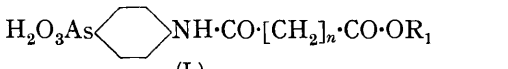
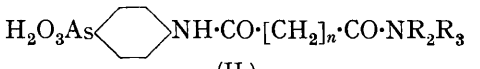
60. *New Derivatives of* p-*Arsanilic Acid. Part VI.* p-*Arsonopimelanilic and* p-*Arsonosuberanilic Acids and Related Compounds.*

By Gilbert T. Morgan and Eric Walton.

Pimelyl and suberyl derivatives of *p*-arsanilic acid have been prepared by condensing the *acid chlorides* of methyl hydrogen pimelate and methyl hydrogen suberate respectively with atoxyl. The products—*methyl* p-*arsonopimelanilate* (I; $n = 5$, $R_1 = Me$) and *methyl* p-*arsonosuberanilate* (I; $n = 6$, $R_1 = Me$)—were treated with various amines to give amides of type II ($n = 5$ and 6).



(I.)



(II.)

In order to purify the amides of the lower series (II; $n = 1, 2, 3$, etc.) it was usually only necessary to isolate them by acidification and recrystallise them from water. In the higher series ($n = 5, 6$, etc.), however, this procedure was often found inadequate, owing mainly to considerable hydrolysis. The amides of the pimelyl series had usually to be purified by alcoholic precipitation of by-products, chiefly p-*arsonopimelanilic acid* (I; $n = 5$, $R_1 = H$), in the form of their sodium salts. In the suberyl series, the sodium salts of the amides, owing to diminished solubility, could be purified by simple crystallisation from water.

Suberyl (II; $n = 6$) and adipyl (II; $n = 4$) derivatives show similar tendencies to hydrolyse readily to p-*arsonosuberanilic acid* and p-*arsonoadipanilic acid* respectively.

These amides have all been tested against experimental trypanosomiasis by Professor Warrington Yorke, F.R.S., and collaborators, with results in summary as follows :

Sodium salts.	M.L.D.	M.C.D.	C.R.
Pimelyl series (I and II; $n = 5$) :			
Ethyl ester	15	—	<1
Methyl ester	25	—	<1
Carboxylic acid	not examined		
Amide	90	20	>4
Methylamide	50	12·5	4
Dimethylamide	100	50	2
Ethylamide	100	50	2
n-Propylamide	100	50	2
Pimelanilide-*pp'*-diarsonic acid	12·5	—	<1

Sodium salts.	M.L.D.	M.C.D.	C.R.
Suberyl series (I and II; $n = 6$) :			
Ethyl ester	25	12·5	2
Methyl ester	25	>25	<1
Carboxylic acid	50	inactive	
Amide	50	12·5	4
Methylamide	25	12·5	2
Dimethylamide	>50	10	>5
Ethylamide	25	6·25	4
n-Propylamide	not prepared		
Suberanilide-*pp'*-diarsonic acid	10	inactive	

M.L.D. = minimum lethal dose, M.C.D. = minimum curative dose (both as mg. per 20 g. of mouse). C.R. = curative ratio.

These data indicate that trypanocidal power is now diminishing with increasing values of *n* (II). In fact, the maximum activity was apparently attained in the series where $n = 2$ and 3 respectively (Part I, J., 1931, 615; Part III, J., 1932, 276).

Sodium succinanilomethylamide-*p*-arsonate (II; $n = 2$; R_2, $R_3 = H$, Me), a highly active substance and one of the most readily prepared compounds in these lower series, is now undergoing clinical trial against both neurosyphilis and sleeping sickness.

Experimental.

Pimelyl Derivatives.

Methyl Hydrogen Pimelate and its Acid Chloride.—Methyl pimelate (20—22 g., b. p. 130—135°/17 mm.) was prepared from salicylic acid (25 g.) by a modification of the method recorded in " Organic Syntheses," XI, 42, whereby drainage of the crude product on a Buchner funnel and porous plate was obviated.

Methyl hydrogen pimelate, prepared from the dimethyl ester by partial hydrolysis according to Blaise and Koehler's method (*Bull. Soc. chim.*, 1910, **7**, 216), boiled at 181—182°/18 mm. (yields from 42 g. of methyl pimelate : methyl hydrogen pimelate, 20 g.; pimelic acid, 4 g.; recovered methyl pimelate, 10 g.).

A mixture of methyl hydrogen pimelate (11·7 g.) and thionyl chloride (8 c.c.), after 24 hours at 20° and 4 hours at 70°, gave the *acid chloride*, b. p. 135—136°/17 mm., in theoretical yield (Found : Cl, 18·6. $C_8H_{13}O_3Cl$ requires Cl, 18·4%).

Ethyl hydrogen pimelate and its acid chloride were also prepared in improved yield by these methods.

Methyl p-*Arsonopimelanilate* (I; $n = 5$, $R_1 = Me$).—Atoxyl (1 g.) in *N*-sodium hydroxide (4 c.c.) was well shaken with the acid chloride (0·5 c.c.) of methyl hydrogen pimelate, and the clear solution poured into an excess of cold dilute hydrochloric acid. The precipitated *methyl* p-*arsonopimelanilate* crystallised from water in small rectangular prisms, readily soluble in alcohol (yield, 12 g. from 30 g. of atoxyl) (Found : As, 20·2. $C_{14}H_{20}O_6NAs$ requires As, 20·1%). The *sodium* salt separated from dilute ethyl alcohol in minute leaflets, p_H 7·5 (Found : As, 17·9. $C_{14}H_{19}O_6NAsNa,H_2O$ requires As, 18·1%).

Ethyl p-*arsonopimelanilate* (I; $n = 5$, $R_1 = Et$), prepared in a similar manner from the acid chloride of ethyl hydrogen pimelate, crystallised from water in flattened prisms, readily soluble in warm alcohol (yield, 7 g. from 30 g. of atoxyl) (Found : As, 19·6. $C_{15}H_{22}O_6NAs$ requires As, 19·4%). The *sodium* salt was prepared by evaporation of its aqueous solution, p_H 7·5 (Found : As, 18·4. $C_{15}H_{21}O_6NAsNa$ requires As, 18·3%).

p-*Arsonopimelanilic acid* (I; $n = 5$, $R_1 = H$), obtained by hydrolysis of the above esters, crystallised from water in striated needles, soluble in warm alcohol (Found : As, 21·0. $C_{13}H_{18}O_6NAs$ requires As, 20·9%).

p-*Dichloroarsinopimelanilic acid*, from the above acid by reduction with sulphur dioxide and iodine (trace) in concentrated hydrochloric acid, crystallised from benzene in needles, m. p. 114—116°, but gave very low figures for chlorine (Found : Cl, 15·3. $C_{13}H_{16}O_3NCl_2As$ requires Cl, 18·7%). Hydrolysis gave p-*oxyarsinopimelanilic acid*, an amorphous solid, only sparingly soluble in water (Found : As, 23·2. $C_{13}H_{16}O_4NAs$ requires As, 23·1%).

Pimelanilamide-p-*arsonic Acid* (II; $n = 5$; R_2, R_3 = H, H).—The methyl ester (I) (6·3 g.) and concentrated aqueous ammonia (15 c.c.) were heated in a sealed tube for 24 hours at 75°. The crude amide, obtained by removal of the ammonia and acidification, was dissolved in 0·5*N*-caustic soda to p_H 5·5. Ethyl alcohol was then added till milky, and, after boiling, the solution was filtered and evaporated to dryness. Repetition of this process gave a *sodium* salt (2 g.), p_H 5·5 (Found : hydrolysable N, 3·4. $C_{13}H_{18}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·4%). *Pimelanilamide*-p-*arsonic acid*, from this sodium salt, crystallised from water in needles, which, on drying, were suddenly transformed into very loosely packed, rectangular plates, sparingly soluble in alcohol (Found : hydrolysable N, 3·6. $C_{13}H_{19}O_5N_2As$ requires hydrolysable N, 3·9%).

Pimelanilomethylamide-p-*arsonic Acid* (II; $n = 5$; R_2, R_3 = H, Me).—The ethyl ester (I) (2 g.) and 33% aqueous methylamine (4 c.c.), after 2 days at room temperature, followed by evaporation, gave the *methylamine* salt of the *methylamide* (Found : hydrolysable N, 6·6. $C_{15}H_{26}O_5N_3As$ requires hydrolysable N, 7·0%). *Pimelanilomethylamide*-p-*arsonic acid*, from this salt, crystallised from hot water in minute prisms (1·5 g.), sparingly soluble in alcohol (Found : hydrolysable N, 3·8. $C_{14}H_{21}O_5N_2As$ requires hydrolysable N, 3·8%).

The *sodium* salt crystallised from dilute alcohol in flattened needles, p_H 7·5 (Found : hydrolysable N, 3·25. $C_{14}H_{20}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·3%).

Pimelanilodimethylamide-p-*arsonic Acid* (II; $n = 5$; R_2, R_3 = Me, Me).—The methyl ester * (I) (6 g.) and 60% aqueous dimethylamine (15 c.c.) were heated under seal at 75° for 24 hours and then left at room temperature for 30 days. The dimethylamine was removed by evaporation and the crude dimethylamide, obtained on acidification, was converted into its sodium salt, p_H 7·5—8·0, with 2*N*-caustic soda. Ethyl alcohol was added till milky, and the filtrate evaporated to dryness. The *sodium* salt (4 g.) thus obtained was somewhat deliquescent (Found : hydrolysable N, 3·05. $C_{15}H_{22}O_5N_2AsNa,3H_2O$ requires hydrolysable N, 3·0%). *Pimelanilodimethylamide*-p-*arsonic acid*, from this sodium salt, crystallised from water in plates, sparingly soluble in hot alcohol (Found : hydrolysable N, 3·5. $C_{15}H_{23}O_5N_2As$ requires hydrolysable N, 3·6%).

Pimelaniloethylamide-p-*arsonic Acid* (II; $n = 5$; R_2, R_3 = H, Et).—A solution of the ethyl ester † (I) (8 g.) in 33% aqueous ethylamine (16 c.c.), left for 3 days at room temperature and worked up as described for the dimethylamide, gave a *sodium* salt (3 g.), p_H 7·5 (Found : hydrolysable N, 3·15. $C_{15}H_{22}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·2%). *Pimelaniloethylamide*-p-*arsonic acid*, from this salt, crystallised from water in hexagonal prisms, moderately

* Similar treatment of the ethyl ester (I) gave no trace of the dimethylamide.
† By analogy, the methyl ester should react more readily.

soluble in hot alcohol (Found : hydrolysable N, 3·5. $C_{15}H_{23}O_5N_2As$ requires hydrolysable N, 3·6%).

Pimelanilo-n-*propylamide*-p-*arsonic Acid* (II; $n = 5$; R_2, R_3 = H, Pr^n).—The methyl ester (I) (6 g.) and 60% aqueous *n*-propylamine were heated for 8 hours at 80° in a sealed tube. The crude propylamide, obtained in the usual way, was converted into sodium salt, p_H 8, with *N*-caustic soda, and ethyl alcohol added till just milky. The mixture was then warmed, and the filtrate cooled to 0°. The sodium salt crystallised, but at this stage gave low analytical figures for nitrogen. With acid, however, it gave pure *pimelanilo*-n-*propylamide*-p-*arsonic acid*, which, recrystallised from water, formed glistening leaflets (2 g.), fairly soluble in hot alcohol (Found : hydrolysable N, 3·5. $C_{16}H_{25}O_5N_2As$ requires hydrolysable N, 3·5%).

The *sodium* salt, p_H 8·0, from the free acid, crystallised from dilute alcohol in leaflets (Found : hydrolysable N, 3·1. $C_{16}H_{24}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·2%).

Pimelanilido-pp'-*diarsonic acid* was prepared by shaking pimelyl dichloride (1 g.) with a solution of atoxyl (3 g.) in water (6 c.c.) and sufficient 2*N*-caustic soda to maintain alkalinity, and acidifying the product. The *diarsonic acid*, after purification through its sodium salt (p_H 8), was an amorphous solid, almost insoluble in hot water and alcohol (yield, 1·5 g. from 6 g. of atoxyl) (Found : As, 26·6. $C_{19}H_{24}O_8N_2As_2$ requires As, 26·9%). The *disodium* salt, p_H 8, was precipitated from aqueous solution by addition of alcohol (Found : As, 24·8. $C_{19}H_{22}O_8N_2As_2Na_2$ requires As, 24·9%).

Suberyl Derivatives.

Methyl Hydrogen Suberate and its Acid Chloride.—Suberic acid (69·2 g.), methyl alcohol (24 c.c.), and sulphuric acid (3·5 c.c.), heated at 100° for 12 hours and worked up as described for methyl hydrogen adipate (Part IV; J., 1933, 91), gave recovered suberic acid (8 g.), methyl suberate (27 g.), and methyl hydrogen suberate (33 g.), b. p. 185—189°/17 mm., m. p. 17—19°. With thionyl chloride (1·3 mols.) the last gave a theoretical yield of its *acid chloride*, b. p. 163—165°/34 mm. (Found : Cl, 16·5. $C_9H_{15}O_3Cl$ requires Cl, 17·2%).

Ethyl hydrogen suberate and its acid chloride were prepared by the same methods.

Methyl p-*arsonosuberanilate* (I; $n = 6$, R_1 = Me), prepared as described for methyl *p*-arsonopimelanilate (p. 291), was found to be contaminated with *p*-arsanilic acid and suberic acid. These were removed by washing with hydrochloric acid, followed by Soxhlet extraction with hot benzene. The *methyl* ester then crystallised from water in curved leaflets, soluble in hot alcohol (yield, 9 g. from 32 g. of atoxyl) (Found : As, 19·3. $C_{15}H_{22}O_6NAs$ requires As, 19·35%). The *sodium* salt crystallised from water in large plates, p_H 6·5 (Found : As, 17·2. $C_{15}H_{21}O_6NAsNa,H_2O$ requires As, 17·5%).

Ethyl p-*arsonosuberanilate* (I; $n = 6$, R_1 = Et), prepared from the acid chloride of ethyl hydrogen suberate and purified as described above for the corresponding methyl ester, crystallised from water in irregular leaflets, soluble in alcohol (Found : As, 19·3. $C_{16}H_{24}O_6NAs$ requires As, 18·7%). The *monosodium* salt, p_H 6·5, crystallised from water in large plates, p_H 6·5, almost insoluble in cold water (Found : As, 17·6. $C_{16}H_{23}O_6NAsNa$ requires As, 17·7%). The *disodium* salt, p_H 8·5, was very soluble in cold water (Found : As, 17·4. $C_{16}H_{22}O_6NAsNa_2$ requires As, 16·8%).

p-*Arsonosuberanilic acid* (I; $n = 6$, R_1 = H), readily obtained by hydrolysis of the above esters, crystallised from water in hexagonal needles, insoluble in alcohol (Found : As, 19·8. $C_{14}H_{20}O_6NAs$ requires As, 20·0%). The *sodium* salt, p_H 6·5, was very soluble in water (Found : As, 17·9. $C_{14}H_{19}O_6NAsNa,H_2O$ requires As, 18·1%).

p-*Dichloroarsinosuberanilic acid*, from the above acid (I; R_1 = H) by reduction, crystallised from toluene in ill-defined nodules, m. p. 152—156°, which, like *p*-dichloroarsinopimelanilic acid (p. 291), gave low analytical figures for chlorine (Found : Cl, 17·0. $C_{14}H_{18}O_3NCl_2As$ requires Cl, 18·0%).

Hydrolysis gave p-*oxyarsinosuberanilic acid*, separating from water, in which it is sparingly soluble, as an amorphous solid (Found : As, 21·75. $C_{14}H_{18}O_4NAs$ requires As, 22·1%).

Suberanilamide-p-*arsonic Acid* (II; $n = 6$; R_2, R_3 = H, H).—The methyl ester (I) (6 g.) and concentrated aqueous ammonia (18 c.c.) were heated at 100° for 12 hours. The crude amide, obtained by acidification, was converted into its *sodium* salt (p_H 6·5), which crystallised from water in leaflets, p_H 6·5 (0·75 g.) (Found : hydrolysable N, 3·2. $C_{14}H_{20}O_5N_2AsNa,2H_2O$ requires hydrolysable N, 3·3%). *Suberanilamide*-p-*arsonic acid*, from its sodium salt, crystallised from water in needles, insoluble in alcohol (Found : hydrolysable N, 3·6. $C_{14}H_{21}O_5N_2As$ requires hydrolysable N, 3·8%).

Suberanilomethylamide-p-*arsonic Acid* (II; $n = 6$; R_2, R_3 = H, Me).—The methyl ester (I) (4 g.) and 33% aqueous methylamine (10 c.c.) were kept at 100° for 4 hours, and the crude acid obtained from this mixture converted into *sodium* salt, p_H 6·5, crystallising from water in leaflets (1 g.) (Found : hydrolysable N, 3·4. $C_{15}H_{22}O_5N_2AsNa$ requires hydrolysable N, 3·4%). *Suberanilomethylamide*-p-*arsonic acid*, from its sodium salt, crystallised from water in rosettes of needles, insoluble in alcohol (Found : hydrolysable N, 3·6. $C_{15}H_{23}O_5N_2As$ requires hydrolysable N, 3·6%).

Suberanilodimethylamide-p-*arsonic Acid* (II; $n = 6$; R_2, R_3 = Me, Me).—The methyl ester (I) (10 g.) and 65% aqueous dimethylamine (30 c.c.) were heated at 100° for 12 hours with occasional shaking. The upper layer of dimethylamine was removed, and the lower layer acidified. The crude dimethylamide, thus obtained, was converted into its *sodium* salt (p_H 6·0), which crystallised from water in well-defined prisms (3 g.) (Found : hydrolysable N, 3·2. $C_{16}H_{24}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·2%). *Suberanilodimethylamide*-p-*arsonic acid*, from this sodium salt, was indefinitely crystalline and fairly soluble in hot alcohol (Found : hydrolysable N, 3·25. $C_{16}H_{25}O_5N_2As$ requires hydrolysable N, 3·5%).

Suberaniloethylamide-p-*arsonic Acid* (II; $n = 6$; R_2, R_3 = H, Et).—The *sodium* salt of this acid, prepared from the methyl ester (I) and 65% aqueous ethylamine as described above for the corresponding dimethylamide, crystallised from water in rectangular plates (yield : 0·6 g. from 4 g. of methyl ester) (Found : hydrolysable N, 3·2. $C_{16}H_{24}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·2%).

The *ethylamide* from this salt crystallised from water in minute leaflets, fairly soluble in hot alcohol (Found : hydrolysable N, 3·3. $C_{16}H_{25}O_5N_2As$ requires hydrolysable N, 3·5%).

Suberanilide-pp′-*diarsonic Acid*.—Suberyl dichloride (10 g.) and 6*N*-caustic soda (35 c.c.) were shaken in small portions with atoxyl (30 g.) in water (100 c.c.) at 50°. The solid obtained by acidification was twice washed with boiling water and further purified through its sodium salt. The *diarsonic acid* was a white amorphous solid, insoluble in water and alcohol (Found : As, 25·8. $C_{20}H_{26}O_8N_2As_2$ requires As, 26·2%). The *disodium* salt (p_H 8) was isolated by alcoholic precipitation (Found : As, 23·2. $C_{20}H_{24}O_8N_2As_2Na_2,2H_2O$ requires As, 23·0%).

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