THE PREPARATION OF 3-CARBAMIDO-4-HYDROXYPHENYL-ARSONIC ACID.*

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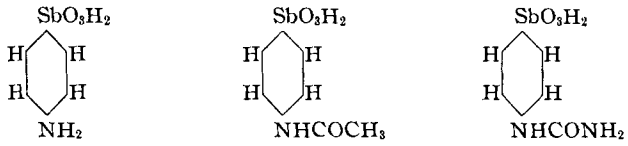
Stovarsol, 3-acetamino-4-hydroxyphenylarsonic acid, has been known for some time and has been used widely in the treatment of amœbic dysentery and, more recently, as a prophylactic against syphilis. Brahmachari (1) prepared a series of antimony compounds and found that of the three given below the carbamido compound III was superior to either the amino or acetylamino compounds in pharmacological action.



By analogy 3-carbamido-4-hydroxyphenylarsonic acid should be superior to Stovarsol. It is proposed here to describe in detail the preparation of 3-carbamido-4-hydroxyphenylarsonic acid.

Ehrlich and Bertheim (2) describe briefly the preparation of both the 3-acetamino-4-hydroxyphenylarsonic acid, Stovarsol, and the 3-carbamido-4-hydroxyphenylarsonic acid. The method described here is similar to that of Ehrlich and Bertheim but is given in greater detail as follows:

Eleven and six-tenth grams of 3-amino-4-hydroxyphenylarsonic acid was dissolved in 100 cc. of $N/2$ sodium hydroxide solution. This solution was then treated with 12 Gm. of potassium cyanate and 12 Gm. of glacial acetic acid, successively, and was then allowed to stand for 24 hours. While standing a small amount of 3-amino-4-hydroxyphenyl arsonic acid separated out. This was removed by filtration and the dark brown filtrate decolorized partially by stirring with a decolorizing carbon. The light brown, clear, alkaline filtrate from the carbon was acidified by the gradual addition of concentrated hydrochloric acid (U. S. P.). Five cc. of acid made the solution acid to litmus, but the 3-carbamido-4-hydroxyphenylarsonic acid did not begin to separate until the solution had been made acid to congo red by the addition of 15 cc. more of hydrochloric acid. When the solution was acid to congo red an additional five cc. of acid were added making a total of 25 cc.; then the product precipitated. The mixture was allowed to stand for four hours and then chilled in ice for two hours more. The white precipitate was collected on a Buechner funnel, washed with water and then air-dried. Yield: 10 Gm. or 77%.

In order to purify this substance and at the same time make it more convenient for biological testing the substance was converted into the sodium salt which is readily water soluble; the free acid is only slightly water soluble. This was accomplished by dissolving 7 Gm. of the acid in 150 cc. of water and 1.14 Gm. of sodium hydroxide and filtering. The clear solution was then poured into 500 cc. of 95% alcohol stirring vigorously. Precipitation was not immediate and was started by removing a small portion in a test-tube, starting crystallization by scratching the

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inner wall of the tube with a glass rod, and then using the crystals thus formed to seed the bulk of the preparation. The large portion crystallized slowly and an additional 200 cc. of alcohol were added. This was then cooled thoroughly in ice for several hours and the precipitate recovered on a Buechner funnel, washed with alcohol and air-dried. The white, microcrystalline solid was readily water soluble and weighed 6.5 Gm., a yield of 80%.

Analysis of the sodium salt: $C_7H_7O_5N_2AsNa$, 4.5 H_2O.
Calculated: Nitrogen—6.99%, arsenic—23.42%.
Found: Nitrogen—7.10%, arsenic—23.26%.

Arsenic was determined by the Ewins Method and Nitrogen by the Kjeldahl Method.

The 3-carbamido-4-hydroxy phenyl arsonic acid was compared to Stovarsol for toxicity by intravenous injection of solutions of the sodium salts and found to be more toxic.

TABLE I.—COMPARATIVE TOXICITIES OF STOVARSOL AND 3-CARBAMIDO-4-HYDROXYPHENYLARSONIC ACID.

Drug.	Dosage in mg. per Kg. body weight.	No. rats injected.	No. rats survived.	No. rats died.
Stovarsol	800	3	0	3
	400	3	0	3
	300	3	3	0
	250	3	1	2
	200	3	3	0
3-Carbamido-4-hydroxy-phenylarsonic acid	800	3	0	3
	400	3	0	3
	200	3	0	3
	150	3	0	3
	100	3	3	0

From these results the minimal lethal dose of Stovarsol appears to be between 200 and 250 mg. per Kg. of body weight whereas that of 3-carbamido-4-hydroxy-phenylarsonic acid is between 100 and 150 mg. per Kg. body weight. It is apparent that 3-carbamido-4-hydroxyphenylarsonic acid is about twice as toxic as 3-acetamino-4-hydroxyphenylarsonic acid, Stovarsol. In this instance, at least, the relation between toxicity and chemical structure in arsenic compounds is not analogous to that in antimony compounds when the nature of the side-chain attached to the amino group is used as the basis of comparison.

On the basis of these results we may conclude that 3-carbamido-4-hydroxy-phenylarsonic acid is of no therapeutic value as it is too toxic for clinical use.

REFERENCES.

(1) Brahmachari, *Indian Jour. Med. Research*, 10 (1922), 508; *Ibid.*, 12 (1924), 423.
(2) Ehrlich and Bertheim, U. S. Patent, No. 1,077,462.

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