38. *New Derivatives of* p-*Arsanilic Acid. Part III.* p-*Arsonoglutaranilic Acid and Related Compounds.*

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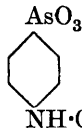
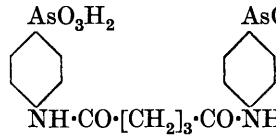
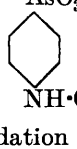
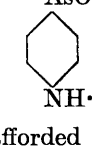
IN continuation of the study of *p*-arsanilic acid derivatives of the general type (I) (J., 1931, 615, 1743) a series of glutaryl derivatives has now been prepared.

(I.)  (II.) 

Methyl and ethyl hydrogen glutarates with thionyl chloride yielded their respective *acid chlorides*, which condensed with atoxyl to give *methyl* and *ethyl* p-*arsonoglutaranilates* (III; R″ = Me or Et). Either the methyl or the ethyl ester, preferably the former in some cases, with ammonia or the appropriate amine gave the amide (I; $n = 3$, RR′ = H_2)—isolated as *ammonium glutaranilamide*-p-*arsonate*—, *methylamide* (R = H, R′ = Me), *dimethylamide* (RR′ = Me_2), *ethylamide* (R = H, R′ = Et), and n-*propylamide* (R = H, R′ = Pr) respectively, but neither the piperidide nor anilide could be prepared by similar methods. The *anilide* (R = H, R′ = Ph) was eventually obtained by condensing *p*-arsanilic acid with glutaranilic acid, but the corresponding *diarsonic acid* (II) alone was isolated from the fusion of atoxyl and glutaric acid or anhydride owing to the solubility of what is probably the main product, *p*-arsonoglutaranilic acid (III; R″ = H), in water. To obtain the latter acid, the following method was adopted : Reduction of (III; R″ = Et) and subsequent hydrolysis of the crude dichloride yielded in turn *ethyl* p-*arsinoglutaranilate* (IV; R‴ = Et) and p-*arsinoglutaranilic acid* (R‴ = H), which was also obtained in smaller yield by reversal of the above reactions on (III) with intermediate production of p-*dichloroarsinoglutaranilic acid.*

(III.)  (IV.) 

Oxidation of IV (R‴ = H) afforded p-*arsonoglutaranilic acid* (III; R″ = H), which, in contrast with *p*-arsonosuccinanilic and *p*-arsonomalonanilic acid (Parts I and II, *loc. cit.*), is readily soluble in cold water. Attempts to prepare the piperidide (I; $n = 3$, NRR′ = Pip.) by way of the anil from (III) were unsuccessful.

The *sodium* salts of many of these derivatives (I) continue to show considerable curative activity on mice infected with trypanosomes, as is evident from the following summary of results obtained by Professor Warrington Yorke, these observations being prolonged during 30 days.

Sodium salts.	M.L.D., mg. per g.	*Tr. equip.* M.C.D., mg. per g.	Chemother. index, M.L.D./M.C.D.
Ester (III; R″ = Me)	0·5	0·5	1
Ester (III; R″ = Et)	0·75	0·75	1
Amide (as NH_4 salt I; $n = 3$)	1·25	1·25	1
Methylamide (I; $n = 3$)	> 5	2	> 2·5
Dimethylamide (I; $n = 3$)	5	< 5	> 1
Ethylamide (I; $n = 3$)	5	0·625	8
n-Propylamide (I; $n = 3$)	> 5	1·25	> 4
* ,, (I; $n = 2$)	> 5	2·5	> 2
* ,, (I; $n = 1$)	5	1·25	4
Anilide (I; $n = 3$)	0·9	> 0·9	< 1
Diarsonic acid (II)	1·5	inactive	

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

* These propylamides of the succinyl and malonyl series were described in J., 1931, 1747.

EXPERIMENTAL.

Methyl and ethyl hydrogen glutarates, prepared from glutaric anhydride and the corresponding sodium alkyloxide (compare Mol, *Rec. trav. chim.*, 1907, **26**, 379), distilled as colourless syrups, b. p.'s 158°/27 mm. and 170°/34 mm. respectively.

γ-Carbomethoxybutyryl Chloride.—A mixture of methyl hydrogen glutarate (9·5 g.) and thionyl chloride (8 c.c.) kept at 20° for 12 hours and then at 30° for 3 hours, yielded on distillation the *acid chloride* (10 g.), b. p. 110°/30 mm. (Found: Cl, 21·6. $C_6H_9O_3Cl$ requires Cl, 21·6%).

γ-Carbethoxybutyryl chloride, prepared in similar manner from ethyl hydrogen glutarate, distilled at 110°/20 mm. (Found: Cl, 20·4. $C_7H_{11}O_3Cl$ requires Cl, 19·9%).

Methyl p-*arsonoglutaranilate* (III; R″ = Me) was prepared best on a small scale by adding γ-carbomethoxybutyryl chloride (0·5 g.) to a cold solution of atoxyl (0·9 g.) in *N*-caustic soda (3·1 c.c.) and shaking till clear; the mixture was then poured into an excess of hydrochloric acid and ice. The precipitated *methyl* p-*arsonoglutaranilate* crystallised from hot water, acidified with hydrochloric acid, in glistening leaflets, soluble in alcohol (yield, 8 g. from 12 g. of atoxyl) (Found: As, 21·1. $C_{12}H_{16}O_6NAs$ requires As, 21·7%). The *sodium* salt is microcrystalline; aqueous solution, p_H 7·5 (Found: As, 20·4. $C_{12}H_{15}O_6NAsNa$ requires As, 20·4%).

Ethyl p-*arsonoglutaranilate* (III; R″ = Et), prepared in similar manner from γ-carbethoxybutyryl chloride and atoxyl, crystallised from hot water in minute rhombic prisms, readily soluble in alcohol

(Found: As, 21·2. $C_{13}H_{18}O_6NAs$ requires As, 20·9%). The ill-defined *sodium* salt is very soluble in water; p_H 8 (Found: As, 19·75. $C_{13}H_{17}O_6NAsNa$ requires As, 19·7%).

Glutaranilamide-p-*arsonic Acid* (I; $n = 3$, $RR' = H_2$).—The *ammonium* salt, prepared by leaving the ester (III; $R'' = Et$) in excess of concentrated aqueous ammonia for 8 days and slowly evaporating the solution, separated as a deliquescent solid, very soluble in water; p_H 5 (Found: As, 20·75; hydrolysable N, 7·6. $C_{11}H_{18}O_5N_3As,H_2O$ requires As, 20·5; hydrolysable N, 7·7%). The free acid was not isolated owing to excessive solubility in water.

Glutaranilomethylamide-p-*arsonic Acid* (I; $n = 3$, $R = H$, $R' = Me$).—A mixture of the ester (III; $R'' = Et$) (4·5 g.) and 33% aqueous methylamine (5 c.c.) was heated at 80° for 3 hours under pressure and acidified with dilute hydrochloric acid. The *methylamide* (3·2 g.), which slowly separated, crystallised from water in massive rhombic prisms, slightly soluble in alcohol (Found: hydrolysable N, 4·0. $C_{12}H_{17}O_5N_2As$ requires hydrolysable N, 4·1%). The *sodium* salt crystallised from dilute alcohol in minute prisms; p_H 6 (Found: H_2O, 6·4. Found in anhydrous salt: hydrolysable N, 3·8. $C_{12}H_{16}O_5N_2AsNa,1\frac{1}{2}H_2O$ requires H_2O, 6·9%. $C_{12}H_{16}O_5N_2AsNa$ requires hydrolysable N, 3·8%).

Glutaranilodimethylamide-p-*arsonic acid* (I; $n = 3$, $RR' = Me_2$), obtained by leaving a mixture of the ester (III; $R'' = Me$) (2 g.) and 33% aqueous dimethylamine (5 c.c.) at room temperature for 6 days, crystallised from hot water in irregular shining leaflets (1·5 g.), practically insoluble in alcohol (Found: hydrolysable N, 3·8. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·9%). The microcrystalline *sodium* salt slowly separated from dilute alcohol; p_H 6·5 (Found: hydrolysable N, 3·4. $C_{13}H_{18}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·4%).

Glutaranilethylamide-p-*arsonic acid* (I; $n = 3$, $R = H$, $R' = Et$), prepared in the same way by means of 33% aqueous ethylamine, crystallised from hot water in small irregular prisms, slightly soluble in alcohol (Found: hydrolysable N, 3·7. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·9%). The *sodium* salt is microcrystalline; p_H 6·5 (Found: hydrolysable N, 3·25. $C_{13}H_{18}O_5N_2AsNa,3H_2O$ requires hydrolysable N, 3·2%).

Glutaranilo-n-*propylamide*-p-*arsonic acid* (I; $n = 3$, $R = H$, $R' = Pr^n$), obtained from the methyl ester (III) and 33% *n*-propylamine after 21 days, separated from water in minute leaflets (Found: hydrolysable N, 3·7. $C_{14}H_{21}O_5N_2As$ requires hydrolysable N, 3·8%). The *sodium* salt is an indefinitely crystalline solid; p_H 8 (Found: hydrolysable N, 3·4. $C_{14}H_{20}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·4%).

Glutaranilic acid was made by stirring together molecular proportions of glutaric anhydride and aniline at 15° and lixiviating the product with dilute hydrochloric acid. The resulting solid was treated with dilute alkali, and the filtrate acidified. Glutaranilic acid crystallised from water in pearly leaflets, m. p. 128° (compare Balbiano and Angeloni, *Gazzetta*, 1905, **35**, i, 150).

Glutaranilide-p-*arsonic Acid* (I; $n = 3$, R = H, R′ = Ph).—A mixture of *p*-arsanilic acid (8·8 g.) and glutaranilic acid (8·4 g.) was kept at 180° for 30 minutes with occasional stirring, and the viscous product lixiviated with warm 0·5*N*-caustic soda. After recrystallisation from alcohol, the residual glutaranilide melted at 223° (compare Beilstein's "Organische Chemie," 1929, **12**, 298). The alkaline filtrate, when acidified with hydrochloric acid, gave the arsonic acid, which was purified by reprecipitation from its alkaline solution (yield, 3·2 g.).

Glutaranilide-p-*arsonic acid*, a microcrystalline solid, was slightly soluble in water and readily so in alcohol (Found: As, 18·75. $C_{17}H_{19}O_5N_2As$ requires As, 18·5%). The *sodium* salt crystallised from dilute alcohol in shining leaflets; p_H 7·5 (Found: As, 16·4. $C_{17}H_{18}O_5N_2AsNa,2H_2O$ requires As, 16·2%).

Glutaranilide-pp′-*diarsonic Acid* (II).—Apparently owing to the instability of glutaryl dichloride (Reboul, *Ann. Chim.*, 1878, **14**, 504), interaction with atoxyl in dilute alkali failed to afford the diarsonic acid, which was, however, readily obtained in small yield by fusing a mixture of glutaric acid (4 g.) and atoxyl (8 g.) at 180° for 30 minutes. The dark mass was lixiviated with very dilute warm hydrochloric acid to dissolve *p*-arsonoglutaranilic acid (see below) and unchanged *p*-arsanilic acid; the insoluble *diarsonic acid* (1·5 g.) was purified through alkali and separated as a white amorphous solid, insoluble in water or alcohol (Found: As, 28·4. $C_{17}H_{20}O_8N_2As_2$ requires As, 28·3%). The *disodium* salt crystallised from dilute alcohol in needles; p_H 7·5 (Found: As, 25·5. $C_{17}H_{18}O_8N_2As_2Na_2,H_2O$ requires As, 25·3%).

p-*Arsinoglutaranilic Acid* (IV; R‴ = H).—(A) A solution of the ester (III; R″ = Et) (5 g.) in concentrated hydrochloric acid (75 c.c.) containing a trace of potassium iodide was saturated with sulphur dioxide and, after 16 hours at 0°, the dichloride was hydrolysed with 2*N*-sodium hydroxide (20 c.c.) at 100°. The filtrate was acidified, made alkaline with sodium carbonate, and the filtered solution again acidified. p-*Arsinoglutaranilic acid* (3·3 g.) was precipitated as a white powder, slightly soluble in water but insoluble in alcohol (Found: As, 24·9. $C_{11}H_{12}O_4NAs$ requires As, 25·2%).

Treatment of the above dichloride with cold sodium carbonate solution afforded *ethyl* p-*arsinoglutaranilate* (IV; R‴ = Et) as a

cream-coloured residue, insoluble in water (Found: As, 22·8. $C_{13}H_{16}O_4NAs$ requires As, 23·1%).

(B) A solution of the ester (III; R = Et) (5 g.) in 6*N*-caustic soda (10 c.c.), heated to 100° and acidified with concentrated hydrochloric acid (85 c.c.), was freed from sodium chloride and reduced as in method (A). The resulting p-*dichloroarsinoglutaranilic acid*, $AsCl_2 \cdot C_6H_4 \cdot NH \cdot CO \cdot [CH_2]_3 \cdot CO_2H$, crystallised from benzene in pink needles, m. p. 156—158° (Found: Cl, 20·4. $C_{11}H_{12}O_3NAsCl_2$ requires Cl, 20·2%). Acidification of a solution of this crude dichloride in sodium carbonate afforded *p*-arsinoglutaranilic acid (2 g.).

p-*Arsonoglutaranilic Acid* (III; R″ = H).—*p*-Arsinoglutaranilic acid (0·5 g.) was suspended in water (10 c.c.), and 2—3 drops of hydrogen peroxide (100 vol.) added. The pale brown solution which rapidly formed on warming was filtered and evaporated. The p-*arsonic acid* separated as an indefinitely crystalline, light brown solid, readily soluble in water and alcohol but insoluble in most organic solvents (Found: As, 22·8. $C_{11}H_{14}O_6NAs$ requires As, 22·65%). Attempts to prepare the anil by heating the acid led to the formation of a black tar.

Note on the Analysis of Arsenic in Organic Compounds.

The following modification of Monthulé's method (*Ann. Chim. anal.*, 1904, **9**, 308) has proved a time-saving procedure for the estimation of arsenic in this series.

The substance containing about 0·05 g. of arsenic is covered with a hot solution (5—8 c.c. for 0·2 g. of substance) of magnesia in nitric acid, *d* 1·38 (10 g. in 100 c.c.), in a silica crucible with a lid, and the mixture is slowly evaporated to dryness and finally ignited. The white residue is treated successively with water (5 drops) and concentrated hydrochloric acid (6—8 c.c.), and the resulting solution washed into a beaker and diluted to 100 c.c. Ammonium chloride (10 g.) is added, to prevent precipitation of magnesium hydroxide, followed by excess of aqueous ammonia (*d* 0·88). After 5 hours, the crystalline precipitate of magnesium ammonium arsenate is collected in a Gooch crucible, washed with dilute aqueous ammonia till free from chloride, dried at 100° for 10 minutes, slowly raised to a bright red heat over a Bunsen flame for a further 5 minutes, and finally weighed as magnesium pyroarsenate.

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