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A method of preparing pure dihydrochloride of diaminodioxyarsenobenzene.

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The synthesis of a pure arsphenamine or salvarsan, in spite of the excellent published work of Ehrlich and Bertheim[1] and their collaborators, is still a vital problem. It is known by those who have given attention to the subject that the toxicity of arsphenamine varies and that batches from individual manufacturers vary more than they can account for in their procedures. Furthermore, as it seems fairly well proven that even Ehrlich's own manufacturers are unable to keep up a uniformly high standard,[2] it is evident there are some factors which are not understood or under control.

In studying this subject, I came to the idea that the toxicity of arsphenamine is largely due to the use of methyl alcohol and ether in the precipitation of the dihydrochloride and therefore made experiments to prepare the arsphenamine in aqueous solutions, free from any extraneous and objectionable substances:

Finding that the dihydrochloride of the salvarsan base was insoluble in excess of chlorides, as might be expected from the Law of Mass Action, an excess of hydrochloride acid was tried in salting out the drug. When first tried by making an aqueous solution of the dihydrochloride directly from the base, by dissolving in two normal sodium hydroxide and adding a slight excess of hydrochloride acid, and pouring the solution of hydrochloride into a strong solution of hydrochloric acid (1–1), a white precipitate was formed which, however, turned to a dark-colored gum. This transformation of the white precipitate into the black gum, as will be shown later, was due simply to coalescence of the particles. To prevent this coalescence three factors were changed: (1) The precipitation was conducted at a low temperature and (2) under more dilute conditions and (3) with vigorous stirring.

[1] *Ber.*, 45, 756, 1912.

[2] Roth, Hygienic Laboratory Bulletin, 113, p. 7, 1918.

Toxicological tests of the arsphenamine made by this method have been favorable but this study is not yet complete. While the physical properties are somewhat different than the usual arsphenamine, which has one molecule of methyl alcohol in its solid or crystal form according to Ehrlich and Bertheim, the chemical tests, analyses and toxicological reactions of the new substance are in harmony with pure dihydrochloride of diaminodioxyarsenobenzene with one or two molecules of water of crystallization.

Our experience with the methyl alcohol method has brought to our attention three possible objections against using this method:

(*a*) Our main objection to the methyl alcohol or any other similar solvent is based on the idea that it is easily oxidized or reduced, and as a concomitant with arsphenamine, a substance easily oxidized to very toxic and dangerous products, is apriori not a safe thing to have. In a subsequent paper we expect to prove these and other points.

(*b*) Our second objection to this method is expense. Even in peace times this method would be expensive.

(*c*) Our third objection is that these solvents are highly inflammable.

The advantages of the hydrochloric acid method are:

(*a*) The medium of precipitation, both the water and the hydrochloric acid can be absorbed by common and inexpensive absorbents and they are not easily oxidized or reduced.

(*b*) It is an inexpensive method, as the excess hydrochloric acid can be recovered ready for use by simple distillation.

(*c*) It is a non-inflammable method.

(*d*) It is pharmacologically more suitable and less open to question.

(*e*) The product seems more stable and less liable to oxidation, when exposed to the air.

(*f*) The method can be used for reprecipitation and is chemically better calculated to eliminate impurities as it is the same method used to obtain chemically pure sodium chloride.