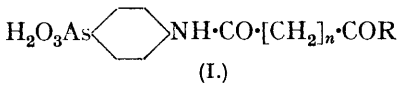
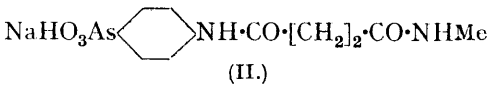
206. *New Derivatives of* p-*Arsanilic Acid. Part VII.* p-*Arsonoazelanilic and* p-*Arsonosebacanilic Acids and Related Compounds.*

By GILBERT T. MORGAN and ERIC WALTON.

AZELAYL and sebacyl derivatives (I; $n = 7$ and 8 respectively, R = NH_2, NHMe, etc.) of *p*-arsanilic acid have been prepared in the general manner already outlined (Part VI,



(I.)



(II.)

J., 1935, 290), and their *sodium* salts tested against experimental sleeping sickness under the direction of Professor Warrington Yorke, F.R.S., at the Liverpool School of Tropical Medicine, with results as follows :

Sodium Salts.	*Azelayl Series.*		*Sebacyl Series.*		
	M.L.D.		M.L.D.	M.C.D.	C.R.
Ethyl ester (R = OEt)	25	Some action	16	8	2
Methyl ester (R = OMe)	12·5	,,	16	Some action	
Carboxylic acid (R = OH)	100	,,	32	Slight action	
Amide (R = NH_2)	25	,,	6	Some action	
Methylamide (R = NHMe)	50	Slight action	5	,,	
Dimethylamide (R = NMe_2)		Not prepared	5	Inactive	
Ethylamide (R = NHEt)	?	Inactive		Not prepared	
Anilide (R = NHPh)		Not prepared	8	Slight action	
pp'-Diarsonic acid		Only free acid prepared	10	Inactive	

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

It will be seen that, in general, there is a considerable rise in toxicity as compared with earlier series, but no corresponding increase in curative action. In view of the lower arsenic content, this enhanced toxicity is a noteworthy feature, which at least illustrates the empirical nature of the search for chemotherapeutic agents.

The results communicated in the present paper represent the continuation of a research which had for its object the preparation of aromatic arsenicals having the general formula (I), where R is an amino- or substituted amino-group.

The series has been ascended from the malonyl group ($n = 1$) to the derivatives of azelaic and sebacic acid ($n = 7$ and 8 respectively) described below.

Some 70 individual compounds have been prepared and tested in the form of sodium salts against sleeping sickness and syphilis. Of this total, 17 have exhibited considerable activity (curative ratios, 4 to 10), whereas only 19 have proved to be quite inactive.

One of the most promising of the active substances, the compound (II), has been prepared on a considerable scale, and employed in systematic clinical trials. It has not only given very satisfactory results in trypanosomiasis but has also proved to be unexpectedly potent in the earlier stages of syphilis. This new drug is now being employed under the name of Neocryl (Yorke, Murgatroyd, and others, *Brit. Med. J.*, 1936, i, 1042).

EXPERIMENTAL.

Azelayl Derivatives.

Methyl Hydrogen Azelate and its Acid Chloride.—Azelaic acid (75 g.), methyl alcohol (40 c.c.) and sulphuric acid (5 c.c.), after 10 hours on the steam-bath, yielded, by distillation, methyl

hydrogen azelate (20 g.), b. p. 190—195°/15 mm., m. p. 21—24°. With thionyl chloride, it gave a theoretical yield of its *acid chloride*, b. p. 150—155°/15 mm. (Found : Cl, 15·8. $C_{10}H_{17}O_3Cl$ requires Cl, 16·1%).

Ethyl hydrogen azelate and its *acid chloride*, b. p. 156—160°/20 mm., were prepared in the same way (Found for acid chloride : Cl, 14·5. $C_{11}H_{19}O_3Cl$ requires Cl, 15·1%).

Methyl p-*Arsonoazelanilate* (I; $n = 7$, R = OMe).—Sodium *p*-arsanilate (1 g.), *N*-sodium hydroxide (4 c.c.), and the acid chloride of methyl hydrogen azelate (1·5 c.c.) were shaken together. The solid obtained on acidification was extracted with benzene to remove azelaic acid and recrystallised from slightly acid solution, *methyl* p-*arsonoazelanilate* being obtained in hair-like needles, readily soluble in warm alcohol (yield, 5 g. from 60 g. of sodium *p*-arsanilate) (Found : As, 19·1. $C_{16}H_{24}O_6NAs$ requires As, 18·7%). The *sodium* salt crystallised in glistening plates, p_H 7·5, readily soluble in warm water (Found : As, 16·9. $C_{16}H_{23}O_6NAsNa,H_2O$ requires As, 17·0%). *Ethyl* p-*arsonoazelanilate* (I; $n = 7$, R = OEt), prepared in the same way, crystallised from water in minute leaflets, slightly soluble in hot alcohol (yield, 1 g. from 20 g. of sodium *p*-arsanilate). It melted in contact with water at 100°, but otherwise has no melting point (Found : As, 18·65. $C_{17}H_{26}O_6NAs$ requires As, 18·1%). The *sodium* salt crystallised in plates, p_H 6·5 (Found : As, 17·1. $C_{17}H_{25}O_6NAsNa$ requires As, 17·1%).

p-*Arsonoazelanilic acid* (I; $n = 7$, R = OH), obtained by hydrolysis of the ester, crystallised from water in glistening leaflets, soluble in warm alcohol (Found : As, 19·5. $C_{15}H_{22}O_6NAs$ requires As, 19·4%). Its *sodium* salt, p_H 7·0, was prepared by precipitation with alcohol (Found : As, 18·0. $C_{15}H_{21}O_6NAsNa$ requires As, 18·3%).

p-*Oxyarsinoazelanilic Acid.*—Reduction of *p*-arsonoazelanilic acid with sulphur dioxide in hydrochloric acid yielded the crude dichloroarsino-compound, which could not be purified. On hydrolysis, however, it gave the *arsinic oxide*, crystallising from water in plates (Found : As, 21·0. $C_{15}H_{20}O_4NAs$ requires As, 21·2%).

Azelanilamide-p-*arsonic Acid* (I; $n = 7$, R = NH_2).—The methyl ester (I; R = OMe) (4 g.) and excess of concentrated aqueous ammonia were heated in a sealed tube at 100° for 24 hours. The crude amide, obtained by acidification, was converted into its *sodium* salt, which crystallised from water in striated leaflets, p_H 6·5 (1·8 g.) (Found : hydrolysable N, 3·3. $C_{15}H_{22}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·3%). *Azelanilamide*-p-*arsonic acid*, from its sodium salt, crystallised from water in branching needles, almost insoluble in alcohol (Found : hydrolysable N, 3·5. $C_{15}H_{23}O_5N_2As$ requires hydrolysable N, 3·6%).

Azelanilomethylamide-p-*arsonic Acid* (I; $n = 7$, R = NHMe).—The methyl ester (I; R = OMe) (4 g.) and 33% aqueous methylamine (12 c.c.) were heated at 70° for 2½ hours, and the gelatinous solid, obtained by acidification, was dried and ground with dilute hydrochloric acid to remove *p*-arsanilic acid. It was purified through its *sodium* salt, which crystallised from water in leaflets, p_H 6·5 (2·5 g.) (Found : hydrolysable N, 3·2. $C_{16}H_{24}O_5N_2AsNa$ requires hydrolysable N, 3·3%).

Azelanilomethylamide-p-*arsonic acid*, from its sodium salt, is an amorphous solid, sparingly soluble in water and alcohol (Found : hydrolysable N, 3·5. $C_{16}H_{25}O_5N_2As$ requires 3·5%).

Azelaniloethylamide-p-*arsonic Acid* (I; $n = 7$, R = NHEt).—The methyl ester (3 g.) and 65% aqueous ethylamine (7 c.c.) were heated at 80° for 6 hours. The crude ethylamide was purified through its sodium salt, which crystallised from water in leaflets, p_H 7·5 (1·3 g.) (Found : hydrolysable N, 2·8. $C_{17}H_{26}O_5N_2AsNa,3H_2O$ requires hydrolysable N, 2·9%).

Azelaniloethylamide-p-*arsonic acid* crystallised from water in plates, slightly soluble in hot alcohol (Found : hydrolysable N, 3·2. $C_{17}H_{27}O_5N_2As$ requires hydrolysable N, 3·4%).

Azelanilide-pp'-*diarsonic Acid.*—Sodium *p*-arsanilate (30 g.), azelayl dichloride (8 g.), and 6*N*-sodium hydroxide (30 c.c.) were shaken together, and the solid, obtained by acidification, washed repeatedly with boiling water to remove azelaic and *p*-arsonoazelanilic acids. The *diarsonic acid* (0·4 g.) after purification through its sodium salt was an amorphous solid, insoluble in alcohol (Found : As, 25·0. $C_{21}H_{28}O_8N_2As_2$ requires As 25·6%).

Sebacyl Derivatives.

Methyl Hydrogen Sebacate.—(*a*) Sebacic acid (100 g.), methyl alcohol (32 c.c.), and concentrated sulphuric acid (2·5 c.c.) were heated for 12 hours on the steam-bath. An ethereal extract of the diluted product yielded, by fractional distillation, methyl sebacate (38 g.), b. p. 175°/20 mm., methyl hydrogen sebacate (40 g.), b. p. 208°/20 mm., and some residual sebacic acid.

(*b*) Methyl sebacate (100 g.) and methyl-alcoholic potassium hydroxide (25 g. in 100 c.c.)

were warmed together for 5 minutes. An ethereal extract of the acidified product yielded unchanged ester (33 g.), methyl hydrogen sebacate (34 g.), and residual sebacic acid.

(*c*) Methyl sebacate (21·4 g.) and sebacic acid (18·5 g.), refluxed together at atmospheric pressure for 6—7 hours, yielded, by direct distillation, unchanged methyl ester (8 g.), methyl hydrogen sebacate (15·7 g.), and residual sebacic acid. The *acid chloride* (b. p. 177°/23 mm.) of methyl hydrogen sebacate was obtained in yields of 60—70% by means of thionyl chloride, but gave low analytical figures (Found : Cl, 11·8, 11·8. $C_{11}H_{19}O_3Cl$ requires Cl, 15·1%). Ethyl hydrogen sebacate (40 g.) was prepared from sebacic acid (100 g.) by method (*a*). Its *acid chloride* also gave low analytical figures (Found : Cl, 10·5. $C_{12}H_{21}O_3Cl$ requires Cl, 14·3%).

Methyl p-*Arsonosebacanilate* (I; $n = 8$, R = OMe).—A solution of sodium *p*-arsanilate (29 g.) and sodium carbonate (7·5 g.) in water (about 150 c.c.) was shaken mechanically with the acid chloride (24 g.) of methyl hydrogen sebacate for 2 hours. The solid, obtained on acidification, was extracted alternately with ether and small quantities of boiling water, and the residual *methyl* p-*arsonosebacanilate* (6 g.) crystallised from a large volume of water, giving parallelogrammatic plates, slightly soluble in hot alcohol (Found : As, 17·9. $C_{17}H_{26}O_6NAs$ requires As, 18·1%).

Its *sodium* salt crystallised from water in glistening leaflets, p_H 7·0, only sparingly soluble in cold water (Found : As, 17·3. $C_{17}H_{25}O_6NAsNa$ requires As, 17·15%).

Ethyl p-*arsonosebacanilate* (I; $n = 8$, R = OEt), prepared in the same way and purified through its sodium salt, crystallised from water in slender prisms, soluble in alcohol (Found : As, 18·1. $C_{18}H_{28}O_6NAs$ requires As, 17·5%). Its *sodium* salt crystallised from water in rhombic plates, p_H 7·0 (Found : As, 16·4. $C_{18}H_{27}O_6NAsNa$ requires As, 16·6%).

p-*Arsonosebacanilic acid*, obtained by hydrolysis, crystallised from water in needles, soluble in warm alcohol (Found : As, 18·4. $C_{16}H_{24}O_6NAs$ requires As, 18·7%). Its *sodium* salt was prepared by evaporation of its solution, p_H 7·0 (Found : As, 16·7. $C_{16}H_{23}O_6NAsNa,H_2O$ requires As, 17·0%).

p-*Dichloroarsinosebacanilic acid*, obtained by the usual reduction method, melted at 130—135°, but gave low analytical figures for chlorine (Found : Cl, 13·4. $C_{16}H_{22}O_3NCl_2As$ requires Cl, 16·8%). p-*Oxyarsinosebacanilic acid*, obtained from the dichloride by hydrolysis, dried to a light fawn solid (Found : As, 19·8. $C_{16}H_{22}O_4NAs$ requires As, 20·4%).

Sebacanilamide-p-*arsonic acid* (I; $n = 8$, R = NH_2), prepared and purified as described for the corresponding azelayl derivative (p. 903), crystallised from water in jagged needles, slightly soluble in hot alcohol (Found : hydrolysable N, 3·5. $C_{16}H_{25}O_5N_2As$ requires hydrolysable N, 3·5%). Its *sodium* salt crystallised from water in leaflets, p_H 7·0, which effloresced on drying at 100° (Found : hydrolysable N, 3·2. $C_{16}H_{24}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·2%).

Sebacanilomethylamide-p-*arsonic Acid* (I; $n = 8$, R = NHMe).—The methyl ester (I; $n = 8$, R = OMe) (9 g.) and 33% aqueous methylamine (25 c.c.) were heated in a sealed tube at 100° for 5 hours. To dissolve the ester, the tube had to be shaken vigorously at intervals. The acid was worked up in the usual manner and purified through its *sodium* salt (yield, 1 g.), which crystallised from water in leaflets, p_H 7·5 (Found : hydrolysable N, 3·0. $C_{17}H_{26}O_5N_2AsNa,H_2O$ requires hydrolysable N, 3·1%).

Sebacanilomethylamide-p-*arsonic acid* crystallised from water in minute needles, sparingly soluble in water, but easily soluble in alcohol (Found : hydrolysable N, 3·25. $C_{17}H_{27}O_5N_2As$ requires hydrolysable N, 3·4%).

Sebacanilodimethylamide-p-*arsonic Acid* (I; $n = 8$, R = NMe_2).—The methyl ester (I; R = OMe) (12 g.) and 65% aqueous dimethylamine (40 c.c.) were heated under seal at 80° for 6 hours. The crystalline solid that separated on cooling was collected and washed with 65% dimethylamine, and its aqueous solution acidified. The resulting free acid was converted into its *sodium* salt, which crystallised from water in well-defined rectangular prisms, p_H 6·5 (6 g.) (Found : hydrolysable N, 3·1. $C_{18}H_{28}O_5N_2AsNa$ requires hydrolysable N, 3·1%).

Sebacanilodimethylamide-p-*arsonic acid*, obtained from its sodium salt, crystallised in feathery needles, soluble in warm alcohol (Found : hydrolysable N, 3·25. $C_{18}H_{29}O_5N_2As$ requires hydrolysable N, 3·3%).

Attempts to prepare *sebacanilide*-p-*arsonic acid* (I; $n = 8$, R = NHPh) by condensing *p*-arsonosebacanilic acid (*q.v.*) or its methyl ester with aniline were unsuccessful. It was, however, eventually obtained as follows :

$$MeO{\cdot}CO{\cdot}[CH_2]_8{\cdot}COCl \longrightarrow MeO{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}NHPh \longrightarrow$$
$$Cl{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}NHPh \longrightarrow H_2O_3As{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO{\cdot}NHPh$$

Methyl Sebacanilate.—The acid chloride of methyl hydrogen sebacate (1 mol.) and aniline

(2 mols.) were stirred together with warming. The mass was washed out with hydrochloric acid, and the *methyl sebacanilate* (yield, 80%) crystallised from petroleum (b. p. 60—80°), giving needles, m. p. 67—68° (Found : C, 70·1; H, 8·7; N, 4·6. $C_{17}H_{25}O_3N$ requires C, 70·1; H, 8·6; N, 4·8%).

Sebacanilic acid (yield, 90%) was obtained by careful hydrolysis of the methyl ester. It crystallised from water in leaflets, m. p. 121—122° (Found : C, 69·9; H, 8·7; N, 4·6. $C_{16}H_{23}O_3N$ requires C, 69·3; H, 8·3; N, 5·0%). It reacted readily with thionyl chloride in chloroform to give its acid chloride, which, after removal of solvent, etc., appeared as a residual yellow syrup.

Sebacanilide-p-*arsonic Acid.*—*p*-Arsanilic acid (12 g.) and the crude acid chloride of sebacanilic acid (7 g.) were stirred together at 150°, the hard mass was washed out with excess of hot dilute hydrochloric acid, and the solid dissolved in dilute aqueous sodium hydroxide to a solution of p_H 8·5—9·0 (75 c.c.). Charcoal and alcohol (150 c.c.) were added, and the solution filtered while hot, to remove brown impurities. On cooling, the *sodium* salt (1 g.) separated in needles, p_H 8·0 (Found : As, 15·0. $C_{22}H_{28}O_5N_2AsNa$ requires As, 15·0%).

Sebacanilide-*p*-arsonic acid was obtained from its sodium salt as a white gelatinous solid, almost insoluble in water. On boiling with water, however, it was converted into minute needles, soluble in hot alcohol (Found : As, 15·2. $C_{22}H_{29}O_5N_2As$ requires As, 15·7%).

Sebacanilide-pp'-*diarsonic acid.*—Sodium *p*-arsanilate (30 g.), sebacyl dichloride (12 g.), and sodium carbonate (5·3 g.) in water (200 c.c.) were shaken together mechanically for 1 hour, and the mixture acidified. After the resulting solid had been washed several times with boiling water, the *diarsonic acid* was obtained as an amorphous solid, insoluble in alcohol (Found : As, 23·6. $C_{22}H_{30}O_8N_2As_2$ requires As, 25·0%). The amorphous *trisodium* salt, p_H 9·5, was obtained by evaporation (Found : As, 20·6. $C_{22}H_{27}O_8N_2As_2Na_3,3H_2O$ requires As, 20·7%).

CHEMICAL RESEARCH LABORATORY, TEDDINGTON, MIDDLESEX. [*Received, May 23rd,* 1936.]