87. *New Derivatives of* p-*Arsanilic Acid. Part VIII.* p-*Arsonooxanilic and* p-*Arsonohexadecanedicarboxylanilic Acids and Related Compounds.*

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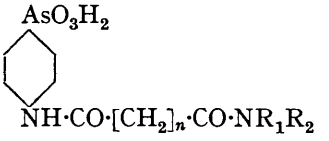
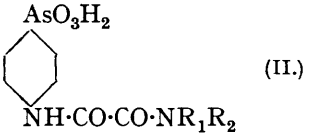
Compounds of type (I) have shown considerable trypanocidal activity throughout the series from $n = 1$ to 8. The activity was at its maximum where $n = 1$, 2, and 3, and tended to diminish higher in the series. This research has now been concluded by the preparation of an oxalyl series ($n = 0$), and one or two compounds where $n = 16$.

THE group of compounds of type (I), described from time to time in this Journal, has now been completed, for all practical purposes, at one end of the series by the synthesis of several

(I.) 

(II.) 

compounds (II) containing an oxalyl residue, and at the other end by the preparation of one or two compounds where $n = 16$ (I).

The oxalyl compounds were readily obtained by treating the *methyl* ester of *p*-arsonooxanilic acid (Bertheim, *Ber.*, 1911, **44**, 3092) with various amines, but compounds in the hexadecanedicarboxylyl series were much more difficult to prepare. p-*Arsonohexadecanedicarboxylanilic acid*, $AsO_3H_2 \cdot C_6H_4 \cdot NH \cdot CO \cdot [CH_2]_{16} \cdot CO_2H$, was obtained in small yield by Schotten–Baumann methods, but, owing to hydrolysis, only traces of its *methyl* ester could be prepared directly by similar methods. Crude methyl ester was eventually obtained in better yield by esterification of the arsonic acid, but neither acid nor ester could be converted into amides.

As might be expected, owing to the exceptional toxicity of oxalic acid, the oxalyl series proved rather more toxic than is usual where n (in I) is low, but in regard to trypanocidal activity, they were still found more or less true to type. We are indebted to Professor Warrington Yorke, F.R.S., for the following summary of pharmacological tests on mice.

Oxalyl Series.

Sodium salts.	M.L.D.	M.C.D.	Sodium salts.	M.L.D.	M.C.D.
Amide	8	Some action in maximum doses	*n*-Propylamide	4	Some action in maximum doses
Methylamide	4		Piperidide	20	
Dimethylamide	64	16–32	Anilide	4	Inactive
Ethylamide	16	Some action in maximum doses	*p*-Arsonohexadecanedicarboxylanilic acid	16	Inactive

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

Experimental.

Oxalyl Derivatives.

Methyl p-*Arsono-oxanilate.*—*p*-Arsono-oxanilic acid (Bertheim, *loc. cit.*) (83 g.), methyl alcohol (240 c.c.), and sulphuric acid (2·5 c.c.) were refluxed together for 5 hours. The *methyl* p-*arsono-oxanilate* was collected and washed with dilute hydrochloric acid to remove *p*-arsanilic acid. It crystallised from water in glistening rhombic plates (47 g.), only slightly soluble in alcohol (Found: As, 25·5; O·CH_3, 9·7. $C_9H_{10}O_6NAs$ requires As, 24·8; O·CH_3, 10·2%). The sodium salt could not be obtained, as the methyl ester was found to be unstable in neutral and in alkaline solutions.

Ethyl p-*Arsono-oxanilate.*—Carbethoxyformyl chloride (18 g.), *p*-arsanilic acid (32 g.) in a little water, and 2N-sodium hydroxide (150 c.c.) were shaken together, acidified, and the solid collected and crystallised from water plus a trace of hydrochloric acid (yield, 15 g.). *Ethyl* p-*arsono-oxanilate* is dimorphous. It crystallised from rapidly cooled water in long needles, which, at room temperature, slowly changed to octagonal platelets, slightly soluble in alcohol (Found: As, 24·1. $C_{10}H_{12}O_6NAs$ requires As, 23·7%). The sodium salt was gelatinous, but too unstable for analysis.

Oxanilamide-p-*arsonic Acid* (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 1597).—Methyl *p*-arsono-oxanilate (2 g.) was stirred into excess of concentrated aqueous ammonia. The latter was removed, and the residue acidified. The amide, thus obtained, crystallised from water in slender prisms, insoluble in alcohol (Found: hydrolysable N, 4·95. Calc. for $C_8H_9O_5N_2As$: hydrolysable N, 4·9%). The *sodium* salt crystallised from dilute alcohol in large prisms (Found: hydrolysable N, 4·7. $C_8H_8O_5N_2AsNa$ requires hydrolysable N, 4·5%).

Oxanilomethylamide-p-*arsonic Acid.*—The methyl ester (3 g.) and an excess of 33% aqueous methylamine were warmed together for 1 minute. The methylamide, obtained by acidification, was purified through its *sodium* salt, p_H 6·5, which crystallised from water in long silky needles (2·1 g.) (Found: hydrolysable N, 3·9. $C_9H_{10}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·9%). *Oxanilomethylamide*-p-*arsonic acid* crystallised from water, in which it was only sparingly soluble, in minute leaflets, insoluble in alcohol (Found: hydrolysable N, 4·7. $C_9H_{11}O_5N_2As$ requires hydrolysable N, 4·6%).

Oxanilodimethylamide-p-*arsonic acid*, prepared by warming the methyl ester with 33% aqueous dimethylamine, crystallised from water in rhombic leaflets, insoluble in alcohol (Found: hydrolysable N, 4·45. $C_{10}H_{13}O_5N_2As$ requires hydrolysable N, 4·4%). The *sodium* salt crystallised from dilute alcohol in fine needles, p_H 6·5 (Found: hydrolysable N, 3·85. $C_{10}H_{12}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·9%).

Oxaniloethylamide-p-*arsonic acid*, prepared as above from 33% aqueous ethylamine, crystallised from water in flocculent micro-needles, insoluble in alcohol (Found: hydrolysable N, 4·3. $C_{10}H_{13}O_5N_2As$ requires hydrolysable N, 4·4%). The *sodium* salt crystallised from dilute alcohol in hexagonal leaflets, p_H 6·5 (Found: hydrolysable N, 3·9. $C_{10}H_{12}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·9%).

Oxanilo-n-*propylamide*-p-*arsonic Acid.*—Methyl *p*-arsono-oxanilate (8 g.) and an excess of 30% aqueous *n*-propylamine were heated at 100° in a sealed tube for 2 hours. The solution was evaporated and acidified, and the resulting n-*propylamide* collected and crystallised from water, forming rectangular plates, slightly soluble in alcohol (Found: hydrolysable N, 4·2. $C_{11}H_{15}O_5N_2As$ requires hydrolysable N, 4·2%). The *sodium* salt crystallised from 50% aqueous alcohol in minute needles, p_H 7·5 (Found: hydrolysable N, 4·0. $C_{11}H_{14}O_5N_2AsNa$ requires hydrolysable N, 4·0%).

Oxanilopiperidide-p-*arsonic Acid.*—The methyl ester (2 g.) and an excess of 50% aqueous piperidine, warmed and acidified, yielded the *piperidide*, which crystallised from water in feathery needles (1·2 g.), soluble in alcohol (Found: hydrolysable N, 3·7. $C_{13}H_{17}O_5N_2As$ requires hydrolysable N, 3·9%). The *sodium* salt crystallised from dilute alcohol in long silky needles, p_H 6·5 (Found: hydrolysable N, 3·5. $C_{13}H_{16}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·5%).

Oxanilide-p-*arsonic Acid.*—The methyl ester (5 g.) and an excess of aniline (20 c.c.) were boiled together until a cream-coloured solid separated from the clear solution. The mixture was acidified, and the solid collected and washed with water and alcohol (yield, 4·5 g.). The crude anilide was converted into its *disodium* salt, which crystallised from alcohol–water in long silky needles, p_H 9·0 (Found: As, 17·6. $C_{14}H_{11}O_5N_2AsNa_2,H_2O$ requires As, 17·6%). The pure *anilide*, from its sodium salt, was a gelatinous solid, which, although almost insoluble, was readily changed into micro-needles on boiling with water. It was insoluble in alcohol (Found: As, 20·8, 20·75. $C_{14}H_{13}O_5N_2As$ requires As, 20·6%).

Aniline Salts of p-*Arsono-oxanilic Acid.*—Three well-defined *salts* were formed on boiling together, in water, *p*-arsono-oxanilic acid and various proportions of aniline. (1) With a trace of aniline, long silky needles, corresponding with the formula $2AsO_3H_2\cdot C_6H_4\cdot NH\cdot CO\cdot CO_2H,C_6H_5\cdot NH_2$ were formed (Found: As, 22·5. $C_{22}H_{23}O_{12}N_3As_2$ requires As, 22·4%). (2) With more aniline, glistening rhombs having the formula $AsO_3H_2\cdot C_6H_4\cdot NH\cdot CO\cdot CO_2H,C_6H_5\cdot NH_2$ were obtained (Found: As, 20·2. $C_{14}H_{15}O_6N_2As$ requires As, 19·6%). (3) With excess of aniline, $AsO_3H_2\cdot C_6H_4\cdot NH\cdot CO\cdot CO_2H,2C_6H_5\cdot NH_2$ was formed in long prisms (Found: As, 16·1. $C_{20}H_{22}O_6N_3As$ requires As, 15·8%).

Hexadecanedicarboxylyl Derivatives.

Methyl hexadecane-αω-dicarboxylate (Chuit, *Helv. Chim. Acta*, 1926, **9**, 264) was prepared by electrolysis of equimolecular proportions of methyl hydrogen sebacate and potassium hydroxide (5N) in small batches (about 20 c.c.) according to the method of Brown and Walker (*Annalen*, 1891, **261**, 125). The material was, however, electrolysed in boiling tubes instead of a platinum crucible, a platinum plate forming the anode. The oily layer, after extraction with ether and three recrystallisations from light petroleum (b. p. 60—80°), gave methyl hexadecanedicarboxylate in leaflets, m. p. 53—56° (yield, 10 g. from 240 g. of methyl hydrogen sebacate) (Found: $O\cdot CH_3$, 16·65. Calc. for $C_{20}H_{38}O_4$: $O\cdot CH_3$, 18·1%).

Methyl Hydrogen Hexadecane-αω-dicarboxylate.—The methyl ester (13·6 g.) in methyl alcohol was treated carefully with 2·25 g. of potassium hydroxide in methyl alcohol. The mixture was evaporated to dryness, and the residue dissolved in water and acidified. The precipitate was crystallised from light petroleum (b. p. 60—80°), whereby three fractions were obtained: (1) an insoluble residue, m. p. 122—124°, consisting largely of dicarboxylic acid, (2) a fraction, crystallising on cooling and consisting largely of *methyl hydrogen hexadecanedicarboxylate*, and (3) mother-liquor, containing mainly methyl ester. Recrystallisation of (2) gave minute needles of the methyl hydrogen ester (6 g.), m. p. 72—74° (Found: C, 69·4; H, 11·0; $O\cdot CH_3$, 7·9. $C_{19}H_{36}O_4$ requires C, 69·5; H, 11·0; $O\cdot CH_3$, 9·4%).

p-*Arsonohexadecanedicarboxylanilic Acid.*—Hexadecanedicarboxylic acid (9 g.) was treated with excess of thionyl chloride for 24 hours. After removal of the thionyl chloride, the residue was vigorously shaken with sodium *p*-arsanilate (10 g.) in water (100 c.c.), sodium carbonate being added from time to time to maintain alkalinity. The solid, obtained by acidification, was dried, extracted with chloroform until the weight was constant, and finally ground with dilute hydrochloric acid (yield, 7 g.). The *acid* was further purified through alcohol (in which it is soluble), and was indefinitely crystalline. On treatment with thionyl chloride, it decomposed at the ·NH·CO· linkage (Found: As, 13·7. $C_{24}H_{40}O_6NAs$ requires As, 14·6%).

The insoluble residue from the alcohol treatment was brown and gelatinous, but its analysis corresponded roughly with *hexadecanedicarboxylanilide*-pp′-*diarsonic acid*,

$$AsO_3H_2\cdot C_6H_4\cdot NH\cdot CO\cdot [CH_2]_{16}\cdot CO\cdot NH\cdot C_6H_4\cdot AsO_3H_2$$

(Found: As, 19·4. $C_{30}H_{46}O_8N_2As_2$ requires As, 21·1%). *Sodium* p-*arsonohexadecanedicarboxylanilate* separated from dilute alcohol as an amorphous solid, giving soapy solutions in warm water. In cold water, it apparently formed a colloidal suspension, p_H 7·5 (Found: As, 12·85. $C_{24}H_{38}O_6NAsNa_2$ requires As, 13·4%).

Methyl p-*Arsonohexadecanedicarboxylanilate.*—Methyl hydrogen hexadecanedicarboxylate (6·5 g.), treated with thionyl chloride (3 c.c.) for 24 hours, yielded its *acid chloride*, which crystallised from light petroleum (b. p. 60—80°) in tufts of micro-needles (Found: Cl, 9·6. $C_{19}H_{35}O_3Cl$ requires Cl, 10·2%). When, however, this acid chloride was shaken with sodium *p*-arsanilate and alkali in the usual way, it yielded mainly *p*-arsonohexadecanedicarboxylanilic acid and only traces of the corresponding methyl ester. Attempts to prepare *methyl* p-*arsonohexadecanedicarboxylanilate* by esterification with hydrogen chloride were also unsuccessful, owing to hydrolysis at the ·NH·CO· linkage, but the crude ester was eventually obtained by refluxing the free acid with methyl alcohol and a trace of sulphuric acid (Found: As, 13·8; $O\cdot CH_3$, 4·0. $C_{25}H_{42}O_6NAs$ requires As, 14·2; $O\cdot CH_3$, 5·9%). A soluble sodium salt of the ester could not be obtained.

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