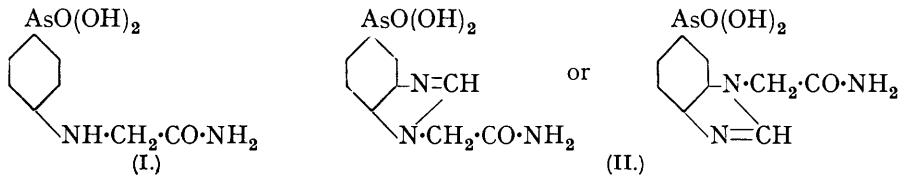
35. *Trypanocidal Activity and Chemical Constitution. Part IV. Derivatives of Benziminazole-5-arsonic Acid.*

By J. Garwood Everett.

The outstanding trypanocidal value of 2-thiolbenziminazole-5-arsonic acid and the corresponding arseno-compound and arylarsenic disulphide and the modification of therapeutic activity due to substitution in the thiol group having already been demonstrated, the effect of the absence of sulphur from these compounds has now been studied; the results obtained with benziminazole-5-arsonic acid and its derivatives are here recorded.

The action of chloroacetic acid and chloroacetamide on benziminazole-5-arsonic acid produced 1(or 3)-*carboxymethylbenziminazole-5-arsonic acid* and 1(or 3)-*carbamylmethylbenziminazole-5-arsonic acid* (II) respectively. The latter acid has special interest owing to its analogy to " Tryparsamide " (I), which is of value for its action in cases where the cerebro-spinal fluid is affected. It has the advantage over " Tryparsamide " that the corresponding *arseno*-compound is soluble and therefore can be used for injection. The arseno-compound is soluble in dilute hydrochloric acid and in excess of dilute sodium hydroxide solution. The latter solubility is surprising, but is also shown by the somewhat

analogous 5 : 5′-arseno-(2-carbamylmethylthiolbenziminazole) (Part II; J., 1930, 2402). This point is of interest in view of the relationship of the compounds concerned to



(I.) (II.)

3 : 4 : 5 : 3′ : 4′ : 5′-hexa-aminoarsenobenzene and its *N*-methyl derivatives, which have the unexpected property of dissolving in alkali carbonate solutions, forming carbamates with the same degree of alkalinity as that of normal blood serum (Baxter and Fargher, J., 1919, **115**, 1373).

Therapeutic Results.—The above-mentioned compounds have been tested against an experimental infection of *T. equiperdum* in mice with the following results : T = maximum tolerated dose in mg./g. of mouse; c = minimum curative dose in mg./g. of mouse, and is the smallest single dose which will cause the disappearance of all trypanosomes from the peripheral blood-stream of all eight mice within seventy-two hours; r = average number of days elapsing between disappearance and reappearance of trypanosomes in the peripheral blood-stream; i = intravenous; o = oral. The relapse figures refer to the minimum curative dose (c).

		T.	c (8 mice).	T/c.	r.
Benziminazole-5-arsonic acid	*i*	1·0	0·4	2·5	7
	o	12·0	0·5	24·0	7
1(*or* 3)-Carboxymethylbenziminazole-5-arsonic acid	*i*	2·0	1·0	2·0	6
	o	10·0	1·0	10·0	6
1(*or* 3)-Carbamylmethylbenziminazole-5-arsonic acid	*i*	2·0	1·0	2·0	6
	o	10·0	1·0	10·0	6
5 : 5′-Arseno(benziminazole)	*i*	0·05	0·005	10·0	10
	o	5·0	0·1	50·0	6
5 : 5′-Arseno-1(*or* 3)-carboxymethylbenziminazole	*i*	0·1	0·025	4·0	15
	o	2·0	0·5	4·0	10
5 : 5′-Arseno-1(*or* 3)-carbamylmethylbenziminazole	*i*	0·05	0·01	5·0	10
	o	>5·0	0·1	>5·0	12
For comparison.					
2-Thiolbenziminazole-5-arsonic acid	*i*	0·5	0·5	1·0	>30
	o	10·0	0·1	100·0	15
5 : 5′-Arseno-(2-thiolbenziminazole)	*i*	0·1	0·005	20·0	>30
	o	>10·0	0·05	>200·0	12
Tryparsamide	*i*	2·5	0·7	3·6	—
	o	14·0	0·6	23·3	—

Experimental.

1(or 3)-*Carboxymethylbenziminazole-5-arsonic Acid.*—Benziminazole-5-arsonic acid (9·68 g. in water, 20 c.c.) and chloroacetic acid (3·78 g. in water, 5 c.c.) were neutralised with sodium hydroxide solution, mixed, and heated at 80° for 1 hour, alkalinity being maintained by the gradual addition of 20% sodium hydroxide solution (8 c.c. required). The mixture was treated with charcoal, filtered, and rendered faintly blue (Congo-red) with hydrochloric acid. On cooling in iced water, 1(or 3)-*carboxymethylbenziminazole-5-arsonic acid* crystallised in small white nodules (4 g.), exceedingly soluble in water. It was dried at 80°, beyond which temperature it became sticky (Found : As, 24·9; N, 9·2. $C_9H_9O_5N_2As$ requires As, 25·0; N, 9·3%).

5 : 5′-*Arseno*-1(or 3)-*carboxymethylbenziminazole.*—The mother-liquor from the above reaction was added to a solution of sodium hyposulphite (62·5 g.) and sodium hydroxide (0·6 g.) in water (1250 c.c.), and the mixture kept at 55° for 1 hour. The *arseno*-compound, precipitated as a yellow amorphous powder (3·3 g.), readily soluble in sodium bicarbonate solution and in dilute hydrochloric acid, was dried in a vacuum over sulphuric acid (Found : As, 29·4; N, 10·7. Atomic ratio As : N = 1·00 : 1·95. $C_{18}H_{14}O_4N_4As_2$ requires As, 30·0; N, 11·2%).

1(or 3)-*Carbamylmethylbenziminazole-5-arsonic Acid* (II).—Prepared in the same way as the carboxymethyl compound, solid chloroacetamide being used in place of a solution of chloro-

acetic acid, this *acid* crystallised in small white prisms (4·2 g.), very soluble in water (Found in acid dried at 80° : As, 25·2; N, 13·9. $C_9H_{10}O_4N_3As$ requires As, 25·1; N, 14·0%).

5 : 5′-*Arseno*-1(or 3)-*carbamylmethylbenziminazole*.—The mother-liquor from the above reaction, treated with sodium hyposulphite and hydroxide (see above), gave the *arseno*-compound as a yellow amorphous powder (3 g.), insoluble in sodium bicarbonate solution (Found : As, 29·2; N, 16·2. Atomic ratio As : N = 1·00 : 2·97. $C_{18}H_{16}O_2N_6As_2$ requires As, 30·1; N, 16·9%).

My thanks are due to the Directors of Messrs. May & Baker, Limited, for permission to publish these results.

RESEARCH LABORATORIES, MESSRS. MAY & BAKER, LTD.,
DAGENHAM, LONDON.

[*Received, May* 22*nd*, 1933.]