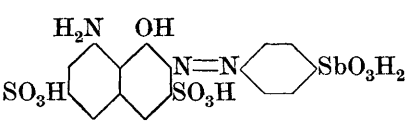
LXXXIX.—*Trypanocidal Action and Chemical Constitution. Part IX. Aromatic Acids containing an Amide Group.*

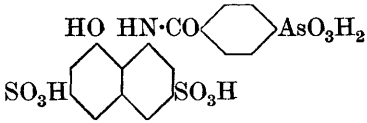
By George Aleck Crocker Gough and Harold King.

The activity of the cotton dye (I) on *Trypanosoma equiperdum* in rats (Dunning and Macht, *J. Pharm. Exp. Ther.*, 1928, **32**, 205) suggested to us an investigation of the colourless substance (II),

which would bear to (I) the same relation as Bayer 205 to trypan-red and afridol-violet (compare Balaban and King, J., 1927, 3068).

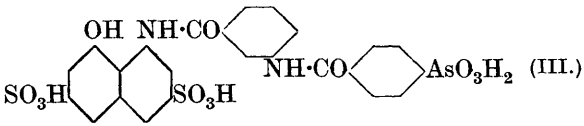


(I.)



(II.)

To facilitate synthesis, antimony was replaced by arsenic. The arsenic analogue of (I) was found to be active but not permanently curative. Arsinous and arsinic acids of type (II) prepared from Freund's acid and H-acid were inactive, even if the substantive character was increased (Balaban and King, *loc. cit.*) by changing the structure to (III). The current theory of the activity of arsinic

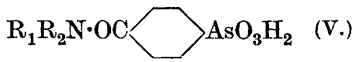


(III.)

acids is that they must first be reduced by living tissues to the much more toxic oxides, and it occurred to us that the amide link might possibly remove these substances out of the range of reduction potential of the mammalian tissues.

Accordingly, *benzamide*-p-*arsinic acid* (IV) was prepared, but it proved to have a therapeutic activity far exceeding that of *p*-amino-

(IV.) 



(V.)

phenylarsinic acid, the starting point of Ehrlich's series of active arsenicals. This interesting discovery made an extensive study of other benzamidearsinic acid derivatives particularly desirable, since no compound of this type had previously been described. A number of substituted benzarsinic acids are known, but no one has converted these carboxylic acids into their simple amides.

The parent substance, benzoyl chloride *p*-dichloroarsine, lends itself to development in a wide variety of ways, for the lone chlorine atom can be replaced by primary or secondary amino-groups or by simple derivatives of these with formation of a series of amides of the type (V). The following table shows the results obtained when a simple series of aromatic amides was 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.

*Amides of Benz-*p*-arsinic and -arsinous Acids.*

Type.	·CO·NR$_1$R$_2$.	Arsinic acid. *T.*	*C.*	*r.*	Arsinous acid. *T.*	*C.*	*r.*
Benzarsinic acid	·CO·OH	0·2	[inactive]		—	—	—
Amide	R$_1$=H, R$_2$=H	1·0	0·3	>30	0·03	0·01	14
Methylamide	R$_1$=Me, R$_2$=H	1·0	0·5	>30	0·01	0·0075	>30
Ethylamide	R$_1$=Et, R$_2$=H	1·25	0·75	>30	0·0075	0·005	>30
Propylamide	R$_1$=Pr, R$_2$=H	0·4	0·2	11	0·005	0·0025	11
*iso*Amylamide	R$_1$=C$_5$H$_{11}$, R$_2$=H	0·1	0·1	6	0·0025	0·0025	9
Dimethylamide	R$_1$=Me, R$_2$=Me	0·6	0·5	5	0·01	0·005	5
Diethylamide	R$_1$=Et, R$_2$=Et	0·1	[inactive]		0·0025	[inactive]	
Piperidinoamide	·NR$_1$R$_2$=C$_5$H$_{10}$N	0·1	[inactive]		0·0025	[inactive]	
Phenylamide	R$_1$=Ph, R$_2$=H	0·1	0·05	>30	—	—	—

If it is borne in mind that the aim of this kind of work is to discover a substance in which the margin between *C* and *T* is as wide as possible, and that the substances should be " permanently " curative, *i.e.*, that *r* should be greater than a month, it will be observed that trypanocidal activity falls off in the monosubstituted alkylamides with increasing weight of the substituting group, and very rapidly in the disubstituted amides.

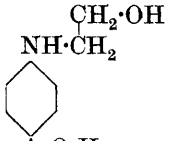
Attention was then directed to the meta-series of amides from benz-*m*-arsinic acid, but they proved to be definitely weaker than those of the para-series.

*Amides of Benz-*m*-arsinic and -arsinous Acids.*

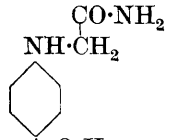
Type.	·CO·NHR$_1$.	Arsinic acid. *T.*	*C.*	*r.*	Arsinous acid. *T.*	*C.*	*r.*
m-Benzarsinic acid	·CO·OH	1·5	[inactive]		—	—	—
Amide	R$_1$ = H	0·6	0·4	>30	0·005	0·005	3
Methylamide	R$_1$ = Me	0·4	0·2	5	0·01	0·0075	>30
*iso*Amylamide	R$_1$ = C$_5$H$_{11}$	0·01	[inactive]		—	—	—

Many of the amides described above, both meta- and para-substituted and containing the arsenic in the quinquevalent state, produced nervous symptoms of chronic poisoning in mice. An attempt was therefore made to prepare derivatives of benzamide-*p*-arsinic acid which would show an equally good therapeutic index without producing any untoward symptoms.

When the modified alkyl groups ·CH$_2$·CH$_2$·OH and ·CH$_2$·CO·NH$_2$ are introduced into the amino-group of *p*-aminophenylarsinic acid,



(VI.)



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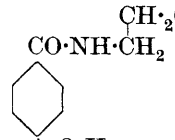

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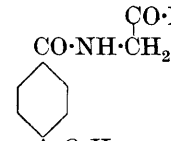
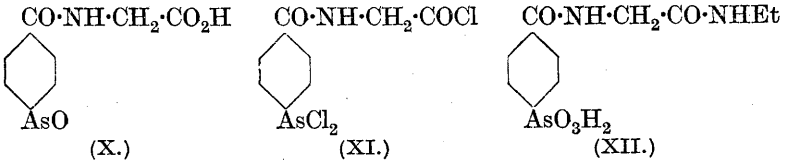


(IX.)

two valuable trypanocidal agents, etharsenol (VI) and tryparsamide (VII) respectively, are known to be obtained. It was, therefore, of

interest to attempt the preparation of their analogues (VIII) and (IX) from benz-*p*-arsinic acid. Although benzoyl chloride *p*-dichloroarsine readily reacted with β-aminoethyl alcohol with formation of an arsinous acid which on oxidation gave (VIII), attempts to prepare (IX) were not immediately successful. Hippuro-*p*-arsine oxide (X) when subjected to the action of phosphorus pentachloride in the presence of acetyl chloride gave the *trichloro*-compound (XI), but this on treatment with ammonia under many conditions always regenerated hippuroarsine oxide. When, however, ammonia was replaced by ethylamine, the *ethylamide* of *hippuro-arsinic acid* (XII) was readily obtained.



(X.) (XI.) (XII.)

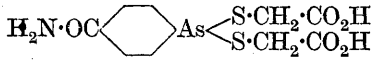
The following table shows the activity of these and some related substances in comparison with benzamide-*p*-arsinic acid. R signifies $-C_6H_4\cdot AsO_3H_2$ and R′ the reduced form $-C_6H_4\cdot AsO_2H_2$.

	T.	*C.*	*r.*
R·CO·NH$_2$	1·0	0·3	>30
R·CO·NH·CH$_2$·CH$_2$·OH	2·0	1·0	6
R′·CO·NH·CH$_2$·CH$_2$·OH	0·01	0·01	>30
R·CO·NH·CH$_2$·CO$_2$H	1·25	[inactive]	
R·CO·NH·CH$_2$·CO·NHEt	>3·0	1·0	>30
R·CO·O·CH$_2$·CH$_2$·NEt$_2$	2·0	[inactive]	

Of this series the ethylamide of hippuroarsinic acid (XII) proved the most useful, and on the highest dose tried there were no nervous symptoms noticeable in mice. The lower homologues of this acid, hippuramide-*p*-arsinic acid and its *N*-methyl derivatives, will be described in a subsequent communication.

Another way of avoiding the undesirable symptoms evoked by benzamide-*p*-arsinic acid would be by use of the corresponding arsinous acid, for since this has more than 30 times the acute toxicity of the acid containing quinquevalent arsenic, and might have a correspondingly high curative power, the amount of arsenic administered would be correspondingly small. Although this arsinous acid produces no nervous symptoms, it is by no means so effective (compare the first table) as the arsinic acid and it occurred to us that it might be possible to render it more effective by esterification with a suitable alcohol. The ester might then be expected to have an increased efficiency, since slow hydrolysis would liberate the toxic arsinous acid over a period of time. For this purpose we chose α-thiolacetic acid, which had already been condensed with 3-amino-

4-hydroxyphenylarsinous acid by Voegtlin, Dyer, and Leonard (*U.S. Public Health Rep.*, 1923, **38**, 1911). When an aqueous suspension of benzamide-*p*-arsinous acid was boiled with α-thiolacetic acid, condensation took place rapidly with formation of crystalline *di(carboxymethyl) benzamide*-p-*thioarsinite* (XIII).



(XIII.)

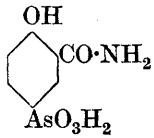
On its maximum tolerated dose, this substance produced no nervous symptoms and it was more effective than the arsinous acid.

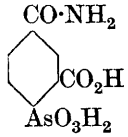
	T.	*C.*	*r.*
Benzamide-*p*-arsinous acid	0·03	0·01	14
Benzamide-*p*-thioarsinite	0·05	0·03	>30

We had made this compound and had examined its oxidation with iodine when an important paper appeared by Barber (J., 1929, 1020) on the condensation of thiol acids with arsinic acids. We believe, however, that some of the results of this author bear a simpler interpretation than that given by him. Barber observed that the arylthioarsinites in alkaline solution, with sodium hydrogen carbonate, for instance, give an intense nitroprusside reaction which he attributed to the intact arylthioarsinite molecule. In support of this he states that the arylthioarsinites do not undergo hydrolytic fission with alkali, because the alkali-metal salts of the di(carboxymethyl) arylthioarsinites can be obtained from strongly alkaline solution. Such a view is, however, untenable. Di(carboxymethyl) benzamide-*p*-thioarsinite (XIII) is soluble in cold sodium hydrogen carbonate solution and gives an intense nitroprusside reaction indistinguishable in tint from that due to α-thiolacetic acid. The free acid also dissolves sparingly in water and gives the transient blue colour with ferric chloride characteristic of α-thiolacetic acid. Both these reactions are specific for thiol groups, and indicate partial hydrolysis of the thioarsinites in weakly alkaline solution and even in water. When a feebly alkaline solution of di(carboxymethyl) benzamide-*p*-thioarsinite was treated with one molecular proportion of hydrogen peroxide, benzamide-*p*-arsinic acid was isolated together with unchanged thioarsinite. This result is inconsistent with an exclusive initial addition of oxygen to the arsenic atom of the intact ester molecule, followed by hydrolysis, a process which would seem to follow on Barber's view of the properties of these compounds, but is consistent with oxidation of the hydrolytic products, arylarsinous acid and α-thiolacetic acid, formed in alkaline solution. The occurrence of some oxidation of the intact ester molecule is not, however, excluded. In further support of the ease of hydrolysis of di(carboxymethyl) benzamide-

p-thioarsinite is the observation of our biological colleagues, Miss Durham and Miss Strangeways, that at high dilutions trypanosomes exposed to its action are rendered non-infective, a property usually recognised as specific for the arylarsinous acids or oxides.

The effect of introducing a second substituent into the phenyl nucleus of benzamidearsinic acid has been examined in a few cases and others are still under investigation. *Salicylamide-5-arsinic acid* (XIV) and iso*phthalamic acid* 6-*arsinic acid* (XV) have been prepared, but not *iso*phthalamide-4-arsinic acid. The toxicities and

(XIV.) 



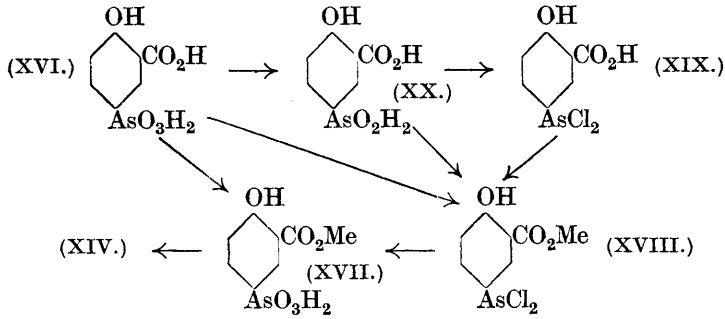
(XV.)

therapeutic activities of these substances compared with some intermediate and allied products are recorded below.

	T.	*C.*	*r.*
p-Tolylarsinic acid	0·005	[inactive]	
m-Xylylarsinic acid	0·03	[inactive]	
*iso*Phthalic acid 4-arsinic acid	0·03	[inactive]	
Methyl *iso*phthalate-4-arsinic acid	0·3	[inactive]	
*iso*Phthalamic acid 6-arsinic acid	0·05	[inactive]	
Salicylic acid 5-arsinic acid	1·5	[inactive]	
Methyl salicylate-5-arsinic acid	0·02	[inactive]	
Salicylamide-5-arsinic acid	0·75	0·3	5

The preparation of salicylamide-5-arsinic acid and *iso*phthalamic acid 6-arsinic acid presents some points of interest. When salicylic acid 5-arsinic acid (XVI) prepared by the Bart–Schmidt reaction from 5-aminosalicylic acid is esterified with methyl-alcoholic sulphuric acid, the degree of esterification increases with the amount of sulphuric acid used. At the same time fission of arsenic as arsenious acid increases so that the most favourable conditions for the esterification are uncertain. If the sulphuric acid is replaced by dry hydrogen chloride, the *methyl* ester (XVII) may again be isolated together with some *methyl salicylate-5-dichloroarsine* (XVIII). The latter substance is formed by loss of labile chlorine atoms which react with the solvent. Similarly in the esterification of *iso*phthalic acid 4-arsinic acid by methyl-alcoholic hydrogen chloride in boiling solution, reduction to *methyl* iso*phthalate dichloroarsine* is complete. Indeed, this action of dry hydrogen chloride on arsinic acids appears to be a general one. For the preparation of methyl salicylate-5-arsinic acid (XVII) it is, however, preferable to reduce salicylic acid 5-arsinic acid by sulphurous acid in concentrated hydrochloric acid solution directly to *salicylic acid dichloroarsine* (XIX), as this is more easily isolated than the intermediate product *salicylic acid*

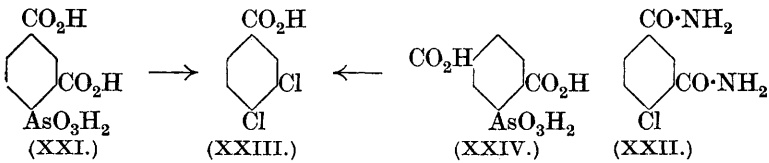
arsinous acid (XX), which separates when the reaction is carried out in dilute hydrochloric acid solution. Salicylic acid dichloro-



arsine (XIX), like salicylic acid arsinous acid (XX), is then readily esterified by methyl-alcoholic hydrogen chloride to methyl salicylate-5-dichloroarsine (XVIII). Careful oxidation of a suspension of this in aqueous sodium hydrogen carbonate at 0° with hydrogen peroxide gives methyl salicylate-5-arsinic acid (XVII), and by the action of ammonia on the ester in dilute methyl alcohol at 100° salicylamide-5-arsinic acid (XIV) is obtained.

The difficulties attending the preparation of *iso*phthalamide-4-arsinic acid have not yet been surmounted. When *iso*phthalic acid 4-arsinic acid (XXI) is allowed to react with thionyl chloride, it gives almost exclusively the half acid chloride of *iso*phthalic acid dichloroarsine, for on treatment with ammonia and oxidation with hydrogen peroxide *iso*phthalamic acid 6-arsinic acid (XV) is obtained.

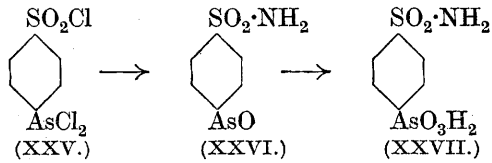
With $5\frac{1}{2}$ molecular proportions of phosphorus pentachloride, the products isolated are the same *iso*phthalamic acid 6-arsinic acid, 4-*chloro*iso*phthalamide* (XXII), and 3 : 4-dichlorobenzamide; and with $6\frac{1}{2}$ molecular proportions, only the last two substances are obtained, the whole of the arsinic acid group having been replaced by chlorine. The constitution of 4-chloro*iso*phthalamide follows from its hydrolysis to 4-chloro*iso*phthalic acid, and that of 3 : 4-dichlorobenzamide follows from its hydrolysis to 3 : 4-dichlorobenzoic acid (XXIII) which was identical with the acid obtained (later communication) by a similar series of reactions from terephthalic acid arsinic acid (XXIV).



When *iso*phthalic acid 4-arsinic acid is esterified in synthetic methyl alcohol by saturation with hydrogen chloride at 0°, crystalline *methyl* iso*phthalate arsinetetrachloride* separates after a few hours. This tetrachloride dissolves in sodium hydrogen carbonate solution at 0° and yields *methyl* iso*phthalate*-4-*arsinic acid* on acidification. If, however, purified methyl alcohol (wood spirit) is used in the esterification, no separation of an arsinetetrachloride occurs at 0°, but when the solution is boiled, reduction takes place with formation of methyl *iso*phthalate dichloroarsine, which is isolated as *methyl* iso*phthalate*-4-*arsinous acid* by pouring the reaction mixture into sodium hydrogen carbonate solution. On oxidation the arsinous acid yields methyl *iso*phthalate-4-arsinic acid.

When methyl *iso*phthalate-4-arsinic acid is allowed to react with ammonia (*d* 0·88) at 0° for 14 days, the sole product of amidation is the same *iso*phthalamic acid 6-arsinic acid as is obtained from the acid chlorides.

The marked influence on the trypanocidal activity of benz-*m*- and -*p*-arsinic acids effected by their conversion into amides, recorded in the foregoing pages, made it desirable to prepare benzenesulphonamide-*p*-arsinic acid. *p*-Sulphophenylarsinic acid had been previously prepared by Hewitt, King, and Murch (J., 1926, 1355) and had been shown to be devoid of activity. By the action of phosphorus pentachloride in boiling carbon tetrachloride solution it was converted into *benzenesulphonyl chloride* p-*dichloroarsine* (XXV), which on graded hydrolysis with water gave *benzenesulphonyl chloride* p-*arsenoxide* and *sulphophenylarsinous acid*. By the action of ammonia *benzenesulphonamide*-p-*arsenoxide* (XXVI) was obtained, and this on treatment with hydrogen peroxide gave *benzenesulphon-*



(XXV.) (XXVI.) (XXVII.)

amide-p-*arsinic acid* (XXVII). With hydrochloric acid, however, the arsinous acid gave *benzenesulphonamide*-p-*dichloroarsine*. The trypanocidal activity of some of these compounds was examined with the following results:

	T.	*C.*	*r.*
Sulphophenyl-*p*-arsinic acid	0·5	[inactive]	
Benzenesulphonamide-*p*-arsinic acid	>1·5	1·0	16
Benzenesulphonamide-*p*-arsenoxide	0·03	0·01	>30

Therapeutic Considerations.

Analysis of the results described in the foregoing pages reveals some underlying principles of considerable interest. The first of

these is the important influence of the amide group in converting trypanocidally inactive carboxylic and sulphonic acids into substances of marked activity. It was known that phenylglycineamide-*p*-arsinic acid (tryparsamide) could cure both experimental and clinical trypanosomiasis, but the significance of the aliphatically bound amide group was obscure, since data on analogous derivatives were lacking. In this communication it has, however, now been demonstrated that benz-*m*- and -*p*-arsinic acids, hippuro-*p*-arsinic acid, salicylic acid 5-arsinic acid, *p*-sulphophenylarsinic acid, and the corresponding arsinous acids where tested, are quite inactive on experimental trypanosomiasis in mice; and yet, when they are converted into the corresponding amides, trypanocidal activity appears in every case. The interpretation is simple. Following the injection of these arsinic or arsinous acids into the blood stream as soluble sodium salts, two main processes become operative, excretion and reduction. Those substances containing solubilising groups such as carboxyl or sulpho, whether they are reduced to the arsinous acids or not, will remain as soluble salts by reason of the carboxyl or sulpho-groups, and their excretion will be rapid. On the other hand, those containing amide groups will also be excreted, though possibly at a slower rate, so long as they contain the arsinic acid group and can form neutral soluble salts. When, however, reduction to the arsinous acid has taken place, they will no longer form neutral salts and will, accordingly, be liberated in the colloidal state as free arsinous acids by hydrolysis at the p_H of the blood stream, and will not be excreted as such. The mechanism of the reduction process and subsequent events may also be pictured from analogous reactions *in vitro*.

It is known that hydrogen sulphide is a very powerful reducing agent, having in fact a reduction potential negative to the hydrogen electrode. It is, therefore, not surprising to find, as Barber (*loc. cit.*) does, that various thiol derivatives of aliphatic acids can reduce arsinic to arsinous acids, condensation then taking place between the arsinous acids and excess of the thiol compound with production of arylthioarsinites, operations which can take place at the ordinary

$$R{\cdot}AsO_3H_2 + 4R'{\cdot}SH \longrightarrow R{\cdot}AsO_2H_2 + 2R'{\cdot}SH \longrightarrow RAsS_2R'_2$$

temperature in neutral solution. It is very probable that similar processes operate in mammalian tissues, for there is abundant evidence of the presence of thiol compounds in tissues, and some for their being concerned in oxidative-reductive processes. That the excess of thiol groups should act as receptors for the arsinous acid group is also very probable; it was, in fact, foreshadowed by Ehrlich many years ago (*Ber.*, 1909, **42**, 42). The occurrence of

arsenic in hair after arsenic medication is possibly a manifestation of the property. The further important point, however, now emerges from our experiments, that the arylthioarsinites are slowly hydrolysed even in neutral solution with regeneration of small amounts of arsinous acids.

$$R{\cdot}As\begin{matrix}SR'\\SR'\end{matrix} + 2H_2O \rightleftharpoons R{\cdot}As(OH)_2 + 2R'{\cdot}SH.$$

The view we advanced in the preceding communication of this series (Gough and King, J., 1928, 2432), that the arsinic acids are "reduced to the reactive oxides, and stored as such by condensation in a reversible form," thus receives experimental support. The arylthioarsinites would be formed from proteins of all degrees of complexity containing sulphydryl groups, and would in general escape excretion, and the continuous production of minute amounts of highly toxic arsinous acids by hydrolysis of such complex thioarsinites in the tissues, maintained over an extended period, would be responsible for the complete disappearance of the trypanosomes with resultant cure.

Lastly, the wide variation in the chemotherapeutic efficiency of arsenicals with change of constitution might be ascribed to difference in the ease of reduction of the arsinic to the arsinous acid, difference in the ease of condensation of the arsinous acid with thiol complexes, and difference in the ease of hydrolysis of such complexes. In fact, the striking results obtained for the series of similarly constituted amides shown in the first table (p. 671), where other factors affecting trypanocidal activity might be expected to be reasonably constant, support such a view. As this table shows, introduction of methyl into the amide group causes a diminution in activity, and this diminution is intensified by increase in the size of the alkyl group or by the introduction of more than one. Introduction of weakly positive alkyl groups will cause a drift of electrons towards the arsenic atom relative to the effect of the unsubstituted amide group, and this will be reflected (*a*) in a diminished ease of reduction of the arsinic acid, since the oxygen atom will be more firmly held, and (*b*) in a decreased tendency to co-ordinate with hydroxyl (Gough and King, *loc. cit.*, p. 2429), since the arsenic atom has become more negative, with resultant increased difficulty of hydrolysis. Both properties would lead to diminished trypanocidal activity, as is actually found.

We are deeply indebted to Miss F. M. Durham and Miss W. I. Strangeways for the whole of the biological findings recorded in this paper.

EXPERIMENTAL.

Derivatives of Naphthylaminesulphonic Acids.

1-*Amino*-3 : 6-*disulpho*-8-*naphthol*-7-*azobenzene*-4′-*arsinic Acid* (compare D.R.-P. 212018).—4-Aminophenylarsinic acid (8·7 g.) in 80 c.c. of 2*N*-hydrochloric acid was treated at 0° with 3·0 g. of sodium nitrite in 30 c.c. of water and then added slowly to 13·6 g. of H-acid in 150 c.c. of 3*N*-sodium hydroxide solution. After being kept at 0° for 45 minutes, the solution was made just acid to Congo-paper by addition of concentrated hydrochloric acid. After 12 hours the deep-coloured solid was collected on porous plate and purified by solution in the minimum volume of boiling water and addition of one-fifth of that volume of concentrated hydrochloric acid. This operation was repeated three times and gave finally 2·8 g. of homogeneous brick-red needles (Found : loss at 105°, 8·0. $C_{16}H_{14}O_{10}N_3S_2As,2\frac{1}{2}H_2O$ requires H_2O, 7·6%. Found in dried acid : As, 13·3. $C_{16}H_{14}O_{10}N_3S_2As$ requires As, 13·7%). When pure, this *acid* requires over 12 parts of boiling water for solution, but will not crystallise therefrom on cooling It is, however, almost completely precipitated by addition to the solution of one-fifth of its volume of 32% hydrochloric acid.

1-*Benzamido*-3 : 6-*disulphonaphthalene*-4′-*arsinous Acid*.—Freund's acid (9 g.), dissolved in *N*-sodium hydroxide (90 c.c.), was treated in presence of benzene (10 c.c.) with three successive portions of benzoyl chloride *p*-dichloroarsine (each 5·7 g.) in benzene (13 c.c.). *N*-Sodium hydroxide (30 c.c.) was added concurrently with vigorous shaking. After removal of the benzene, the liquid was diluted with an equal volume of water and acidified to Congo-paper and the precipitated benz-*p*-arsinous acid (9·8 g.) was removed. The liquid was then concentrated to 100 c.c. and a further small amount of benz-*p*-arsinous acid removed (0·1 g.). After addition of concentrated hydrochloric acid (7 c.c.) and keeping for 2 hours at −5°, clusters of fine needles separated (11·2 g.). These were recrystallised by solution in warm water (24 c.c.) and addition of concentrated hydrochloric acid (4 c.c.) (Found : loss at 140°, 7·5. $C_{17}H_{13}O_9NS_2AsNa,H_2O$ requires H_2O, 6·5% for conversion into oxide. Found in anhydrous oxide : As, 13·1; Na, 4·2. $C_{17}H_{11}O_8NS_2AsNa$ requires As, 13·5; Na, 4·1%).

1-*Benzamido*-3 : 6-*disulphonaphthalene*-4′-*arsinic Acid*.—The crude arsinous acid (7 g.), dissolved in water (35 c.c.), was treated with the calculated amount of 30% hydrogen peroxide in water (14 c.c.). The solution, which became warm and slightly brown on oxidation, was neutralised to litmus-paper, warmed at 50° for ½ hour, and evaporated under reduced pressure to 20 c.c., and the reaction

adjusted to neutrality to Congo-paper. The solution was then heated to 100° and, after addition of concentrated hydrochloric acid (3 c.c.), allowed to cool. The resultant paste of fine rectangular needles (5·7 g.) was removed and recrystallised by solution in the minimum volume of boiling water, followed by the addition of concentrated hydrochloric acid (5·5 c.c.) (Found: loss at 140°, 12·6; As, 12·7; Na, 3·8. $C_{17}H_{13}O_{10}NS_2AsNa,3H_2O$ requires H_2O, 11·9 for conversion into the dioxide; As, 12·3; Na, 3·8%).

1-*Benzamido*-3 : 6-*disulpho*-8-*naphthol*-4′-*arsinous Acid*.—H-Acid (6·8 g. monosodium salt + $1·5H_2O$), dissolved in *N*-sodium hydroxide (20 c.c.), was treated with 0·5 c.c. portions of a solution of benzoyl chloride *p*-dichloroarsine (11·4 g.) in benzene (20 c.c.) with vigorous shaking. *N*-Sodium hydroxide (40 c.c.) was added concurrently at such a rate as to maintain a slightly alkaline reaction. The liquid was made acid to Congo-paper, and the precipitated benzarsinous acid (3·3 g.) removed. The filtrate was concentrated (to 104 c.c., to 76 c.c., and until salt began to separate) at 50° and the three successive crops were united and boiled with water (25 c.c.) containing norit. The undissolved portion yielded a further quantity of benzarsinous acid (1·8 g.), and the filtrate, on the addition of concentrated hydrochloric acid, gave the desired *amide* (11·4 g.). This was recrystallised three times from hot water (28, 21, and 16·5 c.c.), concentrated hydrochloric acid (2 c.c.) being added to the clear solution in each operation (Found: loss at 140°, 23·8; As, 10·3; Na, 3·8. $C_{17}H_{13}O_{10}NS_2AsNa,8H_2O$ requires H_2O, 23·2 for conversion into the arsenious oxide; As, 10·7; Na, 3·3%).

1-*Benzamido*-3 : 6-*disulpho*-8-*naphthol*-4′-*arsinic Acid* (II).—A slightly alkaline solution of the foregoing arsinous acid (11·3 g. in 150 c.c.) was treated with the calculated amount of hydrogen peroxide, kept for ½ hour, and concentrated to 95 c.c. The mass of stout needles which separated was dissolved by warming, and the solution made acid to Congo-paper. On cooling, the desired *arsinic acid* (8·8 g.) separated in fine needles. This, together with a further amount (1·4 g.) obtained from the mother-liquor, was recrystallised from water (18 c.c.) with the addition of concentrated hydrochloric acid (4 c.c.) (Found: loss at 150°, 24·8; As, 10·0. $C_{17}H_{13}O_{11}NS_2AsNa,10H_2O$ requires H_2O, 24·6 for conversion into the dioxide; As, 10·2%).

1-*Benzamido*-m-*benzamido*-3 : 6-*disulpho*-8-*naphthol*-4″-*arsinous Acid*.—A solution of 1-*m*-aminobenzamido-8-naphthol-3 : 6-disulphonic acid (7·1 g.; Balaban and King, J., 1927, 90) in *N*-sodium hydroxide (40 c.c.) with benzene (10 c.c.) was treated with 0·5 c.c. portions of a solution of benzoyl chloride *p*-dichloroarsine (9·8 g.) in benzene until it no longer gave a red colour when diazotised and

coupled with β-naphthol. After removal of the benzene, the liquid was made slightly acid to Congo-paper, filtered from benzarsinous acid (1·4 g.), and evaporated (to 35 c.c.) at 50°. After further filtration the liquid was saturated with sodium chloride and kept at 0° for 12 hours, and the crude *arsinous acid* was then removed and recrystallised from water (140 c.c.) by the addition of concentrated hydrochloric acid at 50° until a slight turbidity was produced. The desired product separated in characteristic bunches of needles (Found: loss at 140°, 18·5; As, 9·0. $C_{24}H_{18}O_{11}N_2S_2AsNa,8H_2O$ requires H_2O, 19·9 for conversion into the oxide; As, 9·2%).

1-*Benzamido*-m-*benzamido*-3:6-*disulpho*-8-*naphthol*-4″-*arsinic Acid* (III).—The foregoing arsinous acid (3·5 g.) was dissolved in half-saturated sodium hydrogen carbonate solution (50 c.c.) and oxidised by the addition of 30% hydrogen peroxide (0·6 g.) in water (10 c.c.). After ½ hour, the liquid was made slightly acid to Congo-paper and saturated with sodium chloride. The precipitated *arsinic acid* was collected and crystallised by solution in water (18 c.c.) at 50°, followed by the addition of concentrated hydrochloric acid (10 c.c.). On keeping, light pink needles of the required acid separated. These were again recrystallised by the use of water (15 c.c.) and hydrochloric acid (8 c.c.) (Found: loss at 140°, 29·1; As, 7·5. $C_{24}H_{18}O_{12}N_2S_2AsNa,14H_2O$ requires H_2O, 28·7 for conversion into the oxide; As, 8·0%).

Derivatives of p- *and* m-*Benzarsinic Acids.*

Benzamide-p-*arsenious Oxide.*—Benzoyl chloride *p*-dichloroarsine (15 g.), dissolved in benzene (20 c.c.), was added slowly to 2*N*-aqueous ammonia (200 c.c.) and benzene (10 c.c.) with vigorous shaking. The precipitate, which began to separate after the first few additions, was collected (11 g.). Acidification of the filtrate gave benzarsinous acid (1·1 g.). For purification the crude product was reprecipitated from 2*N*-sodium hydroxide. This *arsenious oxide*, like all the benzalkylamidoarsenious oxides examined, is insoluble in dilute ammonia and cold sodium hydrogen carbonate solution and does not show any visible crystalline structure (Found: N, 6·4; As, 35·7. $C_7H_6O_2NAs$ requires N, 6·6; As, 35·6%).

Di(*carboxymethyl*) *Benzamide*-p-*thioarsinite* (XIII).—A suspension of the above arsenious oxide (1 g.) in boiling water (19 c.c.) was treated with α-thiolacetic acid (1·1 g.). The solid rapidly passed into solution and on cooling, fine needles (1·7 g.) of *di*(*carboxymethyl*) *benzamidethioarsinite*, m. p. 168—169°, separated. It was recrystallised from boiling water (25 c.c.) containing a small amount of thiolacetic acid (Found: As, 20·1. $C_{11}H_{12}O_5NS_2As$ requires As, 19·9%). When titrated with iodine in the presence of starch, one

molecule of this substance reacts rapidly with four atoms of iodine in agreement with the formation of disulphidoacetic acid and benzamide-*p*-arsinic acid. When a slightly alkaline solution of the thioarsinite (0·41 g.) in sodium hydrogen carbonate solution was treated with half the quantity of hydrogen peroxide (0·13 g.) requisite for complete oxidation, the original material (0·21 g.) and benzamide-*p*-arsinic acid (0·08 g.) were readily isolated.

The parent thioarsinite is readily hydrolysed, for a solution in aqueous sodium hydrogen carbonate gives an intense nitroprusside reaction and an aqueous solution of the free acid gives a transient blue colour with ferric chloride. These reactions are not due to traces of α-thiolacetic acid contaminating the crystalline material, since they are given by odourless samples of the thioarsinites which have been exposed to the air for several months.

Benzamide-p-*arsinic Acid* (IV).—The corresponding arsenious oxide (11 g.) was suspended in water (70 c.c.) containing hydrogen peroxide (5·7 g. of 30% " perhydrol ") and heated on the water-bath until solution was complete. On cooling, large plates of *benzamide*-p-*arsinic acid* (9·1 g.) separated, which were recrystallised from water (58 c.c.). The arsinic acid (7·1 g.) thus obtained is unmelted at 300° and forms crystalline barium and calcium salts (Found: N, 5·5; As, 30·4. $C_7H_8O_4NAs$ requires N, 5·7; As, 30·6%).

Benzomethylamide-p-*arsinous acid* was prepared similarly by means of aqueous methylamine (Found: As, 30·6. $C_8H_{10}O_3NAs$ requires As, 30·3%). The corresponding *arsinic acid* crystallised from water in stout needles, unmelted at 300° (Found: N, 5·7. $C_8H_{10}O_4NAs$ requires N, 5·4%).

Benzodimethylamide-p-*dichloroarsine*.—Benzoyl chloride *p*-dichloroarsine was allowed to react with aqueous dimethylamine in the usual way. After removal of benzene, addition of concentrated hydrochloric acid gave a copious precipitate of small rectangular plates of *benzodimethylamide*-p-*dichloroarsine*, m. p. 192° (Found: As, 25·4. $C_9H_{10}ONCl_2As$ requires As, 25·5%). On oxidation in alkaline solution it gave *benzodimethylamide*-p-*arsinic acid*, m. p. 216—218°, which crystallised from water in small plates (Found: N, 5·0. $C_9H_{12}O_4NAs$ requires N, 5·1%).

Benzethylamide-p-*arsinous acid* was obtained when benzoyl chloride *p*-dichloroarsine in benzene was allowed to react at 0° with anhydrous ethylamine in benzene, and the mixture treated with acidified water (Found: As, 29·3. $C_9H_{12}O_3NAs$ requires As, 29·2%). On oxidation it gave star-shaped leaflets of *benzethylamide*-p-*arsinic acid*, unmelted at 300° (Found: N, 5·3. $C_9H_{12}O_4NAs$ requires N, 5·1%).

Benzodiethylamide-p-*dichloroarsine* was prepared by digesting

benzoyl chloride *p*-dichloroarsine and diethylamine in boiling benzene, the gum remaining on evaporation being dissolved in caustic alkali and extracted with ether to remove diethylamine. On addition of excess of concentrated hydrochloric acid to the residue *benzodiethylamide*-p-*dichloroarsine*, m. p. 185—186°, was obtained as a crystalline precipitate (Found: Cl, 21·8; As, 23·2. $C_{11}H_{14}ONCl_2As$ requires Cl, 22·0; As, 23·3%). On oxidation it gave *benzodiethylamide*-p-*arsinic acid*, stout prisms, m. p. 193—195°, from water (Found: N, 4·9. $C_{11}H_{16}O_4NAs$ requires N, 4·7%).

Benzo-n-*propylamide*-p-*arsenious oxide* was prepared similarly to the monoethyl derivative (Found: As, 29·6; N, 5·6. $C_{10}H_{12}O_2NAs$ requires As, 29·6; N, 5·5%). On oxidation it gave clusters of needles of *benzo*-n-*propylamide*-p-*arsinic acid*, unmelted at 300° (Found: N, 4·8. $C_{10}H_{14}O_4NAs$ requires N, 4·9%).

*Benz*isoa*mylamide*-p-*arsenious oxide* was prepared similarly (Found: As, 26·5. $C_{12}H_{16}O_2NAs$ requires As, 26·7%). On oxidation it gave crystalline *benz*isoa*mylamide*-p-*arsinic acid*, almost insoluble in boiling water but, unlike the lower homologues, easily soluble in ethyl acetate and in ethyl and methyl alcohols (Found: N, 4·7. $C_{12}H_{18}O_4NAs$ requires N, 4·4%).

Benzopiperidide-p-*dichloroarsine* was prepared from the reactants in boiling benzene solution. The residue obtained on removal of the solvents was treated with chloroform in the presence of concentrated hydrochloric acid. The chloroform solution on concentration and addition of light petroleum gave *benzopiperidide*-p-*dichloroarsine*, needles, m. p. 166—167° (Found: As, 22·4. $C_{12}H_{14}ONCl_2As$ requires As, 22·5%). It gave *benzopiperidide*-p-*arsinic acid*, needles, m. p. 230° (Found: As, 23·8. $C_{12}H_{16}O_4NAs$ requires As, 24·0%).

Benzo-β-*hydroxyethylamide*-p-*arsenious Oxide*.—Benzoyl chloride *p*-dichloroarsine (7·1 g.), dissolved in benzene (20 c.c.), was allowed to react with a solution of ethanolamine (2·3 g.) in water (20 c.c.) and benzene (5 c.c.) with the concurrent addition of 2*N*-sodium hydroxide (50 c.c.) in a manner similar to that used in the preparation of benzamide-*p*-arsenious oxide. When the reaction was complete the liquid was made slightly acid to litmus, saturated sodium hydrogen carbonate solution (50 c.c.) added, and the solid (6 g.) removed. *Benzo*-β-*hydroxyethylamide*-p-*arsenious oxide* is obtained in this way free from benzarsinous acid. It crystallises from a large volume of hot water or better from a mixture of ethyl alcohol and water in clusters of small needles (Found: As, 29·5. $C_9H_{10}O_3NAs$ requires As, 29·4%). On oxidation it gave *benzo*-β-*hydroxyethylamide*-p-*arsinic acid* (VIII), glistening leaflets, m. p. 180° (efferv.) (Found: N, 4·7. $C_9H_{12}O_5NAs$ requires N, 4·8%).

Hippuryl Chloride p-*Dichloroarsine* (XI).—Treatment of benzoyl-

glycine-*p*-arsenious oxide (Hugounenq and Morel, *J. Pharm. Chim.*, 1913, **7**, 383) with a chloroform solution of thionyl chloride did not give the required results. When a method similar to that used by Fischer (*Ber.*, 1905, **38**, 605) for the preparation of hippuryl chloride was used, a crude *hippuryl chloride* p-*dichloroarsine* was readily obtained. The arsenious oxide (1 g.), suspended in freshly distilled acetyl chloride, was shaken with phosphorus pentachloride (2·5 g.) for 1 hour. The amorphous product (2·1 g.) was collected and washed with light petroleum (10 c.c.). Although attempts to purify it failed (Found: Cl, 34·6. $C_9H_7O_2NCl_3As$ requires Cl, 31·1%), it could be used successfully for the next process.

Benzoylglycine-ethylamide-p-*arsinic Acid* (XII).—Finely powdered hippuryl chloride *p*-dichloroarsine (5·3 g.) was added to a solution of anhydrous ethylamine (4·2 g.) in dry ether (75 c.c.) cooled in a freezing mixture. After 2 hours, the solid was collected, ground with water (50 c.c.), and washed with sodium hydrogen carbonate solution. The product was suspended in hot water and treated with 30% hydrogen peroxide, and the resultant solution evaporated at 50° to 10 c.c. On cooling, elongated leaflets, which formed clusters, separated. These were recrystallised from boiling water (34 c.c.) (yield, 6·1 g.). *Benzoylglycine-ethylamide*-p-*arsinic acid* thus obtained melts at 270° (decomp.) (Found: N, 8·6. $C_{11}H_{15}O_5N_2As$ requires N, 8·5%).

Benzoylglycine-n-*propylamide*-p-*arsenious oxide* was prepared by the interaction of *n*-propylamine (0·4 g.) and hippuryl chloride *p*-dichloroarsine (0·3 g.) in ether (30 c.c.). The product was amorphous and very similar to its lower homologue (Found: N, 9·1. $C_{12}H_{15}O_3N_2As$ requires N, 9·0%).

β-*Diethylaminoethyl Benzoate*-p-*arsinic Acid*.—A solution of β-diethylaminoethanol (11·1 g.) and benzoyl chloride *p*-dichloroarsine (7·1 g.) in benzene (50 c.c.) was cautiously prepared and refluxed for 1½ hours. The suspension of waxy solid was shaken with water (50 c.c.), and the benzene removed under reduced pressure. After neutralisation of the residue with sodium hydrogen carbonate solution, the thick oil was dissolved by addition of ether (150 c.c.). The ethereal extract was dried but, after removal of the ether, all attempts to crystallise the crude arsinous acid, either as such or as the dichloroarsine hydrochloride, failed. In this behaviour it resembles its stovaine analogue (Fourneau and Ochslin, *Bull. Soc. chim.*, 1912, **11**, 912). The oil (4·7 g.) was therefore oxidised directly to the arsinic acid by means of hydrogen peroxide in aqueous suspension. The resultant solution was evaporated to dryness, and the residue extracted with boiling alcohol (20 c.c.); cautious addition of dry ether gave fine needles of β-*diethylamino*-

ethyl benzoate-p-*arsinic acid*, m. p. 186° (decomp.) (Found : N, 3·7. $C_{13}H_{20}O_5NAs$ requires N, 3·8%).

Benzoyl Chloride m-*Dichloroarsine*.—*m*-Benzarsinous acid was prepared from *m*-aminobenzoic acid (50 g.) by the Bart reaction, the intermediate arsinic acid being reduced without isolation in the solid state, by sulphur dioxide in the presence of hydrochloric acid; the yield varied between 35 g. and 52 g. In preparing the trichloride, it was found that chilling the light petroleum extract (250—300 c.c.) of the distillation residue of the action of thionyl chloride on the arsinous acid in chloroform gave fluffy bunches of needles of *benzoyl chloride* m-*dichloroarsine* (27 g.), m. p. 54—55° (Found : Cl, 37·6. $C_7H_4OCl_3As$ requires Cl, 37·3%).

m-*Benzarsinous Acid*.—The foregoing chloride (5 g.) was dissolved by warming in 2*N*-sodium hydroxide (20 c.c.), and the solution made slightly acid to Congo-paper with hydrochloric acid. (Owing to the ease of formation of the dichloroarsine, excess of hydrochloric acid must be avoided.) A white mass of microscopic crystals of m-*benzarsinous acid* (4·2 g.) separated (Found : As, 32·3. $C_7H_7O_4As$ requires As, 32·6%).

Benzoic Acid m-*Dichloroarsine*.—*m*-Benzarsinous acid (1 g.) was dissolved in a boiling mixture of water (12 c.c.), ethyl alcohol (9 c.c.), and concentrated hydrochloric acid (7 c.c.), and a further quantity (4 c.c.) of hydrochloric acid cautiously added. An oil tended to separate on cooling, but was prevented by addition of more alcohol or by seeding with crystals of an externally crystallised sample. The resultant mass of white prisms was removed and washed with concentrated hydrochloric acid (Found : Cl, 26·6. $C_7H_5O_2Cl_2As$ requires Cl, 26·6%). This substance is more readily hydrolysed than many other dichloroarsines.

Benzamide-m-*arsenious Oxide*.—This substance (12 g.) was prepared from the corresponding acid chloride and ammonia by the method employed for the *p*-isomeride and obtained as a micro crystalline powder (Found : As, 35·4. $C_7H_6O_2NAs$ requires As, 35·6%).

Benzamide-m-*dichloroarsine*.—The foregoing arsenious oxide (1 g.) was dissolved in a hot mixture of 3*N*-hydrochloric acid (5·5 c.c.) and ethyl alcohol (5·5 c.c.), and concentrated hydrochloric acid (8 c.c.) slowly added at the boiling point. On cooling, large prisms of *benzamide*-m-*dichloroarsine*, m. p. 76—80°, separated (Found : Cl, 26·7. $C_7H_6ONCl_2As$ requires Cl, 26·7%). On oxidation in alkaline solution it gave *benzamide*-m-*arsinic acid*, rhombic plates, unmelted at 300° (Found : N, 5·6. $C_7H_8O_4NAs$ requires N, 5·7%).

Benzomethylamide-m-*arsenious Acid*.—This substance (5·2 g.) was obtained in the same way as its *p*-isomeride (Found : As, 30·6.

$C_8H_{10}O_3NAs$ requires As, 30·9%): on oxidation in alkaline solution it gave fine rods of *benzomethylamide*-m-*arsinic acid*, m. p. 238° (efferv.) (Found: N, 5·5. $C_8H_{10}O_4NAs$ requires N, 5·4%).

Benzisoamylamide-m-*arsinic Acid.*—When the corresponding arsinous acid was prepared by the same method as that used for the *p*-isomeride, a thick brown gum was obtained which remained partly solid after being kept for several days at 0°. Accordingly this impure product was oxidised directly to the *arsinic acid* by treatment with 30% hydrogen peroxide (3 g.) and 2*N*-sodium hydroxide solution (30 c.c.). The arsinic acid obtained resembled the *p*-isomeride in its solubilities in various solvents. It was finally purified by fourfold precipitation from its solution in saturated sodium hydrogen carbonate solution (yield, 6 g. from 7·1 g. of benzoyl chloride *m*-dichloroarsine) (Found: N, 4·5. $C_{12}H_{18}O_4NAs$ requires N, 4·4%).

Nuclear-substituted Benzamidearsinic Acids. Derivatives of Salicylic Acid 5-Arsinic Acid.

5-*Nitrosalicylic Acid.*—The methods for the preparation of this acid have been critically examined by Raiziss and Proskouriakoff (*J. Amer. Chem. Soc.*, 1922, **44**, 784), but neither the method adopted by these authors nor those recorded in the literature gave satisfactory results. After many trials the following conditions were found to give the 5-nitro-acid consistently in 42% yield. Salicylic acid (100 g.) was slowly added (compare Meldola, Foster, and Brightman, J., 1917, **111**, 536) to a solution of nitric acid (100 c.c., *d* 1·42) in water (800 c.c.) heated on the water-bath. The contents first became dark, but on further heating (3·5 hours) a light yellow powder of 5-nitrosalicylic acid remained at the bottom of the flask. On cooling, a mass of fine needles also separated consisting chiefly of the 3-nitro-isomeride. The total solid was collected and boiled with water (400 c.c.), the liquid filtered hot, and the residue washed with boiling water (100 c.c.). The insoluble portion consisted of the 5-nitro-acid, m. p. 228°. 5-Aminosalicylic acid was prepared from the nitro-acid by the method of Weil, Traun, and Marcel (*Ber.*, 1922, **55**, 2665).

Salicylic Acid 5-Arsinic Acid (XVI).—5-Aminosalicylic acid hydrochloride (50 g.) was dissolved in water (400 c.c.) and concentrated hydrochloric acid (55 c.c.) and diazotised by the addition of 10% sodium nitrite solution (210 c.c.) in the presence of ice chippings (500 g.). A solution of arsenious oxide (30 g.) in 4% aqueous sodium hydroxide (400 c.c.) was then slowly added to the resultant suspension of diazo-oxide, and after the subsequent addition of freshly precipitated copper (prepared from 50 g. of copper sulphate)

the mixture was slowly made faintly alkaline to litmus paper. After 12 hours and readjustment of the reaction from time to time, the liquid was treated with 40% sodium hydroxide solution to decompose complex copper salts and filtered. The filtrate was made acid to Congo-paper and evaporated under reduced pressure at 50° to 400 c.c. A mass of cream-coloured needles of salicylic acid 5-arsinic acid (24 g.) separated on cooling and a further amount (8 g.) was obtained by saturating the mother-liquor with sodium chloride and keeping it at 0°. The total product was dissolved in 2*N*-ammonia, treated with norit, and precipitated at 90° with hydrochloric acid and finally recrystallised from boiling 50% aqueous methyl alcohol. The acid showed all the properties assigned to it by Kahn and Benda (*Ber.*, 1908, **41**, 3863), who prepared it from *o*-toluidine (see also O. and R. Adler, *Ber.*, 1908, **41**, 933; Karrer, *ibid.*, 1915, **48**, 1061). So prepared, it crystallises with one molecule of water of crystallisation (Found in air-dried material: loss at 100°, 6·9; As, 26·7. Calc. for $C_7H_7O_6As,H_2O$: H_2O, 6·4; As, 26·8%).

Salicylic Acid 5-Arsinous Acid (XX).—A solution of the above arsinic acid (2 g.) in water (10 c.c.) and concentrated hydrochloric acid (1 c.c.) was saturated with sulphur dioxide in presence of a trace of potassium iodide. After 24 hours, a cream-coloured powder of *salicylic acid 5-arsinous acid* (1·6 g.) separated (Found: As, 30·2. $C_7H_7O_5As$ requires As, 30·5%).

Salicylic Acid 5-Dichloroarsine (XIX).—Salicylic acid 5-arsinic acid (7 g.) was dissolved in a boiling mixture of ethyl alcohol (7 c.c.), water (15 c.c.), and concentrated hydrochloric acid (40 c.c.), a small crystal of potassium iodide added, and the solution saturated with sulphur dioxide. The oil which separated at first rapidly solidified to a mass of compact prisms. After 4 hours, it was collected (6·8 g.) and recrystallised by dissolution in the minimum volume of boiling 50% aqueous methyl alcohol, followed by the addition of concentrated hydrochloric acid until a turbidity was produced (Found: As, 26·4. $C_7H_5O_3Cl_2As$ requires As, 26·5%).

Methyl Salicylate-5-arsinic Acid (XVII).—The esterification of salicylic acid 5-arsinic acid by the Fischer–Speier method proceeds very slowly in 1·5% methyl-alcoholic sulphuric acid; if a 10% methyl-alcoholic solution of salicylic acid 5-arsinic acid containing 10% sulphuric acid is used, the methyl ester may be obtained in 70% yield after 3 hours' refluxing. The ester is most conveniently isolated by removing nearly all the methyl alcohol under reduced pressure at room temperature, followed by addition of water (equal in volume to the residue). *Methyl salicylate-5-arsinic acid*, m. p. 208° (efferv.), crystallises from 4 parts of boiling 50% methyl alcohol in small prisms (Found: MeO, 9·4; As, 27·3. $C_8H_9O_6As$ requires

MeO, 11·2; As, 27·2%). If the solution is refluxed for a longer period or if more sulphuric acid is used, some of the arsinic acid decomposes with formation of arsenious oxide. Saturation of a boiling 10% methyl-alcoholic solution of the arsinic acid (7 g.) with dry hydrogen chloride, followed by removal of most of the methyl alcohol, causes crystals of methyl salicylate-5-dichloroarsine (2 g.) to separate. Addition of water (20 c.c.) to the filtrate from this product gives methyl salicylate-5-arsinic acid (5 g.).

Methyl Salicylate-5-dichloroarsine (XVIII).—(i) *From salicylic acid 5-arsinous acid.* The arsinous acid (10 g.), dissolved in anhydrous methyl alcohol (15 c.c.), was heated with dry hydrogen chloride at 10° until saturated. After 4 hours, methyl salicylate 5-dichloroarsine (10 g.) had separated and was crystallised from boiling benzene. (ii) *From salicylic acid 5-dichloroarsine.* Salicylic acid 5-dichloroarsine (5·1 g.) was dissolved in dry methyl alcohol (6 c.c.) and saturated with hydrogen chloride at 10°. The mass of crystals was removed after 2 hours and a further amount was obtained by adding concentrated hydrochloric acid (5 c.c.) to the filtrate. The total yield was 4·6 g. When crystallised from boiling benzene, *methyl salicylate-5-dichloroarsine,* m. p. 168°, was obtained in small prisms. It proved to be identical both with that obtained from salicylic acid 5-arsinous acid and with that obtained in the treatment of salicylic acid 5-arsinic acid with methyl-alcoholic hydrogen chloride (Found: MeO, 8·2; Cl, 23·8; As, 25·7. $C_8H_7O_3Cl_2As$ requires MeO, 10·5; Cl, 23·9; As, 25·3%). This substance is soluble in sodium hydroxide, but in sodium hydrogen carbonate solution a white solid (methyl salicylate-5-arsinous acid) remains after the effervescence has ceased. When it is treated with ammonia at room temperature, extensive decomposition takes place.

Methyl salicylate-5-arsinic acid may be conveniently prepared from this dichloroarsine; it is essential, however, to keep the reaction mixture at 0° during the manipulations, otherwise most of the product consists of the carboxylic acid. The dichloroarsine (5·1 g.) was ground under saturated sodium hydrogen carbonate solution (10 c.c.), removed, suspended in a further quantity of this reagent (20 c.c.), and slowly treated with 30% hydrogen peroxide (2·2 g.) in water (10 c.c.). After being kept at 0° for 1 hour, the liquid was made acid, and the precipitated methyl salicylate-5-arsinic acid collected (3·1 g.).

Salicylamide-5-arsinic Acid (XIV).—A suspension of the finely ground methyl ester (6 g.) in methyl alcohol (15 c.c.) and aqueous ammonia (20 c.c., *d* 0·88) was heated in a sealed tube at 100° for 5 hours. The free ammonia and part of the solvents were removed under reduced pressure at 50° and the residual solution was made

faintly acid to Congo-paper. Large rhombs separated slowly on keeping. They were purified by dissolving them in the smallest amount of 2*N*-ammonia, adjusting the reaction to faint acidity to litmus, and treating the solution with charcoal. When it was made faintly acid to Congo-paper, *salicylamide-5-arsinic acid*, unmelted at 300°, separated (yield, 3·9 g.) (Found: N, 5·6. $C_7H_8O_5NAs$ requires N, 5·4%). This amide is much more soluble in dilute hydrochloric acid than in water.

m-*Xylyl*-4-*arsinic Acid*.—This acid has been previously prepared by Michaelis from tri-*m*-xylylarsine (*Annalen*, 1902, **320**, 333). After numerous trials the following conditions were found satisfactory for its preparation from *m*-4-xylidine. A solution of *m*-xylidine (40·5 g.) in concentrated hydrochloric acid (60 c.c.) and water (150 c.c.) was diazotised with 10% sodium nitrite (210 c.c.) in the presence of ice-chippings (450 g.). This solution was run into another consisting of arsenious oxide (45 g.) and 50% aqueous sodium hydroxide (160 c.c.) in water (750 c.c.) which had just previously been heated to 90°, and 20% aqueous copper sulphate (20 c.c.) added. The mixing was complete in 15 minutes and after an hour the liquid was made weakly acid to litmus paper and filtered from tar. Evaporation of the filtrate (to 700 c.c.), followed by acidification to Congo-paper, gave cream-coloured *m*-xylyl-4-arsinic acid (42·6 g.) which was sufficiently pure for oxidation. One crystallisation from 20% aqueous alcohol gave fine elongated leaflets, m. p. 210—212° (Michaelis gives m. p. 210°).

iso*Phthalic Acid* 4-*Arsinic Acid* (XXI).—This acid was also obtained by Michaelis (*loc. cit.*) by oxidation of the corresponding xylylarsinic acid with permanganate. The large volumes used by Michaelis can be avoided by the following process (compare Maschmann, *Ber.*, 1924, **57**, 1763). A vigorously stirred solution of *m*-xylyl-4-arsinic acid (23 g.) in 0·2*N*-sodium hydroxide (500 c.c.; 1 mol.) was treated with small amounts of finely powdered permanganate (35 g.) at 70—75° over a period of several hours. The solution was finally boiled and any excess of permanganate destroyed by alcohol. After filtration the press-cake was re-extracted twice by suspending it in 500 c.c. of 0·2*N*-sodium hydroxide and bringing the mixture to the boiling point with stirring. (The acid is retained tenaciously by the manganese oxides.) The combined filtrates were acidified to Congo-paper and concentrated. The total yield of acid was 73·4% of the theoretical. The purity of the successive crops obtained can be controlled by titration under standard conditions in comparison with a sample of the pure acid.

Action of Thionyl Chloride on iso*Phthalic Acid* 4-*Arsinic Acid*.—The acid (5·8 g.) was gently boiled for 3½ hours with excess (47 g.)

of freshly distilled thionyl chloride. The residue obtained on removal of the solvent was dissolved in dry toluene and added portionwise to 140 c.c. of chilled 2*N*-ammonia in a bottle and vigorously shaken. The toluene was removed under reduced pressure and perhydrol (2·3 g.) was added to the clear aqueous solution. On concentration to a small volume and acidification, iso*phthalamic acid* 6-*arsinic acid* (XV) separated (yield, 4·45 g.). For analysis it was recrystallised from 30 volumes of boiling water, separating in well-formed glassy prisms (Found: loss at 100°, 5·9, 6·2. $C_8H_8O_6NAs,H_2O$ requires H_2O, 5·9%. Found in anhydrous acid: N, 4·9; As, 26·1. $C_8H_8O_6NAs$ requires N, 4·85; As, 25·9%). This acid also crystallises in short needles. Both forms are unmelted at 300°.

Action of Phosphorus Pentachloride on iso*Phthalic Acid* 4-*Arsinic Acid.*—(a) *With* 5·5 *molecular proportions of phosphorus pentachloride.* Finely powdered *iso*phthalic acid 4-arsinic acid (5·8 g.) was mixed with 22·9 g. of phosphorus pentachloride and after the vigorous reaction had subsided, during which chlorine was evolved, the product was heated in an oil-bath at 110° (external temperature) for 3 hours. The phosphorus oxychloride was distilled off under reduced pressure and the residue, dissolved in sodium-dried toluene, was added portionwise to 160 c.c. of chilled 2*N*-ammonia with vigorous shaking. The toluene was separated, and the aqueous layer extracted once more with benzene. The combined extracts, evaporated to dryness, left 0·05 g. of 3 : 4-dichlorobenzamide, m. p. 163° (see below, section *b*). The aqueous layer was evaporated at 50° to a small volume and deposited 0·8 g. of crude 4-*chloro*-iso*phthalamide* (XXII), m. p. 223—226°. This amide is soluble in 17 parts of boiling water and crystallises in needles, elongated leaflets, and in square plates, m. p. 232—233° (Found: N, 14·2. $C_8H_7O_2N_2Cl$ requires N, 14·1%). On hydrolysis with boiling *N*-potassium hydroxide solution it gave 4-chloro*iso*phthalic acid. This acid is very sparingly soluble in boiling water, requiring 130 parts for solution. It crystallises therefrom in fine needles, m. p. 290—292° (Found: equiv., 104. Calc., 100·3). In its properties it accords best with those given by Ullmann and Uzbachian (*Ber.*, 1903, **36**, 1799).

The mother-liquor of the chloro*iso*phthalamide was made distinctly alkaline by the addition of sodium hydroxide and perhydrol (2·3 g.) was added. On acidification the half-amide of *iso*phthalic acid 4-arsinic acid (3·25 g.) separated, identical with that obtained by the use of thionyl chloride.

(b) *With* 6·5 *molecular proportions of phosphorus pentachloride.* The acid (10·75 g.) was mixed with powdered phosphorus penta-

chloride (50 g.) in a small distillation flask, and the chlorine and phosphorus oxychloride produced were allowed to distil off. The flask was then immersed in an oil-bath kept at 150—160° for 5 hours. Most of the phosphorus oxychloride had distilled off at the end of the first hour's heating. The product was worked up similarly to the foregoing. The benzene–toluene extract on evaporation deposited 0·25 g. of crude 3 : 4-dichlorobenzamide, m. p. 140—156°, which on recrystallisation from 15 c.c. of water separated in large leaflets, m. p. 166—168°. Of this, 0·05 g. was hydrolysed by boiling *N*-potassium hydroxide (1·25 c.c.) and on acidification gave 3 : 4-dichlorobenzoic acid as a felt of microscopic crystals. It was recrystallised from a large volume of boiling water and separated in microscopic pointed leaflets, m. p. 211—212°. The amount available was insufficient for complete analysis, but 0·0372 g. on titration required 2·05 c.c. of *N*/10-alkali, whereas the calculated figure is 1·95 c.c.

The aqueous layer, freed from ammonia and toluene by distillation at 40°, gave 4-chloro*iso*phthalamide (6·0 g.), m. p. 223—227°; the mother-liquor on concentration gave a further 0·65 g. of the same substance. No other product could be found.

Methyl iso*Phthalate*-4-*arsinous Acid*.—*iso*Phthalic acid 4-arsinic acid (20 g.) was suspended in 150 c.c. of dry purified methyl alcohol (wood spirit), and a current of dry hydrogen chloride passed till saturation was complete at 0°. The clear dark brown solution was then heated for 5 hours under reflux, the passage of dry hydrogen chloride being continued. During this process a dark lower layer containing methyl *iso*phthalate-4-dichloroarsine separated. The major portion of the supernatant layer was removed by heating under reduced pressure, and the residue poured into 250 c.c. of saturated sodium hydrogen carbonate solution cooled below 0°. The insoluble grey rubbery mass gradually disintegrated and solidified. It consisted of almost pure *methyl* iso*phthalate*-4-*arsinous acid* (yield, 19 g.) (Found : MeO, 15·1; As, 24·6. $C_{10}H_{11}O_6As$ requires MeO, 20·5; As, 24·8%). Treatment of this ester with aqueous methyl-alcoholic ammonia at 100° led to extensive decomposition.

Methyl iso*Phthalate*-4-*arsinic Acid*.—The arsinous acid (19 g.) was suspended in water (50 c.c.) at 0° and treated with sodium hydrogen carbonate (2·2 mols.) and 30% hydrogen peroxide (1·1 mols.). Rapid effervescence occurred and when solution was complete acidification gave microscopic square plates of *methyl* iso*phthalate*-4-*arsinic acid* (20·5 g.) (Found : As, 23·6. $C_{10}H_{11}O_7As$ requires As, 23·6%). This acid is fairly readily soluble in hot water and crystallises therefrom in long needles, which effervesce at 196—197° and then rapidly resolidify. The plate form of crystal

effervesces at 185° and then rapidly resolidifies (anhydride formation).

Methyl iso*Phthalate 4-Arsinetetrachloride.* — The dicarboxy-acid (5 g.) was suspended in 35 c.c. of synthetic methyl alcohol at −5°, and the liquid saturated with dry hydrogen chloride. The acid dissolved after 1 hour and after a few more hours pale yellow needles began to separate. When separation was complete the solid was rapidly collected, washed with sodium-dried ether, and quickly dried in a vacuum. The *arsinetetrachloride* (2·5 g.) is highly hygroscopic and has m. p. 110—115° (efferv.) (Found: Cl, 31·7. $C_{10}H_9O_4Cl_4As$ requires Cl, 34·6%). The low chlorine content indicates slight hydrolysis to the oxychloride, since the product was free from tervalent arsenic compounds. When added to saturated sodium hydrogen carbonate solution at 0°, it rapidly dissolved and on acidification gave methyl *iso*phthalate-4-arsinic acid, identical with the product described above. Characteristic is its separation in microscopic plates on acidification but in needles when recrystallised from water.

Action of Ammonia on Methyl iso*Phthalate-4-arsinic Acid.*—Methyl *iso*phthalate-4-arsinic acid (28·4 g. of the plate form) was added to 284 c.c. of ammonia (*d* 0·88) previously cooled to −5°. The mixture was kept below 0° for 14 days, during which the gelatinous ammonium salt which originally separated had disappeared with formation of a loose powder. The ammonia was removed as far as possible at room temperature and then, with some concentration of the solution, at 45°. On strong acidification to Congo-paper, a large crop of crystals separated, and on concentration of the mother-liquor at 50° further crops were obtained, making 25·2 g. in all. This material was subjected to fractional crystallisation, the more sparingly soluble fractions (16·0 g.) consisting of *iso*phthalamic acid 6-arsinic acid identical with that obtained previously. The more soluble fractions were further carefully fractionated, and the nitrogen content and titration equivalents determined. They consisted mainly of the above half-amide mixed with varying proportions of esters. There was no evidence for the presence of a diamide in any fraction.

If the original solution is not acidified strongly to Congo-paper, the product contains an *acid ammonium* salt of *iso*phthalamic acid 6-arsinic acid which, being readily soluble in water, separates in the later fractions. It crystallises in fine silky needles (Found: N, 8·9. $C_8H_{11}O_6N_2As$ requires N, 9·1%). The use of methyl-alcoholic ammonia at higher temperatures was no more successful.

Derivatives of Sulphophenylarsinic Acid.

Benzenesulphonyl Chloride p-*Dichloroarsine* (XXV).—*p*-Sulphophenylarsinic acid (13·2 g., prepared as described by Hewitt, King, and Murch, J., 1926, 1369) was suspended in carbon tetrachloride (132 c.c.), and phosphorus pentachloride (58 g.; 6 mols.) added. On warming, hydrogen chloride and chlorine were rapidly evolved. After 1·5 hours' refluxing, the substances volatile at 50°/20 mm. were removed and the residue was poured into a mixture (200 c.c.) of equal volumes of concentrated hydrochloric acid and water. The precipitated oil rapidly solidified (13·1 g.) and when dry was crystallised from benzene. *Benzenesulphonyl chloride* p-*dichloroarsine* separated in stout rhombs (Found: Cl, 33·2. $C_6H_4O_2Cl_3SAs$ requires Cl, 33·1%).

Benzenesulphonyl Chloride p-*Arsenious Oxide*.—The corresponding dichloroarsine (1 g.) was ground with water and kept for 12 hours. The amorphous product was pure *benzenesulphonyl chloride* p-*arsenious oxide* (0·8 g.), almost insoluble in water or organic solvents (Found: Cl, 13·5. $C_6H_4O_3ClSAs$ requires Cl, 13·3%). The aqueous filtrate contained a small quantity of deliquescent p-*sulphophenylarsinous acid*, which may be more readily prepared by boiling either of the sulphonyl chloride compounds with water and evaporating the resultant solution repeatedly to dryness with water.

Benzenesulphonamide-p-*arsenious Oxide* (XXVI).—Benzenesulphonyl chloride *p*-dichloroarsine (5·8 g.), dissolved in benzene (15 c.c.), was slowly added to 2*N*-aqueous ammonia with vigorous shaking. Towards the end of the reaction a white solid separated (2 g.), and a further precipitate (2·6 g.) was obtained by removing the benzene and evaporating the aqueous solution (to 30 c.c.). The united crops were dissolved in hot sodium hydrogen carbonate solution and precipitated with acid. *Benzenesulphonamide*-p-*arsenious oxide* is an amorphous substance which is much more soluble in water than the corresponding benzamide compound (Found: As, 28·2. $C_6H_6O_3NSAs$ requires As, 28·3%). On treatment with hydrochloric acid it is readily converted into *benzenesulphonamide*-p-*dichloroarsine*. For the preparation of this substance sufficient ethyl alcohol was added to a suspension of the arsenious oxide (1 g.) in water to give a clear solution on boiling, and concentrated hydrochloric acid (15 c.c.) slowly added. On cooling, a mass of fine needles (0·82 g.) separated, m. p. 176—178° (Found: Cl, 23·3; As, 25·0. $C_6H_6O_2NCl_2SAs$ requires Cl, 23·5; As, 24·8%).

Benzenesulphonamide-p-*arsinic Acid* (XXVII).—A suspension of benzenesulphonamide-*p*-arsenious oxide (8·7 g.) in water (30 c.c.) was mixed with a solution of 30% hydrogen peroxide (4·4 g.) in

water (20 c.c.). The mixture became hot, most of the solid dissolved, and the undissolved portion became crystalline. The reaction was completed by heating until a clear solution was obtained. On allowing the liquid to cool, stout rhombic tablets of *benzenesulphonamide*-p-*arsinic acid* separated. They were recrystallised from boiling water (60 c.c.) and gave 6·7 g. of pure amide (Found: N, 4·8. $C_6H_8O_5NSAs$ requires N, 5·0%).

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