[CONTRIBUTION FROM THE LABORATORY OF THE SYNTHETIC DRUG COMPANY, LTD.]

EXAMINATION OF NEOARSPHENAMINE.

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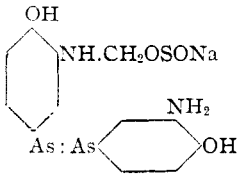
During the last few years many articles have appeared on the chemistry of arsphenamine, but practically nothing on that of neoarsphenamine. This is doubtless owing to the generally admitted obscure nature of the product, which in point of instability and difficulty of preparation stands midway between arsphenamine and sodium arsphenamine. The only references to the preparation of neoarsphenamine are confined to patent literature,[1] and these claim the manufacture of sulfoxylic acid derivatives of arsphenamine by the action of formaldehyde sulfoxylate salts on arsphenamine compounds or their intermediates. Molecular compounds may so be formed, the reaction, in distinction from that of formaldehyde bisulfite, taking place in the presence of either acids or alkalies, the degree of substitution depending on which condition occurs and such factors as temperature, time, concentration and proportion of the reacting substances. The primary products[2] are N-mono- and NN′-dimethylene-sulfoxylate derivatives of dihydroxy-diamino-arsenobenzene, and where technique is not good, mixtures are produced of one or the other, or both, and decomposition products.

Arsphenamine compounds, of course, owing to their amorphous character, cannot be made absolutely pure, this difficulty being increased in the neutral and alkaline derivatives by their lesser stability, so that neo- and sodium arsphenamines, for instance, as usually prepared, are diluted by greater or less amounts of by-products. Account should be taken of this, consequently, in the recognition of neoarsphenamine; *e. g.*, it is not sufficient that a powder should have a definite sulfur : arsenic ratio and be soluble in neutral solution, since it may be shown that preparations nearly always contain mechanically mixed free sulfur salts, and in some cases consist to a great extent of reaction by-products.

Considering the degradation products of neoarsphenamine, one course of decomposition may be represented thus,

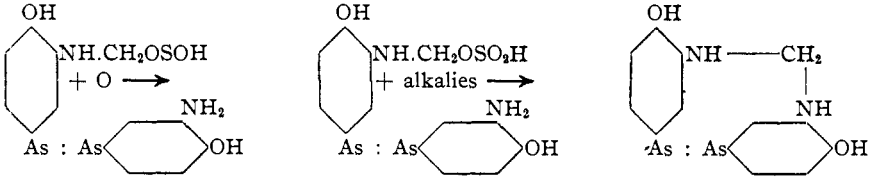
[1] *D. R. P.*, 245,756.

[2] Neoarsphenamine is defined as a compound prepared from arsphenamine by means of formaldehyde sulfoxylate. A monomethylenesulfoxylate formula is claimed for foreign preparations, including Ehrlich's, thus (Fig. 1).



Dihydroxy-diamino-arsenobenzene-*N*-monomethylene-sodium sulfoxylate.

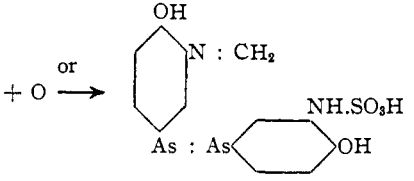
Fig. 1.



Dihydroxy-diamino-arseno-benzene-*N*-monomethylene sulfoxylic acid.

-methylene sulfurous acid.

-methylene compound.



Corresponding sulfamic acid.

Fig. 2.

besides more involved side group and possible nuclear substitution derivatives.[1]

Disintegration of the arseno radical would lead to oxidation and hydrolytic fractures such as appear to occur in the catabolism of arsphenamine.[2] In neoarsphenamine such cleavages are to be detected by biological rather than chemical tests since the introduction of a side chain into the molecule creates colorimetric and reducing properties which would otherwise obscure their occurrence. This is not the case, however, with the above-mentioned sulfur by-products, which it would be a mistake to assume differ greatly in toxicity from the original sulfoxylate derivatives. But therapeutic interest centers on the latter as having the structure attributed to Ehrlich's compound. Considerable importance attaches, therefore, to the identity of the side group in commercial preparation.

Attempts to distinguish the monosulfoxylate derivative by the physical properties of the free acid led to nothing definite: the melting point, though distinct, was not very constant or much removed from those of other arseno compounds. Estimation of its sulfur : arsenic ratio gave better but not uniform results. A method was finally devised by the writer which served to distinguish the sulfoxylate derivative from the more immediate sulfur and non-sulfur by-products and depended on portionwise oxidation of neoarsphenamine solutions by iodine. This method, though having certain limitations, has given consistent analytical figures and possesses an advantage also in that it is effective with relatively small samples of the drug. The error is about 2% and this largely in the arsenic determination. The method is applicable in the toxicological

[1] Binz, *Ber.*, **50**, 1274 (1917).

[2] Sieburg, *Z. physiol. Chem.*, **97**, 53 (1916).

study of the progressive decomposition of neoarsphenamine solutions.[1] Under the conditions described below, oxidation of neoarsphenamine by iodine proceeds quantitatively according to the equation,[2]

$$OH(NH_2)C_6H_3As : AsC_6H_3(OH)NH.CH_2OSOH + 9H_2O + 12I \longrightarrow 2OH(NH_2)C_6H_3AsO(OH)_2 + HCHO + H_2SO_4 + 12HI.$$

Procedure.

Two g. of neoarsphenamine is dissolved in 100 cc. distilled water.

Total Reducing Power.—Ten cc. of this solution is pipetted into a 500-cc. wide-necked glass-stoppered bottle, acidified with 25 cc. of 1–20 hydrochloric acid, immediately treated with 50 cc. of 0.1 *N* iodine from a buret and titrated back with thiosulfate after 3 minutes' shaking. The cc. of iodine required multiplied by 5 is the total reducing power per g. of powder.

Free Reducing Substances.—Simultaneously with the above, 20 cc. of solution is removed to a 100-cc. volumetric flask with well-ground glass stopper, the flask filled with carbon dioxide or nitrogen, 50 cc. of 1–20 hydrochloric acid added, diluted with water to the mark, stoppered and inverted about 120 times in 3 minutes to dissolve the soluble constituents from the precipitate. The suspension is brought onto a dry folded filter, the first few cc. of filtrate discarded, then 25 cc. collected in a dried 50-cc. volumetric flask containing 25 cc. of 0.1 *N* iodine solution. The contents of this flask are poured into a 500-cc. bottle and the residue rinsed twice with water. Titrating back after 3 minutes, the cc. of iodine required multiplied by 10 is that required by the free reducing substances per g. of powder.

Arsenic.—Ten or 20 cc. of solution is oxidized and the arsenic determined by Lehmann's[3] or Rogers'[4] method. The per cent. of As times 5.333 is equivalent to the cc. of iodine required to oxidize the arsenic in 1 g. of powder.

Combined Sulfoxylate.—The iodine required to oxidize the combined sulfoxylate in 1 g. of powder is found by subtracting that required by the arsenic and free reducing substances from the total reducing power. This divided by 3.9553 gives the per cent. of sulfoxylate (as CH_2OSONa).

Calculation.—The ratio of sulfoxylate to arsenic, *e. g.*, M.S.: 2M.As is given by the equation M.S. = 150/% As. × % S./101.13, the theory for neoarsphenamine being unity.

Comment.

Analysis of best preparations has indicated that it is not possible to form products of sulfoxylate : arsenic ratio exactly 1:2, but that products closely approximating to this are quite practicable.

TORONTO, CANADA.

[1] Kolle, *Deut. Med. Wochschr.*, **1918**, p. 1180.
[2] Reinking, *Ber.*, **38**, 1069 (1905).
[3] Fargher, *J. Chem. Soc.*, **115**, 992 (1919).
[4] Rogers, *Can. Chem. J.*, **3**, 398 (1919).