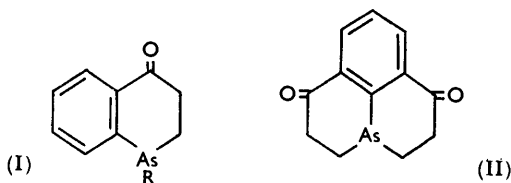


666. *The Synthesis and Properties of Substituted 1 : 2 : 3 : 4-Tetrahydro-4-oxoarsinolines and of 1 : 6-Dioxoarsulolidines.**

By FREDERICK G. MANN and A. J. WILKINSON.

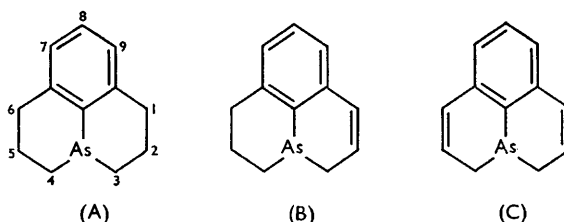
Compounds having a keto- and a tertiary arsine group in one ring have been prepared for the first time. Cyclisation of 2-carboxyethyl-*m*-methoxyphenylmethylarsine gives 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline, and double cyclisation of di-(2-carboxyethyl)-*m*-methoxyphenylarsine affords 7-methoxy-1 : 6-dioxoarsulolidine, which is the first known compound in which two fused rings have one tervalent arsenic atom in common. The properties of these oxo-arsines have been investigated.

FOR the work described in the following paper, cyclic keto-arsines such as a 1-substituted 1 : 2 : 3 : 4-tetrahydro-4-oxoarsinoline (I) or 1 : 6-dioxoarsulolidine (II) were required.



Compounds of this type containing a tertiary arsine group and a keto-group in one ring were unknown. Cookson and Mann¹ had attempted to cyclise 2-carboxyethyldiphenylarsine, $\text{Ph}_2\text{As}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, and also the chloride, $\text{Ph}_2\text{As}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COCl}$, to form

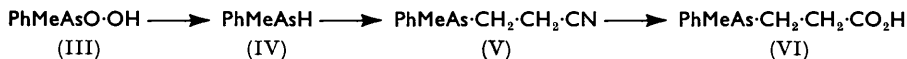
* Following the Editor's advice, the term arsulolidine is applied to the structure (A), in harmony with its nitrogen analogue julolidine. The systems (B) and (C) would thus be arsuloline and arsuline respectively (cf. *J.*, 1951, 1898).



¹ R. C. Cookson and Mann, *J.*, 1949, 67.

1 : 2 : 3 : 4-tetrahydro-4-oxo-1-phenylarsinoline (I; R = Ph) but without success. They failed also to convert di-(2-carboxyethyl)phenylarsine, $\text{Ph}\cdot\text{As}(\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H})_2$, by a double cyclisation into 1 : 6-dioxoarsulolidine (II).

In an attempt to prepare the 1-methyl-oxo-arsine (I; R = Me), dichlorophenylarsine, $\text{Ph}\cdot\text{AsCl}_2$, was converted by a Meyer reaction using aqueous sodium hydroxide and methyl sulphate into methylphenylarsinic acid² (III), which on reduction with amalgamated zinc



dust and concentrated hydrochloric acid at room temperature^{3,4} gave methylphenylarsine (IV). This arsine readily reacted with vinyl cyanide to give 2-cyanoethylmethylphenylarsine (V), in accordance with the experience of Cookson and Mann^{1,4} who found that an alkaline catalyst, although exerting a powerful effect on the cyanoethylation of arsines, was seldom necessary. Hydrolysis then gave 2-carboxyethylmethylphenylarsine (VI).

The arsenic atom in the liquid cyanoethylarsine (V) shows, although to a smaller extent, the partial deactivation shown by that in 2-cyanoethyldiphenylarsine, $\text{Ph}_2\text{As}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$. Thus the arsine (V) is quaternised with cold methyl iodide, and by warm methyl toluene-*p*-sulphonate: the methiodide however readily loses methyl iodide. The arsine is converted into the arsine oxide by hydrogen peroxide in acetone, but is only slowly affected by air at room temperature: in this respect it is intermediate between dimethylphenylarsine, which is readily oxidised, and di-(2-cyanoethyl)phenylarsine, which is stable indefinitely in air.⁴

Attempts to cyclise the nitrile (V) failed. This was not unexpected, for the only method known for the cyclisation of the analogous *N*-2-cyanoethyl-*N*-methylaniline⁵ entails heating with a mixture of aluminium chloride, sodium chloride, and potassium chloride under strictly controlled conditions of time and temperature. The application of this mixture to the nitrile-arsine (V) would probably cause rapid co-ordination of the aluminium chloride with the tertiary arsine, with additional deactivation of the benzene ring.

Cyclisation of the acid (VI) was unsuccessfully attempted by heating the acid (*a*) with phosphoric anhydride suspended in xylene or dissolved in syrupy phosphoric acid, and (*b*) with concentrated sulphuric acid. The acid chloride, when heated with aluminium chloride in various solvents, gave only non-ketonic tars.

These results indicated strongly that activation of the benzene ring by a suitable substituent was necessary to achieve cyclisation. To obtain maximum effect for this purpose, *m*-methoxyphenylarsonic acid (VII) was required. Several routes were available for its preparation. *m*-Anisidine, when subjected to the Bart reaction, gave the acid (VII) in only 22% yield (low yields in this reaction being often obtained with *m*-substituted anilines), and the anisidine is costly to buy and tedious to make. Alternatively, *m*-nitroaniline, which also gives very low yields when subjected to the normal Bart reaction, was converted into *m*-nitrophenylarsonic acid (VIII) in 57% yield by using Doak's application⁷ of Scheller's modification⁸ of the Bart reaction, in which diazotisation is carried out in ethanol and the diazonium salt is coupled with arsenic trichloride in the presence of a cuprous catalyst, hydrolysis then giving the acid (VIII). In view of the consistent yields thus obtained, direct nitration of phenylarsonic acid was not attempted. The acid

² Cragoe, Andres, Coles, Elpern, Morgan, and Hamilton, *J. Amer. Chem. Soc.*, 1947, **69**, 929.

³ Palmer and Adams, *ibid.*, 1922, **44**, 1362.

⁴ R. C. Cookson and Mann, *J.*, 1947, 618.

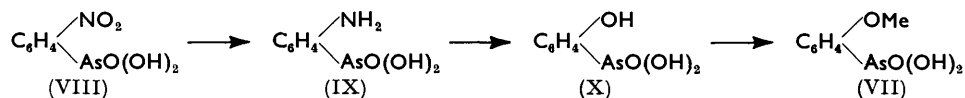
⁵ Allison, Braunholtz, and Mann, *J.*, 1954, 403; cf. also F.P. 806,715/1936.

⁶ Hamilton and Morgan, "The Bart, Béchamp and Rosenmund Reactions" in "Organic Reactions," Vol. II, p. 415, Wiley, New York, 1944.

⁷ Doak, *J. Amer. Chem. Soc.*, 1940, **62**, 167.

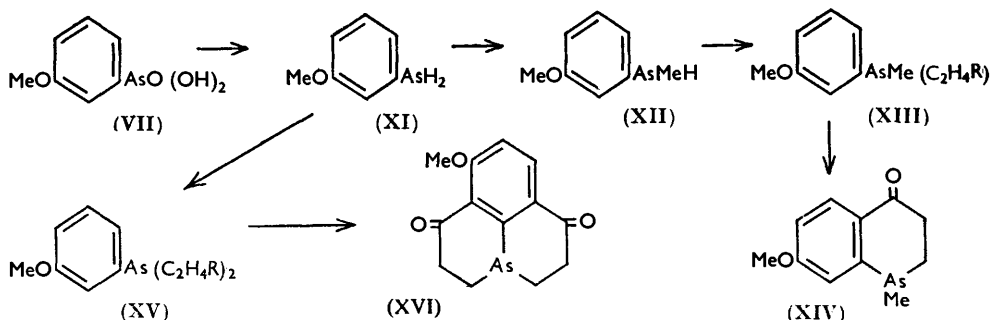
⁸ Scheller, B.P. 261,026/1925; F.P. 624,028/1926.

(VIII) was then reduced by Rozina's method⁹ to *m*-aminophenylarsonic acid (*m*-arsanilic acid) (IX), which after diazotisation gave *m*-hydroxyphenylarsonic acid (X). This acid is very soluble in water, however, and therefore without isolation it was methylated directly in alkaline solution with methyl sulphate to give the much less soluble methoxyacid (VII).



Two methods were available for the next stage, namely, the conversion of *m*-methoxyphenylarsonic acid (VII) into *m*-methoxyphenylmethylarsine (XII). The acid (VII) could be reduced to dichloro-*m*-methoxyphenylarsine, which by a Meyer reaction with methyl sulphate and alkali should furnish *m*-methoxyphenylmethylarsinic acid, $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{AsMe}(\text{O})\cdot\text{OH}$, the reduction of which would give the arsine (XII). This method was long and, in view of the low yields obtained in the comparable reduction of methylphenylarsinic acid, it was not investigated. Alternatively, the acid (VII) was reduced in good yield to *m*-methoxyphenylarsine (XI), which was converted into the methylarsine (XII) by Mann and Smith's method,¹⁰ the arsine in liquid ammonia being converted first into *m*-methoxyphenylsodioarsine by the addition of one equivalent of sodium, and then into the methylarsine (XIII) by the action of methyl iodide. The sharp colour changes which accompany each of these stages are of considerable help in this preparation. It is noteworthy that the reported cleavage¹¹ of alkyl aryl ethers by sodium in liquid ammonia was apparently completely absent during the above reactions, probably because of their great rapidity.

The arsine (XII) was readily converted by vinyl cyanide into the liquid 2-cyanoethyl-*m*-methoxyphenylmethylarsine (XIII; R = CN), which on alkaline hydrolysis gave 2-carboxyethyl-*m*-methoxyphenylmethylarsine (XIII; R = CO₂H). Both these compounds gave methiodides at room temperature, but were stable indefinitely in air: the combined inductive effects of the *m*-methoxyl group and the cyano- or carboxylic group deactivated the tertiary arsine group sufficiently to prevent atmospheric oxidation.



No attempt was made to cyclise the nitrile (XIII; R = CN). The acid (XIII; R = CO₂H) however, when heated in boiling xylene for 2 hours with phosphoric anhydride and "Hyflo Supercel," gave the colourless crystalline 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline (XIV) in 35% yield.

It is of interest that this is only the second recorded example of the formation of a cyclic arsine system by the establishment of a carbon-carbon bond, the first being Das Gupta's claim that chloro-2-chlorovinylphenylarsine, $\text{Ph}\cdot\text{AsCl}(\text{CH}:\text{CHCl})$, undergoes an

⁹ Rozina, *Zhur. priklad. Khim.*, 1950, **23**, 1110; see also Mann and Stewart, *J.*, 1954, 4127.

¹⁰ Mann and Smith, *J.*, 1952, 4544.

¹¹ Birch, *J.*, 1944, 430; 1947, 102.

internal Friedel-Crafts reaction to give 1-chloroarsindole.¹² All other such cyclisations have involved, directly or indirectly, the formation of a carbon-arsenic bond, as in Burrows and Turner's initial synthesis of the parent 1 : 2 : 3 : 4-tetrahydro-1-methylarsinoline by the cyclisation of chloro-methyl-3-phenylpropylarsine.¹³

The fact that the methoxy-group in the arsinoline (XIV) is in the 7- and not the 5-position is clearly shown by the infrared spectrum. This shows a strong band at 12.04 μ and none in the 12.75—13.5 μ region: 1 : 2 : 4- and 1 : 2 : 3-trisubstituted benzenes have a well-defined band at 12.2 and 13.1 μ respectively.

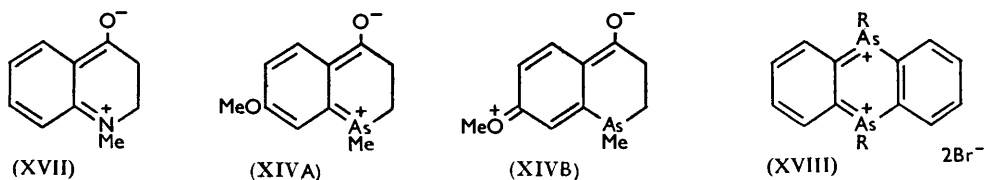
m-Methoxyphenylarsine (XI), when heated with an excess of vinyl cyanide in nitrogen, readily underwent dicyanoethylation to give di-(2-cyanoethyl)-*m*-methoxyphenylarsine (XV; R = CN), which on prolonged alkaline hydrolysis gave the crystalline di-(2-carboxyethyl)-*m*-methoxyphenylarsine (XV; R = CO₂H). Both these compounds are stable indefinitely in the air; the acid readily gave a methiodide at room temperature.

The acid (XV; R = CO₂H), when boiled with phosphoric anhydride in toluene, xylene, or benzene, underwent dicyclisation, forming the highly crystalline 7-methoxy-1 : 6-dioxoarsulolidine (XVI). A number of experiments showed that the maximum yield (11%) was obtained in toluene with only 15 minutes' boiling: in xylene consistently lower yields were obtained, whilst in benzene the dicyclisation was very slow. The acid (XV; R = CO₂H), when heated with a mixture of phosphoric anhydride and syrupy phosphoric acid, also gave the diketone (XVI) in inferior yield, together with an alkali-soluble ketonic gum which was almost certainly 1-(2-carboxyethyl)-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxoarsinoline. This production of the diketone and the keto-acid is analogous to the results of Braunholtz and Mann,¹⁴ who showed that the cyclisation of various *NN*-di-(2-cyanoethyl)anilines gave a mixture of the corresponding 1 : 6-dioxojulolidine and the 1-(2-cyanoethyl)-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline.

It is noteworthy that the arsulolidine (XVI) is the first known compound in which two fused rings have one tervalent arsenic atom in common.

The physical and chemical properties of the oxo-arsine (XIV) and the dioxo-arsine (XVI) will be discussed in turn, omitting reactions which involve the ketomethylene grouping and are discussed in detail in the following paper.

The colourless oxo-arsine (XIV) contrasts markedly with the yellow liquid 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline. The presence of the methoxyl group in the former prevents a strict comparison of the ultraviolet spectra of the two compounds. However, the effect of a methoxyl substituent on benzenoid absorption is usually to cause a shift to longer wavelengths with intensification of the maxima, without greatly altering the general form of the spectrum. The two spectra (Fig. 1) are in fact quite different. Most striking is the complete absence in the spectrum of the oxo-arsine (XIV) of the broad band with a maximum at 384 m μ which is responsible for the yellow colour of the oxo-amine. This absence undoubtedly indicates that whereas the polar form (XVII) makes an appreciable contribution to the oxo-amine, a similar form (XIVA) makes no contribution



to the oxo-arsine (XIV). The absence of the polar form (XIVA) is to be expected, for it is exceedingly rare for an arsenic atom in a ring to be linked to two ring carbon atoms by a single and a double bond respectively. This structure almost certainly exists in the

¹² Das Gupta, *J. Indian Chem. Soc.*, 1935, **12**, 627; 1937, **14**, 231.

¹³ Burrows and Turner, *J.*, 1921, **119**, 426.

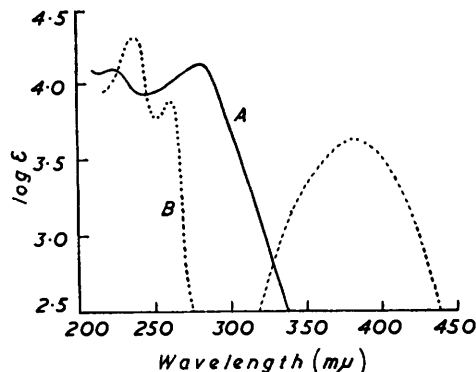
¹⁴ Braunholtz and Mann, *J.*, 1953, 1817; 1954, 651.

5:10-dihydroarsanthronium dibromides (XVIII)¹⁵ where it is stabilised by resonance, and it has been claimed (on insufficient evidence) for arsanthren¹⁶ and phenarsazine.¹⁷

It is of interest that in the infrared spectra of the oxo-arsine and oxo-amine, the carbonyl group appears as a band at 6.05 and 5.97 μ respectively: for comparison, in *o*- and *p*-methoxyacetophenone, this band appears at 6.05 and 6.03 μ respectively.¹⁸ The strong evidence for conjugation of the carbonyl group in the oxo-amine compared with that in the oxo-arsine, which is shown by the ultraviolet spectra, is therefore not shown by the infrared spectra.

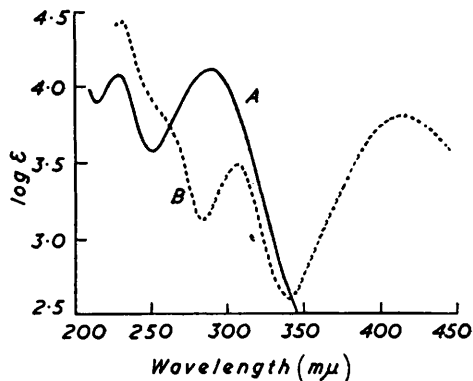
It should be added that the polar form (XIVB) of the oxo-arsine must also make only

FIG. 1.



A, 1:2:3:4-Tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline (XIV) in ethanol.
B, 1:2:3:4-Tetrahydro-1-methyl-4-oxoquinoline in ethanol: there is a minimum at 289 $m\mu$ ($\log \epsilon$, 1.74) not shown in the Figure.

FIG. 2.



A, 7-Methoxy-1:6-dioxoarsulolidine (XVI) in ethanol.
B, 1:6-Dioxojulolidine in ethanol.

a negligible contribution to the structure, otherwise it also would cause the oxo-arsine to be coloured. This factor applies also to the colourless *o*- and *p*-methoxyacetophenone.

The oxo-arsine (XIV) undergoes ready quaternisation at room temperature, but appears to be stable indefinitely in air, in contrast to 1:2:3:4-tetrahydro-1-methylarsinoline which is slowly oxidised.¹³

The carbonyl group in the oxo-arsine (XIV) has normal reactivity in that it gives a phenylhydrazone and a semicarbazone. On the other hand, it could not be induced to react under a wide variety of conditions with a number of compounds containing "reactive" methyl or methylene groups, such as quinaldine methiodide, Fischer's base (1:3:3-trimethyl-2-methyleneindoline), 2-methyl-4:5-diphenylthiazole ethiodide, 2:3:6-trimethylbenzothiazole ethiodide, or malononitrile. 1:2:3:4-Tetrahydro-1-methyl-4-oxoquinoline shows a similar inertness to these reagents¹⁹ except towards malononitrile with which it forms a deep red condensation product.²⁰ This product is undoubtedly stabilised by a considerable contribution from the polar form (XIX), and it is probably the lack of a similar stabilising contribution which inhibits the formation of the arsenic analogue.

The methylene group adjacent to the oxo-group in the arsine showed normal reactivity in condensing with *p*-dimethylaminobenzaldehyde to give the yellow crystalline base (XX), and with *p*-nitrosodimethylaniline to give an anil, which however could not be obtained pure.

¹⁵ Chatt and Mann, *J.*, 1940, 1184; Emrys R. H. Jones and Mann, *J.*, 1955, 411.

¹⁶ Kalb, *Annalen*, 1921, 423, 39.

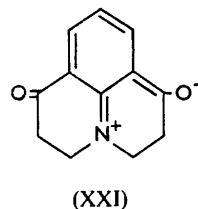
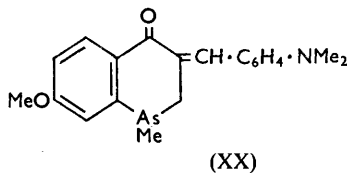
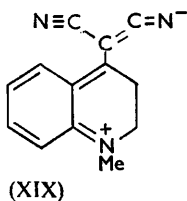
¹⁷ Wieland and Rheinheimer, *ibid.*, p. 1.

¹⁸ Hergert and Kurth, *J. Amer. Chem. Soc.*, 1953, 75, 1622.

¹⁹ Ittyerah and Mann, unpublished work.

²⁰ Ittyerah and Mann, *J.*, 1956, 3179.

The colourless nature of 7-methoxy-1 : 6-dioxoarsulolidine (XVI) is also in contrast to the yellow colour of the nitrogen analogue, 1 : 6-dioxojulolidine, and undoubtedly the difference is again due to the absence in the dioxo-arsine (XVI) of any contribution similar to the polar form (XXI) of the dioxo-amine. The difference in their ultraviolet spectra in ethanol is shown in Fig. 2. The infrared spectrum of the dioxo-arsine shows two carbonyl bands at 5.85 and 5.98 μ , due undoubtedly to the greater influence of the methoxyl group on the neighbouring carbonyl group than upon the more distant one. The symmetric



dioxo-amine shows only one carbonyl band at 5.97 μ . This difference in the carbonyl groups of the dioxo-arsine (XVI) is further shown by the fact that although both, for example, will form phenylhydrazones, one group is more reactive than the other in such condensations.

The dioxo-arsine (XVI) is unaffected by air at room temperature, and by boiling methyl iodide. The fact that 1 : 6-dioxojulolidine is also unaffected by methyl iodide could be attributed to considerable deactivation of the nitrogen atom by the polar contribution (XXI), a factor apparently absent from the dioxo-arsine. It is probable however that in these compounds the nitrogen and the arsenic atom are sufficiently rigidly held in the dicyclic system to make attainment of a tetrahedral configuration, which would accompany quaternisation, exceedingly difficult.

The dioxo-arsine could not be condensed with *p*-dimethylaminobenzaldehyde or with *p*-nitrosodimethylaniline.

EXPERIMENTAL

All compounds were colourless unless otherwise described.

Methylphenylarsinic acid (III) was prepared in 87% yield by the recorded method.²

Methylphenylarsine (IV).—A round-bottomed flask was fitted with a 3-necked adapter carrying a dropping-funnel, an inlet tube for nitrogen, and a reflux water-condenser, which in turn had a long air-condenser loosely plugged with cotton-wool to retard inward diffusion of air. Zinc dust (200 g.) was added in small portions with shaking to a solution of mercuric chloride (8 g.) in dilute hydrochloric acid (80 c.c.). The powdered arsenic acid (100 g.) and then ether (500 c.c.) were then added. Nitrogen was passed through the assembled apparatus in a slow stream throughout the experiment. Concentrated hydrochloric acid (600 c.c.) was added dropwise at the rate of 50 c.c./hr., with occasional shaking. The reaction was allowed to proceed at room temperature for 2 days, fresh ether being added when necessary.

The aqueous layer was extracted several times with ether, which was then forced by nitrogen pressure, first into a flask containing calcium chloride, and then in small portions into a Claisen flask, from which the ether was continuously distilled. The residue gave the arsine (IV) (18.2 g., 22%), b. p. 71—72°/15 mm., which was collected in a receiver suitable for the next operation. A non-volatile residue in the flask, probably dimethyldiphenyldiarsine, PhMeAs·AsMePh, melted at *ca.* 70°, and fumed when exposed to the air.

The low yield of the arsine (IV) is due primarily to evaporation in the current of hydrogen and nitrogen during reduction.

2-Cyanoethylmethylphenylarsine (V).—A mixture of the arsine (18.2 g.) and vinyl cyanide (12 g., *ca.* 2 mols.) was boiled under reflux in nitrogen for 4 hr. Distillation removed unchanged cyanide, and then gave the liquid *arsine* (V) (20.4 g., 85%), b. p. 117°/0.5 mm., 172—174°/14 mm. (Found : C, 54.2; H, 5.4; N, 6.3. C₁₀H₁₂NAs requires C, 54.3; H, 5.5; N, 6.3%). The arsine slowly darkened in air. When mixed with an excess of methyl iodide it gave the *methyl iodide*, m. p. 164.5—165.5°, after repeated crystallisation from acetone (Found : C, 35.8; H, 3.8;

N, 3.9. $C_{11}H_{15}NIAs$ requires C, 36.4; H, 4.2; N, 3.9%). A mixture of the arsine and methyl toluene-*p*-sulphonate (1.1 mols.), when heated under nitrogen at 130° for 3 hr., gave a glass, which afforded crystals when its methanolic solution was cautiously diluted with ether. Recrystallisation in turn from ethanol, methanol-ether, and chloroform-light petroleum (b. p. 80—100°) ultimately gave the pure *metho-toluene-p-sulphonate*, m. p. 144—145° (Found: C, 52.7; H, 5.1. $C_{18}H_{22}O_3NSAs$ requires C, 53.1; H, 5.4%). This gave the yellow *metho-picrate*, m. p. 117—118° after crystallisation from water (Found: C, 44.0; H, 3.7; N, 12.3. $C_{17}H_{17}O_7N_4As$ requires C, 44.0; H, 3.7; N, 12.1%).

An acetone solution of the arsine, when diluted with "10-vol." hydrogen peroxide, became warm. Removal of the solvent left a gum which could not be crystallised. A solution of the gum in warm dilute nitric acid, when evaporated to dryness in a vacuum, deposited the crystalline *hydroxynitrate*, m. p. 118—120° after crystallisation from ethanol (Found: C, 40.6; H, 4.2; N, 9.55. $C_{10}H_{13}O_4N_2As$ requires C, 40.0; H, 4.4; N, 9.3%).

As a brief example of the attempted cyclisation, the cyano-arsine (V) (1.3 g.) was added to a mixture of sodium chloride (1 g.), potassium chloride (1 g.), and aluminium chloride (5 g.) at 130°, with vigorous stirring for 1.5 min. The molten mass was poured on ice, basified with sodium hydroxide, warmed to 70° for 30 min., cooled, and extracted with benzene. Evaporation gave a non-ketonic residue, consisting almost wholly of the unchanged nitrile, characterised as its methiodide, m. p., alone and mixed, 163—165°. When the above melt was heated at 130° for 15 min., and at 180° for 20 min., the nitrile was still unchanged.

2-Carboxyethylmethylphenylarsine (VI).—A mixture of the nitrile (V) (10 g.) and a solution of potassium hydroxide (5 g.) in water (12.5 c.c.) and ethanol (12.5 c.c.) was boiled for 8 hr., evolution of ammonia then ceasing. The cold clear solution, when diluted with water (75 c.c.) and acidified (litmus) with concentrated hydrochloric acid, deposited the *arsine* as an oil (10.9 g., 99%), which when distilled in nitrogen had b. p. 138°/0.3 mm. and formed needles, m. p. 32° (Found: C, 49.7; H, 5.2. $C_{10}H_{13}O_2As$ requires C, 50.0; H, 5.5%).

The arsine in cold methyl iodide deposited the *methiodide*, which after crystallisation from acetone and then from methanol-ether melted at 110°, resolidified, and remelted at 151—153°; when rapidly heated it softened at *ca.* 110° and melted at 154° (Found: C, 34.8; H, 4.3. $C_{11}H_{16}O_2IAs$ requires C, 34.6; H, 4.2%).

An acetone solution of the arsine (VI), when treated with an excess of hydrogen peroxide ("10-vol.") and evaporated, gave the *oxide*, m. p. 165° (from ethanol-ether) (Found: C, 46.8; H, 5.45. $C_{10}H_{13}O_4As$ requires C, 46.9; H, 5.1%).

The arsine gave an *S-benzylthiuronium salt*, m. p. 137° from ethanol-ether (Found: C, 52.8; H, 5.6. $C_{18}H_{23}O_2N_2SAs$ requires C, 53.1; H, 5.7%).

Attempts to cyclise this acid and its chloride under a variety of conditions failed. It is noteworthy that when a solution of the acid (1.2 g.) in concentrated sulphuric acid (4 c.c.) was heated at 100° for 1 hr. and cooled, working up gave a sulphonic acid, presumably *2-carboxyethylmethyl-m-sulphophenylarsine*, m. p. 158—159° (decomp.), from methanol-ether (Found: C, 37.7; H, 4.5. $C_{10}H_{13}O_5SAs$ requires C, 37.5; H, 4.1%).

m-Nitrophenylarsonic acid (VIII), prepared by Doak's method,⁷ was purified by dissolution in aqueous sodium carbonate, filtration, and acidification to Congo-red with concentrated hydrochloric acid. This gave a purer product than recrystallisation from water, which Doak recommends.

m-Aminophenylarsonic Acid (IX).—Fine-mesh cast-iron filings (200 g.) were stirred for 30 min. with a boiling solution of sodium chloride (50 g.) in water (1 l.) under reflux in a 3-necked flask. The arsonic acid (VIII) (100 g.) was then added in small portions during 3 hr., and the mixture boiled for a further 3—4 hr. A solution of sodium hydroxide (40 g.) in water (300 c.c.) was added to the mixture, which was filtered at the pump: the iron residue was extracted with boiling water (200 c.c.). The combined filtrates were concentrated to *ca.* 400 c.c., made just acid (Congo-red) with concentrated hydrochloric acid, and cooled in ice-water. The arsonic acid (IX), m. p. 210—215° (decomp.), crystallised, the mean yield being 75 g. (85%).

m-Methoxyphenylarsonic Acid (VII).—(A) To obtain the pure acid, the acid (IX) was first converted by Jacobs and Heidelberg's method²¹ into *m*-hydroxyphenylarsonic acid (X), m. p. 160—170° (decomp.) when recrystallised from water. A solution of this acid (1.5 g.) in water (2.5 c.c.) containing sodium hydroxide (0.5 g.) was shaken with methyl sulphate until clear: sodium hydroxide (0.25 g.) in water (1 c.c.), and methyl sulphate (0.6 c.c.) were then

²¹ Jacobs and Heidelberg, *J. Amer. Chem. Soc.*, 1919, **41**, 1440.

added with further shaking. Acidification (Congo-red) with dilute hydrochloric acid precipitated the *methoxy-acid* (VII) (1.2 g., 75%), which was recrystallised from water (Found: C, 36.2; H, 4.0. $C_7H_9O_4As$ requires C, 36.2; H, 3.9%). The acid has an indefinite m. p. when heated from room temperature, but melts completely if immersed at 136°.

(B) To obtain the crude acid (VII) suitable for the next stage, a solution of the amino-acid (IX) (180 g.) in ice-water (1500 g.) containing concentrated sulphuric acid (89 c.c., 2.0 mols.) was stirred vigorously whilst an aqueous solution of sodium nitrite (60 g., 1.05 mols.) was added dropwise. The solution was diluted with water (2 l.) and warmed to 60° until nitrogen evolution ceased (ca. 2 hr.). Barium hydroxide octahydrate (530 g.) was added, and the hot solution vigorously stirred to precipitate barium sulphate. The filtered solution was treated with sodium hydroxide (100 g.), concentrated to ca. 750 c.c., cooled to 40°, and again stirred whilst methyl sulphate (120 c.c.) was added dropwise, the temperature being kept below 70°. The solution was again cooled to 40°, sodium hydroxide (50 g.) added, and then methyl sulphate (120 c.c.) as before. The process was again repeated with sodium hydroxide (50 g.) and the sulphate (120 c.c.). The filtered solution was cooled, acidified (Congo-red) with concentrated hydrochloric acid, seeded, vigorously stirred, and set aside overnight. The crude yellow acid (VII) slowly separated in mean yield of 164 g. (85%).

(C) The acid (VII) was also prepared in 22% yield by the application of the Bart reaction under normal conditions to *m*-anisidine.

m-Methoxyphenylarsine (XI).—This was prepared precisely as methylphenylarsine (IV), from mercuric chloride (10 g.) in dilute hydrochloric acid (100 c.c.), zinc dust (250 g.), the crude acid (VII) (100 g.), and concentrated hydrochloric acid (750 c.c.). The *arsine* (55 g., 70%) was isolated as a foul-smelling, rapidly oxidised liquid, b. p. 107–108°/16 mm., 60–61°/1 mm. (Found: C, 46.0; H, 4.9. C_7H_9OAs requires C, 45.7; H, 4.9%).

m-Methoxyphenylmethylarsine (XII).—Freshly and finely cut sodium (2.5 g., 1 atom-equiv.) was added to liquid ammonia (ca. 150 c.c.) in a 250 c.c. flask fitted with a dropping-funnel, mercury-sealed stirrer, and an air-condenser loosely plugged with cotton-wool. The deep blue solution was allowed to boil for 2–3 min to expel all air, and the flask was then cooled in acetone-solid carbon dioxide. The dropping-funnel was filled with nitrogen and a solution of *m*-methoxyphenylarsine (XI) (20.2 g.) in dry ether (60 c.c.), which was then added dropwise to the stirred liquid ammonia, the blue colour of which changed ultimately to yellow. A few very small pieces of sodium (0.03–0.05 atom-equiv.) were now added until the blue colour which was formed locally took several seconds to disappear. A solution of methyl iodide in ether was finally added dropwise until the yellow colour was just discharged.

The ammonia was allowed to evaporate, and the ethereal residue was forced by nitrogen in portions into a Claisen flask, from which ether was distilled; the residual arsine was finally distilled under reduced pressure of nitrogen. The arsine (XII) (18.4 g., 85%) had b. p. 117–119°/15 mm.; it contained only a trace of *m*-methoxyphenyldimethylarsine (see below). Satisfactory analytical results could not be obtained (Found: C, 46.6; H, 5.9. Calc. for $C_8H_{11}OAs$: C, 48.5; H, 5.6%), probably owing to atmospheric oxidation, although this was less rapid than that of methylphenylarsine (IV).

2-Cyanoethyl-*m*-methoxyphenylmethylarsine (XIII; R = CN).—A mixture of the arsine (XII) (20 g.) and vinyl cyanide (10.7 g., 2 mols.) was heated under nitrogen at 100° for 6 hr. After the removal of the excess of vinyl cyanide, the residue, distilled under nitrogen at 1 mm., gave the fractions: (i) b. p. 76–78°; (ii) b. p. 78–148°; (iii) b. p. 148–152°. The very small fraction (i) was *m*-methoxyphenyldimethylarsine, present in the arsine (XII) used. Fraction (iii) was the *cyano-arsine* (XIII; R = CN), in ca. 90% yield; after redistillation it was isolated as an odourless oil (Found: C, 52.9; H, 5.8; N, 5.8. $C_{11}H_{14}ONAs$ requires C, 52.5; H, 5.6; N, 5.6%). It gave a *methiodide*, prisms, m. p. 148°, from methanol-ether (Found: C, 36.6; H, 4.3; N, 3.7. $C_{12}H_{17}ONAs$ requires C, 36.7; H, 4.4; N, 3.6%), and a *methopicrate*, bright yellow crystals, m. p. 117–118°, from methanol (Found: C, 44.0; H, 4.4; N, 11.2. $C_{18}H_{18}O_8N_4As$ requires C, 43.7; H, 3.9; N, 11.3%).

The combined fractions (i) from several preparations, when redistilled under nitrogen, gave the pure *m*-methoxyphenyldimethylarsine, b. p. 123–124°/15 mm., which oxidised only very slowly in the air (Found: C, 51.2; H, 6.25. $C_9H_{13}OAs$ requires C, 51.0; H, 6.2%). It reacted vigorously with methyl iodide, giving a *methiodide*, prisms, m. p. 248–250°, from methanol (Found: C, 34.0; H, 4.8. $C_{10}H_{16}OAs$ requires C, 33.9; H, 4.6%).

2-Carboxyethyl-*m*-methoxyphenylmethylarsine (XIII; R = CO_2H).—The cyanoarsine (XIII;

R = CN) (43.5 g.) was added to a solution of potassium hydroxide (20 g.) in water (50 c.c.) and ethanol (50 c.c.), which was boiled under nitrogen for 12 hr. The cold solution was diluted with water (300 c.c.) and twice extracted with benzene, the extracts being rejected. The solution was acidified (litmus) with concentrated hydrochloric acid and again extracted with benzene. The extract was dried (Na_2SO_4) and the benzene removed by distillation in nitrogen. The carboxy-arsine (XIII; R = CO_2H) (45.3 g., 97%) remained as an almost colourless syrup; distillation gave a clear syrup, b. p. 166—172°/0.02 mm., 138—146°/0.003 mm., which did not solidify.

It readily gave a *methiodide*, crystals, m. p. 138°, from acetone and then methanol-ether (Found: C, 35.0; H, 4.4. $\text{C}_{12}\text{H}_{18}\text{O}_3\text{IAs}$ requires C, 35.0; H, 4.4%), and an *S-benzylthiuronium salt*, m. p. 138°, from ethanol (Found: C, 52.0; H, 6.1; N, 6.65. $\text{C}_{19}\text{H}_{25}\text{O}_3\text{N}_2\text{SAs}$ requires C, 52.3; H, 5.8; N, 6.4%).

1 : 2 : 3 : 4-*Tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline* (XIV).—Phosphoric anhydride (40 g.) and "Hyflo Supercel" (20 g.) (included to prevent caking of the anhydride) were added to a solution of the carboxyarsine (XIII; R = CO_2H) (10 g.) in xylene (200 c.c.), which was boiled under reflux with vigorous stirring, in nitrogen for 2 hr. The xylene was separated by decantation, and the sticky residue extracted with boiling xylene (2×100 c.c.). The residue was then decomposed by the addition of ice, and the solution filtered to remove the Supercel, and extracted with benzene. The combined yellow xylene and benzene extracts were shaken with aqueous sodium carbonate, dried (Na_2SO_4), and evaporated under reduced pressure of nitrogen. The residual gum, when distilled in nitrogen, had b. p. 109—111°/0.02 mm., and the pale yellow distillate solidified on being scratched. In all subsequent preparations, the gum could be crystallised directly by dissolving in a minimum of ethanol and cooling the filtered solution in acetone-solid carbon dioxide, with scratching and seeding if required, the crystals being collected in a cooled filter. Repetition of this recrystallisation gave the pure *oxo-arsine* (XIV) (3.5 g., 38%), m. p. 52° (Found: C, 52.2; H, 5.2%; *M*, in boiling ethanol, 260. $\text{C}_{11}\text{H}_{13}\text{O}_2\text{As}$ requires C, 52.4; H, 5.2%; *M*, 252).

Alternatively, a solution of the carboxy-arsine (5 g.) in a mixture of phosphoric anhydride (25 g.) and syrupy phosphoric acid (25 c.c.) was heated under nitrogen at 100° for 3 hr. The hot red mixture was poured into cold water (100 c.c.), and the solution extracted with benzene. The benzene extract, treated as before, gave the residual gum, which on crystallisation afforded the *oxo-arsine* (XIV) (1.2 g., 26%).

The *oxo-arsine* readily gave a *methiodide*, prisms, m. p. 239°, from methanol (Found: C, 37.0; H, 4.4. $\text{C}_{12}\text{H}_{16}\text{O}_2\text{IAs}$ requires C, 36.6; H, 4.1%), and a *methopicate*, yellow crystals, m. p. 226°, from water (Found: C, 43.7; H, 4.1; N, 8.6. $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_3\text{As}$ requires C, 43.65; H, 3.7; N, 8.5%). When fused with methyl toluene-*p*-sulphonate (1.1 mol.) under nitrogen at 130° for 10 min., it gave the *methotoluene-p-sulphonate*, prisms, m. p. 180—205° (decomp.) from methanol (Found: C, 52.1; H, 5.6. $\text{C}_{16}\text{H}_{23}\text{O}_5\text{SAs}$ requires C, 52.1; H, 5.3%). The *semicarbazone* formed needles, m. p. 208°, from ethanol (Found: C, 46.55; H, 5.25; N, 13.7. $\text{C}_{12}\text{H}_{16}\text{O}_2\text{N}_3\text{As}$ requires C, 46.6; H, 5.2; N, 13.6%).

The *phenylhydrazone* was best prepared by heating a solution of the *oxo-arsine* (1 g.) and pure phenylhydrazine (0.45 g., 1.05 mol.) in ethanol (10 c.c.) and acetic acid (1 c.c.) under reflux in nitrogen for 8 hr. On cooling, the hydrazone separated as plates (92% yield), m. p. 121—122° after recrystallisation from ethanol (Found: C, 59.9; H, 5.7; N, 8.2. $\text{C}_{17}\text{H}_{19}\text{ON}_2\text{As}$ requires C, 59.7; H, 5.6; N, 8.2%). The 2 : 4-dinitrophenylhydrazone, when prepared in ethanol, separated as deep purple crystals, m. p. 183° after crystallisation from ethyl acetate or much ethanol, but a satisfactory analysis was not obtained (Found: C, 48.0; H, 4.5; N, 12.5. Calc. for $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}_4\text{As}$: C, 47.2; H, 4.0; N, 13.0%).

The *oxo-arsine* in acetone underwent vigorous oxidation when hydrogen peroxide was added, but only a dark tar was obtained.

3-(*p*-*Dimethylaminobenzylidene*)-1 : 2 : 3 : 4-*tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline* (XX).—A solution of the *oxo-arsine* (0.50 g.) and *p*-dimethylaminobenzaldehyde (0.33 g., 1.1 mols.) in ethanol (10 c.c.) and 10% aqueous sodium hydroxide (0.5 c.c.) was boiled under reflux in nitrogen for 4 hr., and then concentrated to half-bulk and cooled. The orange solution deposited the *compound* (XX) as yellow needles (0.25 g.), m. p. 159° after crystallisation from ethanol: they were dried by heating at 60°/0.1 mm. for 6 hr. (Found: C, 61.8; H, 5.9; N, 3.6. $\text{C}_{20}\text{H}_{22}\text{O}_2\text{NAs}$ requires C, 62.7; H, 5.8; N, 3.7%).

The *oxo-arsine* (500 mg.) and then *p*-nitrosodimethylaniline (325 mg., 1.1 mol.) were added

in turn to a solution of sodium (50 mg., 1.1 atom-equiv.) in ethanol, and the brown mixture was shaken for 3 hr. The orange-brown crystals (400 mg.) which separated had m. p. 157° after crystallisation from ethanol: they were 3-(*p*-dimethylaminophenylimino)-1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-methyl-4-oxoarsinoline (Found: C, 60.2; H, 5.9; N, 7.85. $C_{19}H_{21}O_2N_2As$ requires C, 59.4; H, 5.5; N, 7.3%), possibly slightly contaminated with azoxydimethylaniline (Calc. for $C_{16}H_{20}ON_4$: C, 70.1; H, 6.6; N, 18.2%), which *p*-nitrosodimethylaniline is known to give in the presence of potassium ethoxide even at 0°. ²² The same product was obtained in ethanol, more slowly and in smaller yield, when the sodium ethoxide was replaced by an equivalent of aqueous 10% sodium hydroxide.

The hydrolysis of this compound by acids, in the hope of obtaining the 3 : 4-dioxo-arsine, gave solely dark brown tars.

Di-(2-cyanoethyl)-*m*-methoxyphenylarsine (XV; R = CN).—The arsine (XI) (38.4 g.) and vinyl cyanide (33.5 g., 3 mols.) were heated under reflux in nitrogen at 100° for 6 hr. The excess of vinyl cyanide was removed by distillation, leaving a yellow viscous residue of the *dicyano-arsine* (XV; R = CN) (60.2 g., 100%), which was normally used without purification. A small quantity, distilled under nitrogen, afforded the cyano-arsine as a pale yellow odourless distillate, b. p. 206—212°/0.03 mm. (Found: N, 9.6. $C_{13}H_{15}ON_2As$ requires N, 9.7%): a slight residue of arsenic remained in the distilling-flask. The arsine reacted with methyl iodide to form a gum which gave an oily methopicate.

Di-(2-carboxyethyl)-*m*-methoxyphenylarsine (XV; R = CO₂H).—This arsine was prepared by alkaline hydrolysis of the dicyano-arsine, precisely as the acid (XIII; R = CO₂H), and obtained as a colourless gum (95% yield), which slowly crystallised. It was too soluble in organic solvents for crystallisation: a sample reprecipitated from sodium hydroxide solution by hydrochloric acid had m. p. 54°, but was not pure (Found: C, 48.5; H, 5.05. Calc. for $C_{13}H_{17}O_5As$: C, 47.6; H, 5.2%). It readily gave a *methiodide*, m. p. 162° from methanol-ether (Found: C, 36.4; H, 4.2. $C_{14}H_{20}O_5IAs$ requires C, 35.8; H, 4.3%), which appeared to lose methyl iodide when dried; and a *bis*-*S*-benzylthiuronium salt, prisms, m. p. 134°, from methanol-ether (Found: C, 52.5; H, 5.3; N, 8.6. $C_{29}H_{37}O_5N_4S_2As$ requires C, 52.7; H, 5.65; N, 8.5%).

7-Methoxy-1 : 6-dioxoarsulolidine (XVI).—Phosphoric anhydride (20 g.) and "Hyflo Supercel" (10 g.) were added to a solution of the dicarboxy-arsine (XV; R = CO₂H) (10 g.) in dry toluene (200 c.c.), which was boiled under reflux with vigorous stirring for 15 min. The toluene was decanted from the sticky residue, which was extracted with boiling toluene (2 × 100 c.c.). The combined toluene extracts were shaken with aqueous sodium hydroxide, dried (Na₂SO₄), and evaporated under reduced pressure in nitrogen. The highly crystalline residual *arsulolidine* (XVI) formed rods, m. p. 150°, from ethanol or benzene (Found: C, 53.5; H, 4.8%; M, in freezing ethylene dibromide, 280. $C_{13}H_{13}O_3As$ requires C, 53.45; H, 4.5%; M, 292). The *arsulolidine* was recovered unchanged from the dibromide solution: the mean yield was 1.0 g., 11%. The dioxo-arsine is slightly volatile in boiling toluene, and the distillate was therefore used as solvent for the next cyclisation.

The sodium hydroxide extracts were acidified and extracted with benzene, but the extracts on evaporation gave only a trace of gummy residue.

The phosphoric anhydride residue, when treated as described on p. 3344, yielded a small quantity of the dioxo-arsine.

The dicarboxy-arsine (XV; R = CO₂H) (5 g.) was also treated with phosphoric anhydride and phosphoric acid for 1 hr. (see p. 3344). The yellow benzene extract, when shaken with aqueous sodium hydroxide, dried, and evaporated in nitrogen, gave a brown gum (0.85 g.), which on recrystallisation from benzene (seeding) gave the pure dioxo-arsine (XVI) (0.3 g., 7%). The alkaline extract was acidified and extracted with benzene, which on evaporation in nitrogen gave a brown ketonic gum (0.75 g.), apparently crude 1-(2-carboxyethyl)-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxoarsinoline, which did not crystallise. The only crystalline derivative isolated was the 2 : 4-dinitrophenylhydrazone, m. p. ca. 100° after crystallisation from ethanol-ethyl acetate, but this was still impure (Found: C, 47.6; H, 3.9; N, 12.0. Calc. for $C_{19}H_{19}O_7N_4As$: C, 46.5; H, 3.9; N, 11.4%).

A solution of the dioxo-arsine (XVI) (1 g.) and phenylhydrazine (0.82 g., 2.2 mols.) in ethanol (20 c.c.) and acetic acid (2 c.c.), when boiled under reflux in nitrogen for 6 hr., deposited the very pale cream crystalline *bisphenylhydrazone* (1.44 g., 89%), m. p. 169—171° after

²² Hantzsch and Lehmann, *Ber.*, 1902, **35**, 897.

crystallisation from ethanol-benzene (Found: C, 63.95; H, 5.5; N, 11.8. $C_{25}H_{25}ON_4As$ requires C, 63.6; H, 5.3; N, 11.9%).

The *bismethylphenylhydrazone*, similarly prepared, separated as pale cream needles (32%), m. p. 160° when recrystallised from ethanol (Found: C, 64.7; H, 5.4. $C_{27}H_{29}ON_4As$ requires C, 64.8; H, 5.8%. Low and inconsistent nitrogen values were always obtained).

The bisdiphenylhydrazone, similarly prepared, formed a brown gum.

When the dioxo-arsine in ethanol was warmed with a deficit of ethanolic 2:4-dinitrophenylhydrazine for 1—2 min., small deep purple crystals separated, and after crystallisation from ethanol afforded the *mono-2:4-dinitrophenylhydrazone ethanolate*, m. p. 125° (decomp.) (Found: C, 49.0; H, 4.3. $C_{19}H_{17}O_6N_4As, C_2H_6O$ requires C, 48.7; H, 4.5%). The use of an excess of the reagent, with boiling under reflux for 30 min., gave the very insoluble bright red crystalline *bis-2:4-dinitrophenylhydrazone*, m. p. 140° (decomp.) after washing with hot ethanol (Found: N, 17.3. $C_{25}H_{21}O_9N_8As$ requires N, 17.2%).

The dioxo-arsine in ethanolic solution, when heated for 15 min. with aqueous hydroxylamine hydrochloride (1.1 mol.) and sodium carbonate, gave the *mono-oxime*, prisms, m. p. 181°, from ethanol (Found: C, 51.3; H, 4.3; N, 4.4. $C_{13}H_{14}O_3NAs$ requires C, 50.9; H, 4.6; N, 4.6%).

The dioxo-arsine was recovered unchanged after its solution in methyl iodide had been boiled in nitrogen for 6 hr. A mixture of the arsine and methyl toluene-*p*-sulphonate (1.1 mol.), when fused under nitrogen at 130° for 15 min., cooled, and extracted with ether, gave a red-brown gum.

No satisfactory product could be isolated on interaction of the dioxo-arsine with *p*-dimethylaminobenzaldehyde or with *p*-nitrosodimethylaniline under various conditions.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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