Fractional extractions of the extracts of man-root and sweet potato with several organic solvents showed them, like other Convolvulaceous resins, to be of complex composition, and partly of glucosidal nature.

A limited number of tests of all the resins showed only the man-root resin to possess marked physiological activity. This resin proved a mild cathartic. Although the yield (4.65 percent) is rather higher than that previously reported, this product because of its mild action and hygroscopic nature appears unlikely to attain commercial or medicinal importance as a competitor of scammony, jalap or orizaba resin.

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THE MANUFACTURE OF ARSPHENAMINE (SALVARSAN) AND NEO-ARSPHENAMINE (NEO-SALVARSAN).*

BY H. A. KRUMWIEDE.

INTRODUCTION.

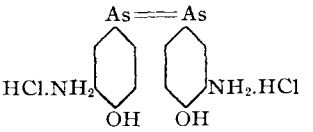
Salvarsan or Arsphenamine, as the Federal Trade Commission has named the drug, is now being successfully manufactured in this country. Previous to the war, it was made in Germany under Ehrlich's supervision, but since the taking over of all alien-enemy patents, there are at least three firms, besides several Health Departments, making it in the United States, and several more are making application for the license to manufacture it.

* Read before Scientific Section A. Ph. A., New York Meeting, 1919.

Arsphenamine is also called by other names according to the firm making it, as for example—arsenobenzol, diarsenol, kharsivan, hydrosan, and arsaminol.

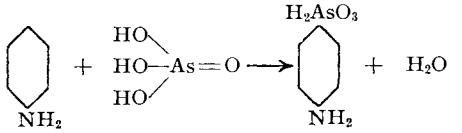
METHOD OF MANUFACTURE.

Arsphenamine is the dihydrochloride of diamino-dioxy-arsenobenzene and its successful preparation has required long and painstaking research.



Of the various possible methods of manufacture, the one most favored is the so-called oxalic method; while it may seem long on paper, it is simpler than some of the others and is now being used by several firms.

The initial step is the formation of para-arsanilic acid by the combination of aniline oil and arsenic acid at a temperature around 180° C.

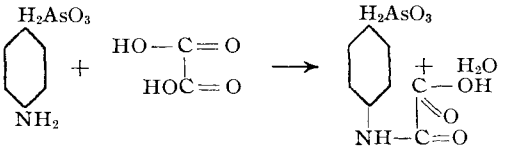


The fusion mixture is dissolved in caustic and is precipitated out by means of acid.

The sodium salt of *p*-arsanilic acid is the "atoxyl" of commerce, and was first made in 1863 by Bechamp. It was also used as a remedy for sleeping sickness and syphilis but the uncertainty of results, with the possibility of blindness, has caused it to be used with caution.

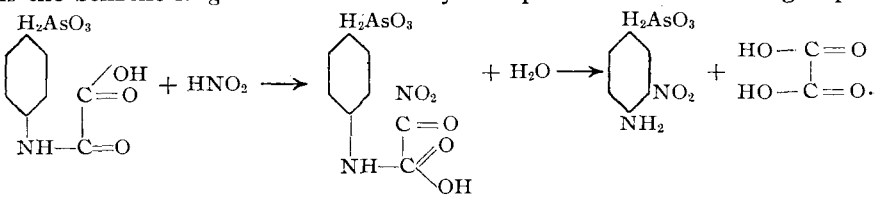
This seemingly simple process is the most difficult one of all the various steps that follow it, because on it depends not only the purity of the final product, but the percentage yield has to be sufficiently large to make it commercially practical.

A nitro- or NO_2 group has to be next attached to the benzene ring, but before this can be done, the amino- or NH_2 group has to be fixed by an oxalic acid group.



This is accomplished by heating the arsanilic acid with oxalic acid until the mixture is perfectly dry, which requires several hours of baking at a moderately high temperature.

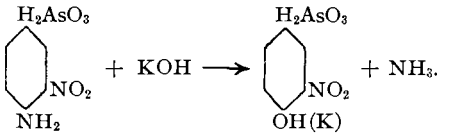
So the third step is the nitration process by means of which the NO_2 group joins the benzene ring in the ortho or adjacent position to the amino group.



To do this the oxalic acid derivative or oxanil-arsenic acid is dissolved in sulphuric acid and a molecule of nitric acid added at low temperature. By diluting and cooking with water, the oxalic acid is again split off, and the nitro-arsanilic is thrown down as a yellow crystalline mass.

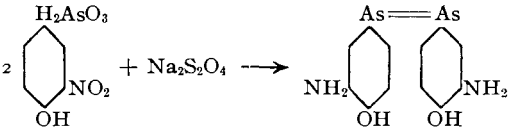
The three subsequent changes while they are very important do not materially alter the general structure of the substance as we finally have it, and the skeleton framework of Arsphenamine is now practically completed.

The three steps are as follows:



The amino group is saponified by means of a strong caustic solution to an OH or phenol group with the natural loss of ammonia. The purified nitrophenol-arsenic acid has only a pale yellow color.

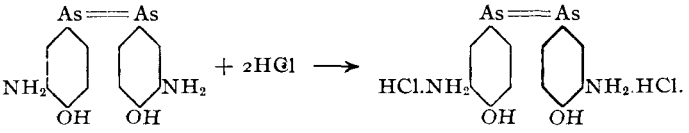
By treating this with sodium hydrosulphite, the nitro group is reduced,



likewise the pentavalent form of arsenic is reduced to a trivalent form, which is very important, as the trivalent form is more valuable therapeutically than the pentavalent variety; this eliminates most of oxygen from the molecule, thus causing two arsenic atoms to unite, which gives us the substance known as Arsphenamine Base, which is the active portion in any of the allied preparations found on the market.

As the base is very insoluble in water, and in order to change it into a form whereby it can be more easily handled clinically, it is necessary to change it into a dihydrochloride. According to the Ehrlich method, the base is dissolved in anhydrous methyl alcohol and hydrochloric acid, and re-precipitated from a large volume of ether. In view of the fact that both the alcohol and ether used are anhydrous, there is no justification for the general assumption, that the Arsphenamine contains two molecules of water of crystallization.

By the Kober method, the base is dissolved in caustic and reprecipitated with an excess of hydrochloric acid with rapid stirring and at a low temperature.

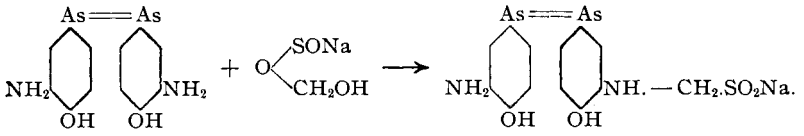


A yellow-white, curdy precipitate is formed, which rapidly turns to a greenish yellow gum, if left exposed to the air, but if filtered and dried under anaerobic conditions, a light yellow powder is obtained which is the product you see in the ampoules—Arsphenamine.

Too much stress cannot be laid on the importance of having the filtering and drying done with the exclusion of air or in an atmosphere of some inert gas, such

as nitrogen or hydrogen, as otherwise the product undergoes rapid oxidation, turning dark brown in color, forming, according to Ehrlich, a substance known as oxyphenyl-arsenic oxide, which is many times more toxic than Arsphenamine.

Neo-Arsphenamine is the sodium salt of diamino-dioxy-arsenobenzene-methanal sulphoxylate, and is made by adding to a solution of Arsphenamine an aqueous solution of formaldehyde sulphoxylate (which is made by combining formaldehyde with sodium hydrosulphite); a precipitate is formed which is called the Neo-Base; this is dissolved in sodium carbonate solution and re-precipitated by the alcohol method.



A modified method has been developed in this laboratory by which the alcohol has been eliminated, which method will be published at a later date elsewhere.

One big advantage Neo-Arsphenamine has over Arsphenamine is, that it is less toxic and can, therefore, be administered in large doses. It is also more soluble in water, forming a neutral solution; but to offset these advantages it is less stable and is oxidized by air even more rapidly than the Arsphenamine.

In testing either of these drugs for decomposition, the best way is to see if the ampoule is air-tight, or if the ampoule had been partially evacuated when it was filled; if such is the case we can readily assume the product is in good condition.

PROPERTIES.

Arsphenamine and the Neo-derivative are both somewhat similar in color, the Arsphenamine being a pale yellow while the Neo is more of an orange-yellow shade.

Chemically, they can be readily distinguished from one another by simple tests, as for example their behavior toward 36% acetic acid, which with Neo-Arsphenamine gives an orange-yellow precipitate on heating, while the Arsphenamine gives none at all; or again, the diazotation of Arsphenamine yields a greenish yellow fluorescent compound, while Neo-Arsphenamine gives a brown solution.

The color of Arsphenamine is no criterion of its toxicity, as some light colored preparations were very toxic and others darker in shade were comparatively non-toxic.

According to some recent investigators, the variations of the toxicity in the drug are largely due to the fact that methyl alcohol and ether are used in the Ehrlich method of precipitating the dihydrochloride, in the final step of the preparation, and due to this fact the methyl alcohol is either occluded in the molecule or the product has been methylated, with the alcohol and ether bound chemically as an ester or ether. In the method used, modified by Kober, no alcohol or ether are employed, thus eliminating that toxicity factor.

It has been found that despite careful methods of manufacture, there is a possibility that variable amounts of arsenic, in an inorganic form, will be present, although theoretically all the arsenic should exist in the organic form only; and to complicate matters still further, various organic arsenic combinations with a higher toxicity than Arsphenamine enter into the final composition.

As these combinations cannot be analyzed chemically, you can readily see how highly essential it is that before this drug can be placed on the market its toxicity has to be determined by means of biological assays, using rabbits, guinea pigs or rats.

The arsenic content of the various Arsphenamine preparations on the market averages around thirty percent, which is the standard set by the Hygienic Laboratory of the United States Public Health Service, while the arsenic content in the Neo-derivative should average around nineteen percent.

The present biological standard set by the same Laboratory, for the Maximum Tolerated Dose, is 100 milligrammes per kilo-body-weight of animal for Arsphenamine; it is 200 milligrammes per kilo-body-weight for Neo-Arsphenamine.

The dose for Arsphenamine usually given to adults is from 0.4 to 0.6 gramme, while from 0.6–0.75 gramme is the usual dose for Neo-Arsphenamine.

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THE PERMANENCE OF ALKALOIDAL FLUIDEXTRACTS AND TINCTURES.*

(SECOND PAPER.)

BY WILBUR L. SCOVILLE.

Nine years ago, at the Richmond meeting, I reported, under the above title, upon the keeping qualities of some fifty alkaloidal fluidextracts and tinctures over a period of two to three years. The remaining portions of those preparations were set aside in a closed case having glass doors where they have been stored during the intervening time. The preparations are now ten to twelve or more years old, and have been stored during that period under conditions which simulate the ordinary storage of business, namely, in partially filled bottles, in a fairly even temperature, and in a diffused light. They were each assayed by the same method as used ten years ago, and the results are shown in the following table.

The column headed "standard" shows the strength (grammes per 100 mils) to which the preparations were adjusted by assay when made.

TABLE OF RESULTS.

Abbreviations in tabular matter: F.—fluidextract; T.—tincture. Under "physical condition," the extent and character of the precipitate are indicated as follows: Slight precipitate—s; very slight—v. s.; moderate—m.; dense—d.; heavy—h.; considerable—c.; gelatinous—g.; wholly gelatinized—w. g. For fluidextracts of cinchona, guarana, ipecac and kola see also statements indicated by key number to foot-notes. Abbreviated references to preparations without precipitates are: O—clear; N—nearly clear; A—acetic.—EDITOR.

Made.	Percent alcohol.	Preparation.	Standard.	Assay 1910.	Assay 1919.	Percent loss.	Physical condition.
7–'07	40	F. Aconite lf.....	0.40	0.50	0.44	00.0	s.
1–'08	65	F. Aconite rt.....	0.40	0.43	0.407	00.0	N
1–'07	63	T. Aconite rt.....	0.050	0.051	0.0486	3.0	s.
10–'07	75	F. Anhalonium.....	5.50	6.48	5.6	00.0	v.s.
7–'08	50	F. Aspidosperma.....	1.00	1.04	0.53	47.0	h.
3–'08	60	F. Belladonna lf.....	0.30	0.297	0.277	8.0	m.

* Read before Scientific Section, A. Ph. A., New York Meeting, 1919.