CCXXXV.—*New Derivatives of* p-*Arsanilic Acid. Part II.* p-*Arsonomalonanilic Acid and Related Compounds.*

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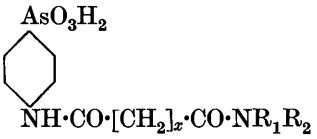
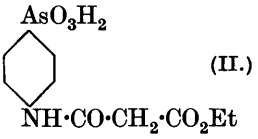
THE object of this investigation is a study of derivatives of *p*-arsanilic acid having the general formula (I) similar to tryparsamide. Members of the succinyl series (I; $x = 2$) have been described (this vol., p. 615); the present paper deals with the synthesis of malonyl compounds (I; $x = 1$). When treated in a variety of ways with ethyl malonate, *p*-arsanilic acid failed to yield *p*-arsonomalonanilic acid (D.R.P. 191,548), but the corresponding *ethyl* p-*arsonomalonanilate* (II), which was prepared by condensing *p*-arsanilic acid with carbethoxyacetyl chloride, readily gave *malonanilomethylamide*-p-*arsonic acid* (I; $x = 1$, $R_1 = H$, $R_2 = Me$) with cold aqueous methylamine, whereas under pressure at 75° with aqueous ammonia, dimethylamine and ethylamine, this ester yielded respectively the corresponding *amide* ($R_1 = H$, $R_2 = H$), *dimethylamide* ($R_1 = Me$, $R_2 = Me$) and *ethylamide* ($R_1 = H$, $R_2 = Et$).

(I.) 

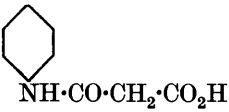


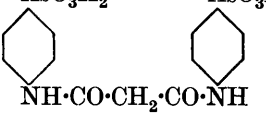
(II.)

Attempts to obtain the piperidide by heating either the ester (II) or its hydrolytic product, *p*-arsonomalonanilic acid, with piperidine under a variety of conditions failed, but *malonanilopiperidide*-p-*arsonic acid* (I; $x = 1$, $NR_1R_2 = Pip.$) was eventually prepared by treating the ester (II) with piperidine at 0°. Similar attempts to obtain the anilide by heating (II) or the corresponding acid with aniline yielded only complex products of ill-defined character.

Ultimately the anilide was prepared as follows: *p*-arsonomalonanilic acid was reduced with sulphur dioxide in the presence of concentrated hydrochloric acid to p-*dichloroarsinomalonanilic acid*, from which p-*arsinomalonanilic acid* (III) was obtained by addition of alkali. By the action of thionyl chloride on either the preceding

dichloride or (in larger proportion) on *p*-arsonomalonanilic acid, *p*-dichloroarsinomalonanilyl chloride was obtained, and, with aniline, the trichloride furnished p-*arsinomalonanilide*, which was readily oxidised by hydrogen peroxide to *malonanilide*-p-*arsonic acid* (I; $x = 1$, $R_1 = H$, $R_2 = Ph$).

(III.) 



(IV.)

Malonanilide-pp'-*diarsonic acid* (IV) was obtained by condensing malonyl dichloride with *p*-arsanilic acid.

A summary of the pharmacological reports from Professor Warrington Yorke of The Liverpool School of Tropical Medicine on the *sodium* salts of several of the new acids is tabulated below. The therapeutic activity of the malonyl series is, on the average, slightly lower than that of the succinyl series (compare Part I, *loc. cit.*), but it may be significant that *malonanilethylamide*-p-*arsonic acid* and succinanilomethylamide-*p*-arsonic acid—the most active members of their respective series—are compounds with identical molecular weights.

Sodium salts.	M.L.D., mg. per g. mouse.	*Tr. equip.* M.C.D., mg. per g. mouse.	Chemother. index, $\frac{\text{M.L.D.}}{\text{M.C.D.}}$.
Amide (I; $x = 1$)	about 5	4	1·25
Methylamide (I; $x = 1$)	>5	4	>1·25
Dimethylamide (I; $x = 1$) ...	5	2·5	2
Ethylamide (I; $x = 1$)	>5	1	>5
Piperidide (I; $x = 1$)	1	>0·75	<1·33
Anilide (I; $x = 1$)	0·75	>0·5	<1·5
Ester (II)	0·75	0·5	1·5
Diarsonic acid (IV)	0·02	>0·02	<1·0

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

EXPERIMENTAL.

Carbethoxyacetyl chloride was prepared in improved yield (70%) from 20 g. of potassium ethyl malonate (Freund, *Ber.*, 1884, **17**, 780) by slow addition of the equivalent quantity of thionyl chloride (14 g.) at 0°, and immediate fractionation; the acid chloride (12·5 g.) was then obtained as a colourless oil, b. p. 75—77°/17 mm. (Staudinger and Becker, *Ber.*, 1917, **50**, 1023).

Ethyl p-*Arsonomalonanilate* (II).—2*N*-Sodium hydroxide (20 c.c.) and carbethoxyacetyl chloride (6 g.) were added alternately in small equivalent proportions to a solution of atoxyl (12 g.) in water (80 c.c.) at 10°. The liquid was well shaken throughout this addition

and then poured into a slight excess of hydrochloric acid and ice; after 2 hours, the precipitated *ethyl* p-*arsonomalonanilate* was crystallised from hot water, containing a few drops of hydrochloric acid, forming long silky needles (6·5 g.), soluble in warm alcohol (Found : As, 22·6, 22·7. $C_{11}H_{14}O_6NAs$ requires As, 22·7%).

The *sodium* salt, an ill-defined crystalline solid, gave an aqueous solution of p_H 6 (Found : As, 20·2. $C_{11}H_{13}O_6NAsNa,H_2O$ requires As, 20·2%).

Malonanilomethylamide-p-*arsonic Acid* (I; $x = 1$, $R_1 = H$, $R_2 =$ Me).—The ester (II) (5 g.) and 33% aqueous methylamine (8 c.c.) were stirred together and warmed at 100° for 1 minute. When cold, the solution was acidified with hydrochloric acid. The *methylamide* crystallised from hot water in small leaflets (3·2 g.), insoluble in alcohol (Found : hydrolysable N, 4·4, 4·5. $C_{10}H_{13}O_5N_2As$ requires hydrolysable N, 4·4%).

The *sodium* salt gave a solution of p_H 6—6·5 (Found : As, 20·6; hydrolysable N, 3·9. $C_{10}H_{12}O_5N_2AsNa,H_2O$ requires As, 21·1; hydrolysable N, 3·9%).

Malonanilamide-p-*arsonic Acid* (I; $x = 1$, $R_1 = H$, $R_2 = H$).—The ester (II) (2 g.) and concentrated aqueous ammonia (8 c.c.) were heated in a sealed tube at 75° for 2 hours, and, after removal of most of the ammonia by evaporation, the solution was diluted with water (5 c.c.) and acidified with hydrochloric acid. The *amide* crystallised from hot water in long prisms (1 g.), insoluble in alcohol (Found : hydrolysable N, 4·5. $C_9H_{11}O_5N_2As$ requires hydrolysable N, 4·6%).

The *sodium* salt crystallised from dilute alcohol in rhombic prisms, p_H 6·0—6·5 (Found : hydrolysable N, 3·6. $C_9H_{10}O_5N_2AsNa,3H_2O$ requires hydrolysable N, 3·7%).

Malonanilodimethylamide-p-*arsonic acid* (I; $x = 1$, $R_1 =$ Me, $R_2 =$ Me), prepared in similar yield by substituting 33% aqueous dimethylamine for ammonia in the preceding experiment, crystallised from hot water in elongated prisms, insoluble in alcohol (Found : hydrolysable N, 4·2, 4·1. $C_{11}H_{15}O_5N_2As$ requires hydrolysable N, 4·2%).

The *sodium* salt, obtained by evaporation of its aqueous solution, showed p_H 6·5 (Found : hydrolysable N, 3·7. $C_{11}H_{14}O_5N_2AsNa,H_2O$ requires N, 3·8%).

Malonanilethylamide-p-*arsonic acid* (I; $x = 1$, $R_1 = H$, $R_2 =$ Et), prepared by heating the ester under pressure with aqueous ethylamine, crystallised from hot water in minute needles, soluble in warm alcohol (Found : hydrolysable N, 4·2. $C_{11}H_{15}O_5N_2As$ requires hydrolysable N, 4·2%).

The *sodium* salt crystallised from dilute alcohol in silky prisms,

p_H 7·5 (Found : hydrolysable N, 3·95. $C_{11}H_{14}O_5N_2AsNa$ requires hydrolysable N, 4·0%).

Malonanilopiperidide-p-*arsonic Acid* (I; $x = 1$, NR_1R_2 = Pip.).—A solution of the ester (II) (9·5 g.) in piperidine (20 c.c.) was left at 0° for 3 days, until two layers appeared; the excess of piperidine was then removed, and the residual yellow syrup acidified with very dilute hydrochloric acid. The precipitated *piperidide* crystallised from hot water in leaflets (3·8 g.), soluble in warm alcohol (Found : hydrolysable N, 3·8. $C_{14}H_{19}O_5N_2As$ requires N, 3·8%).

The *sodium* salt was ill-defined and deliquescent, giving a solution having p_H 7·3 (Found : hydrolysable N, 3·4. $C_{14}H_{18}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·4%).

p-Arsonomalonanilic acid was prepared by boiling 3 g. of the ester (II) with 2*N*-caustic soda (15 c.c.) for 2 minutes, cooling the solution, and acidifying it with dilute hydrochloric acid. The arsonic acid crystallised from water in prisms (2·5 g.), decomp. 188—193° (Found : As, 24·9. Calc. for $C_9H_{10}O_6NAs$: As, 24·8%).

p-*Dichloroarsinomalonanilic acid*, obtained by saturating a solution of *p*-arsonomalonanilic acid (5 g.) in concentrated hydrochloric acid (35 c.c.) containing a trace of iodine, with sulphur dioxide, crystallised from benzene in prisms, decomp. 128—133° (Found : Cl, 20·9. $C_9H_8O_3NCl_2As$ requires Cl, 21·9%).

p-*Arsinomalonanilic acid* (III), prepared by acidifying a filtered solution of *p*-dichloroarsinomalonanilic acid in a little dilute caustic soda, separated from water as an ill-defined crystalline solid (Found : As, 28·3. $C_9H_8O_4NAs$ requires As, 27·9%).

Malonanilide-p-*arsonic Acid* (I; $x = 1$, R_1 = H, R_2 = Ph).—A mixture either of *p*-arsonomalonanilic acid (12 g.) and thionyl chloride (12 c.c.) or of *p*-dichloroarsinomalonanilic acid (12 g.) and thionyl chloride (7 c.c.) was left at 20° for 2 hours, and the resulting yellowish-red solution poured into excess of aniline at 0° with vigorous stirring. The mixture was acidified with very dilute hydrochloric acid, and the precipitate purified by boiling with aqueous sodium carbonate, acidifying its filtered caustic soda solution with dilute hydrochloric acid and finally boiling the precipitate with water. p-*Arsinomalonanilide* (6 g.) was thus obtained as a pale buff-coloured compound, indefinitely crystalline and practically insoluble in water (Found : As, 21·4. $C_{15}H_{13}O_3N_2As$ requires As, 21·8%).

An alkaline solution of the *p*-arsinomalonanilide was treated with 1 c.c. of hydrogen peroxide (100 vol.) and, after a few minutes, acidified with hydrochloric acid. The precipitated *malonanilide*-p-*arsonic acid* crystallised from hot water containing 1 or 2 drops of hydrochloric acid, in minute colourless prisms (2 g.), insoluble in

alcohol (Found: As, 20·1. $C_{15}H_{15}O_5N_2As$ requires As, 19·8%). The *sodium* salt crystallised from dilute alcohol in prisms, p_H 8·5 (Found: As, 17·1, 16·7. $C_{15}H_{14}O_5N_2AsNa,2\frac{1}{2}H_2O$ requires As, 16·85%).

Malonanilide-pp'-*diarsonic Acid* (IV).—It was ultimately found that, owing to the reactivity of malonyl dichloride, this compound could best be prepared, in the absence of water, when *p*-arsanilic acid (0·2 g.) and malonyl dichloride (1 drop) were vigorously stirred together, warmed at 100° for $\frac{1}{2}$ minute, and water (8 c.c.) added. The *pp'*-diarsonic acid thus obtained was purified by acidifying its hot aqueous solution, containing 2 or 3 drops of ammonia, and filtering it if necessary. On cooling, *malonanilide*-pp'-*diarsonic acid* separated as a pale buff-coloured solid, which darkened on drying (yield from 7 g. of malonyl dichloride, 2 g.) (Found: As, 29·95. $C_{15}H_{16}O_8N_2As_2$ requires As, 29·9%).

The *sodium* salt is yellow and deliquescent.

Note on the Preparation of Malonyl Dichloride.—In conformity with the observations of Black, Shaw, and Walker (this vol., p. 276), attempts to prepare malonyl dichloride by the method of Staudinger and Bereza (*Ber.*, 1908, **41**, 4463) yielded only traces of the dichloride. However, by leaving a mixture of powdered malonic acid (10 g.) and thionyl chloride (32 g.) for 2 months, and then fractionating the product, malonyl dichloride was obtained in improved yield (6 g.) as a yellow fuming oil, b. p. 53—58°/25 mm., which slowly darkened and became fluorescent.

Addendum.—Since the foregoing results were written the Committee for Chemotherapy has suggested the preparation of the *n*-propylamides of the malonanilo- and succinanilo-series.

Malonanilo-n-*propylamide*-p-*arsonic acid* (I; $x = 1$, $R_1 = H$, $R_2 = n\text{-}C_3H_7$) has been prepared by leaving a solution of 2 g. of the ester (II) in *n*-propylamine (1 g.) and water ($1\frac{1}{2}$ c.c.) at room temperature for 2 days. The product separated on acidification with dilute hydrochloric acid and crystallised from water in needles (1·2 g.), soluble in warm alcohol (Found: hydrolysable N, 4·3. $C_{12}H_{17}O_5N_2As$ requires hydrolysable N, 4·1%). The *sodium* salt separated as a microcrystalline solid from dilute alcohol, p_H 6·5 (Found: hydrolysable N, 3·8. $C_{12}H_{16}O_5N_2AsNa$ requires hydrolysable N, 3·8%).

Succinanilo-n-*propylamide*-p-*arsonic acid* was formed when a mixture of succinanilo-*p*-arsonic acid (2 g.), *n*-propylamine (2 c.c.), and alcohol (3 c.c.) was left for 24 hours at room temperature. Water (40 c.c.) was added, and the solution acidified with dilute hydrochloric acid. The *propylamide* crystallised from water in large needles (1·3 g.), practically insoluble in alcohol (Found: hydro-

lysable N, 3·8. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·9%). The monosodium salt was ill-defined, but the *disodium* salt crystallised from dilute alcohol in small needles, p_H 10 (Found: hydrolysable N, 3·2. $C_{13}H_{17}O_5N_2AsNa_2,2H_2O$ requires hydrolysable N, 3·2%).

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