LXXXIII.—*New Derivatives of* p-*Arsanilic Acid. Part I.* p-*Arsonosuccinanilic Acid* and Related Compounds.*

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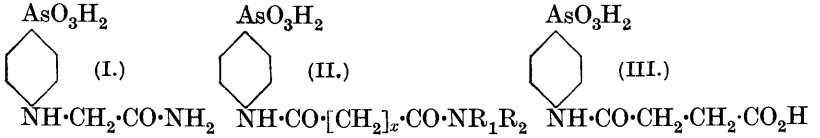
A COMPARISON of the published data concerning the pharmacological properties of *p*-arsanilic acid and its simple derivatives reveals the fact that, in general, *N*-acylation of *p*-arsanilic acid decreases the toxicity of the resulting compound, whereas *N*-alkylation enhances the toxic properties.

Nevertheless, tryparsamide (I) (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 1587), the molecule of which contains an alkylated nitrogen atom, is extremely efficacious in the treatment of certain forms of trypanosomiasis, and accordingly compounds of the general type (II), from which the apparently toxic $NH{\cdot}CH_2$ group is absent, have been examined. In the present communic-

* The group AsO_3H_2, hitherto named "arsinic acid," will in future be named "arsonic acid" (suffix) or "arsono" (prefix).—EDITOR.

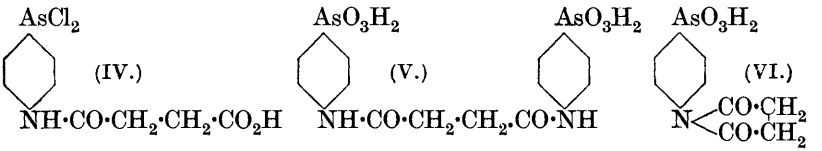
ation a number of succinyl derivatives (II; $x = 2$) of *p*-arsanilic acid are described.



Monosodium *p*-arsanilate (atoxyl) and excess of succinic anhydride condensed at 180° to give p-*arsonosuccinanilic acid* (III), whereas substitution of succinic acid in smaller proportions for the anhydride led to the formation of *succinanilide*-pp′-*diarsonic acid* (V). The diarsonic acid was also obtained by heating atoxyl and *p*-arsonosuccinanilic acid in equimolecular proportion. *p*-Arsonosuccinanilic acid, refluxed with excess of aniline, yielded the *anilide* (II; $x = 2$, $R_1 = H$, $R_2 = Ph$) and, treated with monomethylamine and monoethylamine, the same acid (III) yielded the *monomethylamide* ($R_1 = H$; $R_2 = Me$) and *monoethylamide* ($R_1 = H$; $R_2 = Et$), respectively.

Since neither the amide nor the dimethylamide could be prepared directly from *p*-arsonosuccinanilic acid, the latter was reduced by means of sulphur dioxide to p-*dichloroarsinosuccinanilic acid* (IV), but attempts to convert this into the corresponding acid chloride with either phosphorus pentachloride or thionyl chloride were unsuccessful.

The required derivatives were eventually prepared as follows: By heating *p*-arsonosuccinanilic acid at 240°, the anil (VI) was obtained, and the latter, on treatment with alcoholic ammonia, dimethylamine and piperidine, yielded respectively the corresponding *amide* (II; $x = 2$, $R_1 = H$, $R_2 = H$), *dimethylamide* ($R_1 = Me$; $R_2 = Me$), and *piperidide* ($R_1R_2 = Pip.$).



Preliminary pharmacological reports on the monosodium salts of compounds of type (II) and of succinanilide-*pp*′-diarsonic acid (V) indicate very low toxicities combined with therapeutic activity against trypanosomes in all cases except that of the diarsonic acid, as will be seen from the following tabulated summary of figures obtained by Prof. Warrington Yorke, at The Liverpool School of Tropical Medicine. The corresponding figures obtained by Pearce

and Brown (*J. Exp. Med.*, 1919, **30**, 437; 1921, **33**, 193) for tryparsamide are included for purposes of comparison.

Sodium Salts.		M.L.D., mg. per g. mouse.	*Tr. equip.* M.C.D., mg. per g. mouse.	Chemo-ther. index, M.L.D./M.C.D.	*Tr. rhod.* M.C.D., mg. per g. mouse.	Chemo-ther. index, M.L.D./M.C.D.
V		>5	inactive	—	inactive	—
Anilide	(II; $x=2$)	0·5	0·2—0·4	1·2—2·5	0·5	1
Piperidide	,,	>5	about 2	>2·5	not tried	—
Dimethylamide	,,	>5	not tried	—	1·25—2·5	>2—>4
Monomethylamide	,,	>5	0·75—1·25	>4—>6·5	not tried	—
Amide	,,	>5	not tried	—	2·5	>2
Tryparsamide	,,	2—2·75	0·35—0·6	3—8	0·75—1·5	1·2—3·6

M.L.D. = Minimum lethal dose. M.C.D. = Minimum curative dose.

In view of these promising results, more extended trials are in progress.

Experimental.

p-*Arsonosuccinanilic Acid* (III).—An intimate mixture of atoxyl (12·8 g.) and succinic anhydride (12 g.) was heated at 170—180° for 1 hour, and the cooled mass lixiviated with water at 90—100°; the warm solution was digested with charcoal, and the filtrate acidified with hydrochloric acid and cooled to 0°. The p-*arsonosuccinanilic acid*, which separated (10 g.), crystallised from hot water in silky prisms, insoluble in absolute alcohol * (Found: As, 23·2, 23·7. $C_{10}H_{12}O_6NAs$ requires As, 23·6%).

Succinanilide-pp′-*diarsonic Acid* (V).—(a) A mixture of atoxyl (6·4 g.) and succinic anhydride (2·4 g.) was heated at 170—180° for 1 hour, and the resulting mass boiled with water slightly acidified with hydrochloric acid. The insoluble succinanilide-*pp*′-diarsonic acid was digested with water at 100° to remove soluble products (yield, 1 g.). (b) A mixture of atoxyl (5 g.) and *p*-arsonosuccinanilic acid (5 g.), treated in a similar manner to experiment (a), also yielded the diarsonic acid (1·7 g.).

Succinanilide-pp′-*diarsonic acid* was an ill-defined solid, insoluble in water and organic solvents (Found: As, 28·8, 29·0. $C_{16}H_{18}O_8N_2As_2$ requires As, 29·1%).

The *disodium* salt, obtained by dissolving the acid in the calculated quantity of 2*N*-caustic soda, was precipitated by adding absolute alcohol to the filtered solution, and further purified by repetition of the alcoholic treatment. It was an amorphous solid, readily dissolving in water to give a solution of p_H 7·5 approx. (Found: As, 26·2. $C_{16}H_{16}O_8N_2As_2Na_2,H_2O$ requires As, 26·0%).

* Except where indicated, the *p*-arsonosuccinanilic acid derivatives described in this communication are without definite melting points.

Succinanilide-p-*arsonic Acid* (II; $x = 2$, $R_1 = H$, $R_2 = Ph$).—Powdered *p*-arsonosuccinanilic acid (3·2 g.) and aniline (7·4 g.) were heated together for 2 minutes in an open flask. The resulting solid was washed successively with ether and with water containing 2 or 3 drops of aniline, added to dissolve *p*-arsonosuccinanilic acid. The *anilide* was purified either by lixiviation with hot water containing a little hydrochloric acid or through its sodium salt (yield, 2·3 g.). It crystallised from hot water, in which it was only slightly soluble, in small leaflets, insoluble in alcohol (Found : As, 19·5. $C_{16}H_{17}O_5N_2As$ requires As, 19·1%).

The monosodium salt was obtained on adding alcohol to a solution of the acid in the calculated quantity of 2*N*-caustic soda. It separated after some hours at 0°, and was recrystallised from dilute alcohol, forming needles readily soluble in water, giving a solution of p_H 8 *

Succinanilomethylamide-p-*arsonic Acid* (II; $x = 2$, $R_1 = H$, $R_2 = Me$).—*p*-Arsonosuccinanilic acid (5 g.) was dissolved in aqueous 33% methylamine (10 c.c.), the solution warmed at 75° for 2 minutes, diluted with water (15—20 c.c.), and digested with charcoal (higher temperatures caused hydrolysis to *p*-arsanilic acid). The filtrate was acidified with dilute hydrochloric acid and cooled; the *monomethylamide* then separated as a white crystalline solid (4·5 g.). It crystallised from hot water in glistening prisms, insoluble in alcohol (Found : As, 22·4; hydrolysable N, 3·8, 3·8. $C_{11}H_{15}O_5N_2As$ requires As, 22·7; hydrolysable N, 4·2%).

The *monosodium* salt crystallised with 2 molecules of water (Found : H_2O, 9·7; As, 18·9; hydrolysable N, 3·4. $C_{11}H_{14}O_5N_2AsNa,2H_2O$ requires H_2O, 9·3; As, 19·3; hydrolysable N, 3·6%).

Succinanilethylamide-p-*arsonic acid* (II; $R_1 = H$; $R_2 = Et$) was prepared by substituting monoethylamine for monomethylamine in the above experiment. It crystallised from hot water in silky prisms, insoluble in alcohol (Found : hydrolysable N, 4·1, 4·0. $C_{12}H_{17}O_5N_2As$ requires hydrolysable N, 4·1%).

The *monosodium* salt crystallised from concentrated aqueous solution in needles, and from dilute alcohol in leaflets (Found : hydrolysable N, 3·8, 3·8. $C_{12}H_{16}O_5N_2AsNa$ requires hydrolysable N, 3·8%)

p-*Dichloroarsinosuccinanilic Acid* (IV).—A solution of *p*-arsonosuccinanilic acid (3 g.) in a mixture of concentrated hydrochloric acid (15 c.c.), water (5 c.c.), and a trace of iodine was saturated with sulphur dioxide. After 12 hours in the cold, the *dichloroarsine* (3 g.) separated. It crystallised in pale buff-coloured needles (1st crop) and prisms (2nd crop) from anhydrous

* The subsequently described sodium salts, all prepared in this way, are extremely soluble in water, their dilute solutions showing a p_H of approximately 6.

xylene, both varieties melting at 210—211° (Found: Cl, 21·0, 21·2. $C_{10}H_{10}O_3NCl_2As$ requires Cl, 21·0%).

Succinanil-*p*-arsonic acid (VI) was obtained, by heating powdered *p*-arsonosuccinanilic acid (3·2 g.) at 240° for 1½—2 hours, as an amorphous powder (2·9 g.), insoluble in alcohol and regenerating *p*-arsonosuccinanilic acid on addition of water.

Succinanilamide-p-*arsonic Acid* (II; $x = 2$, $R_1 = H$, $R_2 = H$).—The crude anil (2 g.) and a large excess of 15% anhydrous alcoholic ammonia (about 8 c.c.) were heated in a sealed tube at 75—80° for 3—4 hours. The resulting solution was treated with 1 or 2 drops of water, whereupon the *monoammonium* salt of the amide rapidly appeared as a crystalline solid (Found for ammonium salt: hydrolysable N, 8·0. $C_{10}H_{16}O_5N_3As,H_2O$ requires hydrolysable N, 8·0%).

The ammonium salt was washed with alcohol, and its filtered solution in water (10 c.c.) acidified with hydrochloric acid and cooled. The *amide* (1·5 g.) thus obtained crystallised from hot water in jagged leaflets, insoluble in alcohol (Found: As, 23·8; hydrolysable N, 4·4; total N, 8·5. $C_{10}H_{13}O_5N_2As$ requires As, 23·8; hydrolysable N, 4·4; total N, 8·9%).

The *sodium* salt crystallised in platelets (Found: H_2O, 7·6; As, 20·8; hydrolysable N, 3·8, 3·9. $C_{10}H_{12}O_5N_2AsNa,H_2O$ requires H_2O, 5·1; As, 21·0; hydrolysable N, 3·9%).

Succinanilodimethylamide-p-*arsonic Acid* (II; $x = 2$, $R_1 = Me$, $R_2 = Me$).—The anil (3 g.) and excess of 33% alcoholic dimethylamine (8 c.c.) were heated in a sealed tube at 75—80° for 2—3 hours, and the filtered solution evaporated on the steam-bath. Water (10 c.c.) was added to the residue, and the resulting solution acidified with hydrochloric acid and cooled. The *dimethylamide* (2·6 g.) thus obtained crystallised from hot water in microcrystalline leaflets, slightly soluble in alcohol (Found: As, 22·0; hydrolysable N, 3·9. $C_{12}H_{17}O_5N_2As$ requires As, 21·8; hydrolysable N, 4·1%). The *sodium* salt crystallised in minute prisms (Found: H_2O, 5·0; As, 19·6; hydrolysable N, 3·5, 3·7, 3·5. $C_{12}H_{16}O_5N_2AsNa,H_2O$ requires H_2O, 4·7; As, 19·5; hydrolysable N, 3·6%).

Succinanilopiperidide-p-*arsonic Acid* (II; $x = 2$, $R_1R_2 =$ Pip.).—The anil (4 g.), excess of piperidine (6 g.), and absolute alcohol (7 c.c.) were heated in a sealed tube at 75—80° for 3—4 hours and the filtrate was acidified with dilute hydrochloric acid and cooled to 0°. The *piperidide* (3·5 g.) thus obtained crystallised from hot water in well-defined needles, easily soluble in alcohol (Found: As, 19·6. $C_{15}H_{21}O_5N_2As$ requires As, 19·5%).

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