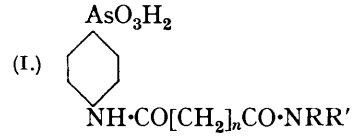
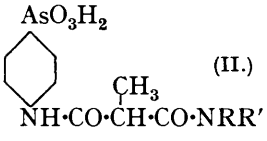
253. *New Derivatives of* p-*Arsanilic Acid. Part V.* p-*Arsonomethylmalonanilic Acid and Related Compounds.*

By Gilbert T. Morgan and Eric Walton.

It is now well established that, of the arsenicals of general type (I; where $n = 1, 2, 3$, or 4), a large proportion show marked trypanocidal activity, and since there are as yet no signs of decreasing activity with increasing numerical values for n, synthetic experiments in this



(I.)



(II.)

direction are being continued. Variations of this structural type, however, are very numerous when alkyl and other substituent groups in both nucleus and side chain are considered, and examples of one such modification, namely, a series of methylmalonyl derivatives (II) of *p*-arsanilic acid, have now been prepared for therapeutic examination.

For this purpose, pure methyl and ethyl methylmalonates were synthesised thus: α-Bromopropionic acid ⟶ α-cyanopropionic acid ⟶ methyl or ethyl methylmalonate. The yield of the ethyl ester (58%, calculated on the α-bromopropionic acid used) obtained in this way was approximately double that afforded by the usual method employing

ethyl α-bromopropionate (Steele,* *J. Amer. Chem. Soc.*, 1931, **53**, 286); further, the conversion into the α-cyano-acid took place in about 3 minutes, as compared with 10 hours required for the reaction ethyl α-bromopropionate ⟶ ethyl α-cyanopropionate.

Methyl and ethyl hydrogen methylmalonates, from the corresponding di-esters, were converted into *α-carbomethoxy-* and α-carbethoxy-propionyl chlorides respectively, and these with atoxyl afforded *methyl* and *ethyl* p-*arsonomethylmalonanilates* (III), from which a series of amides (II; R,R′ = H_2; H, Me; H, Et; H, *n*-Pr) was obtained in the usual manner.

Additional compounds belonging to this group were prepared according to the following scheme (where X = ·C_6H_4·NH·CO·CHMe·) :

(III.) Ethyl *p*-arsonomethylmalonanilate (AsO_3H_2·X·CO_2Et)

↓ NaOH, then HCl and SO_2

p-*Dichloroarsinomethylmalonanilic acid* ($AsCl_2$·X·CO_2H)

↓ $NaHCO_3$ | ↓ $SOCl_2$, then NH_2Ph

p-*Oxyarsinomethylmalonanilic acid* (AsO·X·CO_2H) | p-*Oxyarsinomethylmalonanilide* (AsO·X·CO·NHPh)

↓ H_2O_2 | ↓ H_2O_2

(IV.) p-*Arsonomethylmalonanilic acid* (AsO_3H_2·X·CO_2H) | *Methylmalonanilide*-p-*arsonic acid* (AsO_3H_2·X·CO·NHPh)

Owing to its excessive solubility in water, acid (IV) cannot well be obtained direct from the ester (III).

A summary of recent pharmacological results from Prof. W. Yorke, M.D., M.R.C.P., F.R.S., including data for glutaranilodimethylamide-*p*-arsonic acid,† showing a further improvement on that recorded in Part IV (this vol., p. 91), is here appended.

Sodium salts.	M.L.D.	M.C.D.	C.R.	Sodium salts.	M.L.D.	M.C.D.	C.R.
Ethyl ester (III)	6·25	6·25	1	*n*-Propylamide (II)	50	>50	<1
Methyl ,,	10	>10	<1	Anilide (II)	6	inactive	—
Amide (II)	>100	50	>2				
Methylamide (II)	100	10—12	8—10				
Ethylamide (II)	50	15	3·3	†Dimethylamide (I; *n* = 3)	100	6—10	10—16

M.L.D. = Minimum lethal dose. M.C.D. = Minimum curative dose. (Both as mg. per 20 g. of mouse.) C.R. = Curative ratio.

Experimental

Ethyl Methylmalonate.—α-Bromopropionic acid (76·5 g.) and ice (75 g.), carefully neutralised with sodium hydroxide (20·5 g.) in water (50 c.c.), were treated in a beaker with sodium cyanide (35 g.) in water (60 c.c.), and the mixture heated to 100°, whereupon a fairly vigorous reaction occurred. After being maintained at 100° for 2 minutes, the mixture was cooled, acidified with concentrated hydrochloric acid, and rapidly extracted 5 times with ether (about 1500 c.c. altogether). The extract, after drying and removal of ether, yielded crude α-cyanopropionic acid (50 g.) as a residual syrup, b. p. (some decomp.) 142—145°/15 mm. (Found : N, 14·18. Calc. for $C_4H_5O_2N$: N, 14·15%).

A solution of the crude acid (50 g.) in ethyl alcohol (150 c.c.) and concentrated sulphuric acid (2 c.c.) was saturated at 0° with hydrogen chloride. After 24 hours at 0°, a further quantity of ethyl alcohol (75 c.c.) was added, the mixture refluxed for 30 minutes, and the alcohol removed from the ammonium chloride-free filtrate in a partial vacuum. The residue, treated with water and extracted with ether, afforded, on distillation, ethyl methylmalonate (51 g. or 58%), b. p. 192—198°. Methyl methylmalonate (37 g.), b. p. 172—175°, was prepared in the same way from crude α-cyanopropionic acid (50 g.), methyl alcohol (150 c.c.), and sulphuric acid (2 c.c.).

Partial hydrolysis of ethyl methylmalonate (17·4 g.) and treatment of the ethyl

* This author interprets 118 g. of ethyl methylmalonate from 127 g. of ethyl α-cyanopropionate as a 93% yield; actually it is 68%.

hydrogen methylmalonate (9·5 g.), b. p. 139°/16 mm., thus obtained with thionyl chloride according to the method of Marguery (*Bull. Soc. chim.*, 1905, **33**, 546) afforded α-carbethoxypropionyl chloride (10·5 g.), b. p. 82°/16 mm. Similar hydrolysis of the methyl ester (14·6 g.) with potassium hydroxide (5·6 g.) in methyl alcohol (100 c.c.) gave *methyl hydrogen methylmalonate* (10 g.), b. p. 131°/16 mm. (Found : C, 44·9; H, 5·95. $C_5H_8O_4$ requires C, 45·4; H, 6·1%), and the latter (29 g.) with thionyl chloride (23 c.c.) yielded *α-carbomethoxypropionyl chloride* (31 g.), b. p. 73°/16 mm. (Found : Cl, 23·23. $C_5H_7O_3Cl$ requires Cl, 23·58%).

Ethyl p-*Arsonomethylmalonanilate* (III).—α-Carbethoxypropionyl chloride (0·5 c.c.) was shaken with atoxyl (1 g.) in *N*-sodium hydroxide (5 c.c.), and the solution poured into an excess of cold dilute hydrochloric acid and left for several hours at 0°. The precipitated *ethyl* p-*arsonomethylmalonanilate* crystallised from water in leaflets, soluble in alcohol and slightly so in cold water (Yield, recrystallised, 10 g. from 17 g. of atoxyl) (Found : As, 21·6. $C_{12}H_{16}O_6NAs$ requires As, 21·7%). The *sodium* salt crystallised from dilute alcohol in small leaflets, p_H 6·0 (Found : As, 20·4. $C_{12}H_{15}O_6NAsNa$ requires As, 20·4%).

Methyl p-*arsonomethylmalonanilate* (18·5 g.), prepared in the same way from α-carbomethoxypropionyl chloride (10 c.c.), crystallised from water in tufts of needles, soluble in alcohol and cold water (Found : As, 23·1. $C_{11}H_{14}O_6NAs$ requires As, 22·65%). The *sodium* salt separated from dilute alcohol as a granular precipitate, p_H 8 (Found : As, 20·3. $C_{11}H_{13}O_6NAsNa,H_2O$ requires As, 20·2%).

Methylmalonanilamide-p-*arsonic Acid* (II; R,R′ = H_2).—The ester (III) (4 g.) and concentrated aqueous ammonia (10 c.c.) were heated at 70° under pressure for 4 hours. The ammonia was removed, the residue acidified, and, after 24 hours at 0°, the *amide* was collected, and crystallised from water in large prisms (1·7 g.), insoluble in alcohol but moderately soluble in cold water (Found : hydrolysable N, 4·34. $C_{10}H_{13}O_5N_2As$ requires hydrolysable N, 4·43%). The *sodium* salt, p_H 7·0—7·5, which separated from dilute alcohol is indefinitely crystalline (Found : hydrolysable N, 3·90. $C_{10}H_{12}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·94%).

Methylmalonanilomethylamide-p-*arsonic acid* (II; R = H, R′ = Me) was prepared by leaving the ester (III) (4·5 g.) and 33% aqueous methylamine (9 c.c.) at room temperature for 24 hours and working up the solution as described above for the amide. The *methylamide* crystallised from water in glistening rectangular prisms (2·3 g.), soluble in alcohol and moderately so in cold water (Found : hydrolysable N, 4·24. $C_{11}H_{15}O_5N_2As$ requires hydrolysable N, 4·25%). The *sodium* salt, p_H 6·0, was prepared by evaporation of its aqueous solution (Found : hydrolysable N, 4·03. $C_{11}H_{14}O_5N_2AsNa$ requires hydrolysable N, 3·98%).

Methylmalonanilethylamide-p-*arsonic acid* (II; R = H, R′ = Et), from the ester (III)(12 g). and 33% aqueous ethylamine (25 c.c.), after 12 days at 0°, crystallised from water in small hexagonal plates (3·5 g.), soluble in alcohol and cold water (Found : hydrolysable N, 4·05. $C_{12}H_{17}O_5N_2As$ requires hydrolysable N, 4·07%). The *sodium* salt, p_H 7·0—7·5, was prepared by evaporation of its aqueous solution (Found : hydrolysable N, 3·68. $C_{12}H_{16}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·65%).

Methylmalonanilo-n-*propylamide*-p-*arsonic acid* (II; R = H, R′ = *n*-Pr), from either ester (III) (4 g.) or the corresponding methyl ester (4 g.) and 50% aqueous *n*-propylamine (8 c.c.), after 6 days at room temperature, crystallised from water in tufts of minute needles (1 g.), moderately soluble in alcohol but not in cold water (Found : hydrolysable N, 3·94. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·91%). The *disodium* salt crystallised from dilute alcohol in leaflets, p_H 9·5 (Found : hydrolysable N, 3·35. $C_{13}H_{17}O_5N_2AsNa_2,H_2O$ requires hydrolysable N, 3·33%).

p-*Dichloroarsinomethylmalonanilic Acid.*—The ester (III) (4 g.) and 6*N*-sodium hydroxide (4 c.c.) were boiled for about 1 minute, and, after addition of concentrated hydrochloric acid (50 c.c.) and removal of salt, the solution was saturated with sulphur dioxide at 0°, in the presence of a trace of iodine. After 15 hours at 0°, the *dichloroarsino*-derivative (2·5 g.) was collected, and crystallised from benzene in rectangular prisms, m. p. 158—160° (decomp.) (Found : Cl, 20·6. $C_{10}H_{10}O_3NAsCl_2$ requires Cl, 21·0%).

Acidification of a solution of this dichloride in sodium bicarbonate furnished p-*oxyarsinomethylmalonanilic acid*, an ill-defined solid, almost insoluble in water and alcohol (Found : As, 26·8. $C_{10}H_{10}O_4NAs$ requires As, 26·5%). On treatment with very dilute hydrogen peroxide and evaporation to dryness, the arsine oxide was converted into p-*arsonomethylmalonanilic acid*, a fawn-coloured solid, readily soluble in water and alcohol (Found : As, 23·01. $C_{10}H_{12}O_6NAs$ requires As, 23·65%).

Methylmalonanilide-p-*arsonic Acid* (II; R = H, R = C_6H_5).—A solution of the crude dichloride (2·4 g.) in thionyl chloride (3 c.c.), after 15 hours at room temperature, was poured

into an excess of aniline, and the mixture acidified. The precipitated p-*oxyarsinomethylmalonanilide* (1·2 g.), after purification through its sodium hydroxide solution, appeared as a cream-coloured solid, insoluble in water (Found : As, 20·95. $C_{16}H_{15}O_3N_2As$ requires As, 20·95%). A warm suspension of the anilide in aqueous sodium bicarbonate was treated with hydrogen peroxide (100 vol.) (1 c.c.) and the filtered solution acidified. The precipitated *methylmalonanilide*-p-*arsonic acid* recrystallised from water in microcrystalline leaflets (0·9 g.), soluble in warm alcohol (Found : As, 19·1. $C_{16}H_{17}O_5N_2As$ requires As, 19·1%). The *sodium* salt, prepared by evaporation of its aqueous solution, is a cream-coloured solid, p_H 9·0 (Found : As, 16·8. $C_{16}H_{16}O_5N_2AsNa,2H_2O$ requires As, 16·65%).

Methylmalonanilide-pp′-*diarsonic acid*, $AsO_3H_2{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH(CH_3){\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO_3H_2$, was prepared in small quantity by shaking an alkaline solution of atoxyl with methylmalonyl dichloride (Meyer and Bock, *Annalen*, 1906, **347**, 104), followed by an excess of dilute hydrochloric acid. It separated from water, in which it was only slightly soluble, as a microcrystalline solid, sparingly soluble in hot alcohol (Found : As, 29·1. $C_{16}H_{18}O_8N_2As_2$ requires As, 29·1%).

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