solution in boiling water, followed by crystallization from alcohol. It was formed of pearly needles, which were found to be diisobutyloxamide. Elemental analysis showed that it contained, by weight, 60.61% carbon, 14.43% nitrogen, 10.14% hydrogen, and 14.82% oxygen. Treated with KOH produced a slightly aromatic liquid and a chloroplatinate derivative, sparingly soluble in alcohol and extremely like the butylamine chloroplatinate prepared by Würtz (Würtz, 1854). The second fraction, purified by successive crystallization from water, appeared as fine silver needles, melting at about 100 °C, with fuming. Elemental analysis indicated that it was dipropyloxamide. The third fraction was purified as the first one. Elemental analysis indicated that it composed of dimethyoxamide contaminated with dipropyloxamide. A portion of it, decomposed by KOH, yielded a base forming a yellow chloroplatinate extremely like the monomethylamine chloroplatinate prepared by Würtz (Würtz, 1850). These results indicated that commercial trimethylamine contained monomethylamine, monopropylamine, monoisobutylamine, dimethylamine (about 50% of the total), and traces of monoethylamine (Duvillier and Buisine, 1879c).

Duvillier and Buisine showed that heating to 100 °C, in a closed vessel, a solution of ammonia in methanol mixed with methyl nitrate resulted in the formation of a large amount of monomethylamine, a small amount of tetramethylammonium nitrate and traces of dimethylamine and trimethylamine. Under the same conditions, the reaction between monomethylamine and methyl nitrate produced almost only tetramethylammonium nitrate and traces of dimethylamine and trimethylamine (Duvillier and Buisine, 1880a). Additional papers reported the action of methyl bromide and iodide on monomethylamine (Duvillier and Buisine, 1880b), and the action of ethyl chloride on ethylamines (Duvillier and Buisine, 1880c). A long memoir (60 pages) described in more detail all the information presented above (Duvillier and Buisine, 1881).

In following papers, Duvillier and Hippolyte Malbot reported the action of ammonia gas on methyl nitrate and the action of methyl nitrate on an aqueous solution of ammonia (Duvillier and Malbot, 1883, 1885, 1887). In a first series of experiments, they observed that bubbling ammonia gas through a solution of methyl nitrate in methanol resulted in an exothermic reaction until the liquid became saturated with ammonia. The solution was then distilled to eliminate the ammonia that had not reacted with the alcohol and the residue

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treated with an excess of KOH and then neutralized with nitric acid. After purification, the liquid was found to contain tetramethylammonium nitrate accompanied by a significant proportion of monomethyl amine, accompanied by traces of dimethyl and trimethylamine (Duvillier and Malbot, 1887). These results led them to investigate the action of methyl nitrate on an aqueous solution of ammonia. Mathew Carey-Lea (1823-1897) had already reported that leaving alone for five to six days a mixture of an aqueous solution of ammonia with an equal volume of methyl nitrate resulted in the disappearance of the latter and formation of the three methyl amines (Carey-Lea, 1882). Duvillier and Malbot repeated the experience of Carey-Lea in a more careful manner. For this purpose, they let react at room temperature one mole of methyl nitrate with a concentrated aqueous solution of ammonia (one mole), with constant agitation. The methyl nitrated disappeared after six weeks. The solution was treated with an excess of boiling KOH to remove the volatile ammonia compounds, neutralized exactly with nitric acid, and the potassium nitrate eliminated. The filtrate was mixed with alcohol and then evaporated to dryness. The tetramethylammonium nitrate was extracted with alcohol and purified by repeated crystallization. The analytical results indicated that this procedure provided an abundance of this salt, accompanied by the four-methyl bases (Duvillier and Malbot, 1885, 1887).

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