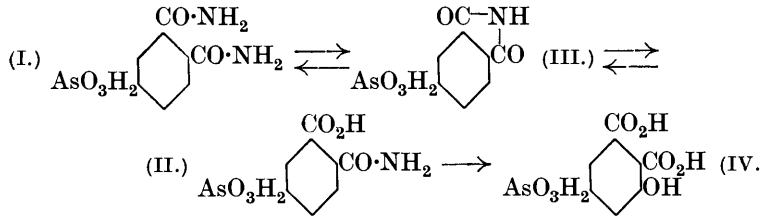
CCCCL.—*Trypanocidal Action and Chemical Constitution. Part XI. Aromatic Arsonic Acids containing Amide Groups.*

By AARON COHEN, HAROLD KING, and WINIFRED I. STRANGEWAYS.

IN Part IX (Gough and King, J., 1930, 669) the discovery was reported that benzamide-*p*-arsonic acid possessed marked trypanocidal activity. Unfortunately this activity was accompanied by the production of nervous symptoms in mice and to avoid this a preliminary survey was made of compounds containing additional substituents, either in the amide group or in the benzene nucleus. The present communication is in amplification of the previous paper and is designed to illustrate the effect of additional amido-, hydroxy-, amino-, and acetamido-groups on the trypanocidal activity as shown by the preparation of phthalimide- and phthalamide-4-arsonic acids, terephthalamidearsonic acid, anthranilamide-4-arsonic acid, salicylamide-4-arsonic acid, *N*-acetylanthranilamide-4- and -5-arsonic acids, hippuramide-*p*-arsonic acid, and a number of allied substances.

When methyl 4-arsonophthalate is treated with concentrated aqueous ammonia it is converted into *phthalamide-4-arsonic acid* (I), under conditions which it has not been found possible to define. The usual product is 5-*arsonophthalamic acid* (II), which on being

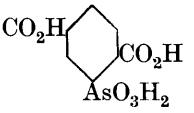


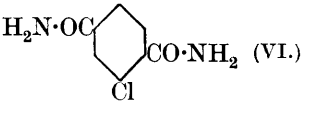
heated to 225° passes into *phthalimide-4-arsonic acid* (III). The latter by the action of concentrated aqueous ammonia at 50° yields a mixture of phthalamide-4-arsonic acid (I) and 5-arsonophthalamic acid (II), whilst at 150° the product is mainly 5-arsonophthalamic acid.

When an attempt was made to orientate 5-arsonophthalamic acid (II) by the action of alkaline hypobromite at 0°, nitrogen was evolved and an acid was isolated as an *acid potassium* salt to which the constitution 3-*hydroxy*-5-*arsonophthalic acid* (IV) is given. It probably arises through an intermediate bromo-acid where the bromine atom is activated by the adjacent carboxyl group (compare Hurtley, J., 1929, 1870).

The approach to the terephthalic acid series was made through *p*-xylidine, which by the Bart–Schmidt reaction gives *p*-xylylarsonic acid, m. p. 191—192°. Michaelis (*Annalen*, 1902, **320**, 271) obtained an acid, m. p. 223°, to which he attributed this constitution, from bromo-*p*-xylene, through tri-*p*-xylylarsine. The m. p. 191—192° recorded in the present communication has been repeatedly confirmed; specimens of *p*-xylidine from a variety of sources and characterised by the m. p. of the acetyl derivative always give the same arsonic acid. The acid, m. p. 191—192°, gives an arsine dichloride, m. p. 60°, crystallising from light petroleum in plates. Michaelis records a m. p. 63°, but describes his product as crystallising in needles from light petroleum. A repetition of Michaelis's procedure with a view to clarifying these discrepancies is in progress.

On oxidation with permanganate *p*-xylylarsonic acid yields 2-*arsonoterephthalic acid* (V), which by the action of phosphorus

(V.) 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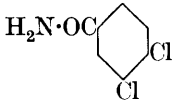
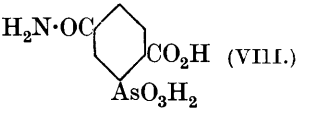
(VII.) 


(VIII.)

pentachloride, followed by treatment with ammonia, gives chloroterephthalamide (VI), 3 : 4-dichlorobenzamide (VII), and 2-*arsonoterephthalamic acid* (VIII).

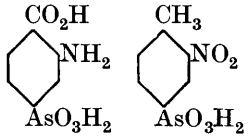
The first two on hydrolysis give acids with melting points in agreement with those recorded in the literature. The constitution of (VII) also follows from its production by a similar series of reactions from 4-arsono*iso*phthalic acid (Gough and King, *loc. cit.*). The results in this series thus parallel those obtained in the *iso*-phthalic acid series, it being found impossible to detect any formation of a diamide provided that the arsenic atom remains attached to the nucleus.

When, however, *methyl arsonoterephthalate* reacts with concentrated aqueous ammonia a product can be obtained containing 80% of *terephthalamidearsonic acid* mixed with 20% of 2-arsonoterephthalamic acid. Both acids are characterised by their very sparing solubility in boiling water; attempts to isolate the pure diamide through salts or other means led to further hydrolysis of one amide group. A by-product isolated in the preparation of methylarsonoterephthalate was 4-*methyl* 1-*hydrogen* 2-*arsonoterephthalate*, which by the action of ammonia gave 2-arsonoterephthalamic acid identical with that obtained through the acid chloride.

The following table shows the results obtained with the above-described amides when tested on an experimental infection of *Trypanosoma equiperdum* in mice, *T* signifying the maximum dose tolerated, expressed in milligrams per gram of mouse, *C* the minimum curative dose, and *r* the number of days during which the blood stream remained free from trypanosomes.

	T.	*C.*	*r.*
Phthalamide-4-arsonic acid	2·0	[inactive]	
Phthalimide-4-arsonic acid	0·25	0·2	4
5-Arsonophthalamic acid	1·75	[inactive]	
Terephthalamidearsonic acid	0·075	0·075	3
2-Arsonoterephthalamic acid	0·05	[inactive]	
p-Xylylarsonic acid	0·005	[inactive]	

To investigate the effect of an amino- or hydroxy-group ortho to the amide group in benzamide-*p*-arsonic acid, the synthesis of 4-*arsonoanthranilic acid* (IX) seemed desirable. The Bart–Schmidt reaction on 2-nitro-4-aminobenzoic acid proved unsatisfactory, but the nitration of *p*-tolylarsonic acid to 2-nitro-*p*-tolylarsonic acid (X), followed by oxidation with permanganate and reduction with



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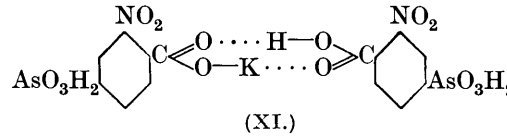
(X.)



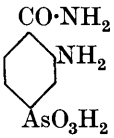
(XI.)

ferrous salts, proved suitable, although Michaelis (*loc. cit.*) had failed to effect this reduction of 3-nitro-4-benzarsonic acid to (IX).

When 2-nitro-*p*-tolylarsonic acid (X) is oxidised to 3-nitro-4-benzarsonic acid by potassium permanganate the product is obtained as an *acid potassium* salt containing one atom of potassium to 6 centres of acidity. The same phenomenon is seen in the above-mentioned acid potassium salt of 3-hydroxy-5-arsonophthalic acid (IV), where there is one atom of potassium to 8 centres of acidity. Whether the hydrogen or the potassium exerts co-valencies or whether both function as in (XI) is undecided, but a related and analogously constituted salt was described by La Coste (*Annalen*, 1881, **208**, 6) in the acid potassium salt of *p*-benzarsonic acid.

From 4-arsonoanthranilic acid (IX), the corresponding *arseno*-compound and *arsine dichloride* are readily obtained, and from the latter by esterification and oxidation methyl 4-arsonoanthranilate. This ester when subjected to the action of concentrated aqueous ammonia at 50° gives the desired *anthranilamide*-4-*arsonic acid* (XII), which on acetylation gives *acetanthranilamide*-4-*arsonic acid*. When, however, the parent 4-arsonoanthranilic acid (IX) is acetylated in alkaline solution it yields *acetic* 4-*arsono*-N-*acetanthranilic*

anhydride (XIII), a substance stable to cold *N*-caustic alkali but converted by brief boiling in 3*N*-sodium hydroxide solution mainly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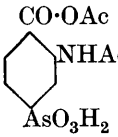
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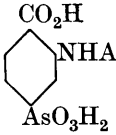
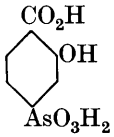
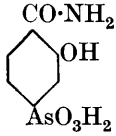

(XIV.)

into 4-*arsonoacetanthranilic acid* (XIV). The latter acid by the usual reactions gives an *arseno*-derivative and the corresponding *oxide*.

4-Arsonoanthranilic acid (IX) readily furnishes 4-*arsonosalicylic acid* (XV), which behaves anomalously when attempts are made to

(XV.) 

 (XVI.)

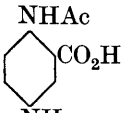
prepare its arseno-derivative. By using synthetic methyl alcohol, 4-arsonosalicylic acid (XV) can be esterified without reduction of the arsonic acid group, and the methyl ester on treatment with concentrated aqueous ammonia at 55° gives *salicylamide*-4-*arsonic acid* (XVI).

The toxicities and therapeutic activities of these substances are recorded below.

	T.	*C.*	*r.*
p-Tolylarsonic acid	0·005	[inactive]	
4-Arsonoanthranilic acid	0·75	[inactive]	
4-Arsenoanthranilic acid	0·15	0·15	>30
Anthranilic acid 4-arsine dichloride	0·02	[inactive]	
Anthranilamide-4-arsonic acid	1·0	0·5	>30
Acetanthranilamide-4-arsonic acid	3·0	1·5	>30
Acetic 4-arsonoacetanthranilic anhydride	0·5	0·5	3
4-Arsonoacetanthranilic acid	1·5	1·0	5
4-Arsenoacetanthranilic acid	0·04	0·02	5
Acetanthranilic acid 4-arsenoxide	0·01	0·005	5
4-Arsonosalicylic acid	0·05	[inactive]	
Salicylamide-4-arsonic acid	0·1	[inactive]	

The preparation of the isomeric 5-arsonoanthranilic acid and certain derivatives had already been described by O. and R. Adler (*Ber.*, 1908, **41**, 933) and by Kahn and Benda (*ibid.*, p. 3861), but the amides to which the greater interest is attached remained unknown. These authors used as their starting material *o*-toluidine, which by the Béchamp reaction with arsenic acid gave 6-amino-*m*-tolylarsonic acid. To avoid the unsatisfactory yield in the Béchamp reaction, a new mode of approach to this series seemed desirable, and this was found in the nitration of acetanthranilic acid

with fuming nitric acid. The products are 3- and 5-nitroacetanthranilic acids, which are readily separable, and the latter on reduction with ferrous sulphate and ammonia gives 5-aminoacetanthranilic acid (XVII), as *sulphate*, in almost quantitative yield. On diazotisation and treatment with sodium arsenite this acid furnishes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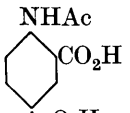
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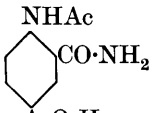
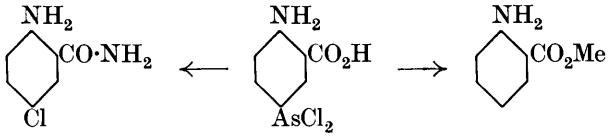

(XIX.)

5-arsonoacetanthranilic acid (XVIII), which is converted through its silver salt into the *methyl* ester. The latter by the action of concentrated aqueous ammonia at 55° gives *acetanthranilamide-5-arsonic acid* (XIX).

It has not been found possible to prepare the parent amide, anthranilamide-5-arsonic acid, for when attempts were made to esterify 5-arsonoanthranilic acid or its *arsine dichloride* (XX), it was converted into methyl anthranilate (XXI) with complete fission of arsenic from the nucleus. Furthermore, when anthranilic acid arsine dichloride was digested with thionyl chloride, and the product

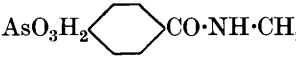

(XXII.) (XX.) (XXI.)

treated with ammonia, 5-chloroanthranilamide (XXII) was formed, agreeing in properties with a substance of this constitution obtained by Dorsch (*J. pr. Chem.*, 1886, **33**, 50) by the action of ammonia on chloroisatoic acid anhydride.

The toxicities and therapeutic activities of these substances and certain related compounds are shown below.

	T.	*C.*	*r.*
5-Arsonoacetanthranilic acid	1·5	[inactive]	
5-Arsenoacetanthranilic acid	0·1	0·05	7
Acetanthranilamide-5-arsonic acid	1·5	1·5	>30
5-Arsonoanthranilic acid	2·5	[inactive]	
5-Arsenoanthranilic acid	0·07	[inactive]	

Of the compounds described in Part IX, the ethylamide of *p*-arsonohippuric acid (XXIII) was the most efficient, having a


(XXIII.)

chemotherapeutic index of 1/3 and curing with great regularity within this range. The preparation of the parent amide was not possible

by the process then employed, but it has now been obtained by the action of ammonia on the ester, *methyl* p-*arsonohippurate*. It proved to be inferior to the ethylamide. Further investigation of this promising series to find where the maximum of activity lies has not been undertaken owing to the difficulties attendant on their preparation.

The following table records the therapeutic activities of these amides and certain related substances :—

	T.	*C.*	*r.*
Phenylglycine-*p*-arsonic acid	1·5	1·25	3
p-Arsenophenylglycine	0·2	0·075	>30
p-Arsonohippuric acid	1·0	[inactive]	
p-Arsenohippuric acid	0·1	0·1	5
Hippuramide-*p*-arsonic acid	4·5	3·0	>30
Hippuroethylamide-*p*-arsonic acid	4·5	1·5	>30
Arsenobenzoic acid	0·03	[inactive]	

Therapeutic Considerations.

The therapeutic results recorded in the preceding tables bring out clearly certain underlying principles. Gough and King (*loc. cit.*) showed that a series of arsonic or arsinic (arsinous) acids containing carboxyl or sulpho-groups were quite inactive when tested on experimental trypanosomiasis (*T. equiperdum*) in mice, but that when they were converted into primary amides, carboxyamides or sulphonamides, the products were trypanocidally active in all cases. Further examples are recorded in this paper. Thus, whilst 5-arsonophthalamic acid, 2-arsonoterephthalamic acid, 4-arsonoanthranilic acid, 5-arsonoacetanthranilic acid, and 5-arsonoanthranilic acid are without activity, the corresponding imides and amides, phthalimidearsonic acid, terephthalamidearsonic acid, anthranilamide-4-arsonic acid, acetanthranilamide-4-arsonic acid and acetanthranilamide-5-arsonic acid all show some curative action, though of varying intensities in relation to the toxic dose.

The explanation for this behaviour seems to be that when these substances are injected into the blood stream in the form of neutral sodium salts, they are subjected to two main processes, excretion and reduction. Those substances containing sulpho- or carboxyl groups will be rapidly excreted, whether they are reduced to arsenoxides or not, since they contain solubilising groups. On the other hand, those containing amide groups will be excreted rapidly so long as they remain arsonic acids; but when once reduction to an arsenoxide has taken place, excretion will be slow, since the only solubilising group, the arsonic acid group, has disappeared.

Slow excretion.	Rapid excretion.
$NH_2 \cdot CO \cdot C_6H_4 \cdot AsO$	$NH_2 \cdot CO \cdot C_6H_4 \cdot AsO_3H_2$
	$CO_2H \cdot C_6H_4 \cdot AsO_3H_2$
	$CO_2H \cdot C_6H_4 \cdot AsO$

Such a view is supported by the results of Voegtlin and Thompson (*J. Pharm. Exp. Ther.*, 1922, **20**, 91), who showed in the case of 4-arsonic acids studied in the rat, that over 80% was excreted through the kidneys within 6 hours, whereas certain arsenoxides devoid of groups capable of forming neutral salts were only excreted to an extent less than 20% in 24 hours.

The difference between the two groups of substances, arsonic acids containing amide groups and those containing carboxy-groups, is naturally only relative. It is not surprising, therefore, to find that certain arsonic acids and arsenoxides containing carboxyl groups do show border-line trypanocidal activity. Thus 4-arsono-acetanthranilic acid, the corresponding arsenoxide, and phenylglycine-*p*-arsonic acid, all cause trypanosomes to disappear for a few days when given in doses near to the maximum tolerated. On the above view, this would mean that these two acids, 4-arsono-acetanthranilic acid and phenylglycine-*p*-arsonic acid, when reduced to the arsenoxides, are retained sufficiently long, in spite of the solubilising carboxyl groups, for the oxides to exert some lethal action on the trypanosomes. In this discussion the assumption has been made that all these arsonic acids, whatever their category, are capable of being reduced by the reducing systems of the mammalian body.

Additional evidence in support of the view that factors which favour retention by the body of the arsenoxides as such, or potentially as derivatives, favour trypanocidal action, is to be found in the behaviour of certain arseno-compounds described in this communication. It is well known that arseno-compounds are much less readily excreted than the corresponding arsonic acids. We have found, for instance, that when salvarsan is administered to normal mice in its maximally tolerated dose it will still prevent their infection with trypanosomes after the lapse of 14 days, whereas the corresponding arsonic acid will not prevent the infection after 24 hours. This means that, at the end of 14 days, there is more potential arsenoxide present in the mouse's tissues in the case of salvarsan than there is after 24 hours in the case of its arsonic acid, although the absolute amount of arsenic injected in the latter case is much higher. Evidence for this view is also given by the figures in the following table, from determinations of the arsenic content, expressed in parts per million, of the mouse's liver and spleen, the organs chiefly concerned in the storage and metabolism of arsenicals.

Salvarsan. (0·125 mg. per g. injected.)			3-Amino-4-hydroxyphenylarsonic acid. (1·125 mg. per g. injected.)		
	Liver.	Spleen.		Liver.	Spleen.
1 week	120	68	24 hours	7	10
2 weeks	51	11			

One might anticipate, therefore, that the presence of arseno-groups would thus tend to bring out trypanocidal action in compounds containing carboxyl groups. Such is indeed the case, for out of 7 arseno-compounds containing free carboxyl groups recorded in this paper, 5 showed trypanocidal activity. Thus 4-arsenoanthranilic acid, 4-arsenoacetanthranilic acid, 5-arsenoacetanthranilic acid, *p*-arsenophenylglycine and *p*-arsenohippuric acid were trypanocidally active, whereas *p*-arsenobenzoic acid and 5-arsenoanthranilic acid were inactive. The solubilising action of the carboxylic acid group is thus more than counterbalanced by the physical properties conferred by the arseno-linkage. Arseno-compounds usually form colloidal solutions, and in many of them it is possible that the arsenic atoms are linked in long main valency chains, thus

$$\begin{matrix} R & R & R & R & R \\ —As— & As— & As— & As— & As— \end{matrix}$$

It may be that it is the aggregation of such main valency chains to micelles which produces the anisotropy observed in concentrated salvarsan solutions.

Experimental.

Derivatives of Arsono-o-phthalic Acid.

Methyl 4-Arsonophthalate.—Methyl 4-aminophthalate was prepared from phthalide in yields of over 80% at each stage by the processes recommended by Hamilton and Jelinek (*J. Amer. Chem. Soc.*, 1927, **49**, 3167). The drastic conditions used by the same authors for the Bart reaction on this substance, which are said to yield 77—80% of the arsonic acid, were not tried.

Methyl 4-aminophthalate (20·9 g.) in water (100 c.c.) and hydrochloric acid (29 c.c., *d* 1·16) was diazotised at −10°. A solution of arsenious oxide (14·9 g.) in 2*N*-sodium hydroxide (94 c.c.) was run in slowly, the temperature being kept below 0°. During this process nitrogen was evolved, causing the production of a very voluminous froth. 2*N*-Sodium hydroxide solution (75 c.c.) was then gradually added until faint alkalinity was reached. The coupling reaction having become negative, the solution was neutralised to Congo-paper, concentrated under reduced pressure at 50°, and made definitely acid to Congo-paper; the arsonic acid then slowly crystallised. By concentration a succession of crops was obtained, 17·2 g. in all. This crude material contained arsenious oxide, which was separated by solution of the arsonic acid in saturated sodium hydrogen carbonate solution at 0°, filtration and acidification. The yield of pure arsonic acid crystallising in diamond-shaped plates was 41%. It melts at 148—149° and, contrary to the statement of

Hamilton and Jelinek, is insoluble in ether (Found: As, 23·4; MeO, 19·3. Calc.: As, 23·6; MeO, 19·5%).

Action of Ammonia on Methyl 4-Arsonophthalate.—(a) *Isolation of phthalamide-4-arsonic acid* (I). The dimethyl ester (3·45 g.) was added to aqueous ammonia (80 c.c., *d* 0·88) at −5°. After 2 days' keeping below 0°, the crystalline sheen had disappeared. The solution was then kept for 12 hours at room temperature and evaporated to a syrup at or below 30°. On solution in a little water and acidification to Congo-paper, a clear solution resulted which on keeping at 0° for 24 hours gave a felted mass of minute needles (1·25 g.). The *diamide* effervesced at 147° and proved on analysis to be a sesquihydrate (Found: loss at 95°, 8·5. $C_8H_9O_5N_2As,1\frac{1}{2}H_2O$ requires H_2O, 8·6%. Found for dried substance: N, 9·5. $C_8H_9O_5N_2As$ requires N, 9·7%). The diamide was obtained by two different workers using similar conditions, but all attempts to repeat the preparation have failed. The usual product is the half-amide. The diamide is soluble in 3 volumes of boiling water and the dried solid is converted into the imide by the action of heat.

(b) *Isolation of 5-arsonophthalamic acid* (II). Under similar conditions to the above, the dimethyl ester (8·0 g.) gave the *arsonophthalamic acid* (5·9 g.). On crystallisation from $2\frac{1}{2}$ volumes of boiling water it separates in well-formed plates which shrink between 220° and 225° and sometimes effervesce and are thereby converted into the imide. Some samples, however, pass into the imide on heating without any visible change. The arsonophthalamic acid also crystallises in a less stable form of very fine needles (Found: N, 4·7. $C_8H_8O_6NAs$ requires N, 4·8%). If acidification of the ammoniacal parent solution has been insufficient a *monoammonium* salt separates in prisms (Found: loss at 100°, 2·6. $C_8H_{11}O_6N_2As,\frac{1}{2}H_2O$ requires H_2O, 2·9%. Found for anhydrous salt: N, 9·2. $C_8H_{11}O_6N_2As$ requires N, 9·2%).

Phthalimide-4-arsonic Acid (III).—Finely powdered arsonophthalamic acid (4·5 g.) was heated under reduced pressure at 230° (external bath) for 4 hours. The product, dissolved in boiling water, on keeping, gave *phthalimide-4-arsonic acid* (3·0 g.), unmelted at 300°. This is soluble in 23 parts of boiling water and crystallises in small plates (Found: As, 27·3. $C_8H_6O_5NAs$ requires As, 27·7%).

Action of Ammonia on Phthalimide-4-arsonic Acid.—(a) *At* 150°. The imide (1·0 g.) was heated in a sealed tube with ammonia solution (10 c.c., *d* 0·88) at 150° for 12 hours. On removal of excess of ammonia, concentration and acidification, the solution deposited crude 5-arsonophthalamic acid (0·7 g.), crystallising in needles and plates. On recrystallisation from water (2 c.c.) it gave the pure

acid in plates (0·3 g.), shrinking at about 225° (Found : N, 4·7 Calc. : N, 4·8%) with re-formation of the imide.

(b) *At* 50°. The imide (1·0 g.) was heated with ammonia solution (20 c.c., *d* 0·88) for 3 hours at 50°. On acidification a small crop of crude diamide was obtained, crystallising as a felt of needles, m. p. 145° (efferv.). A mixed m. p. with a sample obtained from the dimethyl ester showed no depression. On analysis, however, it still proved to contain about 25% of the half-amide (Found : loss at 100°, 6·9. Calc. for sesquihyrate, 8·6. Found for dried amide : N, 8·2. Calc. for diamide : N, 9·7%).

Repetition on a larger scale gave mainly pure arsonophthalamic acid.

Action of Alkaline Hypobromite on 5-Arsonophthalamic Acid.—The half-amide (5·78 g.), dissolved in 33 c.c. of potassium hydroxide solution (6·7%) and cooled to 0°, was treated with potassium hypobromite solution [1 c.c. of bromine (1 mol.) in 66 c.c. of potassium hydroxide (6·7%)]. The yellow colour of the hypobromite was instantly discharged and nitrogen was gradually evolved. After 12 hours the solution was digested on the water-bath for 75 minutes, neutralised to Congo-paper, and concentrated. Well-formed leaflets of an *acid potassium* salt of *3-hydroxy-5-arsonophthalic acid* (IV) separated (1·7 g.) [Found : (micro) C, 29·2; H, 2·0. $C_8H_6O_8AsK$,$C_8H_7O_8As$ requires C, 29·5; H, 2·0%]. A portion (1 g.) dissolved in hot dilute hydrochloric acid gave on cooling the free *acid* (0·85 g.), crystallising in elongated plates [Found : (micro) C, 31·1; H, 2·3; (macro) As, 23·7, 23·9. $C_8H_7O_8As$ requires C, 31·4; H, 2·3; As, 24·5%).

Arsonoterephthalic Acid and Derivatives.

p-*Xylylarsonic Acid.*—The following conditions were found satisfactory for the rapid preparation of this acid in quantity from *p*-xylidine. A solution of this base (40·3 g.) in concentrated hydrochloric acid (75 c.c.) and water (600 c.c.) was diazotised with 10% sodium nitrite (235 c.c.) below 5°. The solution was then run into another consisting of arsenious oxide (49 g.) in 2*N*-sodium hydroxide solution (600 c.c.) which had been heated to 80° and 20% copper sulphate solution (20 c.c.) added. Mixing was complete in 15 minutes, the temperature being maintained at about 75°. After cooling for 30 minutes, the solution was separated from tar and carefully acidified to Congo-paper with concentrated hydrochloric acid. After removal of several crops of amorphous matter, crystalline *p*-xylylarsonic acid was precipitated. On concentration of the mother-liquor further crops were obtained. The combined crops were dissolved in just sufficient saturated sodium hydrogen carbonate

solution to dissolve the arsonic acid and leave arsenious acid undissolved, and the solution was acidified after filtration. The yield of pure acid was 40% of the theoretical.

p-Xylylarsonic acid is soluble in 33 volumes of boiling water and crystallises in clusters of hard plates, m. p. 191—192° (decomp.). Michaelis (*loc. cit.*) gives m. p. 223°. On titration by the method of King and Rutterford (J., 1930, 2138) *p*-xylylarsonic acid gave an equivalent of 114·5 (calc., 115·0).

On reduction of the arsonic acid by passing sulphur dioxide through a suspension of the acid in *N*-hydrochloric acid in the presence of a little potassium iodide, an amorphous oxide was obtained. This was dissolved in chloroform in the presence of concentrated hydrochloric acid; the residue obtained on evaporation of the chloroform crystallised from low-boiling petroleum. In this way *p*-xylylarsine dichloride, large glassy plates, m. p. 60°, was obtained (compare Michaelis, *loc. cit.*) (Found: As, 29·8. Calc., 29·9%).

2-*Arsonoterephthalic Acid* (V).—A vigorously stirred solution of *p*-xylylarsonic acid (23 g.) in 2*N*-sodium hydroxide (150 c.c.; 3 mols.) and 500 c.c. of water was treated with small amounts of finely powdered permanganate (75 g.*) at 75—80° during 7 hours. On the following day the solution was boiled gently for 8 hours, a further 5 g. of potassium permanganate being slowly added. Excess of permanganate was then destroyed, and the solution filtered. The press-cake was re-extracted twice by suspending it in 1000 c.c. of 0·2*N*-sodium hydroxide, bringing the mixture to the boiling point, and stirring. The combined filtrates were made faintly acid to litmus, concentrated to a small volume, and made acid to Congo-paper. The yield was 82% of the theoretical.

2-*Arsonoterephthalic acid* is very sparingly soluble in boiling water and crystallises in small needles. It is extremely difficult to obtain in a state of complete purity as judged by the titration method. If only 75 g. of potassium permanganate are used in the oxidation and the process is only carried out for 7 hours, the average equivalent over many batches is about 88, whereas by the above process the average equivalent is about 78, the calculated value being 72·5. Only on one occasion has a product been obtained of undoubted purity with an equivalent of 73 (Found: As, 25·7. $C_8H_7O_7As$ requires As, 25·8%).

Terephthalic Acid Arsenoxide.—A suspension of the above arsonic acid (5 g.) in warm water (150 c.c.) and concentrated hydrochloric acid (2 c.c.) was repeatedly saturated with sulphur dioxide in the

* The quantity of permanganate given for the preparation of 4-arsono*iso*-phthalic acid (J., 1930, 689) should be doubled.

presence of a trace of potassium iodide. Complete solution did not occur at any stage and after a few days *terephthalic acid arsenoxide* was left as a white powder (3·7 g.), m. p. 250—255° (decomp.) (Found : As, 29·7. $C_8H_5O_5As$ requires As, 29·3%).

Action of Phosphorus Pentachloride on 2-Arsonoterephthalic Acid. —Phosphorus pentachloride (25·1 g.; 6 mols.) was mixed with finely powdered, dry arsonoterephthalic acid (5·8 g.), and the reaction mixture heated under reflux at 130° (oil-bath) for 5 hours. After removal of phosphorus oxychloride, the residue was dissolved in dry benzene and slowly added to chilled 2*N*-ammonia (150 c.c.) with vigorous shaking. Chloroterephthalamide separated (2·0 g., including a small crop separated from the aqueous liquor after concentration under reduced pressure) insoluble in both layers. This amide is soluble in 50 parts of boiling water and crystallises in square plates, occasionally in needles, m. p. 263—264° (Found : N, 14·3. Calc. : N, 14·1%). Ahrens (*Ber.*, 1886, **19**, 1639) gives m. p. above 300°. Hydrolysis of the chloro-diamide (0·2 g.) with *N*-potassium hydroxide (5 c.c.), followed by acidification, gave chloroterephthalic acid (0·2 g.). On crystallisation from 26 c.c. of boiling water this acid separated in fine felted needles, m. p. 305—306°. It agrees with the description given by Ahrens (*loc. cit.*), who gives m. p. above 300°, and with that of Borsche, Stackmann, and Makaroff-Semljanski (*Ber.*, 1916, **49**, 2240), who give 306—308°.

The benzene layer on slow evaporation deposited 3 : 4-dichlorobenzamide in leaflets, m. p. 169° (Beilstein and Kuhlberg, *Annalen*, 1869, **152**, 225, give m. p. 133°). There was insufficient for analysis, but on hydrolysis with potassium hydroxide it gave 3 : 4-dichlorobenzoic acid, which crystallised from water (0·04 g. in 15 c.c. of boiling water) in small narrow leaflets, m. p. 200°. A mixture with 3 : 4-dichlorobenzoic acid, m. p. 211—212°, obtained under parallel conditions from 4-arsono*iso*phthalic acid and phosphorus pentachloride (J., 1930, 691), melted at 205°. The m. p.'s recorded in the literature range from 200° to 205°.

The ammoniacal filtrate was oxidised with perhydrol (2·5 g.) and on acidification gave 2-*arsonoterephthalamic acid* (VIII) (2·0 g.). This acid is very sparingly soluble in boiling water and crystallises in long pointed leaflets, unmelted at 300° (Found : N, 4·9. $C_8H_8O_6NAs$ requires N, 4·8%).

Methyl Arsonoterephthalate.—A suspension of arsonoterephthalic acid (20 g.) in dry methyl alcohol (wood-spirit) (100 c.c.) was saturated with dry hydrogen chloride at 0°, and the brown solution then boiled for 5 hours with continued passage of the gas. After removal of most of the solvent, the residue was added to sufficient sodium hydrogen carbonate, suspended in 100 c.c. of water at —5°, to

maintain alkalinity. The greyish-brown solid which separated (18 g.) was slightly impure *methyl arsinoterephthalate* (Found: As, 23·9. $C_{10}H_{11}O_6As$ requires As, 24·8%). It was suspended in saturated sodium hydrogen carbonate solution (100 c.c.) below 0° and treated with perhydrol (7·8 g.). Effervescence and solution ensued and acidification after filtration from impurities gave fine needles of *methyl arsonoterephthalate* (13 g.) (Found: As, 23·8. $C_{10}H_{11}O_7As$ requires As, 23·6%). This ester crystallises from water in fine needles which effervesce at 195—196° and resolidify a few degrees higher.

The mother-liquor on evaporation under reduced pressure at 50° or on standing in a refrigerator for some days deposited *methyl hydrogen arsonoterephthalate* (2·4 g.). This is soluble in 11 parts of boiling water and separates in long prismatic needles, unmelted at 300° (Found: As, 24·9. $C_9H_9O_7As$ requires As, 24·7%).

If synthetic methyl alcohol is used in the esterification of arsonoterephthalic acid, an unstable arsine tetrachloride is obtained in much the same manner as the corresponding *iso*phthalic acid arsine tetrachloride (Gough and King, *loc. cit.*).

Action of Ammonia on Methyl Arsonoterephthalate.—The finely powdered ester (28 g.) was added slowly to ammonia solution (420 c.c., *d* 0·88) at −5° and kept below 0° for 9 days. After a further interval of 13 days, the ammonia was removed at room temperature and then at 50°, and the residual solution acidified to Congo-paper. A very sparingly soluble product (24·8 g.) separated in small, pointed, boat-shaped leaflets, the nitrogen content and equivalent value of which indicated the presence of some half-amide. On repeated extraction with boiling water the residual insoluble solid (19·2 g.) became richer in *diamide* (Found: N, 8·7. $C_8H_9O_5N_2As$ requires N, 9·7%). Other methods for the enrichment of the diamide were tried, but hydrolysis of one amide group took place with formation of monoamide.

Action of Ammonia on Methyl Hydrogen Arsonoterephthalate.—The ester (2 g.) was treated with aqueous ammonia (30 c.c., *d* 0·88) as described for the dimethyl ester. The product was arsonoterephthalamic acid (1·95 g.), identical in properties with that described previously (Found: N, 4·7. Calc., 4·8%).

4-*Arsonoanthranilic Acid and Derivatives.*

p-*Tolylarsonic Acid.*—The most economical and rapid method for the preparation of large quantities of this acid is the following. *p*-Toluidine (107·1 g.) was treated with water (1800 c.c.) and concentrated hydrochloric acid (225 c.c.) and then diazotised at 0—5° with 705 c.c. of 10% sodium nitrite solution. The clear resultant

solution was run rapidly within 15 minutes into a mechanically stirred solution of 147 g. of arsenious oxide in 1800 c.c. of 2*N*-sodium hydroxide previously heated to 80° and maintained between 75° and 80° during the addition. The flame was removed, and the solution stirred for a further 30 minutes to complete the aggregation of tarry substances. The cold solution after filtration was made faintly acid to litmus, concentrated under reduced pressure to a small volume, and made acid to Congo-paper. Crude *p*-tolylarsonic acid was precipitated containing some arsenious oxide. Such a product (282 g.) from $2\frac{2}{3}$ such batches was suspended in 650 c.c. of water, and sufficient 2*N*-sodium hydroxide (500 c.c.) added to dissolve tolylarsonic acid and leave the solution still acid to litmus. On filtration from arsenious oxide and acidification, pure tolylarsonic acid (232 g.) was obtained; a further 9·2 g. were isolated from the mother-liquor on concentration. The yield of pure acid is 47% (Found: equiv., 108·3. Calc., 108·0).

The addition of copper sulphate in the above process has no effect on the yield. Palmer and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 1380) describe a process which takes more time for preparing this acid in 50—65% yield, but close repetition of their procedure in our hands only gave a 34·5% yield.

2-*Nitro*-p-*tolylarsonic Acid* (X).—*p*-Tolylarsonic acid is not very readily nitrated. It is essential to use fuming nitric acid and sulphuric acid (compare Michaelis, *Annalen*, 1902, **320**, 321). *p*-Tolylarsonic acid (108·0 g.) in sulphuric acid (160 c.c.) was treated gradually at −5° with 38·0 g. of fuming nitric acid. The solution was finally warmed to 40° for 15 minutes and then poured on ice. The yield was 97% of the theoretical (Found: N, 5·1; equiv., 146·7. Calc.: N, 5·4%; equiv., 145·5).

3-*Nitro*-4-*benzarsonic Acid*.—Nitrotolylarsonic acid (26·1 g.), dissolved in 125 c.c. of *N*-potassium hydroxide and diluted with water (400 c.c.), was heated at 85° and treated over a period of 6 hours with finely powdered potassium permanganate (40·0 g.). Any excess of permanganate was destroyed by addition of alcohol to the boiling solution. After filtration the manganese precipitate was extracted twice by boiling with 500 c.c. of 0·2*N*-potassium hydroxide. The combined filtrates were made definitely blue to Congo-paper and concentrated; an *acid potassium* salt (26·2 g.) then separated in well-formed plates, sometimes in needles. The mother-liquors were treated with excess of hydrochloric acid and evaporated to dryness and the residue was extracted with boiling absolute alcohol, which gave 3-nitro-4-benzarsonic acid (3·0 g.), crystallising in needles.

The acid potassium salt is soluble in $2\frac{1}{2}$ parts of boiling water and

crystallises extremely well in large elongated plates (Found: K, 6·6; equiv., 124·2. $C_7H_6O_7NAs$,$C_7H_5O_7NAsK$ requires K, 6·3%; equiv., 124·0). It readily yields the free acid on crystallisation from *N*-hydrochloric acid (Found: equiv., 98·1. Calc., 97·0). The separation of the acid potassium salt from solutions acid to Congo-paper probably accounts for Michaelis's difficulty in freeing his preparation from mineral matter.

This acid was also prepared by the Bart reaction on 2-nitro-4-aminobenzoic acid, but it could only be isolated with great difficulty.

4-*Arsonoanthranilic Acid* (IX).—Nitrobenzarsonic acid (29·1 g.) was reduced with ferrous chloride and alkali, the process used in previous communications in this series being followed. The yield was 96%. The acid was purified by dissolving 72 g. in 390 c.c. of *N*-hydrochloric acid with addition of 55 c.c. of the concentrated acid and adding saturated sodium acetate solution until the blue reaction to Congo-paper was just removed. The amino-acid crystallised in pointed prisms. Its solution in water shows a fluorescence, discharged by excess of acid or alkali. It is readily soluble in 3*N*-hydrochloric acid, and in concentrated hydrochloric acid, from which a hydrochloride separates in prismatic needles. The sulphate crystallises from 2*N*-sulphuric acid in fine needles, and the nitrate from 3*N*-nitric acid also in fine needles (Found: N, 5·1. $C_7H_8O_5NAs$ requires N, 5·4%).

4-*Arsenoanthranilic Acid.*—The foregoing acid was reduced with hypophosphorous acid and a trace of potassium iodide at 55—60°. The crude *arseno*-compound obtained was purified by solution in dilute caustic alkali solution and reprecipitation by careful addition of hydrochloric acid. The product was collected by centrifuging and washed free from chloride by several re-suspensions in water (Found: As, 35·4. $C_{14}H_{12}O_4N_2As_2$ requires As, 35·5%).

Action of Acetic Anhydride on Arsonoanthranilic Acid.—The acid (10·4 g.) was dissolved in *N*-sodium hydroxide (160 c.c.), the solution chilled, and acetic anhydride (20 c.c.) added in 2 portions with vigorous shaking and intermediate chilling. On acidification to Congo-paper *acetic* 4-*arsono*-N-*acetanthranilic anhydride* (XIII) separated in fine needles (12·1 g.) (Found: As, 21·6; equiv., 165·4. $C_{11}H_{12}O_7NAs$ requires As, 21·7%; equiv., 172·5). This arsonic acid is soluble in 9 volumes of boiling water and is remarkably stable to cold *N*-sodium hydroxide solution. When dissolved in 2*N*-sodium hydroxide (3 mols.) and boiled for 5 minutes, it is converted into 4-*arsono*-N-*acetanthranilic acid monohydrate* (XIV), accompanied by a small proportion of the free amino-acid but readily separable by treatment with 3*N*-hydrochloric acid. This new arsonic acid

crystallised in needles (Found: loss at 95°, 5·4; As, 23·0; equiv., 107·0. $C_9H_{10}O_6NAs,H_2O$ requires H_2O, 5·6; As, 23·3%; equiv., 107·0).

Acetanthranilic Acid 4-*Arsenoxide*.—This oxide was prepared by passing a stream of sulphur dioxide through a fine suspension of the parent arsonic acid (2 g.) in 25 c.c. of water containing in addition 5 c.c. of concentrated hydrochloric acid and a crystal of potassium iodide at 50°. At this temperature reduction is fairly rapid and the *oxide* separates in small needles (1·65 g.) (Found: As, 27·8 $C_9H_8O_4NAs$ requires As, 27·9%). 4-*Arsenoacetanthranilic acid* was obtained by reduction of the parent arsonic acid with hypophosphorous acid in the usual way at 58° for 2 hours (Found: As, 29·5. $C_{18}H_{16}O_6N_2As_2$ requires As, 29·6%).

Anthranilic Acid 4-*Dichloroarsine Hydrochloride*.—The parent arsonic acid (25 g.) was dissolved in a mixture of 60 c.c. of concentrated hydrochloric acid and 60 c.c. of water. Whilst still warm, the solution was saturated with sulphur dioxide after addition of a crystal of potassium iodide. When kept at 0°, the *arsine dichloride* separated in fine needles (88% yield) (Found: As, 23·4. $C_7H_7O_2NCl_3As$ requires As, 23·5%).

Methyl 4-*Arsonoanthranilate*.—The preceding arsine dichloride (26·6 g.) was suspended in 170 c.c. of synthetic dry methyl alcohol, which was then saturated at 0° with dry hydrogen chloride. The solution was boiled with further passage of the gas for 6 hours. A portion of the solvent was boiled off and the crystalline paste left was added to a suspension of 80 g. of sodium hydrogen carbonate in 50 c.c. of its saturated solution. The *methyl anthranilate* 4-*arsenoxide* which separated was straightway collected, washed with ice-cold water, suspended in 200 c.c. of water at 0°, and oxidised with a slight excess of perhydrol. The alkaline solution was acidified at 0°; *methyl* 4-*arsonoanthranilate* then separated in spiked leaflets (20·5 g.). This ester is readily soluble in methyl alcohol and separates on addition of water in broad needles or plates. It readily forms a hydrochloride on addition of 3*N*-hydrochloric acid (Found: As, 27·7; MeO, 11·0. $C_8H_{10}O_5NAs$ requires As, 27·3; MeO, 11·3%).

Anthranilamide-4-*arsonic Acid* (XII).—The preceding ester (5 g.) was added to 150 c.c. of aqueous ammonia (*d* 0·88) at 0° in a pressure bottle and heated at 50° for 8 hours. The clear solution was evaporated at 40° until crystals began to form and then acidified until the reaction was distinctly blue to Congo-paper. (This overcomes the separation of an intermediate ammonium salt.) The *amide* separated as a sandy precipitate (3·45 g.). It crystallised from 55 c.c. of boiling water in plates (Found: N, 10·7. $C_7H_9O_4N_2As$ requires N, 10·8%). When it was acetylated with acetic anhydride in

chilled alkaline solution, *N-acetylanthranilamide-4-arsonic acid* separated in microscopic needles in 93% yield (Found: N, 9·1; equiv., 147·8. $C_9H_{11}O_5N_2As$ requires N, 9·3%; equiv., 151·0).

4-Arsonosalicylic Acid and Derivatives.

4-Arsonosalicylic Acid (XV).—4-Arsonoanthranilic acid (26·1 g.) was dissolved in 300 c.c. of 2*N*-sulphuric acid with addition of 500 c.c. of water. On cooling to 0°, a hydrogen sulphate separated in needles and on addition of sodium nitrite (7·25 g.) a diazonium hydrogen sulphate separated in diamond-shaped plates. After the mixture had been stirred for 15 minutes to ensure complete disappearance of the needles, steam was passed into the solution. At 88° the diazonium salt rapidly disappeared with vigorous evolution of nitrogen. The solution when cold deposited *4-arsonosalicylic acid* in square plates (17·65 g.). It was dissolved in 450 c.c. of boiling water and then separated in perfectly formed hexagonal plates (Found: As, 28·1. $C_7H_7O_6As$ requires As, 28·6%). It gives a clear port-wine coloured solution with a drop of ferric chloride.

4-Arsenosalicylic acid could not be obtained in a state of purity. When the parent arsonic acid was reduced with sodium hyposulphite in the presence of magnesium chloride at 40°, and the alkali-soluble portion of the arseno-compound reprecipitated by acid, a product was obtained with As, 32·6 ($C_{14}H_{10}O_6As_2$ requires As, 35·4%). When hypophosphorous acid was used as the reducing agent at 65°, a product was obtained having the properties of an arseno-compound but was poorer in arsenic content (Found: As in different samples, 26·4, 27·6) than the original acid. The cause of this curious anomaly is not known, but on oxidation the product readily gave the parent acid.

Salicylamide-4-arsonic Acid (XVI).—4-Arsonosalicylic acid (10 g.) was suspended in 80 c.c. of dry synthetic methyl alcohol and esterified by saturation with hydrogen chloride at 0°. After removal of most of the solvent, water (20 c.c.) was added, and the crystalline methyl 4-arsonosalicylate (8·8 g.) collected. This ester is soluble in boiling water and crystallises in clusters of microscopic plates. It was converted into the amide by suspension in 200 c.c. of aqueous ammonia (*d* 0·88) and heating to 55° in a pressure bottle until complete solution had been effected (6 hours). On removal of the excess of ammonia and acidification *salicylamide-4-arsonic acid* separated (8·0 g.). It is soluble in 2½ volumes of boiling water and separates in hard glassy plates, m. p. 270° (efferv.). Its aqueous solution gives a clear wine-red colour with ferric chloride (Found: N, 5·0. $C_7H_8O_5NAs$ requires N, 5·4%).

5-Arsonoanthranilic Acid and Derivatives.

Nitration of Acetanthranilic Acid. Isolation of 3- and 5-Nitroacetanthranilic Acids.—Finely powdered acetanthranilic acid, m. p. 183—184° (100 g.), was added in portions during one hour to fuming nitric acid (180 c.c.) kept vigorously stirred and cooled so that the temperature did not exceed 0° (compare Baly, Tuck, and Marsden, J., 1910, **97**, 1502). A further 20 c.c. of nitric acid were finally added to wash down any solid adhering to the sides of the flask. The reaction mixture was stirred for 4 hours, the temperature being kept below 10°. The crystalline paste was poured on ice, and the solid collected (100 g.), m. p. 201—204°. It was heated on the water-bath for 2 hours with 2000 c.c. of water and filtered whilst hot. The insoluble solid (72 g.) was suspended in water and dissolved by the gradual addition of *N*-sodium hydroxide (310 c.c.), the production of an alkaline reaction being carefully avoided. On saturation with sodium chloride a crystalline sodium salt was precipitated. This was collected, washed with saturated sodium chloride solution, dissolved in warm water (1000 c.c.), and acidified. 5-Nitroacetanthranilic acid (68·7 g.) so prepared melts at 225—226°, the highest m. p. previously recorded being 221° (Ullmann and Uzbachian, *Ber.*, 1903, **36**, 1801).

The mother-liquors which had been used to extract the original solid showed an amino-reaction and deposited 26·1 g. of solid from 610 g. of crude nitration product. This was boiled with 52·2 c.c. of acetic anhydride for 5 minutes, poured into ice-water, and the solid collected (24·3 g.), m. p. 213—215°. On extraction with 500 c.c. of boiling water the yield was 23·3; the solid, m. p. 222—223°, when purified through the sodium salt as described above, gave 20·0 g., m. p. 224—225°.

The combined original mother-liquors from 610 g. of crude nitration product on concentration gave 79 g. of material, m. p. 170—172°, showing an amino-reaction. It was boiled with 79 g. of acetic anhydride until all had dissolved; the solution, poured on ice, gave 67·5 g., m. p. 177—179°. A single crystallisation from 25% acetic acid gave pure 3-nitroacetanthranilic acid (44·2 g.), m. p. 185—186° (Chapman and Stephen, J., 1925, **127**, 1795, give m. p. 180—181°).

5-Aminoacetanthranilic Acid (XVII).—The parent nitro-acid (44·8 g.) in 2*N*-ammonia (120 c.c.) and water (80 c.c.) was run in a thin stream into ferrous sulphate solution (384 g. $FeSO_4,7H_2O$ in 600 c.c. of water) at 50°. Aqueous ammonia (195—200 c.c., *d* 0·88) was then added until the solution was alkaline and the precipitate, which was dark green at first, had become brown, the temperature meanwhile rising to 60°. The reaction mixture, diluted with a

further 500 c.c. of water, was submitted to filtration, the solid well washed with 2*N*-ammonia, and the filtrate made just acid to Congo-paper with 50% sulphuric acid. 5-*Aminoacetanthranilic acid sulphate* separated in woolly needles, yield 95% (Found: N, 11·4. $C_9H_{10}O_3N_2,\frac{1}{2}H_2SO_4$ requires N, 11·5%). The free amino-acid separated from a hot saturated solution of the sulphate which was made neutral to Congo-paper with sodium hydrogen carbonate. It is soluble in 43 parts of boiling water and crystallises in minute glassy prisms, m. p. 233° (Found : N, 14·4. Calc., 14·4%). Treatment of the base with hydrochloric acid (1 H_2O : 1 HCl, *d* 1·16) gave the *hydrochloride* in fine needles (Found : Cl, 15·1. $C_9H_{10}O_3N_2$,HCl requires Cl, 15·4%).

5-*Arsonoacetanthranilic Acid* (XVIII).—Aminoacetanthranilic acid sulphate (48 g.) in water (200 c.c.) and 2*N*-sodium hydroxide (110 c.c.; 1·1 mols.) was mechanically stirred and then treated with hydrochloric acid (57 c.c., *d* 1·16). The paste of finely divided solid was cooled to 0° and diazotised with sodium nitrite (15 g. in 30 c.c. of water). A crystalline diazonium salt separated and to ensure complete conversion of amino-compound the stirring was continued for 15 minutes. Sodium arsenite solution (29·7 g. of arsenious oxide in 188 c.c. 2*N*-sodium hydroxide) was then run in, the temperature being kept at 0°, followed by 2*N*-sodium hydroxide (200 c.c.) until most of the diazonium chloride had disappeared. Moist copper powder (from 50 c.c. of 10% copper sulphate solution) was then added to accelerate the evolution of nitrogen and stirring was continued until the reaction with alkaline β-naphthol was negative, usually about 2 hours being required. The filtered solution was acidified to Congo-paper, quickly filtered from amorphous matter, and kept at 0° for 12 hours. The required arsonic acid separated as a cream-coloured crystalline powder (30·0 g.), m. p. 236—237° (efferv.). It crystallises as a monohydrate from 26 volumes of boiling water in hexagonal-shaped plates (Found : H_2O, 5·6; equiv., 106·3. Calc. : H_2O, 5·6%; equiv., 107·0). Kahn and Benda (*Ber.*, 1908, **41**, 3861) record the substance as a hydrate, m. p. 230°, and crystallising from water in extremely long, fine hairs.

5 : 5′-*Arsenoacetanthranilic Acid.*—The above arsonic acid (5 g.) was suspended in water (40 c.c.) and hypophosphorous acid (40 c.c.; *d* 1·137). A crystal of potassium iodide was added, and the mixture stirred at 60° for 3 hours. The amorphous yellow product was repeatedly washed in the centrifuge and dried in a vacuum (yield, 4·1 g.). The final product was a light voluminous yellow powder, unmelted at 300° (Found : As, 29·4. $C_{18}H_{16}O_6N_2As_2$ requires As, 29·6%).

5-*Arsonoanthranilic Acid.*—The foregoing acetylated acid (20 g.)

was boiled with 3*N*-hydrochloric acid (120 c.c.) for 30 minutes. When kept, the free acid separated in 90% yield. It crystallises from water in fine needles, m. p. 245° (decomp.), and agrees with the description given by Kahn and Benda (*loc. cit.*) (Found : N, 5·4. Calc. : N, 5·4%).

5 : 5′-*Arsenoanthranilic Acid.*—This was prepared as described above for the acetylated acid. The yield was 74% of the theoretical. The product is weakly basic, dissolving with difficulty in 3*N*-hydrochloric acid. On heating it darkens and shrinks at about 280° (Found : As, 35·4. $C_{14}H_{12}O_4N_2As_2$ requires As, 35·5%).

Anthranilic Acid 5-Dichloroarsine Hydrochloride. — 5-Arsonoanthranilic acid (25 g.) was added to 125 c.c. of 16% hydrochloric acid. A trace of potassium iodide was added to the suspension, which was then saturated with sulphur dioxide at 0°. Solution ensued, followed by precipitation of a cream-coloured solid in woolly needles. The mixture was kept cold for several hours, and the product then collected and washed with concentrated hydrochloric acid (yield, 24·8 g.) (Found : As, 23·8. $C_7H_6O_2NCl_2As,HCl$ requires As, 23·6%).

Action of Methyl-alcoholic Hydrogen Chloride on Anthranilic Acid 5-Dichloroarsine Hydrochloride. Isolation of Methyl Anthranilate. —(a) A solution of the above dichloroarsine (24·6 g.) in synthetic methyl alcohol (125 c.c.) was saturated with dry hydrogen chloride at 0° for 2 hours and then heated under reflux with continued passage of the gas for 4 hours. The solution was concentrated to one-third its bulk at 50°, and the resulting crystalline paste added slowly to an aqueous suspension of excess of sodium hydrogen carbonate in water in a freezing mixture. The solid which separated contained much arsenious oxide, and a low-melting substance which was extracted with ether. The extract on evaporation gave methyl anthranilate (9·0 g.), m. p. 25°, which on hydrolysis gave anthranilic acid. The sodium hydrogen carbonate liquors contained unesterified acid.

(b) A solution of the dichloroarsine (15 g.) in synthetic methyl alcohol (100 c.c.) was saturated with hydrogen chloride at 0° and kept at 4° for 3 days. The crystals which separated were found to be unchanged material (7·5 g.). The mother-liquors on careful evaporation and treatment with sodium hydrogen carbonate gave methyl anthranilate (3·2 g.).

When 5-arsonoanthranilic acid was submitted to similar esterification processes, the product was always methyl anthranilate.

Action of Thionyl Chloride on 5-Arsonoanthranilic Acid. Isolation of 5-Chloroanthranilic Acid and Amide.—5-Arsonoanthranilic acid hydrochloride (5 g.) was heated with thionyl chloride (30 c.c.) for

2 hours under reflux. After removal of the excess of thionyl chloride the residue was dissolved in dry benzene and added in portions to chilled 2*N*-ammonia (50 c.c.). The benzene-soluble portion (1·5 g.) crystallised from dilute alcohol in needles, m. p. 172°, of 5-chloroanthranilamide (Found: N, 16·0. Calc.: N, 16·4%). On hydrolysis with aqueous potassium hydroxide it gave 5-chloroanthranilic acid, fine woolly needles from dilute alcohol, m. p. 200°, with previous sintering. The properties of the acid agree with those recorded by Eller and Klemm (*Ber.*, 1922, **55**, 218), who give m. p. 204° (corr.). When the above 5-chloroanthranilamide was heated with soda-lime, an oil distilled which crystallised readily and melted at 65—70° (alone or mixed with *p*-chloroaniline). The main ammoniacal liquors held an amorphous arsenious acid in suspension. It was collected and oxidised with hydrogen peroxide to an amorphous arsonic acid which readily resinified.

Acetanthranilamide-5-arsonic Acid (XIX). — 5-Arsonoacetanthranilic acid (18 g.) in *N*-ammonia (200 c.c.) was treated with silver nitrate (30 g.) in water (50 c.c.). The voluminous buff-coloured precipitate of silver salt was collected, dried, suspended in synthetic methyl alcohol (150 c.c.), and digested with methyl iodide (25 c.c.) on the water-bath for a day. The filtrate was evaporated to dryness; the residue on treatment with a little water rapidly crystallised (yield, 13·0 g.). This *methyl* ester was unmelted at 300° (Found: equiv., 154·0. $C_{10}H_{12}O_6NAs$ requires equiv., 158·5). It was added to ammonia solution (250 c.c., *d* 0·88) at −5° in a pressure bottle and then heated for 3 hours at 55°. When cold, the ammonium salt which had separated was collected and dissolved in water, and the free acid precipitated (yield, 5·15 g.). The original ammoniacal liquors when concentrated and acidified gave a further 5·35 g. of acid. *Acetanthranilamide-5-arsonic acid* is very sparingly soluble in boiling water, acetic acid, or methyl alcohol. It is readily soluble in hot 90% formic acid, but crystallises best from formamide as a felt of needles (Found: loss at 100°, 2·9. $C_9H_{11}O_5N_2As,\frac{1}{2}H_2O$ requires H_2O, 2·9%. Found for dried amide: N, 9·3. $C_9H_{11}O_5N_2As$ requires N, 9·3%).

5-*Arsonosalicylic Acid.*—This acid was prepared from 5-arsonoanthranilic acid by the method of Kahn and Benda (*Ber.*, 1908, **41**, 3863). This route is preferable to that used by Gough and King (J., 1930, 686) from aminosalicylic acid. The yield was 12·9 g. from 20·8 g. of amino-acid. On crystallisation from 200 c.c. of boiling water, it gave 11·65 g. of pure material. When it was reduced with hypophosphorous acid at 50° or with sodium hyposulphite at 20°, an arseno-compound was readily formed but was insoluble in alkalis, apparently through formation of insoluble salts.

Derivatives of Arsonohippuric Acid.

Hippuric Acid p-*Arsenoxide* (*Benzoylglycine*-p-*arsenoxide*).—Arsonohippuric acid (10 g.) was suspended in water (200 c.c.) and hydrochloric acid (15 c.c., *d* 1·16), a crystal of potassium iodide added, and the solution saturated with sulphur dioxide at 50° to ensure solution of the arsonic acid. After keeping and re-saturation at 0°, the oxide separated in white crusts (8·0 g.) (Found: As, 27·8. Calc.: As, 27·9%).

Hippuric Acid Arsine Dichloride.—When the above oxide (1·0 g.) was suspended in concentrated hydrochloric acid, it became a gum which crystallised on rubbing (yield, 1·1 g.) (Found: As, 23·2. $C_9H_8O_3NAsCl_2$ requires As, 23·2%).

Hippuramide-p-*arsonic Acid.*—Benzoylglycine-*p*-arsenoxide (15·7 g.) was suspended in synthetic methyl alcohol (125 c.c.), and the solution saturated with dry hydrogen chloride at 0°. The clear solution was evaporated to a third of its volume at 50° and added to saturated sodium hydrogen carbonate solution (50 c.c.) containing the solid salt (15 g.) in suspension. The voluminous arsenoxide which separated was washed free from chloride, suspended in sodium hydrogen carbonate solution (50 c.c.), and oxidised at 0° with perhydrol (6·6 g.). Rapid solution ensued and on acidification methyl *p*-arsonohippurate separated in microscopic leaflets (9·4 g.). The product was added to ammonia solution (200 c.c., *d* 0·88) at −5° and kept for 2 days below 0° and then for several days at room temperature until a clear solution was obtained. On evaporation at 50° and acidification *hippuramide*-p-*arsonic acid* (7·8 g.) separated. It was soluble in 3 parts of boiling water and crystallised in flattened needles (Found: N, 9·1. $C_9H_{11}O_5N_2As$ requires N, 9·3%).

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