The Pictet Memorial Lecture.

AMÉ PICTET.

1857—1937.

A MEMORIAL LECTURE DELIVERED ON APRIL 1ST, 1938.

BY GEORGE BARGER, Hon. M.D., LL.D., F.R.S.

BY the death, on March 11th, 1937, of Amé Pictet, Swiss chemistry lost its doyen, and this Society a distinguished honorary Fellow, one of the last representatives of the "classical period" of organic chemistry. But little interested in theoretical questions, and not much influenced by modern biochemistry, he was primarily concerned with the constitution of natural products and most of all with their synthesis. The latter he often accomplished by the simplest of means, applying old-established methods with great ingenuity and tenacity, not using elaborate modern technique, always showing a thorough knowledge of the literature. Pictet was not just a chemist, no mere academic recluse. A distinguished citizen of a small republic, "the Rome of the Protestants," the "Conscience of the World," where a traditional devotion to science and learning had long been the attribute of men of leisure, this son of a patrician family did not entirely live the retiring life of an investigator and teacher; he was also a welcome delegate at many international gatherings.

For centuries the Pictet family had supplied distinguished citizens to the state. Marc Auguste, collaborator of de Saussure and his successor to a chair in the old Academy of Calvin, was one of the founders of the Société helvétique des Sciences naturelles. His brother Charles represented Geneva at the Vienna Congress of 1815 and was moreover one of those who originated the *Bibliothèque brittanique*, from which the present *Archives des Sciences physiques et naturelles de Genève* took their origin. This branch of the family later produced Raoul Pictet, physicist and inventor, well known for his work on the liquefaction of gases.

Amé Pictet, our late honorary Fellow, belonged to a younger branch which had included notable biologists among its members. Amé's grandfather, Jules, a historian, was the author of a well-known work, "La Genève ressuscitée," and married a niece of the famous botanist, Augustin-Pyramus de Candolle.

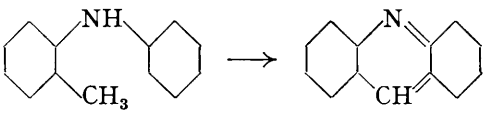
The next generation was not much influenced by science or learning: Amé's father, Ernest Pictet, was a banker, a man of affairs, maire, president of the Geneva Grand Council, representative of his town in the national Parliament; he probably had no enthusiasm for the scientific career of his son, in whom the family tradition of scholarship nevertheless reasserted itself.

Having received a classical education at the local Gymnasium, young Pictet entered the university of his native town in 1875, with the intention of studying medicine, but he was soon deflected towards chemistry by the teaching of the famous Marignac. After obtaining the bachelor's degree in 1877, he migrated to the Polytechnikum (later Technische Hochschule) at Dresden, where in R. Schmitt's laboratory he spent a year on inorganic analyses and a second year on practical organic chemistry. During this period Pictet had as fellow student Arthur Hantzsch, of the same age (both were born in 1857). A lecture in memory of Hantzsch was delivered by Professor T. S. Moore at the annual meeting of this Society at Bristol two years ago. Schmitt, the teacher of Pictet and of Hantzsch, was a former pupil and assistant of Kolbe; he seems to have been a favourite with young students, at a time when there were few laboratories in which systematic instruction in the technique of organic chemistry could be obtained. It was Marignac who induced Pictet to choose chemistry rather than medicine; it was Schmitt who made him choose the organic branch of the subject. Therefore, on leaving Dresden in 1879, Pictet selected Kekulé's laboratory for his first research. At Bonn he did not, however, work with the great master himself; he was put in charge of the latter's assistant,

Anschütz, who suggested an investigation on the isomerism, then not completely understood, of maleic and fumaric acids, and on their relation to the tartaric acids. It was proposed to convert the two unsaturated acids into dibromosuccinic acids without change of configuration, and then to transform the bromo-acids into either pure racemic or pure *meso*tartaric acid; previously only mixtures of these two had been obtained. Hardly had Pictet started his experiments, in the autumn of 1879, when he and Anschütz were chagrined to learn that Kekulé had succeeded in converting succinic acid into *meso*-tartaric. This took away much of the interest from Pictet's research and he therefore confined himself to a systematic examination of esters of tartaric acid, and to an attempt to connect their rotatory powers with the nature of the alkyl group. He did indeed observe some regularities, which were not, however, reproduced when the esters were acetylated or benzoylated. This theoretical question was much later investigated by Pictet's colleague, Philippe Guye. In 1880 Pictet left Bonn for Geneva, where he completed his work and obtained the degree of doctor of science in 1881 with a dissertation entitled: "Recherches sur les éthers tartriques."

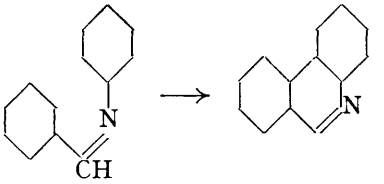
The work in Kekulé's laboratory did not profoundly influence Pictet's career. Yet, in a rather accidental way, his stay in Bonn proved of the greatest importance. According to notes left at his death, he received a deep impression, amounting to an inspiration, on seeing one day in the window of a Bonn bookshop a pamphlet by Koenigs, open at the pages where the author discussed the structure of pyridine. Pictet decided to take up the study of heterocyclic compounds of this type, and thus the nature of his researches was determined for more than 30 years, during his most fruitful period, devoted largely to the study of alkaloids. There was already some evidence of his interest in vegetable bases in the subsidiary propositions, which according to custom he undertook to defend along with his doctoral thesis.

When Pictet returned to Geneva in 1880, Graebe, Marignac's successor, at once appointed him an assistant, and henceforth Pictet worked in his native city, except for the winter of 1881—1882, when he spent a little time in the laboratory of Würtz at Paris. Würtz, like Anschütz and Kekulé, had but little influence on Pictet's further work; not so Graebe. It was Graebe who, on Pictet's final return in 1882, made him a Privatdozent and supplied him with young collaborators. It was also Graebe who suggested a synthesis of *iso*quinoline from phthalomethylimide, and later made more valuable suggestions, directly or indirectly. The first attempt to obtain the hypothetical isomeride of quinoline failed, and once more Pictet suffered a disappointment, when *iso*quinoline was discovered in coal tar by Hoogewerff and van Dorp (1885) and was synthesised by Gabriel (1886). During this period his scientific output was not very large; his work on nicotine had not yet begun. In 1888 he was appointed chemistry master at the Gymnasium, a post which he held for five years. Pictet's first independent paper of any importance was published in 1886, when he was 29 years of age, and consisted in the recognition that the product obtained by Etard in the pyrolysis of benzylidene-*o*-toluidine was not a methyl derivative of the hypothetical phenanthridine, as Etard supposed, but α-phenylindole. Pictet's attention seems to have been directed to this subject by Graebe's work, who a little earlier had synthesised acridine by pyrolysis of phenyl-*o*-toluidine

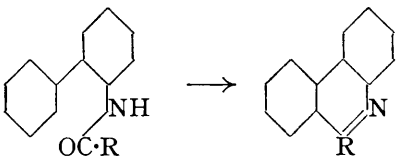


Graebe, however, failed to obtain an isomeric substance "phenanthridine" from benzylideneaniline, and this apparently led Pictet to test Etard's claim to have produced a methylphenanthridine from benzylidene-*o*-toluidine. Since benzylideneaniline did not react in the desired fashion, and, for that matter, benzylidene-*p*-toluidine did not either, Pictet rightly concluded that the methyl group of *o*-toluidine was involved in a ring closure, to an indole derivative, and this he proved by a synthesis of α-phenylindole by reduction of *o*-nitrodeoxybenzoin. In this manner Pictet began to pay attention to pyrogenetic

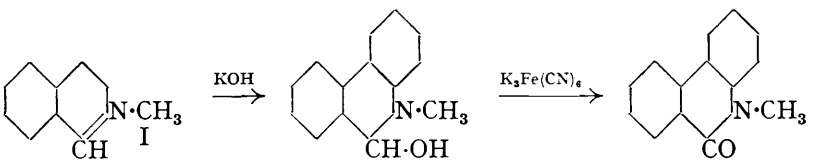
reactions, which played so large a part in his subsequent work. His first success with such a reaction was the synthesis of phenanthridine itself, from benzylideneaniline :



Five years earlier Graebe had failed to achieve this (at a dull red-heat). Pictet used an iron tube packed with pumice and raised the temperature to a bright red-heat (1889). Later he synthesised the base by a less violent method; he prepared also derivatives by intramolecular condensation of 2-acylamidodiphenyls :

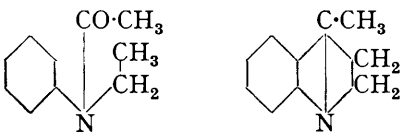


Unlike phenanthrene, phenanthridine proved very difficult to oxidise. In order to obtain phenanthridone, Pictet employed a novel agent, the nascent oxygen given off from bleaching powder and a cobalt salt. Alkylphenanthridones were, however, readily obtained by means of ferricyanide; the latter reaction may be explained by the intermediate formation of what is now called a pseudo-base :

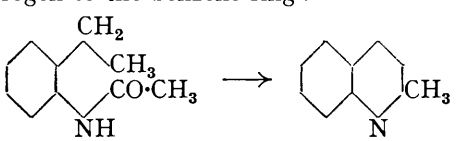


Pseudo-base Methylphenanthridone

Other papers of this early period are concerned with the monoalkylation of primary bases, by treating their acyl derivatives with alcoholic potassium hydroxide and an alkyl halide, a method improved later by Hinsberg, who used sulphonyl derivatives. In this way Pictet occupied himself with acetomethylanilide, and suggested its introduction into medicine to replace the rather undesirable acetanilide or antifebrine. He mentioned his ideas to a partner in a Parisian firm, who began to manufacture acetomethylanilide under the name of exalgine, without in any way acknowledging Pictet's suggestion or work. The latter's train of thought about this time may be illustrated by yet another synthesis. By the action of zinc chloride, a reagent which he also employed much later in his work on sugars, he hoped to convert acetoethylanilide into dihydrolepidine (4-methyldihydroquinoline) :



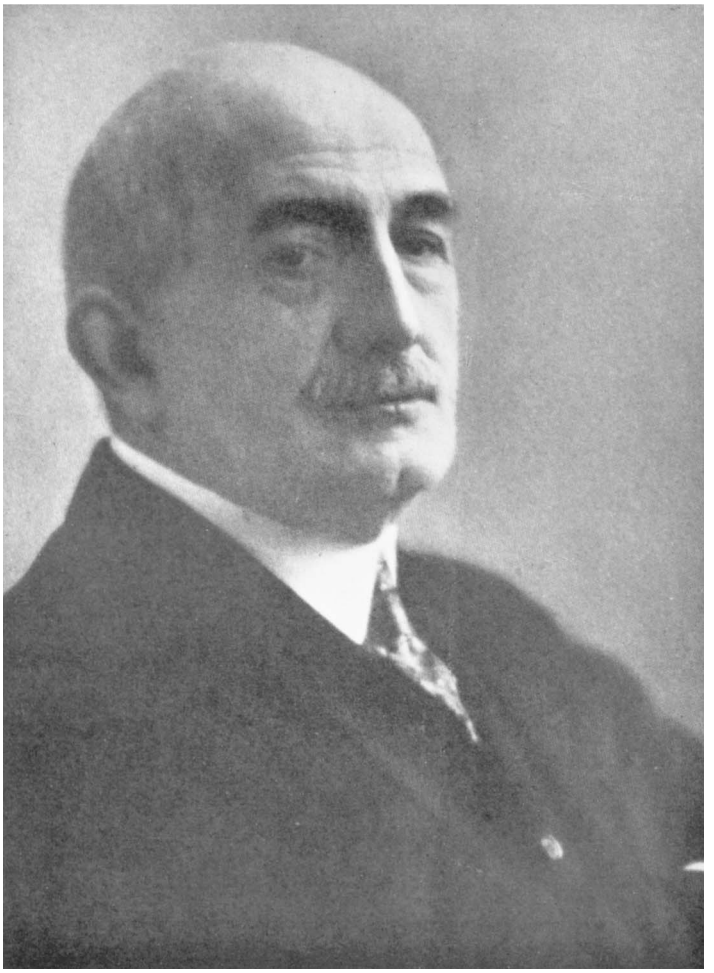
Actually he obtained quinaldine, which probably involves a preliminary wandering of the ethyl group from the nitrogen to the benzene ring :



In 1892 Pictet was one of the secretaries of the congress of chemists, which met in his native city and suggested the Geneva nomenclature of organic compounds. Its origins

were as follows: In connexion with the Paris exhibition of 1889 (which left as a relic the Eiffel tower) there was held an international congress of chemistry, and its organisers had placed on the programme the reform of organic nomenclature. The subject, however, proved to be so difficult that it was remitted to an international standing committee. A Parisian sub-committee met 45 times and considered suggestions from abroad; its report was adopted as the basis for discussion at the congress which met at Geneva on April 19—22, 1892. Membership was by invitation, not by delegation from national chemical societies. Some 35 chemists accepted the invitation and among these France was most largely represented. Not only did the project originate in France, but some of the younger French chemists had contributed much enthusiasm and energy to the preliminary discussions: the reform appealed to their logical minds and was intended to facilitate teaching. The Germans were more concerned with giving every substance a single official name so that it could readily be found in the literature. Britain was represented only by H. E. Armstrong, J. H. Gladstone and W. Ramsay; others who had been invited did not accept. C. Friedel, of Paris, an Alsatian, was chosen as president, von Baeyer, Cannizzaro, Gladstone and Lieben were vice-presidents. Pictet, at that time 35 years of age, and still a schoolmaster, was one of the four secretaries. (The photograph facing p. 1117 is reproduced from an original kindly lent by Prof. E. Briner, Geneva.) During its eight sessions the congress did little more than consider the nomenclature of aliphatic compounds; its recommendations were to some extent a compromise between the French and the German views. Much later, after the World War, a sub-committee of the Union de Chimie pure et appliquée carried the work further, and in this Pictet took an active part, understanding alike the French and the German points of view.

In 1893 Pictet resigned his schoolmastership, and a year later he was appointed extraordinary professor of organic chemistry in the University. In 1895 there appeared one of his best known papers, on phenyl- and pyridyl-pyrroles and the constitution of nicotine (in conjunction with P. Crépieux). It had been shown by Blau that gentle dehydrogenation of nicotine furnishes a monoacid base (nicotyrine) having the properties of a pyrrole, and this had led Hoogewerff and van Dorp to suggest a structural formula for the alkaloid, which was later proved to be correct. Already in 1889, in the laboratory of the Gymnasium, Pictet had begun an attempt to verify this formula, but he made no considerable progress until, on returning to the University in 1894, he secured an abundant supply of tobacco juice from a friendly manufacturer of cigars. The main result in the 1895 paper was the demonstration of the identity of nicotyrine with *N*-methyl-α-(β-pyridyl)pyrrole, which established the constitution of the natural alkaloid. The synthesis was first tried with aniline mucate, which yielded *N*-phenyl- and α-phenyl-pyrrole. The β-aminopyridine was obtained from nicotinic acid *via* the amide; nicotinic acid had already been synthesised, but Pictet obtained the necessary supplies of this acid by oxidising nicotine. The most difficult step was the isomerisation of *N*-(β-pyridyl)pyrrole to the corresponding α-derivative, which was achieved by passing the vapour of the former through a red-hot tube [a synthesis by a different route, at a lower temperature, was worked out by Späth and Bretschneider (*Ber.*, 1928, **61**, 327)]. It should be remembered that in 1895 alkaloidal synthesis was in its infancy and had gone no further than coniine and piperine. A red-hot tube had already become to Pictet a familiar piece of apparatus, and had enabled him to prepare phenanthridine and *iso*quinoline. Nicotyrine was, however, but the first stage in the synthesis of the natural alkaloid; eight more years were required before it could be converted into optically active nicotine. The reduction of the pyrrole ring without affecting the pyridine nucleus caused the greatest difficulty in those days, before the development of catalytic methods. The reduction was accomplished in two stages: hypoiodite yielded iodonicotyrine, which with tin and hydrochloric acid furnished dihydronicotyrine. On repetition of the process (with hypobromite instead of hypoiodite) the second double bond was hydrogenated and the resulting racemic nicotine was resolved *via* the tartrate. The nicotyrine actually used in these experiments was made from the alkaloid, not synthesised; Pictet relied on the proved identity of the synthetic product with nicotyrine from natural sources. The resolution of the racemic alkaloid created interest on account of the difference between



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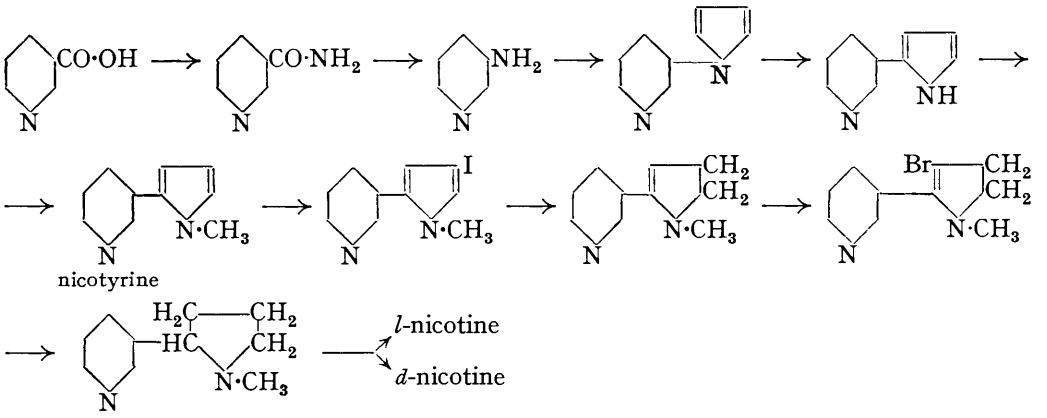
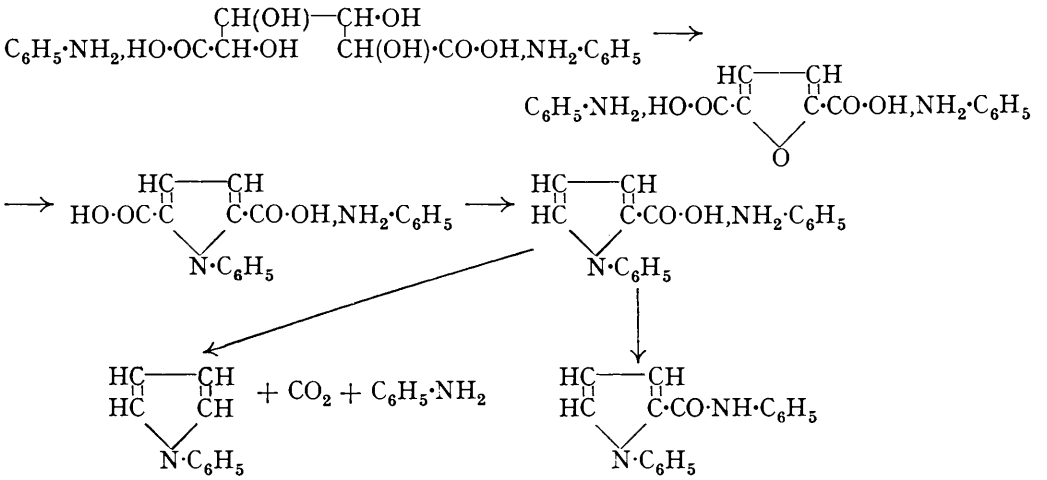
CONGRESS OF ORGANIC NOMENCLATURE, GENEVA, APRIL 19-22, 1892.

the pharmacological properties of the new *d*-enantiomorph and natural *l*-nicotine. Again the racemic nicotine employed was not obtained by reduction of nicotyrine, but by heating *l*-nicotine hydrochloride for 4—5 days with water at 200—210°.

The synthesis may be represented as follows :



The synthesis of nicotine led to some subsidiary investigations, on nicotinic acid, on the methiodides of nicotine, and on the minor alkaloids of tobacco. Of the last he described in 1901 *nicoteine*, $C_{10}H_{12}N_2$ (a dehydronicotine); *nicotelline*, $C_{10}H_8N_2$, a solid, and *nicotinine*, $C_{10}H_{14}N_2$, isomeric with nicotine and a secondary base. Other work was concerned with the mechanism of the pyrrole synthesis, which was studied with aniline mucate. By varying the conditions either *N*-phenylpyrrole-αα′-dicarboxylic acid could be obtained, or the anilide of the monocarboxylic acid. Either compound furnished *N*-phenylpyrrole at a higher temperature :



At a still higher temperature (dull red-heat) the pyrrole ring may be enlarged, if it has a suitable substituent in the α-position. Thus α-methylpyrrole yields pyridine, α-methylindole yields quinoline, *N*-methylcarbazole yields phenanthridine, and α-benzylpyrrole yields β-phenylpyridine.

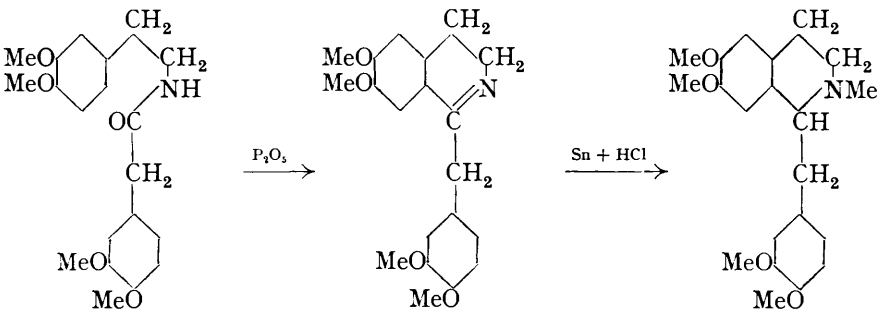
Other investigations of this time were concerned with the dismutation which the methiodides of phenanthridine and acridine undergo on treatment with alkali. Thus phenanthridine methohydroxide is partly oxidised to *N*-methylphenanthridone, partly reduced to a volatile base, dihydrophenanthridine. Similarly methylacridone is obtained along with methyldihydroacridine. A research of a rather different nature involved the preparation of mixed anhydrides of acetic acid with inorganic acids, for instance, tri-

acetyl boric acid, acetyl nitrate and diacetyl orthonitric acid. The last on refluxing with acetic anhydride yielded tetranitromethane:

$$4(CH_3{\cdot}CO{\cdot}O{\cdot})_2N(OH)_3 + 4(CH_3{\cdot}CO)_2O = 15CH_3{\cdot}CO{\cdot}OH + CO_2 + C(NO_2)_4$$

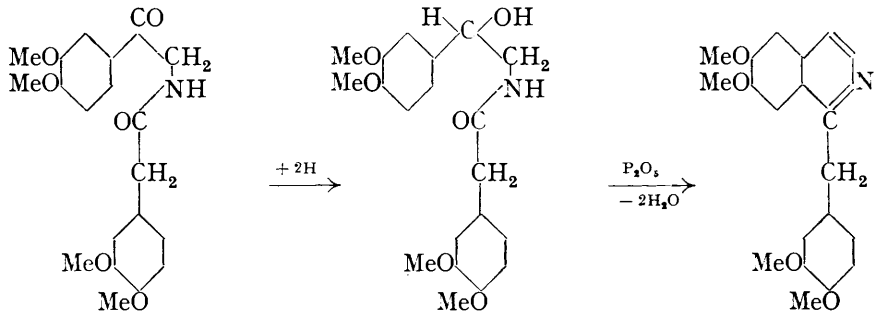
Pictet was, however, gradually becoming more and more interested in alkaloids. Already before the beginning of this work on nicotine he had published "La constitution chimique des alcaloides végétaux," Paris, 1888; this book subsequently had an English and two German editions. Before the synthesis of nicotine had been completed, he entered the field of *iso*quinoline alkaloids by showing that the rare opium alkaloid laudanosine can be obtained by resolution, by means of quinic acid, of the racemic reduction product of papaverine methochloride The constitution of papaverine had already been settled by Goldschmiedt. Other alkaloidal work was concerned with strychnine and brucine oxides, with *iso*strychnine, and with the origin of alkaloids in plants. Whilst Pictet was not much concerned with theoretical explanations in organic chemistry—he as a rule preferred a simple experiment—he was more inclined to speculate in the biological field, where experimentation was difficult or impossible. Thus he was one of the first to put forward the theory, now generally accepted, but by no means so well recognised by the botanists of that time, that alkaloids are break-down products of protein, which the plant couples with other substances, analogous to benzoic acid and indoxyl, and deposits in its tissues because it has no excretory organs which enable the animal to get rid of such substances in the form of hippuric acid and urinary indican. In a search of such analogues of benzoic acid and indoxyl he discovered (1907) in a number of common plants minute traces of simple bases, which he termed proto-alkaloids. For instance, in tobacco he found *N*-methylpyrrolidine, in a quantity corresponding to 0·3% of the total alkaloid, and not formed from nicotine. A similar base obtained in a minute yield (0·01%) from pepper was identified 20 years later as β-methylpyrroline. Whilst Pictet's view as to the source of alkaloids has been generally accepted, his ideas regarding the mechanism of their production, and the significance of his proto-alkaloids, are not in accordance with modern knowledge of the amino-acids of protein, some of which were only being discovered at the time of his speculations. His curiosity as to the presence of alkaloids in fossil plants seems afterwards to have led him to his work on vacuum tar and would thus be a link between his earlier and his later periods.

The five years 1904—1909 after the nicotine synthesis were thus occupied with problems arising out of it, and with minor investigations on other alkaloids. In 1909 he published an improved synthesis of tetrahydro*iso*quinolines which led again to most important work, on laudanosine and papaverine. Bischler and Napieralski had distilled amides with phosphoric oxide and so obtained minute yields of bases which they regarded as *iso*quinolines. With F. W. Kay, apparently his first British pupil, Pictet showed that the reaction is enormously improved by heating the amide in toluene or xylene solution with the suspended pentoxide. This opened the way to the synthesis of laudanosine (with Marie Finkelstein); the method was afterwards much used by others for the synthesis of numerous *iso*quinoline alkaloids. One of the main difficulties is the preparation of the requisite substituted amide; in the case of laudanosine the amide was homoveratroylhomoveratrylamine, which Pictet had to prepare by the somewhat primitive methods then available:



Homoveratroylhomoveratrylamine Laudanosine

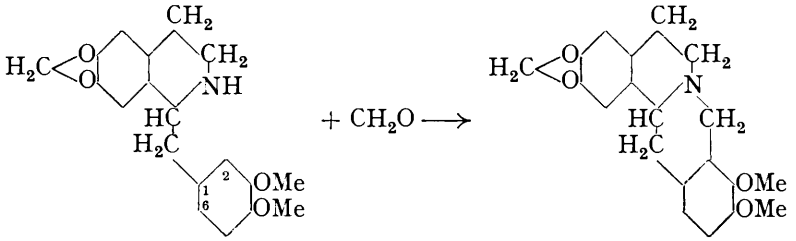
The year 1909 greatly added to Pictet's reputation, and he also published the synthesis of papaverine (with H. Gams). Unlike laudanosine, which is a derivative of tetrahydro-*iso*quinoline, papaverine is a derivative of unreduced *iso*quinoline, so that the dihydro-derivative resulting from the ring closure would have to lose two hydrogen atoms, instead of gaining them. This dehydrogenation Pictet was unable to bring about directly (it was later accomplished by Späth and Burger, *Ber.*, 1927, **60**, 704, by palladised asbestos at 200°). Pictet, however, obtained the desired result indirectly, by introducing a hydroxyl group, and removing this later along with a hydrogen atom to make the necessary double bond. This ingenious modification of the synthesis started with ω-aminoacetoveratrone instead of homoveratrylamine. The homoveratroyl derivative of this ketone was reduced to a hydroxylated amide, from which phosphoric oxide removed in one operation two molecules of water, instead of the single one required for ring closure:



ω-Homoveratroylaminoacetoveratrone — Hydroxylated amide — Papaverine

The synthetic product did not show a colour reaction given by the natural papaverine, and this colour reaction was traced to the presence in the commercial alkaloid of several units % of cryptopine.

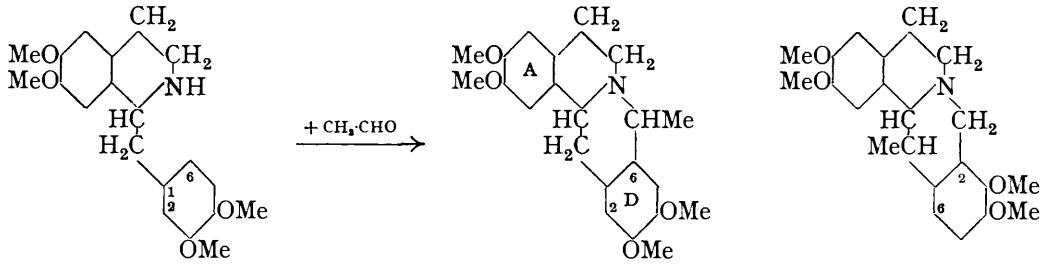
In 1911 Pictet and Gams published two papers, in which they claimed to have synthesised oxyberberine and berberine, containing a fourth ring additional to the three in laudanosine and papaverine. Haworth, Perkin, and Robinson (J., 1924, **125**, 1686) failed to repeat the alleged synthesis of oxyberberine, which is destroyed by 15—20% alcoholic potassium hydroxide at 140—150°, the supposed last reaction in Pictet and Gams's process. It was, however, synthesised by Perkin, Rây, and Robinson (J., 1925, **127**, 740) by another method, so that its constitution is certain. Likewise Buck and Davis (*J. Amer. Chem. Soc.*, 1930, **52**, 660) could not repeat the direct synthesis of berberine. The error, of which Pictet became the victim, can only be a subject for speculation. The reaction aimed at was a simple one, the ring closure of veratrylnorhydrastinine (analogous to laudanosine) by means of an additional carbon atom, supplied as methylal:



Veratrylnorhydrastinine — Tetrahydroberberine

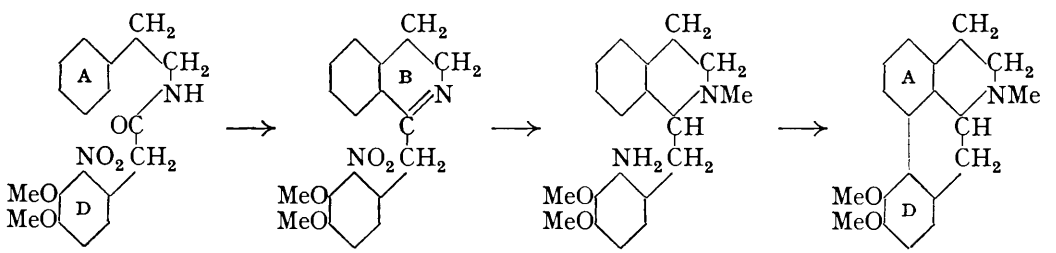
Pictet was himself surprised at the supposed result. "Es ist überraschend, dasz die Methylengruppe des Methylals in Stellung 2 und nicht 6 des Veratrylringes eingreift." Various analogues and theoretical considerations, which he mentions, had led him to expect that the methylene group would attack position 6, and that one methoxy-group would then be in a different position in the final product. "Wir erwarteten eigentlich, durch vorstehende Reaktion zu einem Tetrahydro-*iso*berberin zu gelangen."

This ring closure in position 6 and the production of an isomeride was indeed realised two years later when (with S. Malinowski) he attempted to synthesise corydaline from tetrahydropapaverine and acetal:



The isomeride of corydaline was named by Pictet coralydine; he attributed the isomerism solely to the different position of the 3-methoxy-group. Actually there was a further difference. The *C*-methyl group was much later shown by Perkin and Koepfli (J., 1928, 2990) to be on the side of the molecule opposite to that in which it was supposed to be in 1913. However, the position of the methyl groups in coralydine was established by oxidation, which yielded only metahemipinic (4 : 5-dimethoxyphthalic) acid from both rings (A and D), whereas Dobbie and Lauder had obtained from corydaline both metahemipinic acid (from A) and hemipinic (3 : 4-dimethoxyphthalic) acid (from D). Pictet was thus confronted with the question, why in the experiments of Gams aiming at berberine, methylal reacted with position 2 of ring D, whilst in those of Malinowski, intended to produce corydaline, the 6-position was attacked by acetal. In order to test whether this remarkable result (bemerkenswerte Konsequenz) was due to a difference in the nature of methylal and acetal, he next proceeded to condense tetrahydropapaverine as before, but with methylal instead of acetal. The product, norcoralydine, was shown (in collaboration with Tsan Quo Chou, 1916) to furnish only metahemipinic acid, as its homologue had done previously. The formation of norcoralydine thus "depended again on a condensation in position 6. The cause of the difference in the points of attack of the aliphatic radicle does not therefore seem to depend on the nature of this radicle (methylene or ethylidene) but rather on the diversity of substituents in the *iso*quinoline residue" (two methoxy-groups in coralydine, a methylenedioxy-group in berberine). Thus, in 1916, Pictet came very near to clearing up the discrepancy of the berberine synthesis of five years before. (His energies were then, however, already taken up by quite a different subject.) It was later shown by Späth and Kruta (*Monatsh.*, 1928, **50**, 341) that papaveroline, with four free phenolic groups, condenses with formaldehyde both in the 2- and in the 6-position. It would thus seem that in the plant ring closure precedes the methylation of the phenolic hydroxyls.

Two other papers on alkaloids require mention. That by Kay and Pictet (J., 1913, **103**, 947) is the only one he published in our Journal. It was an ambitious and well-conceived attempt to prepare a member of the extensive group of aporphine alkaloids, which differ from the laudanosine group by a further ring closure through the direct union of the two benzene rings A and D.



This union can be brought about by Pschorr's phenanthrene synthesis, according to which a nitro-group in D is reduced, and the resulting amino-group is diazotised. Pictet's pioneer attempt failed because it was found impossible to close ring B to form the required nitrobenzyldihydro*iso*quinoline (second formula). This reaction had been quite successful in Pictet's earlier synthesis of laudanosine, in which, however, methoxy-groups made ring A more reactive. He unfortunately chose one of the aporphine alkaloids most difficult to synthesise, namely, apomorphine, in which ring A has no substituents to activate it. In later years numerous alkaloids of this group were synthesised, by the method first indicated by Pictet, but among them apomorphine presented considerable difficulty, only overcome by Späth and Hromatka (*Ber.*, 1929, **62**, 325) and, following a different method, by Avenarius and Pschorr (*Ber.*, 1929, **62**, 321).

Pictet's last paper relating to alkaloids was an attempt to imitate their genesis in plants, and is characteristic of his biochemical speculations. He had come to believe that formaldehyde plays a considerable part in this genesis, by condensing with amino-acids to form heterocyclic bases, and he thus conceived the idea of hydrolysing casein in the presence of methylal which was continuously dropped into the boiling acid solution and formed a source of formaldehyde. The resulting mixture, as in many of Pictet's experiments at high temperatures, was very complex. It was worked up by evaporation to dryness and distillation with quick lime; a mixture of bases was obtained in a yield of 9% of the protein hydrolysed. From it pyridine, *iso*quinoline and homologues were isolated.

The remainder of Pictet's publications are almost entirely concerned with non-nitrogenous substances. In 1911, together with the berberine synthesis, he published a paper on the extraction of powdered coal by means of benzene. The extract amounted to only 0·1%, but was mostly volatile and yielded a hexahydrofluorene, which could be oxidised to a mixture of phthalic, adipic and acetic acids. The small yield induced Pictet to distil coal under reduced pressure; a much larger amount (3·5%) of vacuum tar was then obtained, which also yielded hydroaromatic hydrocarbons, including the above-mentioned hexahydrofluorene.

It is of some interest to trace a connection between these researches on coal and those on alkaloids. The first paper on coal merely mentions a desire to know something about the constituents of fossil plants, and does not refer to alkaloids, but Pictet's friend and colleague Cherbuliez is more precise and states in his obituary notice that Pictet was curious to know the fate of vegetable alkaloids during fossilisation. This provides an ideological link between the two sets of researches. Pictet certainly did not find any "fossil" alkaloids, but he found interesting substances in vacuum tar, which directly or indirectly made him give up his alkaloidal researches for the rest of his life. When in 1923 the writer asked Pictet why he had abandoned alkaloids, he answered that he had no students who could be trusted to work with such expensive substances.

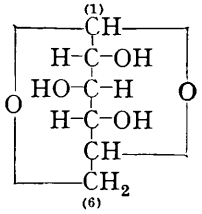
Pictet's apparatus for obtaining vacuum tar was, as always, very simple. With a cast-iron retort, three water pumps, and some Bunsen burners he obtained 1 kg. of vacuum tar from 30 kg. of coal. The tar yielded monocyclic hydroaromatic hydrocarbons, chiefly $C_{10}H_{20}$ and $C_{11}H_{22}$, which were similar to those from Baku petroleum, and apparently identical with two hydrocarbons isolated by Mabery from Canadian petroleum. Pictet thus established for the first time a chemical connection between coal and petroleum, and based on this an argument for the vegetable origin of the latter. Later the hydrocarbon $C_{10}H_{20}$ was shown to be almost certainly hexahydrodurene (tetramethylhexahydrobenzene).

A solid hydrocarbon $C_{30}H_{60}$ was also obtained, both by extraction of coal and by vacuum distillation. It was found to occur also in Galician petroleum and to be identical with melene resulting from the destructive distillation of beeswax. The cracking of vacuum tar was studied and here aluminium chloride was found to be an active catalyst. Realising that this discovery might have technical importance, Pictet took steps to have its practical possibilities investigated, but found himself anticipated by patents, recently taken out by others.

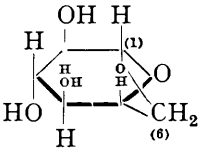
The work on vacuum tar occupied Pictet almost exclusively from 1910 to 1916, while his ideas on alkaloids were being tested by his students. The vacuum tar constitutes

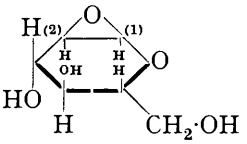
a connecting link between the earlier "alkaloid" period and the later researches on carbohydrates. The connection with carbohydrates is clear. It was but a step from the vacuum distillation of coal to that of one of its precursors, cellulose. In 1918, in the first number of the *Helvetica Chimica Acta*, Pictet and Sarasin reported that the distillation of cotton wool under a pressure of 12—15 mm. yielded a semi-crystalline distillate, from which they were able to isolate lævoglucosan in a yield of 30% of the cellulose employed. Lævoglucosan is a unimolecular inner anhydride of glucose, and was obtained by Tanret (*Bull. Soc. chim.*, 1894, **11**, 949) in small quantity in the hydrolysis of the glucosides picein, salicin and coniferin by baryta, and by Vongerichten and Müller (*Ber.*, 1906, **39**, 241) by the hydrolysis of apiin. It was thus a chemical rarity; it was so named by Tanret, to distinguish it from the dextrorotatory amorphous glucosan obtained in 1860 by Gélis on heating glucose to 170°. Vongerichten and Müller later called the substance β-glucosan, which name, in spite of Tanret's priority, has gained currency because the substance was ultimately recognised to be an anhydride of β-glucose.

Pictet's discovery that a large yield of a crystalline product can be obtained by the distillation of cellulose under reduced pressure at once led him to distil a number of other natural products such as ovalbumin, sodium stearate, sodium oleate, lignin; these experiments yielded little of interest. They show in him the enterprising experimenter, rather than the calculating theorist. Only certain β-glucosides gave (like cellulose) an appreciable yield of β-glucosan (maltose did not), which led Karrer (*Helv. Chim. Acta*, 1920, **3**, 258) to distil β-glucose itself, and he obtained from it almost as good a yield of β-glucosan as Pictet did from cellulose. By the action of acetyl chloride Pictet was able to convert the glucosan into β-acetochloroglucose, whence it was shown to be an anhydride of β-glucose involving the aldehyde carbon atom. He considered it to be a 1 : 6-anhydride, which view was confirmed by various authors, and if we adopt the pyranose structure of glucose, β-glucosan has the formula:



Lævoglucosan of Tanret; β-glucosan (1894).





Glucosan of Gélis (1860); α-glucosan.

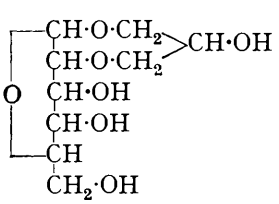
A consideration of the spatial formula shows that in β-glucose the hydroxyl groups of carbon atoms (1) and (6) are on the same side of the pyranose ring, and thus capable of forming an additional oxygen bridge. In α-glucosan there is a 1—2 bridge.

β-Glucosan, or lævoglucosan as Pictet preferred to call it, paying more attention to history than to stereochemistry, was the means of his complete conversion to the chemistry of carbohydrates. With but trifling exceptions all his subsequent papers are devoted to this group. Early on he polymerised lævoglucosan by heating it alone at 240°, or better in the presence of platinum-black at 180°, and thus obtained an amorphous achroodextrin $(C_6H_{10}O_5)_4$. He soon also studied the glucosan of Gélis, and by heating at 150°/14 mm. (without distillation) obtained this substance sufficiently pure to be crystallisable from methanol. In contradistinction to β-glucosan, the α-isomeride is readily hydrolysed to glucose by boiling water; with hydrogen chloride in methanol it yields α-methylglucoside, with concentrated hydrochloric acid an amorphous "chlorure de glucosyle," which acetic anhydride converts into α-acetochloroglucose. By the interaction of this α-glucosyl chloride with the potassium derivative of α-glucosan he obtained an amorphous substance, $C_{12}H_{20}O_{10}$, which on boiling with water was hydrolysed to a crystalline sugar, $C_{12}H_{22}O_{11}$, closely resembling gentiobiose:

$$C_6H_{11}O_5Cl + KO{\cdot}C_6H_9O_4 = C_6H_{11}O_5{\cdot}O{\cdot}C_6H_9O_4 = C_{12}H_{20}O_{10}$$
$$C_{12}H_{20}O_{10} + H_2O = C_{12}H_{22}O_{11}$$

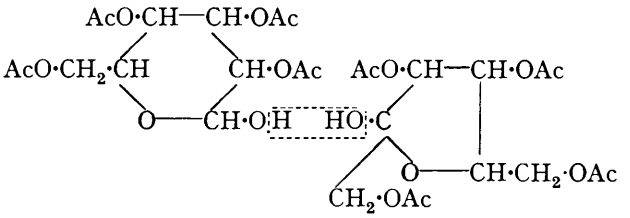
The simplicity of this reaction, reminiscent of an ancient synthesis of mixed ethers, was quite characteristic of Pictet. Having obtained crystalline anhydrides of both forms of glucose, he tried to do the same with other sugars; lævulose (with J. Reilly), galactose, maltose, and lactose yielded only amorphous anhydrides which could not be distilled and were readily hydrolysed by boiling water. Synthetic experiments were therefore mainly conducted with the two glucosans. The effect of pressure on the polymerisation of lævoglucosan was studied with zinc chloride as condensing agent. Under reduced pressure a sweet crystalline non-reducing dimeric product was obtained, under atmospheric pressure an amorphous tetraglucosan, which yielded a crystalline acetate, at 4·6 atmospheres a hexaglucosan, at 13·3 atmospheres an octaglucosan. The latter products were all amorphous and were fractionally dialysed. This investigation is chiefly interesting for the ingeniously simple, almost naive, way in which Pictet obtained the above pressures. He merely heated lævoglucosan with a little zinc chloride and some benzene in a sealed tube to 140°, at which temperature the vapour pressure of benzene is 4·6 atmospheres; similarly ether gave him 13·3 atmospheres. According to Irvine and Oldham (J., 1925, **127**, 2903) pressure does not determine the nature of the products, which in any case have no close relationship to starch. By partial hydrolysis of α-diglucosan Pictet obtained an amorphous disaccharide, yielding a crystalline octa-acetate and not identical with trehalose.

A counterpart to these polymerisation experiments was the depolymerisation of starch by heating in glycerol. Here again nothing was obtained analogous to the crystalline amyloses resulting from the action of *Bacillus macerans* on starch. Hoping to obtain a monoamylose, Pictet pushed the depolymerisation to its extreme limit, by heating starch with glycerol to 200—210°, and obtained instead a crystalline non-reducing anhydride of glucose and glycerol, $C_9H_{16}O_7$. This substance was also formed by heating glucose with glycerol to 165°. Pictet suggested the annexed constitution.



So much had Pictet become absorbed in the chemistry of sugars that he devised a new method for lengthening their carbon chains, by addition of nitromethane to the aldehyde group. Reduction, followed by treatment with nitrous acid, then furnished the next higher alcohol. In this way he converted glycollaldehyde into glycerol, glucose into glucoheptitol. He had not yet synthesised a natural disaccharide, but in 1926 (with Georg) he made the observation that in the condensation of glucose with hydrochloric acid to *iso*maltose, according to Fischer, some 3% of gentiobiose is formed. Very soon afterwards a much more elaborate synthesis of the same sugar was published by Helferich, Bäuerlein, and Wiegand (*Annalen*, 1926, **447**, 27) and afforded an insight into its constitution. Gentiobiose and melibiose are two rather aberrant disaccharides in which a glucose residue is joined by its 6-carbon atom to the aldehyde carbon atom of either glucose (in gentiobiose) or galactose (in melibiose). The observation (made with Georg), that small quantities of the former sugar are formed from glucose and hydrochloric acid, led Pictet to attempt also the synthesis of the latter sugar. Glucose was converted into α-glucosan and this by zinc chloride into α-diglucosan. Similarly digalactosan was prepared, and the mixture of the two, on heating with zinc chloride at 150°/15 mm., furnished a product which, on hydrolysis by concentrated hydrochloric acid in the cold, yielded crystalline melibiose. This and all subsequent syntheses of disaccharides were carried out in conjunction with H. Vogel. They were all done in a simple manner. For instance, a mixture of α- and β-glucose was heated at 160°/15 mm. and after long fractionation from alcohol, of the sugars and of their mixed acetyl derivatives, octa-acetylmaltose was isolated in a yield of 5% of the glucose employed. Sucrose and galactose in the same way gave 1% of raffinose. Finally Pictet and Vogel tackled the still more formidable synthesis of cane sugar. They realised that since the fructose occurs in this sugar as γ-fructose, of the furanose series, and since ordinary fructose is a pyranose, they required acetyl γ-fructose; hence they acetylated fructose and separated the crystalline tetra-acetyl pyranose from a syrup which they regarded as the tetra-acetyl derivative of the

furanose form, believed to be in equilibrium with the pyranose. The syrupy acetyl derivative was condensed in chloroform solution with tetra-acetyl glucopyranose in the presence of phosphoric oxide:



Since various sugar chemists could not repeat this synthesis (published in 1928), Pictet announced in 1930 that he intended to re-investigate it and supply further details. He was unsuccessful; his health declined; he requested a former collaborator, Alfred Georg, to continue the attempt. In 1933 the latter reported unsuccessful experiments in considerable detail. He believed that some sucrose is formed, but he could not himself isolate it from the reaction mixture. To this paper by Georg is appended one by Pictet. He entirely agrees with Georg's results; he reports the isolation of a minute quantity of a copper compound, the melting point of which was not depressed by the copper complex of sucrose. In effect this, Pictet's last paper, is a withdrawal of earlier claims, at best exaggerated, and is to his lasting credit.

It is impossible to say of what error Pictet became the victim during his experiments with Vogel, but it is safe to assume that the inability of himself and others to repeat these experiments saddened the last years of his life. It might almost be argued that the large yield of lævoglucosan, which he so unexpectedly obtained in 1918, was in fact a misfortune, for it led him into a field abounding in subtleties, and requiring an elaboration of technique, very different from the simple methods which so well illustrated his genius. Lævoglucosan brought misfortune in its train; his experimental career ended with a great disappointment. Shortly before his death he still clung to the hope that some day the discovery of a suitable catalyst would clear up the mystery.

As mentioned above, Pictet was appointed extraordinary professor of organic chemistry in 1894. On the death in 1899 of his former teacher Monnier, he became ordinary professor of pharmaceutical, biological and toxicological chemistry, and as such had pharmacists among his pupils, who assisted him in his nicotine work. In 1906, when Graebe returned to Germany, Pictet was transferred to the chair of general (organic and inorganic) chemistry and became director of the laboratories. From this chair he retired in 1932 on attaining the age limit of 75. He died on March 11th, 1937, nearly 80 years of age.

Reference must still be made to Pictet as an organiser of scientific endeavour. His secretaryship of the Geneva congress of 1892 has already been mentioned; the work of this congress was again taken up by the International Union of Pure and Applied Chemistry, founded in 1919. Pictet was chairman of the Swiss national council from 1925 to 1930, and frequently attended the meetings of the Union abroad. Thus he was present at the Cambridge meeting of 1923, during a rare visit to this country; he was much more at home in Paris, where he represented Switzerland on various occasions, notably at the Berthelot centenary in 1927. In his own country he often took the lead in scientific matters; thus he was one of the four founders of the Swiss Chemical Society (1901) and regularly published accounts of its meetings and lists of Swiss chemical publications in the *Archives des Sciences physiques et naturelles de Genève*, with which venerable journal he was closely associated. It was he who devised the name *Helvetica Chimica Acta* (with the stress on Helvetica), when the chemical society of his trilingual country decided in 1918 to start a journal of its own, and in the *Acta* he henceforth published all his papers. Previously they had mostly appeared in the German *Berichte*, in a language with which he was familiar since his student days. His papers are distinguished by brevity and clarity, and those written in French show a great regard for literary style. It has been said that in this respect no one approached so nearly to the famous Würtz.

Education and social environment gave to Amé Pictet an air of natural distinction, to which he joined a rare simplicity of character. His assured position made him free from the suspicions which might have assailed other minds. To those who did not know him well, he seemed to be reserved, almost cold. In the laboratory and in public he was always perfectly correct, in dress, in speech, in manner. At home the amiable host would unbend to his student-guests. His language was very clear, simple, *le mot juste ;* these characteristics were also clearly reproduced in his handwriting.

In conversation annoyance showed itself only by an impatient look, a dry tone of voice, not by words, unless a certain limit had been exceeded, and then his anger or disdain would be expressed coolly, by a remark of the utmost severity. He did not suffer fools gladly and the indolent were worse than fools. He abhorred laziness, being a great worker himself. During the first winter after his succession to Graebe, he regularly rose at five o'clock in order to prepare his daily lecture on inorganic chemistry, with which, at the age of 49, he had become less familiar. Few interests competed with chemistry. He was fond of travel and of music, he collected stamps, but these minor interests occupied little of his time. His talk with collaborators was largely of chemistry and the affairs of the laboratory : Emil Fischer was the greatest of all chemists ; one should never use logarithms, they were wrong by definition ; Werner's theory of hydrates was all very well, but. . . . To remarks of this kind which he was in the habit of making, his students could make no reply.

Pictet was a patriotic Swiss who, like most of his French-speaking countrymen, had a great sympathy for France ; yet his knowledge of other countries made him free from any trace of insularity. He loved his Paris, the French mode of life, and in particular, French cookery ; indeed, he was said to be both gourmet and gourmand, perhaps only because in old age gout forced him to drive to his laboratory. Although he had ample private means, he was reputed to be close-fisted ; he insisted on economy in the laboratory and was apt to complain of the cost of research. This parsimony was, however, a mere affectation ; privately, very discreetly, he often gave generous aid to poor students, and he did much to alleviate the distress of an aged colleague, made penniless by post-war inflation.

Pictet was the recipient of many honours : corresponding member of the Académie des Sciences, 1922 ; honorary member of many societies (French chemical 1921, our own 1923) ; on him were conferred honorary degrees (Cambridge 1923, Brussels 1930) and many other distinctions. In 1927 his 70th birthday was the occasion for a great international celebration.

Amé Pictet was no chemical giant. No fundamental theory, no new class of substances or general reaction is associated with his name, which remains unknown to elementary students of chemistry. Yet he stood out in the last generation, by his classical syntheses of nicotine, of laudanosine, of papaverine, and by his discovery of vacuum tar. He was an interesting personality, a link between French and German chemistry, a remarkable man. It is indeed fitting that we should do honour to his memory.