96. *Amides of* p-*Arsonophenylacetic Acid.*

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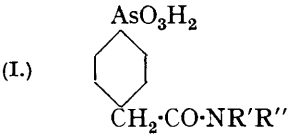
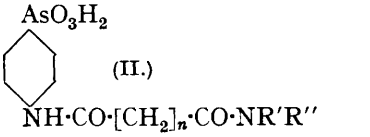
A series of amides (I) has been prepared from *p*-arsonophenylacetic acid for comparison with compounds of type (II). These amides are all well-defined, crystalline compounds, and their sodium salts show fair activity against experimental sleeping sickness.

A SERIES of compounds of type (I) has been prepared for comparison with similar derivatives (II) of *p*-arsanilic acid, which have been described from time to time in this Journal. These amides were prepared from *p*-arsonophenylacetic acid (Robertson and





Stieglitz, *J. Amer. Chem. Soc.*, 1921, **43**, 180) by treating its *methyl* ester with various amines in either aqueous or alcoholic solution. Their sodium salts have been tested for trypanocidal activity under the direction of Professor Warrington Yorke, F.R.S., with results as follows:

Sodium salts.	M.L.D.	M.C.D.	Sodium salts.	M.L.D.	M.C.D.
Methyl ester	4	Some action	Ethylamide	16	8
Amide	64	8—16	*n*-Propylamide	32	32
Methylamide	64	16	Piperidide	2	No action
Dimethylamide	16	16	Anilide	8	Some action

M.L.D. = minimum lethal dose, M.C.D. = minimum curative dose (both in mg. per 20 g. of mouse).

It will be seen that trypanocidal activity is again maintained throughout the series. In fact, from these results and from a survey of the literature, it appears that an amide group in the *p*-position of the unsubstituted phenylarsonic acid nucleus nearly always maintains or confers activity (compare *Chem. and Ind.*, 1937, **56**, 1116).

EXPERIMENTAL.

Methyl p-*Arsonophenylacetate.*—Crude *p*-arsonophenylacetic acid (18 g.), prepared from *p*-aminophenylacetic acid according to the method of Robertson and Stieglitz (*loc. cit.*), was dissolved in methyl alcohol, and the solution slowly saturated with hydrogen chloride. It was then refluxed for 1 hour, and the residue, after removal of methyl alcohol, treated with water. The resulting *methyl* ester (11 g.) crystallised from 50% water–ethyl alcohol in long colourless needles, very soluble in hot water and alcohol (Found: As, 27·5; O·CH_3, 10·9. $C_9H_{11}O_5As$ requires As, 27·4; O·CH_3, 11·3%). The *sodium* salt crystallised from dilute alcohol in leaflets, p_H 8·0 (Found: As, 24·3. $C_9H_{10}O_5AsNa,H_2O$ requires As, 23·9%).

Phenylacetamide-p-*arsonic Acid.*—The methyl ester (6 g.) and excess of concentrated aqueous ammonia were heated at 100° in a sealed tube for 6 hours. The resulting crimson solution gave crystals of *ammonium phenylacetamide*-p-*arsonate*, which crystallised from alcohol–water in parallelepipeds (2 g.), p_H 5·0, and from concentrated aqueous solution in silky needles (Found: N, 10·1. $C_8H_{13}O_4N_2As$ requires N, 10·15%). The free *acid* crystallised from water in prisms, insoluble in alcohol (Found: N, 5·5. $C_8H_{10}O_4NAs$ requires N, 5·4%).

Phenylacetomethylamide-p-*arsonic Acid.*—The methyl ester (3 g.) and excess of 25% aqueous methylamine were heated under pressure at 100°, until the crimson colour that developed faded to yellow (about 5 hours); the syrup was then evaporated and acidified. The resulting *methylamide* (2 g.) crystallised from water in pale yellow, hexagonal prisms, soluble in hot alcohol (Found: N, 4·9. $C_9H_{12}O_4NAs$ requires N, 5·1%). The *sodium* salt, p_H 7·0, prepared by evaporation, was somewhat deliquescent (Found: N, 4·45. $C_9H_{11}O_4NAsNa,H_2O$ requires N, 4·5%).

Phenylacetodimethylamide-p-*arsonic Acid.*—This cannot be prepared under aqueous conditions. The methyl ester (8 g.) and 50% alcoholic dimethylamine (30 c.c.) were heated at 100° in a sealed tube for 5 hours. The dimethylamine was completely removed, and the

residue carefully acidified and cooled in a freezing mixture. Owing to excessive solubility in water, the resulting fawn-coloured precipitate (7 g.) was crystallised from alcohol by slow addition of ether. The *dimethylamide* now crystallised from water plus a trace of hydrochloric acid in large rhombic leaflets, very soluble in alcohol (Found: N, 4·9. $C_{10}H_{14}O_4NAs$ requires N, 4·9%). Its *sodium* salt, p_H 7·0, was white and indefinitely crystalline (Found: N, 4·6. $C_{10}H_{13}O_4NAsNa$ requires N, 4·5%).

Phenylacetoethylamide-p-*arsonic acid* was prepared as above, 33% alcoholic ethylamine being used. It was purified by dissolution in alcohol and addition of ether until a brown flocculent precipitate appeared. This was removed, and the filtrate treated with more ether until the *ethylamide* began to separate in micro-crystals. The ethylamide crystallised from water plus a trace of hydrochloric acid in long prisms (Found: N, 4·7. $C_{10}H_{14}O_4NAs$ requires N, 4·9%). Its *sodium* salt, p_H 7·0, was prepared in alcohol (Found: N, 4·4. $C_{10}H_{13}O_4NAsNa$ requires N, 4·5%).

Phenylaceto-n-*propylamide*-p-*arsonic Acid.*—The methyl ester (4·8 g.) and 50% alcoholic *n*-propylamine were heated under pressure until the crimson colour had disappeared. The propylamine was completely removed by repeated evaporation and addition of alcohol. As the residue failed to give a solid on acidification, it was dissolved in alcohol (about 30 c.c.), to which ether (about 30 c.c.) was added to precipitate impurities. The filtrate was treated with more ether until milky, and cooled to 0°; the n-*propylamine* salt of *phenylaceto*-n-*propylamide*-p-*arsonic acid* (3·8 g.) then separated in micro-needles (Found: N, 8·1. $C_{14}H_{25}O_4N_2As$ requires N, 7·8%). The free *propylamide* crystallised from water plus a trace of hydrochloric acid in needles, soluble in alcohol (Found: N, 4·8. $C_{11}H_{16}O_4NAs$ requires N, 4·7%). Its *sodium* salt, p_H 7·0, crystallised from alcohol–water in rhombic plates (Found: N, 4·5. $C_{11}H_{15}O_4NAsNa$ requires N, 4·3%).

Phenylacetopiperidide-p-*arsonic Acid.*—The methyl ester (7 g.) and piperidine (25 c.c.) were refluxed together for about 3 hours. The excess of piperidine was completely removed, and the residue acidified. The *piperidide* (4·5 g.), thus obtained, crystallised from water in cream-coloured hexagonal prisms, soluble in warm alcohol (Found: N, 4·3. $C_{13}H_{18}O_4NAs$ requires N, 4·3%). The *sodium* salt, p_H 6·5, was prepared by evaporating its alcoholic solution (Found: N, 4·2. $C_{13}H_{17}O_4NAsNa$ requires N, 4·0%).

Phenylacetanilide-p-*arsonic Acid.*—*p*-Arsonophenylacetic acid (5 g.) was heated in an open beaker with excess of aniline (15 c.c.). The mixture first tended to solidify, but, on further heating, liquefied and boiled. As soon as the water had been removed, the mixture was cooled and acidified. The resulting *anilide*, after purification through sodium carbonate solution, crystallised from water, in which it was only slightly soluble, in needles, soluble in hot alcohol (Found: As, 22·3. $C_{14}H_{14}O_4NAs$ requires As, 22·4%). The *disodium* salt crystallised from dilute alcohol in glistening leaflets, p_H 9 (Found: As, 19·4. $C_{14}H_{12}O_4NAsNa_2$ requires As, 19·7%).

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