LXVIII.—*Diphenylaminearsinic Acids. Part I. Derivatives of Diphenylamine-4-arsinic Acid.*

By HARRY JAMES BARBER.

INVESTIGATIONS of the relation between trypanocidal action and chemical constitution have resulted in an exhaustive study of the effects of substitution in a single aromatic nucleus containing an arsenic group, and to a less extent in arsenic derivatives containing more than one aromatic nucleus.

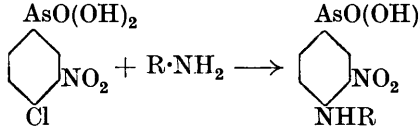
Derivatives in which other substituted aromatic nuclei are attached to that containing the arsenic group by linkages of the types ·CO·NH· and ·NH·CO·NH· are numerous, but those involving a closer union, such as diphenylamine, have not been extensively studied.

The reactivity of the various chloronitrophenylarsinic acids in which the chlorine is in the ortho- or the para-position with respect to the nitro-group suggested the use of these for the preparation of considerable quantities of certain types of diphenylamines. Since this paper is restricted to the consideration of diphenylamine-4-arsinic acids, only the reactions of 4-chloro-3-nitrophenylarsinic acids will be discussed here, but the reactions of the other chloronitrophenylarsinic acids mentioned are being investigated.

The reactivity of the chlorine atom is shown by its replacement by NH_2, NHMe, NMe_2, and $NH{\cdot}CH_2{\cdot}CO_2H$ groups when the arsinic acid

is heated in aqueous media with the corresponding amine (D.-R.P. 285,604, 412,171, 446,545). It also reacts with piperidine (King, J., 1927, 1053) and with ethylenediamine and piperazine (Fourneau and Funke, *Bull. Soc. chim.*, 1928, **43**, 889).

It was found that 4-chloro-3-nitrophenylarsinic acid reacted very readily with most aromatic amines when an aqueous solution of its sodium salt was warmed with a suspension or solution of the amine at 95° for several hours. The products obtained by using aniline, 4-aminophenol, 4-aminoacetanilide, 4-amino-2-acetamidophenol, or anthranilic acid are described here, but *o*-chloroaniline, *o*-toluidine, and sulphanilic acid have also been found to condense; the nitroanilines are apparently not sufficiently basic to react under the conditions employed.



[R = C_6H_5, C_6H_4·OH, C_6H_4·NHAc, C_6H_3(OH)·NHAc, or C_6H_4·CO_2H.]

The 2-nitrodiphenylamine-4-arsinic acids thus obtained were reduced to the corresponding amino-compounds, and certain derivatives were also prepared. The biological results, for which I am indebted to Mr. J. G. Everett, B.Sc., A.I.C., of this laboratory, are summarised in the following table.

The tolerated dose (*T*) was determined by intravenous injection in normal mice, and the curative dose (*C*) on mice infected with *Trypanosoma equiperdum*; both are expressed as mg./g. of mouse. The period of observation was 7 days. For comparison, 3-amino-4-piperidinophenylarsinic acid (King, *loc. cit.*), 3-amino-4-piperazinophenylarsinic acid (Fourneau and Funke, *loc. cit.*), and 3 : 4-diaminophenylarsinic acid are included.

Arsinic acids.	*T*.	*C*.	*C*/*T*.
3 : 4-Diaminophenylarsinic acid	2·0	0·15	1/13
3-Amino-4-piperidinophenylarsinic acid	<0·1	>0·1	—
3-Amino-4-piperazinophenylarsinic acid	0·5	>0·5	—
2-Aminodiphenylamine-4-arsinic acid	0·05	0·05	1
2-Acetamidodiphenylamine-4-arsinic acid	0·1	0·1	1
2-*iso*Propylideneaminodiphenylamine-4-arsinic acid (or *N*-phenyl-2 : 2-dimethyl-2 : 3-dihydrobenziminazole)	0·1	>0·1	—
2 : 4′-Diaminodiphenylamine-4-arsinic acid	0·1	0·1	1
2-Amino-4′-acetamidodiphenylamine-4-arsinic acid	0·6	0·1	1/6
2 : 4′-Diacetamidodiphenylamine-4-arsinic acid	2·0	—	—
2-Amino-4′-hydroxydiphenylamine-4-arsinic acid	0·5	0·25	1/2
2-Amino-3′-acetamido-4′-hydroxydiphenylamine-4-arsinic acid	1·0	>1·0	—
Arsenobenzenes (administered orally).			
3 : 3′-Diamino-4 : 4′-dianilinoarsenobenzene	>10·0	0·5	<1/20
3 : 3′-Diamino-4 : 4′-di-*p*-acetamidoanilinoarsenobenzene	>10·0	1·0	<1/10

In this series of compounds the introduction of an unsubstituted phenyl group in the 4-amino-group of 3 : 4-diaminophenylarsinic acid results in a very marked increase in toxicity, despite the lower arsenic content, and somewhat greater trypanocidal effect; this unexpected and interesting discovery is being further investigated. Substitution in the non-arsenated phenyl nucleus results in modification of the toxicity and curative action, which follows, in general, that of similar substitution in phenylarsinic acid. As is usual, the introduction of an acetyl group in the amino-group results in a decrease of both toxicity and curative action.

EXPERIMENTAL.

4-Chloro-3-nitrophenylarsinic acid (D.-R.P. 245,536) is prepared by nitration of 4-chlorophenylarsinic acid, obtained by a modification of the Bart reaction from *p*-chloroaniline, but as precise details of the nitration are not given, the preparation is described here.

To 4-chlorophenylarsinic acid (24 g.) dissolved in concentrated sulphuric acid (70 c.c.), nitric acid (*d* 1·52; 7·5 c.c.) was added without cooling. The mixture was heated on a water-bath for 1 hour and poured on ice, and the arsinic acid separated; yield, 24 g. (85%). Nitration does not occur at 0°, and despite the statement (D.-R.P. 285,604) that 4-chloro-3 : 5-dinitrophenylarsinic acid is prepared by " energetic nitration," no trace of this has been obtained even under the most drastic conditions. The acid crystallises from hot water in diamond plates (Found : As, 27·0. Calc. for $C_6H_5O_5NClAs$: As, 26·7%); the calcium salt crystallises in needles and the barium salt in plates.

2-*Nitrodiphenylamine*-4-*arsinic Acid*.—The foregoing acid (28 g.), dissolved in 2*N*-caustic soda (50 c.c.) and water (150 c.c.), was heated for 16—20 hours on a steam-bath with aniline (10 g.; 5% excess of 2 mols.). Part of the required acid crystallised, and the remainder was obtained by acidification (Congo red) with hydrochloric acid. The yield was almost quantitative but the crude material was contaminated by aniline. The crude acid was converted into the sodium salt in concentrated aqueous solution; this was salted out with sodium chloride and dissolved in a large volume of water, the solution was heated to boiling in the presence of charcoal and filtered, and the *acid* precipitated hot with hydrochloric acid. It separated in fine yellow needles (Found : As, 21·9, 22·0; N, 8·5. $C_{12}H_{11}O_5N_2As$ requires As, 22·2; N, 8·3%), sparingly soluble in boiling water, almost insoluble in cold. It is somewhat more soluble in dilute and readily soluble in hot glacial acetic acid.

2-*Aminodiphenylamine*-4-*arsinic Acid*.—The 2-nitro-acid was re-

duced with ferrous hydroxide at 80—90° by the method of Jacobs, Heidelberger, and Rolf (*J. Amer. Chem. Soc.*, 1918, **40**, 1581). The crude amino-acid (80% yield) crystallised with a purple colour, which could only be removed by dissolving the acid in sodium hydroxide solution, adding a *trace* of sodium hydrosulphite, boiling the solution with charcoal, filtering it, and acidifying it with acetic acid. The pure *acid* crystallises from hot water in white rectangular plates (Found : As, 24·6; N, 9·4. $C_{12}H_{13}O_3N_2As$ requires As, 24·3; N, 9·1%), which rapidly turn blue on exposure to air; m. p. 170—175° with preliminary darkening.

The *monohydrochloride* forms long slender needles from 2*N*-hydrochloric acid which are readily hydrolysed by water and slowly lose hydrogen chloride in air (Found : As, 22·6; Cl, 9·0. $C_{12}H_{13}O_3N_2As,HCl$ requires As, 21·8; Cl, 10·3%).

On attempting to recrystallise the base from hot acetone, a condensation product was obtained containing acetone, not driven off at 100° but readily lost on warming with dilute acid or alkali; this was either 2-*iso*propylideneaminodiphenylamine-4-arsinic acid or *N*-phenyl-2 : 2-dimethyl-2 : 3-dihydrobenziminazole (Found : As, 21·5, 21·7; N, 7·5, 7·6; $COMe_2$, 14·3, 14·6. $C_{15}H_{17}O_3N_2As$ requires As, 21·5; N, 8·05; $COMe_2$, 16·2%). Treatment of the base with nitrous acid gives quantitatively *N-phenylbenztriazole-5-arsinic acid* (Found : As, 23·4; N, 12·7. $C_{12}H_{10}O_3N_3As$ requires As, 23·5; N, 13·15%).

2-Acetamidodiphenylamine-4-arsinic acid, obtained by acetylation of the amino-derivative in alkaline solution with acetic anhydride, crystallises from alcohol in small diamond-shaped plates (Found : As, 21·8; N, 7·85. $C_{14}H_{15}O_4N_2As$ requires As, 21·5; N, 8·0%). On being boiled (5 g.) with 2*N*-hydrochloric acid (50 c.c.), it gives *N-phenyl-2-methylbenziminazole-5(6)-arsinic acid* (compare *J. pr. Chem.*, 1904, **69**, 40) (Found : As, 22·6. $C_{14}H_{13}O_3N_2As$ requires As, 22·6%).

2-Nitro-4'-hydroxydiphenylamine-4-arsinic acid, prepared by the condensation of 4-chloro-3-nitrophenylarsinic acid with *p*-aminophenol exactly as described for aniline (above), crystallises from alcohol in reddish-brown needles (Found : As, 20·5; N, 8·3. $C_{12}H_{11}O_6N_2As$ requires As, 21·2; N, 7·9%).

2-Amino-4'-hydroxydiphenylamine-4-arsinic acid, obtained by reduction with ferrous hydroxide in the usual way, crystallises from very dilute acetic acid in grey flat needles, which are very susceptible to atmospheric oxidation (Found : As, 22·9; N, 8·4. $C_{12}H_{12}O_4N_2As$ requires As, 23·1; N, 8·65%). *4'-Hydroxy-1-phenyl-1 : 2 : 3-benztriazole-5-arsinic acid* crystallises in colourless needles (Found : As, 22·5; N, 12·4. $C_{12}H_{10}O_4N_3As$ requires As, 22·4; N, 12·5%).

2-*Nitro*-4'-*acetamidodiphenylamine*-4-*arsinic acid*, from *p*-aminoacetanilide and 4-chloro-3-nitrophenylarsinic acid, crystallises in faintly red needles (Found : As, 18·75. $C_{14}H_{14}O_6N_3As$ requires As, 19·0%).

2-*Amino*-4'-*acetamidodiphenylamine*-4-*arsinic acid* forms irregular flat needles (Found : As, 20·7. $C_{14}H_{16}O_4N_3As$ requires As, 20·5%). Acetylation gives 2 : 4'-*diacetamidodiphenylamine*-4-*arsinic acid* (Found : As, 18·6. $C_{16}H_{18}O_5N_3As$ requires As, 18·4%), which crystallises in fine colourless needles from dilute acetic acid.

2 : 4'-*Diaminodiphenylamine*-4-*arsinic acid*, prepared by boiling the 4'-acetyl compound (5 g.) with 2*N*-sulphuric acid (50 c.c.) for 3 hours, forms long slender prisms (Found : As, 23·6. $C_{12}H_{14}O_3N_3As$ requires As, 23·2%).

2-*Nitro*-3'-*acetamido*-4'-*hydroxydiphenylamine*-4-*arsinic acid* forms fine yellow needles from hot water (Found : As, 18·7. $C_{14}H_{14}O_7N_3As$ requires As, 18·7%).

2-*Amino*-3'-*acetamido*-4'-*hydroxydiphenylamine*-4-*arsinic acid* crystallises in fine colourless needles from 50% acetic acid (Found : As, 19·9. $C_{14}H_{16}O_5N_3As$ requires As, 20·2%).

2'-*Carboxy*-2-*nitrodiphenylamine*-4-*arsinic acid* forms yellow needles from hot 50% acetic acid (Found : As, 20·1. $C_{13}H_{11}O_7N_2As$ requires As, 19·6%).

Nitration of 2-*Acetamidodiphenylamine*-4-*arsinic Acid*.—Owing to the failure to condense *o*- and *p*-nitroanilines with 4-chloro-3-nitrophenylarsinic acid, the direct nitration of 2-acetamidodiphenylamine-4-arsinic acid was carried out in the hope of obtaining the 2'- or 4'-nitro-derivative, which on reduction would give 2'- or 4'-amino-2-acetamidodiphenylamine-4-arsinic acid isomeric with the 2-amino-4'-acetamido-compound described above, but it was not possible to obtain a mononitro-derivative, for dinitration occurred even at −10° with only 1 mol. of nitric acid or potassium nitrate.

2' : 4'(?)-*Dinitro*-2-*acetamidodiphenylamine*-4-*arsinic acid* crystallises from 50% acetic acid in clusters of fine yellow needles (Found : As, 16·9, 17·2; N, 12·5. $C_{14}H_{13}O_8N_4As$ requires As, 17·0; N, 12·7%). A satisfactory method of orienting this product has not yet been found.

The two arseno-compounds mentioned in the table (p. 472) were prepared from the arsinic acids by reduction with sodium hydrosulphite in the usual way. They are both yellow amorphous powders, which oxidise rapidly in air and are soluble in excess of hydrochloric acid : 3 : 3'-*diamino*-4 : 4'-*dianilinoarsenobenzene* (Found : As, 28·2. $C_{24}H_{22}N_4As_2$ requires As, 29·1%); 3 : 3'-*diamino*-4 : 4'-*di*-p-*acetamidoanilinoarsenobenzene* (Found : As, 23·8. $C_{28}H_{28}O_2N_6As_2$ requires As, 23·8%).

In conclusion, I wish to record my thanks to Dr. A. J. Ewins for his kindly criticism of this paper, and to Mr. R. H. Klein, F.I.C., for the analytical results.

RESEARCH LABORATORIES, MESSRS. MAY & BAKER, LTD.,
WANDSWORTH, S.W. 18. [*Received, December 29th*, 1928.]