

502. Carbazoles, Carbolines, and Related Compounds. Part IV.* Amino-derivatives of 9-Arsafluorenic Acid.†

By B. N. FEITELSON and V. PETROW.

The chemistry of 9-arsafluorenic acid † (V) has been extended by the preparation of the 2-, 3-, and 4-amino-derivatives. The 2:7-dinitro-derivative (IX; R = NO₂) has been prepared, but its reduction to (IX; R = NH₂) has not been accomplished.

MORGAN and STEWART (*J.*, 1931, 620; 1932, 1634; 1933, 1454) have shown that the introduction of an arsonic acid radical and an amino-group into the fluorene molecule leads to the appearance of trypanocidal properties. Extending these observations, we have now prepared some amino-derivatives of 9-arsafluorenic acid † (V), in which the arsenic acid radical has been transferred to an intracyclic position.

9-Arsafluorenic acid (V), the parent compound of the group, was prepared by Aeschlimann, Lees, McClelland, and Nicklin (*J.*, 1925, 127, 66) by subjecting 2-aminodiphenyl to the Bart reaction, whereby diphenyl-2-arsonic acid (I) was produced, followed by ring closure with sulphuric acid. Experimental details for the preparation of (I) were not given. We have, therefore, carried out a systematic study of the methods whereby the latter compound may be obtained, and find Scheller's modification of the Bart reaction, as described by Oneto and Way (*J. Amer. Chem. Soc.*, 1941, 63, 3068), to be entirely satisfactory. Our results are thus at variance with Cookson and Mann's observations (*J.*, 1949, 2897).

Nitration of the acid (V) with one equivalent of nitric acid in concentrated sulphuric acid led to formation of the 2-nitro-derivative (VIII; R = NO₂), reduced by ammonical ferrous sulphate (Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1918, 40, 1585) to the 2-amino-compound (VIII; R = NH₂).

Preliminary attempts to confirm the constitution assigned to (VIII; R = NH₂), and hence to (VIII; R = NO₂), by its alternative synthesis from 2-amino-4'-nitrodiphenyl (Scarborough and Waters, *J.*, 1927, 89), proved unsuccessful. The latter compound readily gave 4'-nitrodiphenyl-2-arsonic acid (VII; R = NO₂) in excellent yield when submitted to the Scheller-Bart reaction, but attempts to effect ring closure of this compound with concentrated sulphuric acid invariably led to recovery of unchanged material. Heating with phosphorus oxychloride likewise failed to enforce cyclisation, though in this instance a product was obtained which was undoubtedly a di-(4'-nitro-2-diphenyl)arsinic acid (IV), formed by loss of arsenic acid between two molecules of 4'-nitrodiphenyl-2-arsonic acid. A similar transformation has been recorded by Morgan and Davies (*Proc. Roy. Soc.*, 1930, 127, A, 1) in the diphenyl-2-stibonic acid series.

Attention was, therefore, directed to the ring closure of 4'-aminodiphenyl-2-arsonic acid derivatives, whereby it was hoped that the inhibitory influence of the 4'-nitro-group on the cyclisation of (VII; R = NO₂) (cf. Morgan and Walls, *J.*, 1932, 2225) would be avoided (cf. Petrow, *J.*, 1945, 18; Walls, *J.*, 1947, 67). The amino-compound required for this purpose was obtained by reduction of (VII; R = NO₂) with alkaline ferrous sulphate, or, more conveniently, by careful hydrogenation, Raney nickel being used (cf. Doak and Steinmann, *J. Amer. Chem. Soc.*, 1946, 68, 1989). Experiments on its ring closure with concentrated sulphuric acid proved successful, authentic 2-amino-9-arsafluorenic acid (VIII; R = NH₂) being produced, identical in every way with the product obtained from the 2-nitro-acid (above), the constitution of which is accordingly confirmed. The 2-amino-acid was also prepared by cyclisation of 4'-carbethoxyaminodiphenyl-2-arsonic acid (VII; R = NH·CO₂Et), obtained by a Scheller-Bart reaction on 2-amino-4'-carbethoxyaminodiphenyl (Walls, *J.*, 1947, 67).

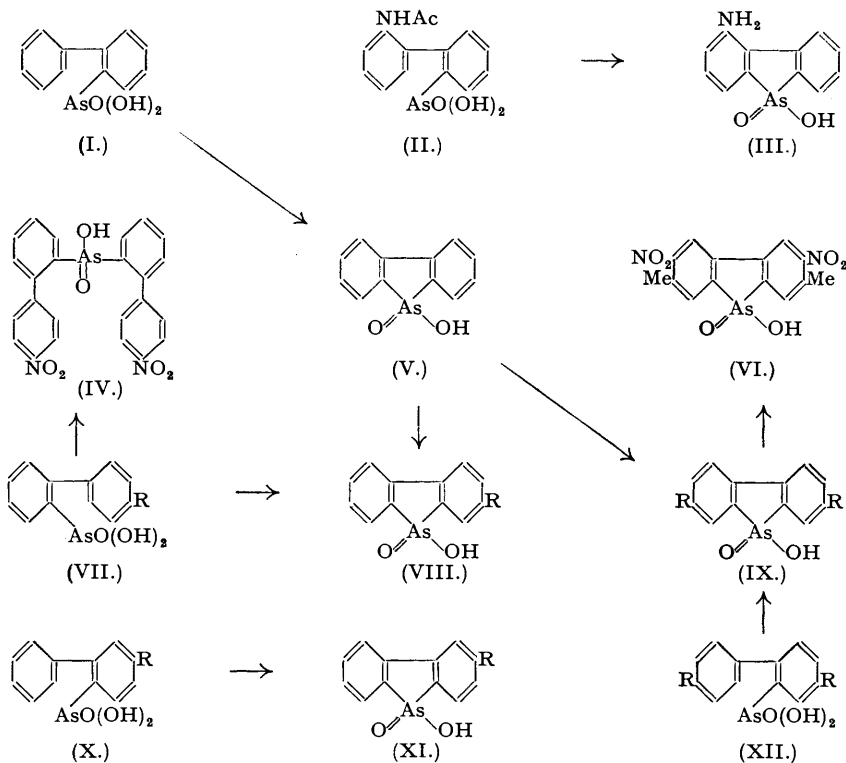
3-Nitro-9-arsafluorenic acid (XI; R = NO₂) was obtained by ring closure of 5-nitrodiphenyl-2-arsonic acid (X; R = NO₂) with concentrated sulphuric acid at 65°. The preparation of the latter compound was achieved through a Scheller-Bart reaction on 2-amino-5-nitrodiphenyl (Bell, *J.*, 1928, 2770). Reduction with alkaline ferrous sulphate furnished

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† The nomenclature used in this paper involves transference of the termination denoting the nature of the arsenic acid to the end of the fundamental skeleton, with elimination of a terminal "e". For the use of the termination "inic" to denote acids of the type R₂AsO·OH, compare the analogous phosphorus acids (*J.*, 1951, 1868, footnote). ED.

3-amino-9-arsafluorenic acid, also obtained by conversion of (X; R = NO₂) into 5-amino-diphenyl-2-arsonic acid (X; R = NH₂), followed by careful ring closure with sulphuric acid.

The preparation of 4-amino-9-arsafluorenic acid (III; R = NH₂) offered considerable experimental difficulty. 2-Amino-2'-nitrodiphenyl, required for this purpose, was first described by Mascarelli and Gatti (*Atti Accad. Lincei*, 1929, **10**, 441), who obtained it in impure condition by partial reduction of 2 : 2'-dinitrodiphenyl with aqueous-alcoholic ammonium sulphide. Its preparation was subsequently improved by Purdie (*J. Amer. Chem. Soc.*, 1941, **63**, 2276), but



this method likewise failed to give satisfactory results in our hands. Acetylation of the sticky product so obtained, however, gave a low yield of 2-acetamido-2'-nitrodiphenyl, which was directly reduced to 2-acetamido-2'-aminodiphenyl. The latter compound was also obtained, albeit in unsatisfactory yield, by partial acetylation of 2 : 2'-diaminodiphenyl as described by Sako (see *Chem. Abs.*, 1932, **26**, 3246). Conversion into 2'-acetamidodiphenyl-2-arsonic acid proceeded fairly well, but cyclisation to 4-amino-9-arsafluorenic acid (III) was accompanied by a very marked drop in yield.

Dinitration of (V) gave 2 : 7-dinitro-9-arsafluorenic acid (IX; R = NO₂). The constitution assigned to this compound follows from the formation of (VIII; R = NO₂) by mononitration of (V), and from the established formation of 2 : 7-dinitrofluorenone from fluorenone (Schultz, *Annalen*, 1880, **203**, 104), an analogous ring system in which the 9-position is likewise occupied by an electrophilic group. The direct preparation of (IX; R = NO₂) from 4 : 4'-dinitrodiphenyl-2-arsonic acid was not possible, however, as 2-amino-4 : 4'-dinitrodiphenyl (Ritchie, *Proc. Roy. Soc. N.S.W.*, 1945, **78**, 177) behaved abnormally in the Scheller-Bart reaction giving a mixture of 4 : 4'-dinitro- and 2-hydroxy-4 : 4'-dinitro-diphenyl.

Attempts to reduce 2 : 7-dinitro-9-arsafluorenic acid by chemical methods proved uniformly unsuccessful owing to the virtual insolubility of the compound in the usual solvents. Failure likewise followed experiments employing catalytic techniques : the compound was recovered unchanged after its hot 1% solution in 2-ethoxyethanol had been shaken with palladised charcoal and hydrogen, and use of Raney nickel and hydrogen under the same experimental conditions led to formation of benzidine. A dinitrodiphenyl-2-arsonic acid of unknown orientation,

obtained by nitration of diphenyl-2-arsonic acid (I), likewise proved too insoluble for reduction to the corresponding diamine.

Attention was, therefore, directed to the possibility of synthesising 2:7-diamino-9-arsafluorenic acid (IX; R = NH₂) by ring closure of 4:4'-diaminodiphenyl-2-arsonic acid derivatives (XII; R = NH₂). Attempts to prepare compounds of the latter type, however, proved disappointing. Thus 2-amino-4:4'-biscarbethoxyaminodiphenyl (Walls, *J.*, 1947, 67) behaved abnormally both in the usual Bart reaction, in which *NN'*-dicarbethoxybenzidine was formed, and in the Scheller modification, *NN'*-dicarbethoxy-2-hydroxybenzidine being obtained. 4:4'-Dicarbethoxy- and 4:4'-dinitro-groups thus seem to exert a similar inhibitory influence upon the replacement of a 2-amino- by a 2-arsonic group in the diphenyl series. The reason for this anomalous behaviour is not evident, however, as previous observations, *inter al.*, by Walls (*loc. cit.*), would appear to indicate that the polar effects of a 4:4'-dinitro- may be reversed by conversion into a 4:4'-diamino-group.

EXPERIMENTAL.

M. p.s are uncorrected.

Diphenyl-2-arsonic acid (I).—2-Aminodiphenyl (15 g.) in absolute ethanol (400 ml.) was treated with concentrated sulphuric acid (7 ml.), cooled to 5°, and the solution diazotised with a saturated solution of sodium nitrite (6.2 g.). The mixture, kept at 0–5°, was mechanically stirred for 2 hours, and arsenic trichloride (28 g.) in absolute ethanol (100 ml.) was then slowly added. After a further ½ hour cuprous bromide (2.0 g.) was added, and the mixture warmed gradually, with vigorous stirring, to 70°, at which temperature it was kept until evolution of nitrogen had ceased. Steam-distillation of the mixture removed ethanol and traces of diphenyl also formed in the reaction. Diphenyl-2-arsonic acid crystallised on cooling, and was purified *via* the potassium salt and by crystallisation from 50% aqueous acetic acid, white needles (40%) being obtained having m. p. 206°. Aeschlimann *et al.* (*loc. cit.*) give m. p. 205° (uncorr.).

9-Arsafluorenic Acid (V).—The foregoing compound (12 g.) was heated in concentrated sulphuric acid (90 ml.) for 1 hour at 50–60°, and the mixture was then poured slowly into ice-water. After some time, the precipitated material was collected and purified from glacial acetic acid. 9-Arsafluorenic acid formed needles (80%), m. p. >300° (Found: C, 54.9; H, 3.5. Calc. for C₁₂H₉O₂As: C, 55.4; H, 3.5%).

2-Nitro-9-arsafluorenic acid (VIII; R = NO₂).—9-Arsafluorenic acid (2.15 g.), dissolved in concentrated sulphuric acid (6 ml.), was treated at 0° with a mixture of nitric acid (0.5 ml., 1.0 mol; *d* 1.42) and concentrated sulphuric acid (0.5 ml.), added dropwise with stirring. Stirring was continued for a further ½ hour, and the mixture was then poured on ice. The precipitate was collected, and crystallised from 50% aqueous acetic acid, giving *2-nitro-9-arsafluorenic acid*, pale yellow crystals (90%), m. p. >345° (Found: C, 46.7; H, 2.7; N, 5.4. C₁₂H₈O₄NAs requires C, 47.2; H, 2.6; N, 4.6%).

2-Amino-9-arsafluorenic Acid (VIII; R = NH₂).—A solution of 2-nitro-9-arsafluorenic acid (1.25 g.) in 2.5*N*-sodium hydroxide (25 ml.) was added in one portion to a solution of ferrous sulphate (8 g.) in water (25 ml.) which had been made just alkaline to litmus with aqueous ammonia. The mixture was shaken vigorously for 10 minutes and filtered, and the filtrate acidified to pH 3. The pink precipitate was collected and purified by reprecipitation to give *2-amino-9-arsafluorenic acid* (75%), m. p. 240° (Found: C, 52.2; H, 3.9; N, 4.5. C₁₂H₁₀O₂NAs requires C, 52.4; H, 3.6; N, 5.1%).

4'-Nitrodiphenyl-2-arsonic acid (VII; R = NO₂), yellow crystals (77%) from methanol or aqueous acetic acid, had m. p. 290° (decomp.) (Found: C, 44.7; H, 3.3; N, 4.1. C₁₂H₁₀O₅NAs requires C, 44.6; H, 3.1; N, 4.3%).

Di-(4'-nitro-2-diphenyl)arsinic Acid (IV).—4'-Nitrodiphenyl-2-arsonic acid (5 g.) was heated under reflux with phosphorus oxychloride (10 g.) for 1½ hours. Excess of halides was removed under reduced pressure, and the residue was extracted with 2*N*-sodium hydroxide solution. The resulting sodium salt was decomposed with dilute hydrochloric acid, and the solids (4.7 g.) thus formed were extracted with boiling ethanol (200 ml.). The insoluble fraction (1.1 g.) yielded *di-(4'-nitrodiphenyl)arsinic acid*, m. p. >260°, on crystallisation from ethanol (Found: C, 57.5; H, 4.1; N, 4.6. C₂₄H₁₇O₆N₂As requires C, 57.2; H, 3.4; N, 5.6%).

4'-Aminodiphenyl-2-arsonic acid (VII; R = NH₂).—(i) 4'-Nitrodiphenyl-2-arsonic acid was reduced with ammoniacal ferrous sulphate, to give *4'-aminodiphenyl-2-arsonic acid*, m. p. 212–213° (Found: N, 4.9. C₁₂H₁₂O₃NAs requires N, 4.8%). (ii) The corresponding nitro-compound (10 g.) was dissolved in ethanol (150 ml.), and the mixture shaken with Raney nickel and hydrogen until the theoretical volume of gas had been absorbed. After filtration, the solution was concentrated under reduced pressure to a small bulk, water was added, and the mixture cooled. 4'-Aminodiphenyl-2-arsonic acid separated in nearly quantitative yield as microcrystals, m. p. 213° (Found: N, 4.9%), not depressed on admixture with a sample prepared by method (i) above.

Ring closure of (VII; R = NH₂) gave (VIII; R = NH₂), m. p. 240°, not depressed on admixture with a sample prepared *via* nitroarsafluorenic acid (see above).

4'-Carbethoxyaminodiphenyl-2-arsonic acid (VII; R = NH·CO₂Et) formed crystals (15%), m. p. 228°, from aqueous ethanol (Found: C, 49.3; H, 4.6; N, 3.8. C₁₅H₁₆O₅NAs requires C, 49.3; H, 4.4; N, 3.8%). Ring closure was effected by heating the arsonic acid (2 g.) with concentrated sulphuric

acid (15 ml.) at 125–130° for 20 minutes. After 30 minutes, the mixture was poured on ice. The precipitated product was collected and crystallised from aqueous ethanol, giving (VIII; R = NH₂) (50%), identical in m. p. and mixed m. p. with an authentic specimen.

5-Nitrodiphenyl-2-arsonic acid (X; R = NO₂), prepared by a Scheller–Bart reaction on 2-amino-5-nitrodiphenyl, formed glistening plates (50%) (from aqueous ethanol), m. p. 228–229° (Found: C, 44.2; H, 3.1; N, 4.3. C₁₂H₁₀O₅NAs requires C, 44.5; H, 3.1; N, 4.3%).

3-Nitro-9-arsafluorenic acid (XI; R = NO₂), obtained by heating the foregoing compound (16 g.) with concentrated sulphuric acid (125 ml.) at 60° for 45 minutes, formed a crystalline powder (75%) from aqueous acetic acid and had m. p. >330° (Found: C, 47.4; H, 2.8; N, 4.7. C₁₂H₈O₄NAs requires C, 47.2; H, 2.6; N, 4.6%).

3-Amino-9-arsafluorenic Acid (XI; R = NH₂).—The foregoing compound (6.2 g.), suspended in sodium hydroxide solution (40 ml., 1 equiv.), was added to reduced iron (3.5 g.) in sodium chloride solution (7 ml. containing 2.6 g. of sodium chloride) at 90°. The mixture was kept at this temperature for 2 hours, sufficient hydrochloric acid being added from time to time to keep the pH at ca. 7–8. Sodium hydroxide solution (5 ml.; 33%) was then added, and the mixture heated to boiling and filtered hot. The residues were twice extracted with alkali, and the bulked filtrates acidified to pH 7. The precipitated material was collected, purified by reprecipitation, and finally crystallised from aqueous acetic acid, giving *3-amino-9-arsafluorenic acid* (87%), orange needles, m. p. >350° (Found: C, 52.0; H, 3.3; N, 5.0. C₁₂H₁₀O₂NAs requires C, 52.4; H, 3.6; N, 5.1%).

5-Aminodiphenyl-2-arsonic Acid (X; R = NH₂).—(i) A solution of 5-nitrodiphenyl-2-arsonic acid (13.3 g.) in sodium hydroxide (2.5–3N.) was added in one portion to ferrous sulphate (80 g., 7 equivs.) dissolved in water (250 ml.) and made alkaline with sodium hydroxide. The mixture was shaken vigorously for 15 minutes, precipitated iron salts were removed by centrifugation, and the liquors concentrated to 200 ml. Acidification to pH 3 precipitated *5-aminodiphenyl-2-arsonic acid*, needles (66%) (from aqueous ethanol), m. p. 187° (Found: C, 49.3; H, 4.1; N, 5.3. C₁₂H₁₂O₃NAs requires C, 49.2; H, 4.1; N, 4.8%). (ii) The foregoing amine was obtained (92% yield) by catalytic hydrogenation of the nitro-compound in ethanol, a Raney-nickel catalyst being used.

Cyclisation with concentrated sulphuric acid for 45 minutes at 60° gave (XI; R = NH₂) (80%), identical in m. p. and mixed m. p. with a specimen prepared by reduction of (XI; R = NO₂) (see above).

2'-Acetamidodiphenyl-2-arsonic acid (II) was prepared from 2'-acetamido-2-aminodiphenyl by the Scheller–Bart reaction, and formed crystals (from ethanol), m. p. 122° (Found: C, 49.6; H, 4.3. C₁₄H₁₄O₄NAs requires C, 50.2; H, 4.2%).

4-Amino-9-arsafluorenic acid (III), obtained in very low yield by ring closure of the foregoing compound, formed microcrystals, m. p. >300° (Found: N, 5.3. C₁₂H₁₀O₂NAs requires N, 5.4%).

2:7-Dinitro-9-arsafluorenic Acid (IX; R = NO₂).—Nitration of 9-arsafluorenic acid (18 g.) in concentrated sulphuric acid (50.0 ml.) with a mixture of nitric acid (8.4 ml.; *d* 1.42) and concentrated sulphuric acid (8.4 ml.) at 2°, gave 2:7-dinitro-9-arsafluorenic acid (87%) as a pale yellow powder, which was purified repeatedly through the potassium salt and then had m. p. >300° (Found: C, 40.6; H, 2.3; N, 7.9. C₁₂H₇O₆N₂As requires C, 41.2; H, 2.0; N, 8.0%).

Dinitrodiphenyl-2-arsonic Acid.—Diphenyl-2-arsonic acid (13.4 g.) in concentrated sulphuric acid (45 ml.) was treated with a mixture of nitric acid (6.8 ml.; *d* 1.42) and concentrated sulphuric acid (6.8 ml.) added dropwise with stirring at 5°. After 1 hour the mixture was allowed to warm to room temperature and then added to a large volume of ice-water. The precipitated material was collected. Purification many times through the potassium salt yielded a *dinitrodiphenyl-2-arsonic acid* (70%), m. p. >300° (Found: C, 39.7; H, 2.0; N, 7.4. C₁₂H₈O₇N₂As requires C, 39.2; H, 2.5; N, 7.6%).

Scheller–Bart Reaction on 2-Amino-4:4'-dinitrodiphenyl.—2-Amino-4:4'-dinitrodiphenyl (4.45 g.) was submitted to the Scheller–Bart reaction, and the product triturated with warm acetone. The fraction insoluble in acetone, on purification from acetic acid, yielded 2-hydroxy-4:4'-dinitrodiphenyl, yellow needles, m. p. 209–210° (Found: C, 55.5; H, 3.3; N, 10.6. C₁₂H₁₀O₅N₂ requires C, 55.4; H, 3.1; N, 10.7%), soluble in alkali. The soluble fraction, when kept in acetone, deposited yellow needles (3.2 g.) which, after repeated crystallisation from aqueous acetone, yielded 4:4'-dinitrodiphenyl, m. p. 235° alone or on admixture with an authentic specimen.

Bart Reaction on 2-Amino-4:4'-biscarbethoxyaminodiphenyl.—2-Amino-4:4'-biscarbethoxyaminodiphenyl (34.3 g.), suspended in 20% hydrochloric acid (70 ml.) and some water, was diazotised with sodium nitrite (7 g.) in water (20 ml.). The cold solution was added to 10% sodium hydroxide solution (250 ml.) at 0°, followed by sodium arsenite (17.5 g.) dissolved in water, and added in one portion with vigorous stirring. The temperature was then gradually raised to 65°, and kept thereat for 3 hours. The cooled solution was acidified with acetic acid, and the precipitated solids (14 g.; m. p. 200–204°) were collected and crystallised from aqueous ethanol, yielding 4:4'-dicarbethoxybenzidine, m. p. 234–235° (Found: C, 65.8; H, 5.8; N, 8.7. C₁₈H₂₀O₄N₂ requires C, 65.8; H, 6.1; N, 8.5), not depressed on admixture with an authentic specimen. The latter was prepared by treating a just boiling solution of benzidine (47.6 g.) in ethanol (600 ml.) with diethylaniline (79 g.), followed dropwise by ethyl chloroformate (70 g.), added at such a rate that moderate refluxing ensued. Heating was discontinued after 2 hours, and the mixture, after being kept overnight, was poured into *n*-hydrochloric acid (1600 ml.). The precipitated solids were collected and crystallised from ethanol, giving *NN'*-dicarbethoxybenzidine as long needles (45 g.), m. p. 235–237° (Found: C, 65.5; H, 6.6; N, 8.6%).

Scheller–Bart Reaction on 2-Amino-4:4'-biscarbethoxyaminodiphenyl.—2-Amino-4:4'-biscarbethoxyaminodiphenyl (34.3 g.) was submitted to the Scheller–Bart reaction. The product (11 g.), isolated in the usual way, on purification from aqueous ethanol, yielded 4:4'-biscarbethoxyamino-2-hydroxydiphenyl, needles, m. p. 128–130° (Found: C, 62.3; H, 5.9; N, 8.2. C₁₈H₂₀O₅N₂ requires C, 62.6; H, 5.5; N, 8.3%). The product was soluble in alkali.

Miscellaneous Experiments.—(i) By submitting 2-amino-4 : 4'-ditolyl (Marler and Turner, *J.*, 1932, 2391) to the Scheller-Bart reaction, 4 : 4'-dimethyldiphenyl-2-arsonic acid (XII; R = Me) was obtained; it formed needles, m. p. 237°, from 75% acetic acid (Found: C, 54.7; H, 4.9. $C_{14}H_{15}O_2As$ requires C, 54.9; H, 4.9%). Extraction of the alkaline solution of the crude product with ether yielded 4 : 4'-ditolyl, pale yellow prisms (from light petroleum), m. p. 122—123° (Found: C, 92.0; H, 7.8. Calc. for $C_{14}H_{14}$: C, 92.3; H, 7.7%) not depressed in admixture with an authentic specimen (m. p. 125°).

(ii) Ring closure of 4 : 4'-dimethyldiphenyl-2-arsonic acid with concentrated sulphuric acid furnished 2 : 7-dimethyl-9-arsaftuoreninic acid (IX; R = Me), white needles (92%) (from acetic acid), m. p. 321—322° (Found: C, 57.8; H, 4.6. $C_{14}H_{13}O_2As$ requires C, 58.3; H, 4.5%).

(iii) Nitration of the foregoing compound (400 mg.) in concentrated sulphuric acid (4 ml.) with a mixture of nitric acid (0.13 ml.; *d* 1.42) and concentrated sulphuric acid (0.15 ml.) at 0—5° gave 2 : 7-dimethyl-3 : 6-dinitro-9-arsaftuoreninic acid (VI), as feathery needles (76%) (from acetic acid), m. p. >300° (Found: N, 7.4. $C_{14}H_{11}O_6N_2As$ requires N, 7.4%). Attempts to reduce this compound to the corresponding diamino-derivative proved unsuccessful owing to its sparing solubility in suitable solvents.

(iv) 4' : 5-Dinitrodiphenyl-2-arsonic acid, m. p. 220° (decomp.) (Found: C, 39.6; H, 2.8; N, 7.8. $C_{12}H_9O_7N_2As$ requires C, 39.2; H, 2.5; N, 7.6%), was obtained in low yield from 2-amino-4' : 5-dinitrodiphenyl. Attempts at ring closure were unsuccessful.

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CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES, LTD., LONDON, N.1.

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