30. *New Derivatives of* p-*Arsanilic Acid. Part IV.* p-*Arsonoadipanilic Acid and Related Compounds.*

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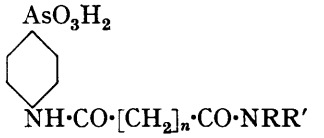
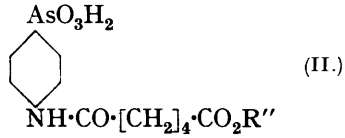
A SERIES of adipyl derivatives of *p*-arsanilic acid (I; $n = 4$; RR′ = H_2; H,Me; Me_2; H,Et; H,*n*-Pr; and H,Ph respectively) has now been prepared by condensing the *acid chloride* of methyl hydrogen adipate with atoxyl, and treating the resulting *methyl* p-*arsonoadipanilate* (II; R″ = Me) with the appropriate amine. The crude amides, in some cases, were admixed through hydrolysis with p-*arsonoadipanilic acid* (II; R″ = H), which was most effectively removed by fractional precipitation of its sodium salt from dilute alcohol, whereas the piperidide could not be prepared owing to hydrolysis of the methyl ester (II) by piperidine.

(I.) 



(II.)

p-Arsonoadipanilic acid was converted into p-*dichloroarsino*- and p-*oxyarsino-adipanilic acids* by the usual methods.

Reports from Professor Warrington Yorke, F.R.S., indicate that trypanocidal activity is being well maintained in the present case, in comparison with members of the lower homologous series, as shown in the following summary, into which more promising data * for two glutaryl derivatives are also introduced (cf. Part III; J., 1932, 276).

Sodium salts.	*M.L.D.*	*M.C.D.*	*C.R.*	Sodium salts.	*M.L.D.*	*M.C.D.*	*C.R.*
Methyl ester (II)	12·5	6·25	2	*n*-Propylamide (I; $n=4$)	<100	<30	3
Ethyl ester (II)	12·5	12·5	1	Anilide (I; $n=4$)	<10	<10	1
Amide (I; $n=4$)	50	12·5	4	Adipanilide-*pp*′-diarsonic acid	20	inactive	—
Methylamide (I; $n=4$) ...	100	25	4	*Dimethylamide (I; $n=3$)	100	12·5	8
Dimethylamide (I; $n=4$)	100	12	8	*Ethylamide (I; $n=3$)	100	12·5	8
Ethylamide (I; $n=4$) .....>50		12	>4	*n*-Propylamide (I; $n=3$)			

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

Several of the more active compounds described in this and the earlier papers are being subjected to more extensive tests.

EXPERIMENTAL.

Methyl Hydrogen Adipate.—A modification of Blaise and Koehler's method (*Bull. Soc. chim.*, 1910, **7**, 216) was employed. Adipic acid (29·2 g.), MeOH (20 c.c.), and conc. H_2SO_4 (4 c.c.) were heated for 3 hr. at 100°. The mixture was diluted with H_2O (250 c.c.), an Et_2O extract (A) well shaken with an excess of $NaHCO_3$ aq., and the aq. layer acidified and again extracted with Et_2O (B). The dried Et_2O solution (B), on fractionation, yielded methyl hydrogen adipate (7 g.), b. p. 178°/30 mm., m. p. 9°, and the solution (A) afforded dimethyl adipate (8 g.), b. p. 128°/30 mm.

Ethyl hydrogen adipate (9 g.), b. p. 185°/35 mm., m. p. 28°, and diethyl adipate (15 g.), b. p. 140°/28 mm., were obtained in the same way from adipic acid (29·2 g.), EtOH (38 c.c.), and conc. H_2SO_4 (4 c.c.) heated for 10—12 hr. at 100°.

Considerable quantities of dimethyl adipate having accumulated from the esterification of adipic acid, an alternative method for the prep. of methyl hydrogen adipate, based on Fourneau and Sabetay's procedure for the ethyl hydrogen ester (*Bull. Soc. chim.*, 1928, **43**, 859), was adopted with success. A mixture of dimethyl adipate (192·8 g.) and adipic acid (166 g.) was heated for 5 hr. at 230° and then distilled in vac., with production of two fractions A and B. Fraction A, b. p. up to 160°/30 mm., was ultimately remixed with the residual adipic acid; B, b. p. 170—180°/30 mm., was shaken with an excess of $NaHCO_3$ aq. and subsequently worked up as already described. Continued repetition of this process yielded 60—70% of methyl hydrogen adipate.

δ-Carbomethoxyvaleryl Chloride.—A mixture of methyl hydrogen adipate (10 g.) and $SOCl_2$

(8 c.c.), kept for 3 hr. at room temp. and then for 3 hr. at 40°, yielded on distillation the *acid chloride* (9 g.), b. p. 141°/36 mm. (Found: Cl, 19·6. $C_7H_{11}O_3Cl$ requires Cl, 19·9%). δ-Carbethoxyvaleryl chloride prepared in the same way from ethyl hydrogen adipate distilled at 145°/35 mm. (Blaise and Koehler, *loc. cit.*).

Methyl p-*Arsonoadipanilate* (II; R″ = Me).—δ-Carbomethoxyvaleryl chloride (0·5 c.c.) was shaken with atoxyl (1 g.) in *N*-NaOH (5·3 c.c.), and the clear solution poured into cold dil. acid. The pptd. *methyl* p-*arsonoadipanilate* crystallised from H_2O in plates, sol. in EtOH (yield recryst., 33 g. from 80 g. of atoxyl) (Found: As, 21·2. $C_{13}H_{18}O_6NAs$ requires As, 20·9%). The *sodium* salt crystallised in leaflets from dil. EtOH at 0°; p_H 9 (Found: As, 18·2; H_2O, 7·4. $C_{13}H_{17}O_6NAsNa,2H_2O$ requires As, 18·0; H_2O, 8·6%).

Ethyl p-*arsonoadipanilate* (II; R″ = Et), prepared in the same way from δ-carbethoxyvaleryl chloride, crystallised from H_2O in prisms, sol. in EtOH (Found: As, 20·3. $C_{14}H_{20}O_6NAs$ requires As, 20·1%). The *sodium* salt is indefinitely cryst.; p_H 8 (Found: As, 19·0. $C_{14}H_{19}O_6NAsNa$ requires As, 19·0%).

p-*Arsonoadipanilic acid* (II; R″ = H), readily obtained by hydrolysis of the foregoing esters, crystallised from H_2O in needles, sol. in hot EtOH (Found: As, 21·7. $C_{12}H_{16}O_6NAs$ requires As, 21·7%).

p-*Dichloroarsinoadipanilic acid*, obtained from II (R″ = H) by reduction with SO_2 in conc. HCl solution, separated from C_6H_6 in felted needles, m. p. 138° (Found: Cl, 19·25. $C_{12}H_{14}O_3NCl_2As$ requires Cl, 19·4%). Hydrolysis with dil. alkali afforded p-*oxyarsinoadipanilic acid*, a white, indefinitely cryst. solid (Found: As, 24·1. $C_{12}H_{14}O_4NAs$ requires As, 24·1%).

Adipanilamide-p-*arsonic Acid* (I; RR′ = H_2).—The methyl ester (II) (7 g.) was treated at 0° with aq. NH_3 (*d* 0·88) (50 c.c.) and sufficient H_2O (about 5 c.c.) to bring it into solution, and after 2 days the solvent was removed in vac. and more aq. NH_3 added to the residue. After a further 7 days the solvent was again removed in vac., and the residue dissolved in H_2O and acidified. The ppt. was dissolved in 2*N*-NaOH to a neutral solution, and an excess of EtOH added. The filtrate, after 12 hr. at 0°, deposited the *sodium* salt (4 g.), which, after repetition of this process, crystallised in rosettes of silky prisms, p_H 5·5 (Found: hydrolysable N, 3·8. $C_{12}H_{16}O_5N_2AsNa$ requires hydrolysable N, 3·8%).

Adipanilamide-p-*arsonic acid*, from the pure Na salt, crystallised from H_2O in rectangular plates, almost insol. in EtOH (Found: hydrolysable N, 3·9, 4·0. $C_{12}H_{17}O_5N_2As$ requires hydrolysable N, 4·1%).

Adipanilomethylamide-p-*arsonic acid* (I; R, R′ = H, Me), obtained from the methyl ester (II) (2·2 g.) and 33% aq. NH_2Me (5 c.c.) after 48 hr. at room temp., separated from H_2O in microcrystals (1·3 g.), slightly sol. in hot EtOH (Found: hydrolysable N, 3·9. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·9%). The *sodium* salt, p_H 6·5, crystallised from dil. EtOH in prisms (Found: hydrolysable N, 3·3. $C_{13}H_{18}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·4%).

Adipanilodimethylamide-p-*arsonic Acid* (I; RR′ = Me_2).—The methyl ester (II) (4 g.) and 58% * aq. $NHMe_2$ (8 c.c.), when heated for 5 hr. at 75° in a sealed tube, separated into two layers; $NHMe_2$ was removed and the residue acidified. The resulting arsonic acid was converted into its Na salt (p_H 6·0) with 2*N*-NaOH, and EtOH (70—90 c.c.) added until milky. The mixture was warmed on the steam-bath, the ppt., consisting of sodium *p*-arsonoadipanilate, removed, and the filtrate evaporated to dryness in vac. The residue, dissolved in H_2O and acidified, gave *adipanilodimethylamide*-p-*arsonic acid* (2·2 g.), crystallising from H_2O in long needles, slightly sol. in hot EtOH (Found: hydrolysable N, 3·6. $C_{14}H_{21}O_5N_2As$ requires hydrolysable N, 3·76%). The *sodium* salt crystallised from conc. solution in cold H_2O in needles and from dil. EtOH in leaflets; p_H 6·0 (Found: hydrolysable N, 3·3. $C_{14}H_{20}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·4%).

Adipaniloethylamide-p-*arsonic acid* (I; R, R′ = H, Et) was prepared from the methyl ester (II) (4 g.) and 33% aq. NH_2Et (8 c.c.), heated for 3 hr. at 75° as described for the dimethylamide, except that the mixture of Na salts (p_H 8) was treated at room temp., to obviate hydrolysis, with EtOH until just milky, and the process repeated on the filtrate with use of more EtOH and charcoal. The ethylamide (2 g.) crystallised from H_2O in slender prisms, sol. in EtOH (Found: hydrolysable N, 3·75. $C_{14}H_{21}O_5N_2As$ requires hydrolysable N, 3·76%). The *sodium* salt, prepared by evaporation of its solution, crystallised in minute irregular leaflets; p_H 8 (Found: hydrolysable N, 3·25. $C_{14}H_{20}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·26%).

Adipanilo-n-*propylamide*-p-*arsonic acid* (I; R, R′ = H, Pr^n), from the methyl ester (II) (5 g.) and 60% * aq. NH_2Pr^n (10 c.c.) heated for 2½ hr. at 75°, crystallised from H_2O in clusters

* The use of weaker amines led to increased production of *p*-arsonoadipanilic acid.

of needles (2·5 g.), sol. in hot EtOH (Found : hydrolysable N, 3·5. $C_{15}H_{23}O_5N_2As$ requires hydrolysable N, 3·6%). The *sodium* salt, p_H 7·5, is microcryst. (Found : hydrolysable N, 3·3, 3·5. $C_{15}H_{22}O_5N_2AsNa$ requires hydrolysable N, 3·4%).

Adipanilide-p-*arsonic Acid* (I; R, R′ = H, Ph).—*p*-Arsonoadipanilic acid (3 g.) and an excess of NH_2Ph were refluxed for 3 min., the crude acid, obtained by acidifying the product, was dissolved in 2*N*-NaOH to p_H 7·5 and treated with EtOH (60—70 c.c.) at 70°, and the filtrate evaporated. When an aq. solution of the residue was acidified, *adipanilide*-p-*arsonic acid* (3 g.) separated as an indefinitely cryst. solid, only slightly sol. in H_2O and EtOH (Found : As, 18·4. $C_{18}H_{21}O_5N_2As$ requires As, 17·9%). The *sodium* salt crystallised from its conc. aq. solution or from dil. EtOH in needles; p_H 7·5 (Found : As, 16·0. $C_{18}H_{20}O_5N_2AsNa,H_2O$ requires As, 16·3%).

Adipanilide-pp′-*diarsonic acid* was prepared by shaking adipyl chloride (0·3 g.) (Blaise and Koehler, *Bull. Soc. chim.*, 1909, **5**, 683) with atoxyl (1 g.) in *N*-NaOH (3·5 c.c.) and acidifying the product. The *diarsonic acid*, washed with boiling H_2O, in which it was almost insol., was a white amorphous solid, insol. in EtOH (yield, 4 g. from 8 g. of atoxyl) (Found : As, 27·5. $C_{18}H_{22}O_8N_2As_2$ requires As, 27·6%). The *disodium* salt separated from dil. EtOH in microcrystals, p_H 7·0 (Found : As, 25·8. $C_{18}H_{20}O_8N_2As_2Na_2$ requires As, 25·5%).

Note on Succinyl Derivatives of p-*Arsanilic Acid.*

The following details amplify the experimental section of " New Derivatives of *p*-Arsanilic Acid," Part I (J., 1931, 617).

1. The fusion of atoxyl and succinic anhydride, as recorded on p. 617 (*loc. cit.*), has been found to yield pure p-*arsonosuccinanilic acid*, $AsO_3H_2{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ (III), only when the crude product is lixiviated with a slight excess of hot alkali. It crystallised from H_2O in needles (Found : As, 23·7, 23·8. $C_{10}H_{12}O_6NAs$ requires As, 23·65%).

2. *Succinanil*-p-*arsonic acid*, $AsO_3H_2{\cdot}C_6H_4{\cdot}N<\begin{matrix}CO{\cdot}CH_2\\ |\\ CO{\cdot}CH_2\end{matrix}$ (IV), prepared as described on p. 619 (*loc. cit.*), crystallised from H_2O, in which it is comparatively stable, in irregular silky plates (Found : As, 25·2, 25·15. $C_{10}H_{10}O_5NAs$ requires As, 25·1%).

3. The methylamide and ethylamide (p. 618, *loc. cit.*) have now been obtained by using the anil (IV) in place of the acid (III), from which they are directly unobtainable.

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