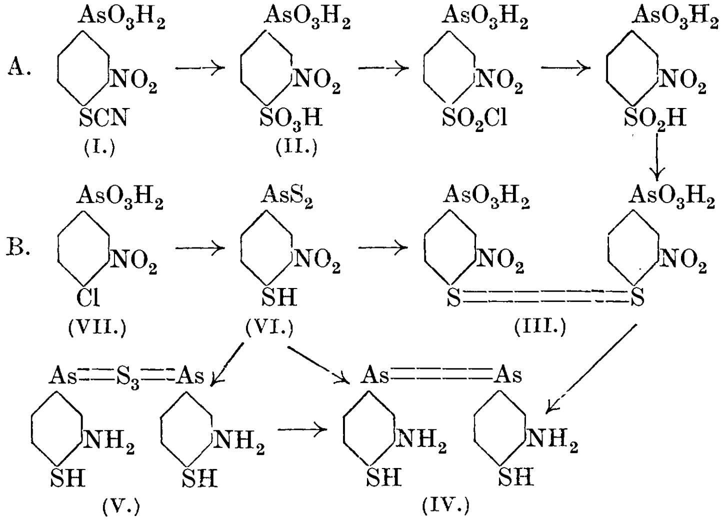
CCCLVI.—*Aromatic Arsenic Compounds containing Sulphur Groups attached to the Nucleus. Part III. 3 : 3′-Diamino-4 : 4′-dithiolarsenobenzene, the Thiol Analogue of Salvarsan.*

By Harry James Barber.

The unique position of salvarsan and its immediate derivatives as therapeutic agents and the view, for which there is increasing evidence, that the thiol group plays an essential rôle in the action of organic arsenicals render the preparation of the thiol analogue of salvarsan of dual interest.

With this object, due regard being given to the properties of sulphur-containing arsenicals (J., 1930, 2047, 2725), the following suitable schemes were investigated :



With regard to scheme A, 3-nitro-4-thiocyanophenylarsonic acid (I) was converted readily into 3-*nitro*-4-*sulphophenylarsonic acid* (II) by oxidation, but the conversion of this into the disulphide by a similar series of reactions to that employed in Part I (*loc. cit.*) for the 2-sulphophenylarsonic acid failed at the first stage. A small quantity of 2 : 2′-*dinitro*-4 : 4′-*diarsonodiphenyl disulphide* (III) was obtained as an intermediate stage of the oxidation of the thiocyano-acid.

With regard to scheme B, alkali sulphides produced with 4-chloro-3-nitrophenylarsonic acid (VII) a yellow amorphous substance, containing one sulphur atom attached to the nucleus and two to the arsenic atom (VI). The action of oxidising agents on this compound was studied quantitatively with the view of determining the nature of the sulphur group (thiol or disulphide) and the state of oxidation of the arsenic atom. Completely satisfactory equations for the formation and oxidation of this substance have not been found, but the following are close approximations :

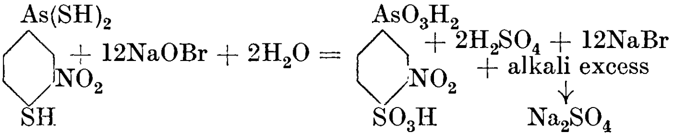
$$1.\ \mathrm{R = NO_2{\cdot}C_6H_3Cl.}$$
$$\mathrm{R{\cdot}AsO_3H_2 + 4KSH = R{\cdot}As(SK)_2 + K_2S_2 + 3H_2O}$$
$$2.\ \mathrm{R = NO_2{\cdot}C_6H_3(AsS_2).}$$
$$\mathrm{2RCl + K_2S_2 = RS{\cdot}SR + 2KCl}$$
$$3.\ \mathrm{R = NO_2{\cdot}C_6H_3(AsO_3H_2).}$$
$$\mathrm{RCl + KSH = R{\cdot}SH + KCl}$$

Equation 1 is analogous to the equation representing the action of mercaptans on arsonic acids (Barber, J., 1929, 1021). It is probable that reaction 3 proceeds simultaneously with 1, since an attempt to produce 4-chloro-3-nitrophenylarsenic disulphide under very mild conditions showed that the halogen atom was very easily replaced.

Oxidation.

Acid 4. $\mathrm{2SH{\cdot}C_6H_3(NO_2){\cdot}As{:}S_2 + 5I_2 + 6H_2O =}$
$\mathrm{[{-}S{\cdot}C_6H_3(NO_2){\cdot}AsO_3H_2]_2 + 10HI + 4S}$

Alkaline 5.



$$\mathrm{C_6H_3(As(SH)_2)(NO_2)(SH) + 12NaOBr + 2H_2O = C_6H_3(AsO_3H_2)(NO_2)(SO_3H) + 2H_2SO_4 + 12NaBr}$$
$$\mathrm{+\ alkali\ excess \downarrow Na_2SO_4}$$

It has not been found possible to isolate the arsenical portions of the reaction products formed under the conditions of the titrations, but equation 5 was confirmed by sulphate determinations. The reaction in acid solution is in accordance with the representation $\mathrm{R{\cdot}AsS_2}$ and in alkaline with $\mathrm{R{\cdot}As(SNa)_2}$. A more detailed discussion of the structure is not attempted here.

The *arsenic disulphide* (VI) can be converted by mild oxidation with iodine into the disulphide arsonic acid (III). This acid has properties similar to those of the other disulphide arsonic acid previously described, but its hydrolysis and oxidation are accompanied by remarkable colour changes. The solution of the acid in caustic alkali has momentarily a red-brown colour, but this rapidly passes through green to an intense blue-violet, which slowly fades : the sequence of changes is accelerated by warming. In weak alkalis such as ammonia or sodium carbonate the normal reddish solution is obtained, but no further change occurs except on the addition of a drop of hydrogen peroxide; the complete reaction is then obtained. The arsenic disulphide (VI) also gives the reaction with alkali and hydrogen peroxide but not with alkali alone. This reaction has already been noted (*loc. cit.*) with the thiocyano-acid (I), but the amino-compound corresponding to (VI) gives no such reactions. It seems probable that the effect is one of oxidation at the sulphur atom in which the hydrogen peroxide or the arsonic acid group is the oxidant. More drastic oxidation of the arsenic disulphide (VI) gives the sulphonic acid (II).

The arsenic disulphide (VI) on reduction with ferrous hydroxide gives an *amino*-compound (V), one sulphur atom between two molecules being eliminated.

Reduction of either (V) or (VI) with sodium hyposulphite gave a product which was undoubtedly an impure thiosalvarsan (IV). The reduction of the arsonic acid (III), which might be expected to give a purer product, was less successful, as the arseno-compound prepared in this way separated in a flocculent form and could not be removed by filtration and washed. Attempts to reoxidise the arseno-compound (IV) or the amino-compound (V) to the corresponding arsonic acid have so far failed.

The arseno-compound (IV) had the usual physical properties, but so far none of the many condensation reactions of salvarsan base has been achieved with this substance. In fact, it appears to be non-basic, as does also the amino-compound (V). The presence of the *o*-aminothiophenol residue has been established satisfactorily by the preparation of a number of cyclic compounds, which will form the subject of Part IV.

EXPERIMENTAL.

3-*Nitro*-4-*sulphophenylarsonic Acid* (II).—(*a*) 3-Nitro-4-thiocyanophenylarsonic acid was evaporated repeatedly with nitric acid (*d* 1·52) and finally several times with water to remove the excess of acid. A solution of the crystalline residue in a little water was filtered from a small quantity of the disulphide (III) and evaporated almost to dryness; the residual crystalline mass, freed from mother-liquor by washing with glacial acetic acid, formed brownish prisms extremely soluble in water or alcohol (Found: As, 23·1; N, 4·3; S, 9·8. $C_6H_6O_8NAs$ requires As, 22·9; N, 4·3; S, 9·8%).

(*b*) The compound (VI) was treated similarly, but the product contained a small amount of inorganic material (Found: As, 22·5; N, 5·0; S, 10·6%).

3-*Nitro*-4-*thiolphenylarsenic Disulphide* (VI).—When solutions of 4-chloro-3-nitrophenylarsonic acid (20 g.) in alcohol (50 c.c.) and of potassium hydrosulphide (140 c.c. of 15%, or an equivalent quantity) were mixed, they became yellow and then dark red. After being boiled for 5 minutes, the mixture was diluted to 500 c.c. with water and made acid with hydrochloric acid. The yellow precipitate was removed at once, washed with hot water, and purified by solution in cold *N*/5-sodium hydroxide (500 c.c.), filtration, and reprecipitation (yield, 17—20 g.). The preparation was carried out similarly with sodium monosulphide or disulphide.

The following table summarises the results :

						Oxidation (atoms of O).	
No.	Mols. KSH or Na_2S.	As.	S(As).	S (total).	N.	Iodine.	Hypo-bromite.
1	3·6	26·0	21·9 21·9	30·5	5·45	2·1	11·7
2	3·5	27·3					
3	4·5	27·7					
4	3·6	27·1	19·7	30·1		3·1	13·8
5		27·5				2·8	13·6
6	4·0	26·2	23·8	31·4		2·5	13·6
7	3·0			30·6		2·5	14·1
8	4·0	26·8		33·4	5·3		
9	5·0	27·5		32·2			

$C_6H_4O_2NS_3As$ requires As, 25·7; S(As), 21·9; S (total), 32·8; N, 4·8%. Nos. 4 and 5 are different fractions of the same crude product obtained by partial extractions with alkali. No. 7 was obtained from 4-chloro-3-nitrophenylarsinic acid. Nos. 8 and 9 were from sodium sulphide preparations. It is evident that, while none is pure, all are essentially the same product.

The titrations were carried out as follows :—*Acid*. The arsenic disulphide (0·1 g.), dissolved in 2*N*-sodium hydroxide (2—3 c.c.) and water (20 c.c.), was added to *N*/10-iodine (25 c.c.), acidified with 2*N*-sulphuric acid (20 c.c.), and kept for 5 minutes; the excess of iodine was then titrated with standard thiosulphate solution.

Alkaline. The arsenic disulphide in dilute alkali solution as before was treated with *N*/5-sodium hypobromite (50 c.c.), warmed at 80° for ¼ hour, and cooled. Potassium iodide solution (20 c.c. of 10%) was added and then 2*N*-sulphuric acid (80 c.c.); the liberated iodine was titrated after 2—3 minutes. The sulphur attached to arsenic [S(As)] was determined gravimetrically as sulphate after hypobromite oxidation as above. Both titrations were tested and gave consistent results on a given sample.

2 : 2′-*Dinitro*-4 : 4′-*diarsonodiphenyl Disulphide* (III).—A suspension of the freshly precipitated compound (VI), kept alkaline by sodium bicarbonate, was treated with a concentrated solution of

iodine in potassium iodide until no more dissolved. The liquid was filtered from the insoluble material, diluted considerably with water, heated at 90° for ½ hour, treated with charcoal, and again filtered. The crude acid, precipitated by addition of hydrochloric acid, was purified as above, the operation being repeated several times (Found: As, 26·3; N, 5·0; S, 11·6. $C_{12}H_{10}O_{10}N_2S_2As_2$ requires As, 27·0; N, 5·0; S, 11·5%).

3 : 3′-*Diamino*-4 : 4′-*dithiolarsenobenzene* (IV).—(*a*) The compound (VI) (5 g.), dissolved in 2*N*-sodium hydroxide (40 c.c.), was reduced at 0—5°, by the addition of sodium hyposulphite (10 g.) and ice (40 g.). The colourless solution obtained was filtered (charcoal) and added to a filtered solution of sodium hyposulphite (40 g.) in water (400 c.c. containing magnesium chloride, 100 c.c. of 40% solution), the whole being then heated at 55—60° for 2 hours. The *arseno*-compound which separated was washed by decantation and then by suction and dried in a vacuum to constant weight. The product was a yellow amorphous powder insoluble in acids, soluble in sodium hydroxide to a pale yellow solution, which usually gave some colour with sodium nitroprusside. The substance was apparently diazotisable and then gave a strong coupling reaction with sodium β-naphthoxide, but the condensation reactions of salvarsan base have not yet been achieved with this product. The analyses show a considerable contamination, which is partly accounted for by inorganic material and partly by sulphur-containing impurities, as is the case with salvarsan [Found: As, 31·2 (mean of 5); N, 5·75 (mean of 5); S, 16·4, 14·4, 17·6 (mean 16·1); C, 31·1; H, 3·0. As : N : S : C : H = 1 : 0·99 : 1·2 : 6·2 : 7·2. $C_{12}H_{12}N_2S_2As_2$ requires As, 37·7; N, 7·05; S, 16·1; C, 36·2; H, 3·0%].

(*b*) The compound (V) (5 g.), dissolved in 2*N*-sodium hydroxide (50 c.c.), was added to sodium hyposulphite solution (50 g.; 500 c.c.) containing magnesium chloride (120 c.c. of 40% solution) at 0°, the mixture treated with charcoal, and the liquid filtered rapidly before the arseno-base began to separate. The reduction was carried out at 55—60°, and the product worked up in the usual way; prepared by this method, it separated in a form more suitable for filtering and washing, and this probably accounts in part for its greater purity (Found: As, 34·8; N, 6·0; S, 16·9%).

3 : 3′-*Diamino*-4 : 4′-*dithioldiphenyldiarsenic Trisulphide* (V).—The compound (VI) (10 g.) was dissolved in just sufficient 2*N*-sodium hydroxide and reduced at 90° with ferrous hydroxide (60 g. of ferrous sulphate in 60 c.c. of water; 20 g. of sodium hydroxide in 40 c.c. of water). After filtration the solution was made acid to Congo-red with hydrochloric acid, and the product was removed, dissolved in sodium hydroxide solution, and reprecipitated with acid.

The pale yellow, amorphous powder obtained had apparently very feebly basic properties; it gave, however, a coupling reaction with β-naphthol after diazotisation. The sulphur atom which is detached from arsenic presumably forms alkali sulphide during the reduction, since hydrogen sulphide is evolved on acidification of the reduction mixture (Found: As, 29·1; N, 5·8; S, 30·4. $C_{12}H_{12}N_2S_5As_2$ requires As, 30·4; N, 5·7; S, 32·4%).

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