Furthermore the very general use of glycerin as a means of preventing precipitation in galenical preparations, and the observance that sugars act in a similar and very effective way, is best explained on the ground of their dehydrolyzing action in the menstrua.

Thus not simply the experiments conducted for the purposes of this paper, but much of the evidence of experience and established pharmaceutical practice point to a hydrolyzing action as the main factor in precipitation in galenicals.

European pharmacists have long favored stronger alcohol for tinctures and fluidextracts than has been used in America, and it would look as though they are nearer to right in this. In Europe a diluted alcohol is not equal volumes of alcohol and water but is usually a mixture containing 68 to 70 per cent by volume of absolute alcohol. This strength of alcohol is often used as a menstruum in preparations which correspond to those made with our 49% alcohol. Thus many of the European preparations are approximately 1.4 times as strong in alcohol as the corresponding American preparations.

The stronger alcohols tend to prevent hydrolysis and thus to preserve drug principles in their original condition. Change by hydrolysis is not always evidenced by precipitation, as we have learned from the deterioration of Aconite, Digitalis and other potent preparations, as well as some astringent tinctures, but the value of the preparation depends upon its activity, and hydrolysis usually destroys this. The tendency of recent years to reduce the alcoholic content of pharmaceutical preparations to a minimum may easily result in inferior preparations for therapeutic use through the ignoring or forgetting the stabilizing effect of stronger alcohols. Therapeutic power and dependability should be the first consideration in all such cases.

The most prominent development in pharmacy during the past generation has been that of standardization of medicines. We are now facing the logical sequence of this—the development of conditions or methods that make for stability in standardized medicinals. Standards in many cases need to be made more trustworthy by stabilizing the preparations. This is one of the most important problems of the immediate future.

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PHARMACEUTICAL PRODUCTS FROM MUCIC ACID.

BY F. F. BLICKE AND J. L. POWERS.

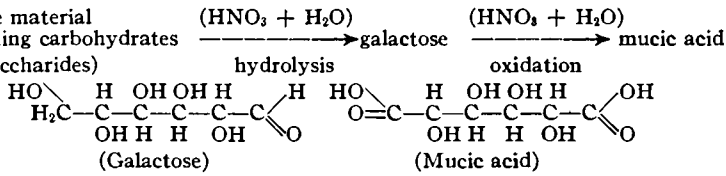
About 1780 Scheele, the celebrated Swedish apothecary, published the results of an investigation entitled "Milk and Its Acids."[1] During this investigation milk sugar was treated with nitric acid; a white powder was obtained thereby which resembled saccharic acid. An aqueous solution of the material tasted sour, turned blue-litmus red and reacted with calcium carbonate with the evolution of carbon

[1] Carl Wilhelm Scheele, "Sämtliche Physische und Chemische Werke," edited by Hermbstadt (Berlin, 1793), Vol. II, p. 261.

dioxide. In view of these properties Scheele called the new substance "Milchzuckersäure," that is, milk-saccharic acid.[1]

Some years later Fourcroy obtained the above compound by the action of nitric acid on gums and mucilages (gum arabic and tragacanth). The latter investigator named the substance "acids muqueux" from which the name mucic acid is derived.

The production of mucic acid in small amounts by the action of nitric acid on milk sugar has been a standard laboratory preparation for many years;[2] in general it has been found that this acid can be obtained from any carbohydrate vegetable material which yields galactose on hydrolysis:[3]



About 1921 the Montana Products Company of Eureka, Montana, began the manufacture of mucic acid on a large scale. Scrap larch wood, the raw material for this industry, is converted by hydrolysis into galactose and the latter product is then oxidized by nitric acid. The commercial mucic acid is said to be 99.7 per cent pure and sells for 28 cents a pound in large quantities. Since scrap material from larch wood is available in large quantities in some of the western States, the utilization of this material represents an achievement of considerable commercial importance.

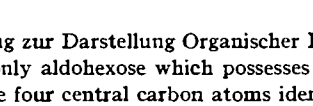
At present mucic acid finds its most extensive use as a substitute for potassium bitartrate in baking powder. We have found that this acid can also be used satisfactorily in place of tartaric acid in the preparation of granular effervescent salts. In view of the fact that the price of mucic acid is approximately two-thirds that of tartaric acid it is obvious that this substitution is advantageous from the commercial standpoint.

The use of mucic acid for the two above-mentioned purposes is only justifiable, provided it can be proven that this acid exerts no deleterious action. In order to determine this point as far as baking powders are concerned, physiological tests with mucic acid were conducted by Rose and Jackson.[4] The material was administered orally to fasting rabbits; in small amounts, 1 to 5 Gm. given during the course of a single day no effect upon renal activity was observed; with larger

[1] Liebig ("Annalen der Chemie und Pharmacie," 113, 4 (1860)) found that in addition to the compound of Scheele three other acids are formed in this reaction, namely, saccharic, tartaric and oxalic acids.

[2] Emil Fischer, "Anleitung zur Darstellung Organischer Praparate" (8th Edition), p. 82.

[3] Since galactose is the only aldohexose which possesses a special arrangement of the H atoms and the OH groups on the four central carbon atoms identical with that of mucic acid, it is obvious from the configuration formulas that this acid could not be obtained by the oxidation of any other aldohexose, such as glucose:



[4] *Journal of Laboratory and Clinical Medicine*, 11, 824 (1926).

quantities, 5 to 19 Gm., nephritis occasionally developed and in few instances post mortem examinations showed marked tubular involvement of the kidney.

From the experimental data obtained by Rose and Jackson it might be assumed that mucic acid would be harmless in the quantities which would be present in baking powders; however, the above-mentioned investigators consider that their results do not entirely justify such a conclusion. They say, "Although the doses of mucic acid employed in our experiment are infinitely larger than could be obtained in man from the quantities of baking powders ordinarily ingested, it is not impossible that the habitual ingestion over long periods of time of minute traces of the substance might lead eventually to renal effects in some individuals." Baumgarten[1] administered doses of mucic acid as large as 50 Gm. to a normal man but was unable to detect any untoward effect.

Pearce and Ringer[2] were able to induce nephritis by the oral administration of tartaric acid to laboratory animals, but it has been shown by Post[3] that the usual therapeutic doses of tartrates are not injurious to man.

In drawing conclusions from physiological experiments it should be kept in mind that a fasting animal is not a normal animal, and that the effects produced by exceedingly large doses administered to starving animals can hardly be comparable to those produced by the amounts ordinarily taken by man.

It has been known for a long time[4] that the ammonium salt of mucic acid, when heated, decomposes with the formation of pyrrole. Although pyrrole itself has no important pharmaceutical or industrial use at the present time it seemed to us, nevertheless, that if pyrrole could be manufactured cheaply and in large quantities the material might eventually become a commercial product of considerable value. Since it was by no means certain that the above reaction would be suitable for the preparation of pyrrole on a large scale we carried out a series of experiments in which five-pound portions of ammonium mucate were heated at one time. It was found that yields as high as fifty per cent of pure pyrrole could be obtained without difficulty.

According to a German patent[5] the conversion of pyrrole into indole, a product of great importance in the perfume industry, is a simple process. Indole, in turn, according to another patent[6] is easily transformed into indigo. Pyrrole dyes[7] and synthetic resins prepared from pyrrole have also been described in the chemical literature.

In view of the unusually great activity of the four hydrogen atoms which are attached to carbon in pyrrole it might be expected that all of these hydrogen atoms could be replaced by mercury. In this event the mercury derivative would represent one of the most highly mercurated organic compounds known and might

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[1] *Zeitschrift für Experimentelle Pathologie und Therapie*, 2, 59 (1911).

[2] *Journal of Medical Research*, 29, 57 (1913).

[3] *J. A. M. A.*, 62, 592 (1914).

[4] Schwanert, *Ann.*, 116, 270, 278 (1860). Goldschmidt, *Zeitsch., für Chemie, Neue Folge*, 3, 280 (1867). Khotinsky, *Ber.*, 42, 2506 (1909).

[5] *D. R. P.*, 125, 489 (1902).

[6] *D. R. P.*, 130, 629 (1903).

[7] "Thorpe, Dict. of Ap. Chem.," Vol. 1, 635; Vol. 5, 526 (1929). *Chemical Abstracts*, 11, 782 (1917). *J. Soc. Chem. Ind.*, 36, 210 (1917).

possibly possess therapeutic value. We made a preliminary investigation of the action of aqueous and of alcoholic mercuric acetate on pyrrole. Amorphous mercury derivatives were obtained which were extremely difficult to purify because of their colloidal nature. During the preparation of this manuscript we found that a compound claimed to be pyrrole tetramercuric acetate has been prepared very recently.[1] It is interesting to note that certain mercury derivatives of indole, to be used for therapeutic purposes, have been made the subject of a German patent.[2]

Iodole, the proprietary name for tetraiodopyrrole, was the first compound to be used as a substitute for iodoform. Michelman[3] considers that this product would be used to a greater extent if pyrrole could be obtained more cheaply. We are of the opinion that a dichlorodiiodopyrrole might be just as efficient an iodoform substitute as tetraiodopyrrole and could be prepared much cheaper since the cost of chlorine is considerably less than that of iodine. The action of sodium iodide on tetrachloropyrrole is now being investigated in the expectation that dichlorodiiodopyrrole may be obtained in this way.

In conclusion it should be mentioned that the chemistry of pyrrole is of paramount importance in connection with the study of the alkaloids, atropine, cocaine and nicotine and of such physiologically important compounds as chlorophyl and hæmoglobin, since all of these compounds contain modified pyrrole nuclei.

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THE ANALYSIS AND CHARACTERIZATION OF NEOARSPHENAMINE.

BY A. E. JURIST AND W. G. CHRISTIANSEN.

Neoarsphenamine is described as the condensation product of 3,3′-diamino, 4,4′-dihydroxyarsenobenzene and sodium formaldehyde sulphoxylate. Inasmuch as it is not a chemical individual but a mixture which has been diluted with sodium chloride, the characterization of the various commercial products is difficult. Several investigators have published methods of determining the composition of neoarsphenamine, among them are Macallum,*[1] Raiziss and Falkov,[2] Freedman,[3] de Myttenaere,[4] and Elvove.[5] Of these methods Elvove's gives the most satisfactory results, but it still leaves much to be desired because it is based on certain assumptions which have not been substantiated. Therefore it is proposed to give certain modifications of Elvove's method which enable one to determine the composition of neoarsphenamine and show thereby that different types of neoarsphenamines exist.

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[1] Ciusa and Grilla, *Gazz. chim. ital.*, 57, 323 (1927). *C. A.*, 21, 2686 (1927).
[2] *D. R. P.*, 236, 893 (1911).
[3] *A. J. P.*, 97, 350 (1925).
* A. D. Macallum, *J. A. C. S.*, 43, 643 (1921).
[1] A. D. Macallum, *Ibid.*, 44, 2578 (1922).
[2] G. W. Raiziss and M. Falkov, *J. Biol. Chem.*, 46, 209 (1921).
[3] L. Freedman, *J. Lab. Clin. Med.*, 11, 6 (1926).
[4] F. de Myttenaere, *J. pharm. Belg.*, 45 (Nov. 8 1925).
[5] E. Elvove, "U. S. P. H. S. Reports" (June 12, 1925); 40, No. 24, p. 1235.