178. *The Hydrolysis of Arylthioarsinites.**

By Harry James Barber.

In a previous communication (J., 1929, 1021) dealing with the formation of thioarsinites from aromatic arsonic acids and thiol compounds according to the equation

$$(1)\quad Ar{\cdot}AsO(OH)_2 + 4RSH = Ar{\cdot}As(SR)_2 + R{\cdot}S{\cdot}S{\cdot}R + 3H_2O$$

it was stated that hydrolytic fission of these substances does not occur in alkaline solution. Gough and King (J., 1930, 673) express the view that all thioarsinites undergo partial hydrolysis in weakly alkaline and even in neutral aqueous solution. In view of the fact that these compounds, either in their formation, oxidation, or hydrolysis or some more complex mechanism involving all three processes (Voegtlin, Dyer, and Leonard, *U.S. Public Health Rep.*, 1923, **38**, 1911; Gough and King, *loc. cit.*; King, *Chem. and Ind.*, 1930, 786; Barber, *loc. cit.*; *Chem. and Ind.*, 1930, 802), probably play an essential rôle in trypanocidal action and that studies of their activity *in vitro* and *in vivo* are being made (Warrington Yorke and Murgatroyd, *Ann. Trop. Med. Liverpool*, 1930, 449), it is desirable that this supposed hydrolysis should be discussed and some further evidence submitted.

The evidence for the hydrolysis is as follows :—

(i) Alkaline solutions of thioarsinites give with sodium nitroprusside solution the characteristic colour reaction associated with the presence of a free aliphatic thiol group.

(ii) "When a feebly alkaline solution of di(carboxymethyl) benzamide-*p*-thioarsinite was treated with one molecular proportion of hydrogen peroxide, benzamide-*p*-arsinic [*p*-arsonic] acid was isolated together with unchanged thioarsinite. This result is inconsistent with an exclusive initial addition of oxygen to the arsenic atom of the intact ester molecule, followed by hydrolysis, a process which would seem to follow on Barber's view of the properties of these compounds," (Gough and King, *loc. cit.*).

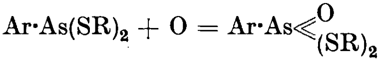
The two suggested mechanisms are :

$$(2)\quad (a)\ Ar{\cdot}As(SR)_2 + 2H_2O \rightleftharpoons Ar{\cdot}As(OH)_2 + 2RSH$$

$$(b)\ Ar{\cdot}As(OH)_2 + O = Ar{\cdot}AsO_3H_2$$

$$(c)\ 2RSH + O = R{\cdot}S{\cdot}S{\cdot}R + H_2O$$

(3) (a)



$$Ar{\cdot}As(SR)_2 + O = Ar{\cdot}As{\lessdot}\begin{matrix}O\\(SR)_2\end{matrix}$$

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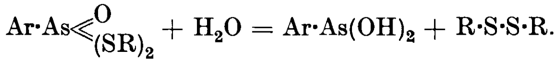
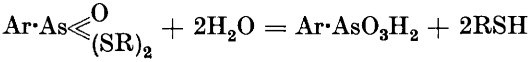
* Since this work, which was done in 1930, was submitted for publication a further investigation on the subject has been made by Cohen, King, and Strangeways (J., 1931, 3043).

(b) 

$$\mathrm{Ar{\cdot}As}{\lessdot}^{\mathrm{O}}_{(\mathrm{SR})_2} + \mathrm{H_2O} = \mathrm{Ar{\cdot}As(OH)_2} + \mathrm{R{\cdot}S{\cdot}S{\cdot}R}.$$

(c) 

$$\mathrm{Ar{\cdot}As}{\lessdot}^{\mathrm{O}}_{(\mathrm{SR})_2} + \mathrm{2H_2O} = \mathrm{Ar{\cdot}AsO_3H_2} + \mathrm{2RSH}$$

According to Gough and King, (2) represents the process of oxidation, in which the reactions (b) and (c) are obviously competing for the one atom of oxygen available (in Gough and King's experiment). If (b) is favoured to the exclusion of (c), the result will be $\mathrm{Ar{\cdot}AsO_3H_2} + \mathrm{2RSH}$, which will react according to equation (1) to give $\frac{1}{2}\mathrm{Ar{\cdot}As(SR)_2} + \frac{1}{2}\mathrm{Ar{\cdot}AsO_3H_2}$: this is the result actually obtained. But if, as is the more likely [since measurements of rates of oxidation indicate that α-thiolacetic acid is more rapidly oxidised than an aromatic arsinic acid, $\mathrm{Ar{\cdot}As(OH)_2}$], (c) is favoured, the result should be *complete conversion* into $\mathrm{Ar{\cdot}As(OH)_2} + \mathrm{R{\cdot}S{\cdot}S{\cdot}R}$. Intermediate results are of course possible and would seem to be the more likely, but the result obtained by Gough and King can only be obtained by the mechanism (2) if reaction (b) proceeds exclusively.

In process (3), the oxygen addition compound postulated can obviously be hydrolysed in the two directions (b) and (c). If (b) is followed exclusively, the result will be $\mathrm{Ar{\cdot}As(OH)_2} + \mathrm{R{\cdot}S{\cdot}S{\cdot}R}$; if (c), then $\mathrm{Ar{\cdot}AsO_3H_2} + \mathrm{2RSH}$ will be produced exactly as in process (2), the same considerations will apply, and the result will be $\frac{1}{2}\mathrm{Ar{\cdot}As(SR)_2} + \frac{1}{2}\mathrm{Ar{\cdot}AsO_3H_2}$.

The experiment cited by Gough and King thus does not differentiate between the two processes. With regard to process (2), any marked preponderance of reaction (c) would be shown by a smaller iodine titration with sodium nitroprusside as indicator (external) than with starch. This has not been observed.

Against the hydrolysis is the fact that separation of the arsinic acid from feebly alkaline solutions of a thioarsinite has not been observed. In the equilibrium 2(a), the $\mathrm{Ar{\cdot}As(OH)_2}$ component, being extremely sparingly soluble, should be removed from the sphere of action as a solid phase and the reaction should proceed to completion with gradual separation of the arsinic acid. Sodium 8-acetamido-3-hydroxy-1 : 4-benz*iso*oxazine-6-thioarsinite (" Parosan ") is apparently stable in sodium bicarbonate solution, although the arsinic acid is practically insoluble : in this case, at any rate, the hydrolysis cannot proceed to any appreciable extent. An aqueous solution containing 10% of the disodium salt of di(carboxymethyl) 3-amino-4-hydroxyphenylthioarsinite, kept in an evacuated ampoule at 90°, slowly deposits *o*-aminophenol : the form in which the arsenic is eliminated has not been determined, but this can hardly be regarded as a hydrolysis.

It has been shown that, if equimolecular mixtures of two arsonic acids are treated with sufficient thiolacetic acid to react with only one molecular proportion of acid, the thiol compound distributes itself in a certain ratio between the two arsenicals. These experiments were devised with the special object of ascertaining if there was any parallelism between physiological activity of arsenicals and their affinity for thiol groups. For the present purpose one or two results only need be discussed. It is sufficient to consider the supposed equilibrium 2(a). If a second arsinic acid $Ar'\cdot As(OH)_2$ is added to the solution of the thioarsinite $Ar\cdot As(SR)_2$, some $Ar'\cdot As(SR)_2$ should be formed according to the distribution ratio. So far it has only been found practicable to study pairs of arsenicals in which one residue contains an amino-group and the other is non-basic. In this way a separation on acidification is effected. This presupposes that no change occurs on acidification. This assumption may not be strictly true, but will affect only the quantitative aspects of the case. Actually this migration of the thiol residue

$$Ar\cdot As(SR)_2 + Ar'\cdot As(OH)_2 \longrightarrow Ar'\cdot As(SR)_2$$

has been observed where Ar = p-aminophenyl and Ar′ = 3-acetamido-4-hydroxyphenyl and with ‘ Parosan.’ It has been observed in neutral solution, moreover, where $R = CH_2\cdot CO\cdot NH_2$. This is the most definite evidence yet given for the hydrolysis, but it is not conclusive. Attempts to demonstrate the hydrolysis without the introduction of a second arsenical or metallic residue, by using a thioarsinite in which the thiol compound involved was aromatic and might therefore be the more readily split and the thiol residue isolated, did not succeed.

Several new thioarsinites, including types derived from an aromatic thiol compound and also a derivative of a secondary arsenical, have been prepared. Cacodylic acid reacts with thiolacetamide according to the equation

$$(CH_3)_2AsO(OH) + 3SH\cdot CH_2\cdot CO\cdot NH_2 = (CH_3)_2As\cdot S\cdot CH_2\cdot CO\cdot NH_2 + (S\cdot CH_2\cdot CO\cdot NH_2)_2 + 2H_2O$$

The reaction is probably general for secondary arsonic acids, as is also the equation for the oxidation with iodine in bicarbonate solution :

$$2(CH_3)_2As\cdot S\cdot CH_2\cdot CO\cdot NH_2 + 3I_2 + 4H_2O = 2(CH_3)_2AsO(OH) + (S\cdot CH_2\cdot CO\cdot NH_2)_2 + 6HI$$

EXPERIMENTAL.

Distribution of α-Thiolacetic Acid between Two Arsonic Acids.— General procedure. Thiolacetic acid (0·04 mol., determined by titration with iodine immediately prior to use) was dissolved in *N*-sodium hydroxide (40 c.c.), and to the neutral solution of monosodium thiolacetate was added a solution of 0·01 mol. of each arsonic acid in *N*-sodium hydroxide (20 c.c.). The solution was acidified with concentrated hydrochloric acid (7 c.c.) after ¼ hour and the crystalline mixture of arsonic acid and thioarsinite was removed after 3 hours, washed with a little cold water, dried in a vacuum, and weighed (fraction A). The mother-liquor was neutralised with 2*N*-ammonia (12 c.c.) and kept over-night, and the product treated as before (fraction B). The separate fractions were analysed by titration of 0·2 g. in sodium bicarbonate solution with *N*/10-iodine.

Control experiments were carried out with the arsonic acids separately so as to make corrections for losses due to solubility in water. The experiments were done in duplicate and have a probable error of not more than 10%.

3-*Acetamido*-4-*hydroxyphenylarsonic acid* (A) *and* 4-*aminophenylarsonic acid* (B).

Controls.	5·5 G. A →	6·3 g. mixture.
	0·2 G. mixture	10·5 c.c. 10·25 c.c. 0·996*N*/10-iodine.
	2 Mols. A →	thioarsinite 0·815 mol. arsonic acid 1·07 mols.
		Recovery of thioarsinite, 81·5%.
	4·34 G. B →	4·25 g. mixture.
	0·2 G. mixture	16·9 c.c. 16·4 c.c. 0·996*N*/10-iodine.
	2 Mols. B →	thioarsinite 0·89 mol. arsonic acid 0·53 mol.
		Recovery of thioarsinite, 89%.

It is assumed that in dealing with the mixtures of arsonic acids the same percentage recoveries apply, since the concentrations are kept the same.

Experiment	1.	2.	
2·75 G. A } →	2·0 g.	2·1 g.	Fraction A.
2·17 G. B }	2·4 g.	2·25 g.	,, B.
0·2 G. of fraction A required	7·6 7·65 } 7·6 c.c.	8·0 c.c. 8·0 c.c.	0·996*N*/10-iodine.
0·2 G. of fraction B required	19·5 19·2 } 19·35 c.c.	19·3 19·0 } 19·15 c.c.	,,

Whence, in molecular quantities:

A, 1 mol.	Acid	0·45 mol.	0·47 mol.
	Thioarsinite	0·19 ,,	0·21 ,,
B, 1 mol.	Acid	0·10 ,,	0·09 ,,
	Thioarsinite	0·58 ,,	0·54 ,,

Correcting for A = 81·5% and B = 89%,

A →	0·23	0·25	Mean ratio 0·24
B →	0·65	0·61	,, 0·63

A = 28%; B = 72%.

Similarly for 4-aminophenylarsonic acid (B) and " Parosan " (C):

$$B = 17{\cdot}1\%;\ C = 83\%.$$

Interaction of Thioarsinites and Arsenoxides.—(1) Di(carboxymethyl) 4-aminophenylthioarsinite (1·75 g.) was dissolved in water (30 c.c.) containing sodium bicarbonate (1 g.), " Parosan " oxide (1·5 g.) added, and the whole heated for 1 hour at 95—100°. After being cooled and filtered from unchanged oxide (1·3 g.), the solution was made strongly acid (Congo-red) with hydrochloric acid; 0·22 g., m. p. 198—205°, crystallised. Recrystallisation gave the pure " Parosan " thioarsinite, m. p. 212—215°. Other experiments gave 0·48 g. (crude) after 1 hour's and 0·55 g. after 2 hours' heating. Both gave the pure thioarsinite on recrystallisation.

(2) Di(carbamylmethyl) 4-aminophenylthioarsinite (0·9 g.), dissolved in water (25 c.c.) at 100°, was heated for ¾ hour with 3-acetamido-4-hydroxyphenylarsenoxide (0·6 g.). The liquid was filtered hot and acidified (Congo-red); 0·45 g., m. p. 157—160°, was obtained, giving 0·3 g., m. p. 163—165°, on recrystallisation.

(3) As in (2), " Parosan " oxide (0·7 g.) being used. The product (0·2 g.), m. p. 210° (*ca.*), had m. p. 225° after recrystallisation.

Di-p-*tolyl 4-Chloro-3-nitrophenylthioarsinite.*—Alcoholic solutions of 4-chloro-3-nitrophenylarsonic acid (7 g. in 100 c.c.) and of *p*-thiocresol (12·5 g. in 50 c.c.) were mixed and boiled for a few minutes. On cooling, the *thioarsinite* separated in flat, pale yellow prisms (12 g.), m. p. 88—90° (Found: As, 15·2. $C_{20}H_{17}O_2NClS_2As$ requires As, 15·7%).

Di-p-*tolyl 3-acetamido-4-hydroxyphenylthioarsinite*, similarly prepared (yield, 85%), had m. p. 173—174° (Found: As, 16·0. $C_{22}H_{22}O_2NS_2As$ requires As, 15·9%).

Carbamylmethyl Dimethylthioarsinite.—Cacodylic acid (0·5 g.), added to a hot solution of α-thiolacetamide (1 g.) in water (10 c.c.), dissolved. The *thioarsinite* crystallised on cooling and was recrystallised from a little water; m. p. 107° (Found: As, 38·8; *M*, by iodine titration, the equation on p. 1367 being assumed, 199, 194. $C_4H_{10}ONSAs$ requires As, 38·5%; *M*, 195).

Dicarboxymethyl 4-amino-3-hydroxyphenylthioarsinite has m. p. 161—162° (Found: *M*, 364. $C_{10}H_{12}O_5NS_2As$ requires *M*, 365) and *dicarboxymethyl 4-acetamido-3-hydroxyphenylthioarsinite* m. p. 156—158° (Found: *M*, 412. $C_{12}H_{14}O_6NS_2As$ requires *M*, 407).

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