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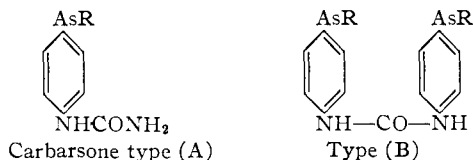
## Arsenic Derivatives of Diphenylurea

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RECEIVED APRIL 29, 1954

A series of diphenylureas has been prepared, in which the aromatic rings were symmetrically substituted by arsono and arsonoso substituents. Some of the compounds have shown activity against *E. histolytica in vitro*.

Pentavalent arsenic compounds such as carbarsone and acetarsone have been used in the treatment of amebiasis for many years. More recently, Anderson<sup>2</sup> showed that the trivalent arsenic compounds (Type A)—carbarsone oxide and its thioglycolic acid and thiosalicylic acid derivatives—were active in human and monkey amebiasis. We have prepared this series of penta- and trivalent arsenic compounds of type B in which the nitrogen atoms of the ureido linkage were symmetrically substituted.



These compounds were prepared by the reaction of phosgene with the corresponding arsonoaniline and arsonosoaniline in an aqueous alkaline solution, except compounds VI, XI and XII. An aqueous solution of 3-amino-4-hydroxyphenyldichloroarsine hydrochloride was used in the synthesis of VI. Compound XI was obtained by the reduction of the corresponding arsenic acid using phosphorus trichloride in ethyl acetate. Compound XII was prepared from *p*-arsonobenzylamine.

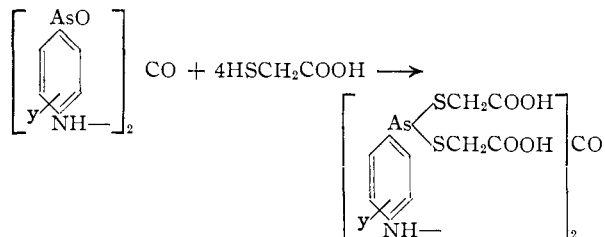
The arsenic and nitrogen analyses on compounds II, V and VI indicated the presence of two moles of water which could not be determined by loss on drying or by the Karl Fischer method. Therefore the arsenious acid [ $-\text{As}(\text{OH})_2$ ] structure is proposed for these products. Analyses of compounds III, XI and XII indicated the presence of only one molecule of water which also could not be determined. A possible structure



is proposed to explain this fact.

The arsonoso compounds II, V and VI were suspended in water and refluxed with an excess of thioglycolic acid to yield the *N,N'*-carbonyl-bis-(substituted phenylarsylenedithio)-diacetic acids, VII, VIII and IX, respectively.

The compounds were screened against *Endameba histolytica*, N.R.S. strain, using a modification of the Bradin and Hansen method.<sup>3</sup> This involved



the use of a liquid liver-proteose-peptone medium. Readings were made 48 hours after introduction of the drug. Carbarsone in this test showed an activity at 1:20,000 dilution. The comparative activities of the series of compounds is shown in Table I and the biological data will be published elsewhere.

## Experimental

**Procedure A. Method of Preparation of Arsonic Acid (I) and Arsonoso Compounds II and III.**—The procedure was essentially that of King and Murch.<sup>4</sup> The product was purified by the reprecipitation of the acid from a filtered alkaline solution. The material was washed on the filter with two 200-cc. portions of hot water. The purified product was dried in a vacuum oven at 60°.

The starting material for the preparation of II and III was *p*-arsonoaniline<sup>5</sup> and *m*-arsonoaniline.<sup>6</sup>

**Procedure B. Method of Preparation of Arsonoso Compounds V, VI and Arsonic Acid (IV).** *N,N'*-Bis-(5-arsono-2-hydroxyphenyl)-urea (VI).—The procedure was essentially that of King.<sup>7</sup> A solution of the dichloroarsine hydrochloride<sup>8</sup> in 250 cc. of water was cooled to 10–15°. A slow stream of phosgene was introduced below the surface of the stirred solution for about two hours. The foaming was controlled by the addition of a few milliliters of benzene or toluene, or by intermittent gassing.

The white solid, which separated during the gassing, was dissolved by making the reaction mixture strongly alkaline with sodium hydroxide solution. The alkaline solution was extracted with ether, if necessary, to remove the benzene or toluene, and the aqueous phase filtered to remove any insoluble material. By treating the clear filtrate with a saturated solution of ammonium chloride, a precipitate separated which was isolated by filtration.

This solid was slurried with water, then separated by filtration, and washed on the filter until the filtrate gave no test for chlorides with silver nitrate solution. The product was dried in a vacuum oven at 60°.

*N,N'*-Bis-(5-arsono-2-chlorophenyl)-urea (IV) and *N,N'*-Bis-(5-arsono-2-chlorophenyl)-urea (V).—The procedure for the preparation of these compounds was the same as for compound VI using a dilute alkaline solution as the reaction solvent. The products were precipitated from the alkaline solution by the addition of concentrated hydrochloric acid.

*N,N'*-Bis-(*p*-arsonophenyl)-thiourea (X).—Procedure A was followed using an equivalent amount of thiophosgene. The product was isolated and purified in the same manner.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{As}_2\text{N}_2\text{O}_6\text{S}$ : As, 31.47; N, 5.88. Found: As, 31.45; N, 5.71.

(1) Presented at the 125th meeting of the American Chemical Society, Division of Medicinal Chemistry, at Kansas City, March, 1954.

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(3) J. L. Bradin and E. L. Hansen, *Am. J. Trop. Med.*, **30**, 27 (1950).

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(6) C. S. Hamilton and J. F. Morgan, in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, 1944, p. 425; G. O. Doak, H. Eagle and H. S. Steinman, *THIS JOURNAL*, **62**, 168 (1940).

(7) H. King, *J. Chem. Soc.*, 1049 (1927).

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TABLE I<sup>a</sup>

No.	x	y	Pro- cedure	Formula	Analyses, %				Activity <i>E. hist.</i>
					Arsenic Calcd.	Arsenic Found	Nitrogen Calcd.	Nitrogen Found	
I	4-AsO <sub>3</sub> H <sub>2</sub>	H	A	C <sub>13</sub> H <sub>14</sub> As <sub>2</sub> N <sub>2</sub> O <sub>7</sub>	32.56	32.30	6.09	6.03	1:50,000
II	4-As(OH) <sub>2</sub>	H	A	C <sub>13</sub> H <sub>14</sub> As <sub>2</sub> N <sub>2</sub> O <sub>5</sub>	34.99	35.02	6.54	6.53	1:50,000
III	3-As(OH)O <sup>c</sup>	H	A	C <sub>13</sub> H <sub>12</sub> As <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	36.54	36.49	6.83	6.72	1:10,000
IV	5-AsO <sub>3</sub> H <sub>2</sub>	2-Cl	B	C <sub>13</sub> H <sub>12</sub> As <sub>2</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>7</sub>	26.52	26.76	4.96	4.75	Inactive
V	5-As(OH) <sub>2</sub>	2-Cl	B	C <sub>13</sub> H <sub>12</sub> As <sub>2</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>5</sub>	30.15	30.75	5.64	5.35	1:100,000
VI	5-As(OH) <sub>2</sub>	2-OH	B	C <sub>13</sub> H <sub>14</sub> As <sub>2</sub> N <sub>2</sub> O <sub>7</sub>	32.56	33.33	6.09	5.80	1:200,000
VII	4-As $\begin{cases} \text{SCH}_2\text{COOH}(\text{Na}) \\ \text{SCH}_2\text{COOH}(\text{Na}) \end{cases}$	H		C <sub>21</sub> H <sub>22</sub> As <sub>2</sub> N <sub>2</sub> O <sub>3</sub> S <sub>4</sub> (4Na)	18.46 <sup>b</sup>	17.95	3.45 <sup>b</sup>	3.41	1:2000
VIII	5-As $\begin{cases} \text{SCH}_2\text{COOH}(\text{Na}) \\ \text{SCH}_2\text{COOH}(\text{Na}) \end{cases}$	2-Cl		C <sub>21</sub> H <sub>20</sub> As <sub>2</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub> S <sub>4</sub> (4Na)	16.49 <sup>b</sup>	17.02	3.18 <sup>b</sup>	3.15	1:10,000
IX	5-As $\begin{cases} \text{SCH}_2\text{COOH} \\ \text{SCH}_2\text{COOH} \end{cases}$	2-OH		C <sub>21</sub> H <sub>22</sub> As <sub>2</sub> N <sub>2</sub> O <sub>11</sub> S <sub>4</sub> (4Na)	19.78	19.49	3.7	3.5	1:200,000

<sup>a</sup> On heating to 300°, all of these compounds charred without melting. <sup>b</sup> Calculated as the tetrasodium salt. <sup>c</sup> This structure is the postulated anhydride, see text.

**Anhydride of N,N'-Bis-(*p*-arsonosophenyl)-thiourea (XI).**—The procedure is essentially that of Ehrlich and Bertheim.<sup>9</sup> The *sym*-diphenylthioureadiarsonic acid was suspended in dry ethyl acetate and an excess of phosphorus trichloride was added dropwise with vigorous shaking. The mixture warmed up and the solid gradually went into solution. The solution was filtered to remove any insoluble material and the clear filtrate was shaken with an excess of concentrated ammonium hydroxide whereupon a white product separated, which was isolated by filtration.

The solution obtained by dissolving the precipitate in 10% sodium hydroxide solution was filtered and the product reprecipitated by adding an excess of saturated ammonium chloride solution. The solid was washed with water until the filtrate gave a negative chloride test and was then dried in a vacuum oven at 60°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>As<sub>2</sub>N<sub>2</sub>O<sub>3</sub>: As, 35.16; N, 6.58. Found: As, 35.19; N, 6.68.

**Anhydride of N,N'-Bis-(*p*-arsonosobenzyl)-urea (XII).**—The *p*-arsonosobenzylamine was prepared using the procedure of Fox,<sup>10</sup> and was treated with phosgene using procedure A.

The crude product was precipitated from an alkaline solution with a saturated solution of ammonium chloride. The solid product was isolated by filtration and washed on the filter until the silver nitrate test of the filtrate was negative. The product was dried in a vacuum oven at 60°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>16</sub>As<sub>2</sub>N<sub>2</sub>O<sub>4</sub>: As, 34.20; N, 6.40. Found: As, 33.96; N, 6.44.

**N,N'-Carbonyl-bis-(3-amino-4-hydroxyphenylarsylenedithio)-diacetic Acid (IX).**—A suspension of 42.4 g. (0.1 mole) of N,N'-bis-(5-arsono-2-hydroxyphenyl)-urea in 500 cc.

of water was treated with 46 g. (0.5 mole) of thioglycolic acid. The mixture was refluxed until all of the solid dissolved. The clear hot solution was filtered and allowed to cool slowly. The oil, which separated, solidified on further cooling in an ice-bath. The solid was broken up and isolated by filtration.

The crude product was dissolved in 100 cc. of ethanol, treated with charcoal and filtered. The clear filtrate was diluted with 1.5 liters of warm water and the clear solution cooled in an ice-bath. The white solid, which slowly separated, was isolated by filtration and dried in a vacuum oven at 60°.

**Tetrasodium N,N'-Carbonyl-bis-(4-aminophenylarsylenedithio)-diacetate (VII) and Tetrasodium N,N'-Carbonyl-bis-(3-amino-4-chlorophenylarsylenedithio)-diacetate (VIII).**—A suspension of 0.1 mole of the arsonoso compound in 500 cc. of water was refluxed with 0.5 mole of thioglycolic acid for 15 minutes. The mixture was cooled and the aqueous layer decanted from the oily layer. The oil was dissolved in a minimum quantity of 10% sodium hydroxide solution, treated with charcoal and filtered. The clear filtrate was treated with a large excess of ethanol. The water-alcohol layer was decanted from the gummy solid which formed. The gummy product was refluxed 15 minutes with 200 cc. of ethanol. On cooling the mixture the insoluble product solidified and was isolated by filtration and dried in a vacuum oven at 60°.

**Acknowledgment.**—The authors wish to thank Mr. E. F. Shelberg and the microanalytical staff for the microanalyses and Mr. C. J. Rickher and Miss Daisy Herman for the *in vitro* amebicidal tests.

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