in two ways: in small concentrations they influence its activity but do not permanently destroy it, in larger concentrations they accomplish its destruction. The destruction by acid at 30° reaches a barely noticeable rate at 0.01 normal acidity and increases rapidly with the acidity until it becomes almost instantaneous at 0.05 normal. The rate of destruction follows the formula for unimolecular reactions. The alkaline destruction begins a little below 0.01 normal and is almost instantaneous at 0.045 normal. The rates of destruction are shown in Fig. 2.

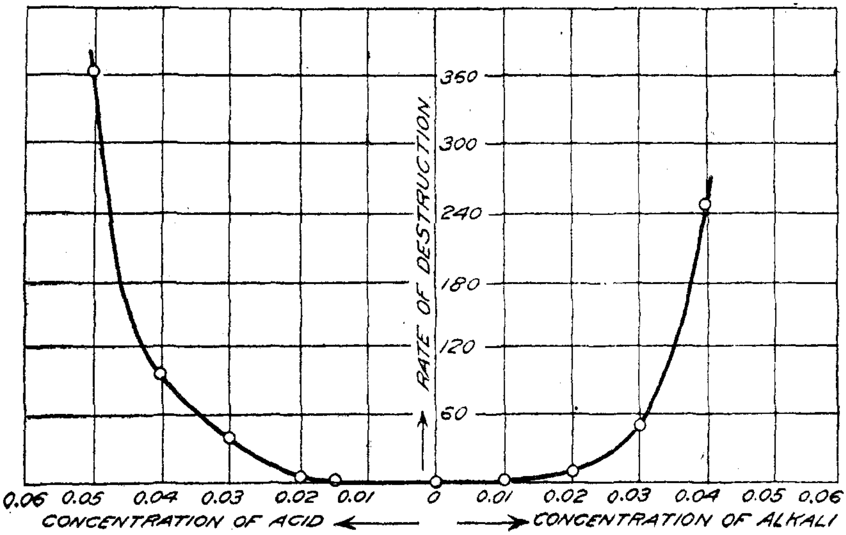


Fig. 2.—The rate of destruction of invertase at 30° C. by acid and alkali.

The activity of invertase in acid solutions which are not strong enough to destroy the enzyme was measured for hydrochloric, hydrobromic, nitric, phosphoric, sulphuric, boric, oxalic, tartaric, citric, and acetic acids; the activity depends almost entirely on the concentration of hydrogen ions in the acid solution and the various acids thus show typical differences which correspond with their recognized degrees of dissociation. The activity of invertase is zero in alkaline solutions, rises to a maximum in very weakly acid ones, and decreases with stronger acidity.

FEHLING'S SOLUTION.

A CONTRIBUTION TO THE HISTORY OF CHEMICAL REAGENTS.

By B. Herstein.

Received March 11, 1910.

A history of chemical reagents would form no small and not the least interesting part of the history of chemistry generally, and for obvious reasons. In studying the intramolecular changes of matter, chemistry follows strictly inductive methods, taking for granted only the results of direct observation, and while for the purpose of unification we are compelled to classify such results into some comprehensive and consistent system arrived at by logical induction, such hypothetical assumptions are not permitted to influence the direct results of the experiments.

Intramolecular changes of matter however are not always directly observable, and to bring them into a condition where our perception would be able to grasp them, we must in the majority of cases resort to what may be described as secondary reactions induced by foreign substances, the so-called chemical reagents. Our processes of differentiation, upon which chemistry in general and analytical chemistry especially ultimately rest, are based upon the behavior of the various forms of matter towards different chemical reagents, and it follows from this that the progress of chemistry to a very large degree depends upon the introduction of such chemical reagents and an intimate knowledge of their working.

Thus to quote but one modern instance it is only necessary to point to the fact that the wonderful insight which we have gained within the last generation into the nature of sugars and carbohydrates generally is due almost exclusively to the introduction of phenylhydrazine as a chemical reagent. Previous to this our knowledge of this group of substances was very limited indeed, and of the few reactions characteristic for this group of substances none was better known than their behavior towards a solution of copper salts. The reaction upon which the value of this reagent in all its various modifications depends is, as is well known, based upon the reducing effect which certain sugars exert upon such solution, and although analytical chemistry has only within comparatively recent years made use of this reaction, its history runs nevertheless far back into the primitive period of human knowledge.

It undoubtedly must first have been observed by the man who introduced the so-called *unguentum Ægyptiacum*—Egyptian ointment—into materia medica, and this probably was none other than an Egyptian priest, if we may draw such conclusions from the name. This *unguentum Ægyptiacum*, which has long since disappeared from all the modern pharmacopoeias, but which for long ages was considered a very valuable medicine, forming the basis of various ointments and cosmetical preparations, was prepared by boiling together a mixture of verdigris and honey to which a few drops of vinegar were added. During the boiling the color of the mass changes considerably owing to the interaction between the glucose and the copper acetate, a change of color so striking that it could not have escaped notice. Nevertheless it has never occurred to any of these pharmacists, who in those days were the principal guardians of whatever chemistry there was, to make these changes the independent object of their studies. The first to attempt an explanation of the phenomena observed during this reaction was Antoine Baumé, a celebrated pharmacist of the eighteenth century, who wrote his name indelibly into the history of chemical technology by the device of his spindle. In accordance with the theory then prevailing he said in his "Traité de Pharmacie Théorique et Pratique," that in boiling honey with verdigris and vinegar it is the phlogiston of the acetic acid which, uniting with the verdigris, orms metallic copper, which is deposited. For almost one-half a century this explanation was accepted as satisfactory. During this time, however, the phlogiston theory had been entirely overthrown by Lavoisier, and a period of reconstruction had set in, which may be best described by Hegel's phrase "the re-evaluation of all values." Speculative deductions gave place to experimental research, and the balance was made the chief arbiter of the laboratory. A thorough overhauling of all chemical knowledge was undertaken, and in course of time the phenomena observed during the reaction in question were also subjected to renewed scrutiny.

In January, 1815, Dr. Vogel, of Paris, read before the French Academy of Science a paper entitled "A Research Concerning the Decomposition of Salts and Metallic Oxides by Sugars."[1] As indicated by the title, the principal object sought in this investigation was an insight into the mechanism of the reaction, while the products formed during the reaction were studied as closely as the means then permitted, both qualitatively and quantitatively, but only with a view of obtaining light upon the reaction itself. Vogel was able to show that the reddish or brown precipitate which formed on boiling copper acetate with honey and several other sugars then known was not metallic copper, but cuprous oxide, or as it was then called, copper protoxide, that the color of the precipitate depended very much on the length of time the mixture was heated, and that the precipitation is obtained only from cane, starch and grape sugar, sugar of milk, also from molasses, manna, and honey, but not from the so-called sweet principle of Scheele.[2] Vogel also observed the evolution of carbonic acid gas and acetic acid, which, however, he attributed to the high temperature to which the mixture had been subjected. Using copper sulphate instead of the acetate he claims to have precipitated metallic copper while copper chloride and copper nitrate, which were likewise tried, seemed not to be influenced at all. Similar observations made almost simultaneously with the preceding were given by J. A. Buchner, Professor of Chemistry in Munich, and published in the succeeding number of the same periodical.[3] On the whole he merely confirmed the result

---

[1] *Abstracted in Schweigger's Journal*, 1815, Vol. XIII, page 162.

[2] By this name glycerol, discovered in 1779 by Scheele, was known until well up into the first part of the 19th century.

[3] *Schweigger's Journal*, 1815, Vol. XIV, p. 224.

obtained by Vogel with this exception, that while Vogel had proved the red precipitate to consist of cuprous oxide, Buchner states that during the reaction the sugar is split up and that one of these cleavage products combines with the copper to form the precipitate.

From time to time other chemists were attracted by the same subject.[1] Their work, however, did not materially broaden the problem, which remained one more of theoretical than practical value until the year 1841, when Trommer published his paper, "The Differentiation between Dextrin, Cane and Grape Sugar."[2] Here the subject was approached from an entirely different and more practical point of view. Trommer was able to show that in making the copper salt solution alkaline, it became a valuable reagent for the differentiation between the various sugars and sugar-giving substances. He used an alkaline solution of copper sulphate, and showed that such a solution will yet give a distinctive precipitate of cuprous oxide when boiled with solutions of grape sugar containing only one part in one hundred thousand, and that when the solution of the grape sugar is ten times more dilute, *i. e.*, containing one part to one million, the reaction is yet noticeable in reflected light. The fact that the reaction takes place only in the presence of certain sugars such as glucose, for instance, while cane sugar or dextrin are not acted upon, was fully noticed and made the basis of the differentiation between the different sugars. To Trommer thus belongs the credit of having first introduced the alkaline copper sulphate solution into analytical chemistry, though it was at first used only for qualitative purposes. But the next step was not long in coming, and within a very short time the very same reagent was recommended for use in quantitative chemical analysis.

The estimation of sugars in those days was far from being satisfactory to the chemist engaged in this line of work, depending entirely on two methods. First, the fermentation process devised by Lavoisier and others, and second, the process introduced by Biot, which was based on the deflection of polarized light by sugar solutions. Both methods have their disadvantages, the first requiring considerable time for its completion, quite aside from the fact that the decomposition into alcohol and carbonic acid gas is by no means quantitative, by-products being formed which interfere with the accuracy of the results. The polariscope gives quick and fairly accurate results; requires however clear and colorless solutions containing no foreign substances which would deflect the polarized ray. The necessity for an improved method of estimating sugars became so imperious that in 1838 a prize of 3000 francs was offered by the "Société d'encouragement pour l'industrie nationale" to the chemist who would devise a successful

---

[1] Buchholtz, Peschier, Busch, see *Annalen der Chem. und Pharm.*, 1832, Vol. IV, p. 57.

[2] *Annalen der Chem. und Pharm.*, 1841, Vol. XXXIX, page 360.

method for the quantitative estimation of sugar. Of the answers received none was acceptable to the committee, and the offer was renewed from year to year until in 1844 Ch. Barreswil submitted his solution.[1] The referee of the committee, the well-known Peligot, did not consider the answer entirely satisfactory, but he nevertheless recommended that one-third of the prize, *viz.*, 1000 francs, be awarded to Barreswil for his solution, which, in his opinion,[1] though limited in its application, nevertheless offered a valuable improvement on the existing methods. Barreswil's proposal consisted merely in the extension of the method suggested by Trommer for qualitative differentiation to the quantitative estimation of sugars. The main principle of Trommer's suggestion, *i. e.*, the use of the alkaline copper sulphate solution, was maintained, and the improvement introduced consisted in the addition of a solution of potassium tartrate to prevent the decomposition of the solution on heating. As proposed by Barreswil, the method was a volumetric one, the copper solution being standardized against a pure grape sugar solution of known strength, which latter was added drop by drop to the boiling copper solution, the end point of the reaction being reached when the blue color of the solution had disappeared. He also points to the necessity of inverting the cane sugar to glucose, and making two determinations, before and after inversion, where mixtures of the sugars are to be analyzed.

The principle of the method was thus established, and its practicability depended very largely upon the stability of the copper solution, which was not very satisfactory. The further efforts of the chemists who studied the subject were therefore directed mainly in this direction, although the use of the method was fully recognized and extended, as by H. Schwartz,[2] who in 1849 proposed it for the estimation of starch, which had previously to be hydrolyzed by dilute sulphuric acid to glucose. H. Fehling, by whose name the method is apparently destined to remain known in chemistry, published his first paper concerning the subject in 1848 in a medical publication, and only in 1849 he gave a more detailed account of his work to the chemical fraternity.[3] Fehling's merit consisted chiefly in having worked out with great care the details of the method, giving some account of the stoichiometrical equivalents, but neither did his solution keep for any length of time, nor did he, any more than his predecessors, recognize the fact that the reaction is quantitative only within very narrow restrictions as to the concentration of the solutions and the time of reaction. This point has been established only by the concerted efforts of the many chemists, who worked on the subject after Fehling, the necessity for keeping the copper solution divided into two parts

---

[1] Reported in *Journal de Pharmacie*, [3] **6**, 301 (1844).

[2] *Ann.*, **70**, 54 (1849).

[3] *Ibid.*, **72**, 106 (1849); **106**, 75 (1858).

being soon recognized. Soxhlet especially devoted much of his time to the study of the method and established[1] the exact conditions under which the determination must be carried out in order to get satisfactory results.

BUREAU OF CHEMISTRY, WASHINGTON, D. C.

A REVIEW OF SOME RECENT INVESTIGATIONS IN THE QUINAZOLINE GROUP.[2]

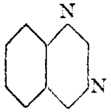
BY MARSTON TAYLOR BOGERT.

Received March 31, 1910.

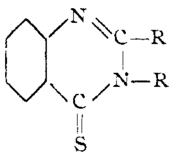
For several years past, the Organic Laboratory of Columbia University has been engaged in the synthesis and study of compounds belonging to that group of organic heterocycles known as quinazolines or phenmiazines.

To us, the work has been most interesting and enjoyable. The compounds obtained have been generally crystalline solids, quite readily purified, stable, and very satisfactory to work with.

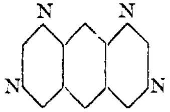
Our investigations have included—A. Quinazolines, B. Thioquinazolines, and C. Naphthotetrazines of quinazoline structure:



(Quinazoline)



(Thioquinazoline)



(1,3,7,9-Naphthotetrazine)

Incidentally, a great many new preparatory, intermediate and subsidiary products have been obtained. From the standpoint of new substances, the field has been an unusually fruitful one.

It is, therefore, not only an honor but also a pleasure to present on this occasion a brief synopsis of the major lines of the work to date.

A. Quinazolines.

Colby and Dodge,[3] as the result of their investigations of the interaction of nitriles and organic acids, under conditions of heat and pressure, came to the following conclusions:

I. Fatty nitriles and aromatic acids give fatty acids and aromatic nitriles.

II. Aromatic nitriles and fatty acids give mixed secondary amides.

III. Aromatic nitriles and aromatic acids give secondary amides, unless the temperature is very high, when the nitrile of the higher radical may form.

Mathews,[4] in continuation of this work, heated acetonitrile and anthranilic acid together under pressure, hoping thereby to obtain the

---

[1] *Z. anal. Chem.*, 18; **20,** 425. For other references to modern investigators see standard text-books.

[2] Address at the Twentieth Anniversary Celebration of Clark University, Worcester, Mass., Sept. 14, 1909.

[3] *Am. Chem. J.*, 13, 1 (1891).

[4] THIS JOURNAL, **20,** 654 (1898).