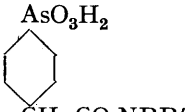
37. *Amides of β-p-Arsonophenylpropionic Acid.*

By E. Walton.

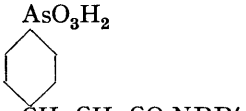
A number of arsenical compounds of type (II) have been prepared from β-*p*-aminophenylpropionic acid. These amides show some trypanocidal activity, but they are all more toxic than their homologues of type (I).

The object of this investigation was the preparation of organic arsenicals showing progressive structural changes, and thereby likely to be of value in the correlation of trypanocidal activity with chemical constitution.

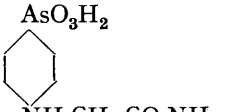
The amides of *p*-arsonophenylacetic acid (I) have already been described (J., 1938, 471). The present paper deals with the corresponding β-*p*-arsonophenylpropionic acid series (II), which bear some resemblance to tryparsamide (III) in structure. They were prepared by



(I.)



(II.)



(III.)

converting β-*p*-aminophenylpropionic acid into β-p-*arsonophenylpropionic acid*, the *methyl* ester of which yielded a series of *amides* with amines under various conditions.

The *sodium* salts of these amides have been tested for trypanocidal activity, on behalf of the Chemotherapy Committee (Medical Research Council), by Professor Warrington Yorke, F.R.S., with the following results:

Sodium salts.	M.L.D.	M.C.D.	Sodium salts.	M.L.D.	M.C.D.
Carboxylic acid	64	Some action	Ethylamide	8	Some action
Methyl ester	2	No action	*n*-Propylamide	1	Some action
Amide	8	4	Piperidide	1	No action
Methylamide	16	4	Anilide	0·5	No action
Dimethylamide	2	Slight action			

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

Although their chemotherapeutic ratios (M.L.D./M.C.D.) are of the same order, compounds of type (II) are, in general, much more toxic than those of type (I).

Experimental.

β-p-*Arsonophenylpropionic Acid.*—β-*p*-Aminophenylpropionic acid (13 g.) in 4N-hydrochloric acid (90 c.c.) was diazotised at 0° (sodium nitrite, 5·75 g., in a little water) and poured into a solution of arsenious oxide (8·25 g.) and anhydrous sodium carbonate (58 g.) in water (400 c.c.) containing a little electrolytic cuprous oxide. The mixture was stirred vigorously until frothing subsided, warmed at 60° for 10 minutes, and acidified with hydrochloric acid. The filtered liquid was evaporated to dryness, the residue ground and extracted with absolute alcohol, the solution evaporated to dryness, and the residue dissolved in hot water. The insoluble oil was discarded; when the filtrate cooled, a solid separated, consisting largely of β-*p*-hydroxyphenylpropionic acid, m. p. 132°. The mother-liquor, on evaporation, yielded a second crop, consisting mainly of β-p-*arsonophenylpropionic acid.* These acids were purified by repeated washing with boiling xylene, in which the *p*-hydroxy-compound alone was soluble (yields, 4—5 g. each of *p*-hydroxy- and *p*-arsono-phenylpropionic acids). β-*p*-Arsonophenylpropionic acid crystallised from water in clusters of rectangular prisms (Found: As, 26·9. $C_9H_{11}O_5As$ requires As, 27·4%). Its *sodium* salt, p_H 7·0, prepared in alcohol, was granular (Found: As, 23·1. $C_9H_9O_5AsNa_2$ requires As, 23·6%).

Methyl β-p-*Arsonophenylpropionate.*—A solution of β-*p*-arsonophenylpropionic acid (28 g.) in methyl alcohol (150 c.c.) was saturated with dry hydrogen chloride at 0°. After 12 hours the alcohol was removed, and water (150 c.c.) added to the residue. The *methyl* ester, which separated rapidly, crystallised from water in flat needles (15 g.) (Found: As, 25·8. $C_{10}H_{13}O_5As$ requires As, 26·0%). Its *sodium* salt, a white, indefinitely crystalline solid, p_H 7·5, was prepared in alcohol (Found: As, 24·0. $C_{10}H_{12}O_5AsNa$ requires As, 24·2%).

β-*Phenylpropionamide*-p-*arsonic Acid.*—Recrystallised methyl *p*-arsonophenylpropionate (4·0 g.) and excess of concentrated aqueous ammonia were heated at 100° for 4 hours in a sealed tube. The ammonia was removed from the resulting yellow solution, and the residue acidified. The *amide* (2·8 g.) crystallised from water in hexagonal leaflets, soluble in hot alcohol (Found: N, 5·0. $C_9H_{12}O_4NAs$ requires N, 5·1%). The *sodium* salt, p_H 7·0, separated from dilute alcohol in granular form (Found: N, 4·55. $C_9H_{11}O_4NAsNa,H_2O$ requires N, 4·5%).

β-*Phenylpropionomethylamide*-p-*arsonic acid*, prepared as above, excess of 33% aqueous methylamine being used, crystallised from water in octagonal leaflets, soluble in alcohol (Found: N, 4·85. $C_{10}H_{14}O_4NAs$ requires N, 4·9%). Its *sodium* salt, p_H 8·0, crystallised from dilute alcohol (Found: N, 4·3. $C_{10}H_{12}O_4NAsNa_2$ requires N, 4·2%).

β-*Phenylpropionodimethylamide*-p-*arsonic Acid.*—Only traces of this substance could be obtained by means of 33% aqueous dimethylamine. The methyl ester (5 g.) and excess of 50% alcoholic dimethylamine were heated at 100° for 4—5 hours in a sealed tube. The residue after removal of alcohol was acidified, and the resulting solid dried and purified by slow precipitation from alcoholic solution by addition of ether. The *dimethylamide* (3 g.) thus obtained crystallised from water in well-defined hexagonal tablets (Found: N, 4·6. $C_{11}H_{16}O_4NAs$ requires N, 4·65%). The *sodium* salt, p_H 7·5, being very soluble in dilute alcohol, was prepared by evaporation of its aqueous solution. It formed pearly leaflets (Found: N, 4·0. $C_{11}H_{15}O_4NAsNa,H_2O$ requires N, 4·1%).

β-*Phenylpropionoethylamide*-p-*arsonic Acid.*—This compound was likewise only obtainable from alcoholic solution. 4 G. of the methyl ester and 15 c.c. of 60% alcoholic ethylamine were heated at 100° in a sealed tube for 3 days. At no stage was solution complete. The *ethylamine* salt of the ethylamide, which ultimately separated in fairly pure form, was readily isolated by addition of more alcohol and ether to the reaction product. It crystallised from alcohol–ether in

minute rectangular prisms, p_H 5·5, extremely soluble in water (Found : N, 7·85. $C_{13}H_{23}O_4N_2As$ requires N, 8·1%). The free *ethylamide*, on the other hand, was obtained by evaporation of the reaction mixture and acidification of the residue. The resulting solid was purified by careful precipitation from alcoholic solution by addition of ether (yield, 3 g.). It now crystallised from water in clusters of octagonal leaflets (Found : N, 4·4. $C_{11}H_{16}O_4NAs$ requires N, 4·65%). The *sodium* salt, p_H 8·0, separated from dilute alcohol in minute rhombic leaflets (Found : N, 3·8. $C_{11}H_{15}O_4NAsNa,2H_2O$ requires N, 3·9%).

β-*Phenylpropiono*-n-*propylamide*-p-*arsonic acid* was prepared from the methyl ester (4 g.) and 50% alcoholic *n*-propylamine, as described above for the ethylamide. It crystallised from water in needles (1·3 g.) (Found : N, 4·35. $C_{12}H_{18}O_4NAs$ requires N, 4·45%). Its *sodium* salt separated from alcohol in pearly leaflets, p_H 7·0 (Found : N, 3·9. $C_{12}H_{17}O_4NAsNa,H_2O$ requires N, 3·95%).

β-*Phenylpropionopiperidide*-p-*arsonic Acid*.—The methyl ester (4 g.) and pure piperidine (10 c.c.) were refluxed together for 4 hours. The excess of piperidine was removed, and the residue acidified. The solid obtained (3·3 g.) was purified through alcohol–ether as described above. The *piperidide* crystallised from water in granules (Found : N, 4·1. $C_{14}H_{20}O_4NAs$ requires N, 4·1%). Its *sodium* salt separated from dilute alcohol, on the addition of a little ether, in leaflets, p_H 7·0 (Found : N, 3·8. $C_{14}H_{19}O_4NAsNa$ requires N, 3·86%).

β-*Phenylpropionanilide*-p-*arsonic Acid*.—4 G. of β-*p*-arsonophenylpropionic acid and 10 c.c. of aniline were refluxed together for 3—4 minutes. The product was stirred with hot water and acidified. The *anilide* thus obtained, after purification through mild alkali (yield, 2 g.), separated from alcoholic solution on addition of water in minute hexagonal needles, very sparingly soluble in water (Found : As, 21·4. $C_{15}H_{16}O_4NAs$ requires As, 21·5%). The *sodium* salt separated from dilute alcohol, after boiling and leaving for 12 hours, as a white, indefinitely crystalline solid, p_H 8 (Found : As, 20·0. $C_{15}H_{15}O_4NAsNa$ requires As, 20·2%).

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