126. *The Preparation and Properties of 2-Substituted* iso*Arsindolines and of* As-spiro-*Bis*iso*arsindolinium Salts.*

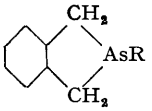
By Donald R. Lyon, Frederick G. Mann, and (in part) Gerald H. Cookson.

A number of 2-aryl*iso*arsindolines (I) have been prepared by the action of *o*-xylylene dibromide and sodium on the corresponding aryldichloroarsines. Oxidation derivatives of these compounds proved, however, to have no greater activity against *T. congolense* in mice than those of the 2-phenyl member previously described. These 2-aryl*iso*arsindolines when heated with hydriodic acid readily give 2-*iodo*iso*arsindoline*, which by the action of the appropriate Grignard reagent can be converted into other 2-alkyl- or 2-aryl-*iso*arsindolines.

A new method has been devised for the preparation of 2-aryl*iso*arsindolines by the thermal decomposition of the arsonium salt formed by the union of *o*-xylylene dibromide with an appropriate tertiary dimethylarsine. This method should afford a synthesis of substituted *iso*arsindolines the preparation of which by the sodium method is not possible.

As-spiro-*Bis*-5-*chloro*iso*arsindolinium bromide* has been synthesised; this compound possesses molecular dissymmetry, but attempts to resolve it into optically active forms have failed.

It has been shown by Lyon and Mann (*J.*, 1945, 30) that *o*-xylylene dibromide in ethereal solution reacts with phenyl- and methyl-dichloroarsine in the presence of sodium to form 2-phenyl*iso*arsindoline (I; R = Ph) and 2-methyl*iso*arsindoline (I; R = Me) respectively. These compounds possessed two particular points of interest. The phenyl compound when treated with nitric acid was readily oxidised to the corresponding hydroxynitrate (II; R = Ph, X = NO_3), which with alkali gave the dihydroxide (II; R = Ph, X = OH), and the latter on dehydration formed 2-phenyl*iso*arsindoline oxide (III; R = Ph). The preliminary tests showed that the dihydroxide possessed slight activity against *Trypanosoma rhodesiense*, *T. cruzi*, and *T. congolense* in mice. Secondly, the methylarsine (I; R = Me) readily combined



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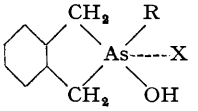

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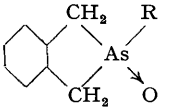

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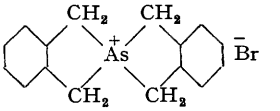


(IV.)

with a further molecule of *o*-xylylene dibromide, and the arsonium salt thus produced lost methyl bromide on heating with the formation of *As-spiro*-bis*iso*arsindolinium bromide (IV). This constituted the first synthesis of a spirocylic arsonium salt having the arsenic atom covalently joined to four carbon atoms. We have consequently investigated in greater detail both these aspects of the *iso*arsindolines.

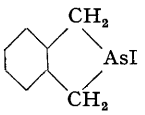
We have first prepared analogues of (I) containing aryl groups other than phenyl in the 2-position in order to determine whether the therapeutic action could thus be increased. *o*-Xylylene dibromide reacted readily with *p*-tolyldichloroarsine and sodium to form 2-p-*tolyl*iso*arsindoline* (I; R = *p*-C_6H_4Me); this compound resembled its phenyl analogue in that even after distillation it remained contaminated with cyclic hydrocarbons (cf. Lyon and Mann, *loc. cit.*). It was therefore converted into its *hydroxynitrate* (II; R = *p*-C_6H_4Me, X = NO_3) which was then purified by recrystallisation, converted into the *dihydroxide* (II; R = *p*-C_6H_4Me, X = OH), and the latter then reduced to the pure liquid arsine.

p-Chlorophenyldichloroarsine similarly furnished 2-p-*chlorophenyl*iso*arsindoline* (I; R = *p*-C_6H_4Cl); this arsine, initially liquid, had also to be purified *via* the *hydroxynitrate* (II; R = *p*-C_6H_4Cl, X = NO_3) and the *dihydroxide* (II; R = *p*-C_6H_4Cl, X = OH) and was thus obtained as colourless crystals, m. p. 64°.

p-Anisyldichloroarsine furnished 2-p-*anisyl*iso*arsindoline* (I; R = *p*-C_6H_4·OMe), which readily solidified after an initial distillation, and was purified by direct crystallisation without the necessity for the intermediate formation of the *hydroxynitrate* (II; R = *p*-C_6H_4·OMe, X = NO_3) and the *oxide* (III; R = *p*-C_6H_4·OMe). The arsine is dimorphic, having two forms,

m. p. 69—70° and 91—92°; the first form was obtained only in the initial experiment, and when it had once been converted into the second form, all subsequent preparations gave the higher melting and more stable form.

Many attempts to demethylate the *p*-anisylarsine, in order to obtain 2-*p*-hydroxyphenyl*iso*arsindoline (I; R = *p*-C_6H_4·OH), failed, but revealed a remarkable reaction. When the anisylarsine was heated with hydriodic acid of constant b. p. under the usual conditions, the product was the colourless crystalline 2-*iodo*iso*arsindoline* (V), the aryl group having been removed from the molecule; this reaction is apparently general for the 2-aryl*iso*arsindolines, since the iodoarsine (V) was similarly obtained from the 2-phenylarsine (I; R = Ph). Now although *p*-anisylphosphines when heated with hydriodic acid undergo smooth demethylation without fission of the P–C bonds (Davies and Mann, *J.*, 1944, 276), *p*-anisylarsines under these conditions are usually converted ultimately into arsenic tri-iodide (Michaelis and Weitz, *Ber.*, 1887, **20**, 48). The fact that our 2-*aryl*iso*arsindolines* even under the prolonged effect of boiling hydriodic acid gave the iodoarsine (V), and that no further fission of the As–C bonds occurred, is striking evidence of the stability of the cyclic *iso*arsindoline system.



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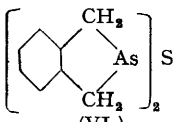

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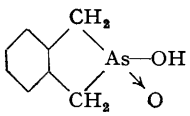
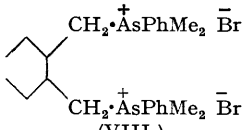


(VII.)

The iodoarsine (V) has many interesting reactions; for example with sodium sulphide it forms the highly crystalline *bis*-2-iso*arsindolyl sulphide* (VI), whereas oxidation and hydrolysis furnish o-*xylylenearsinic acid* (VII). Its greatest value is that by reaction with an appropriate Grignard reagent other aryl or alkyl groups can be inserted in the 2-position, and a very convenient method of converting one tertiary *iso*arsindoline into another is thus available (*vide infra*).

The use of sodium in the initial formation of 2-aryl*iso*arsindolines (I) imposes severe limitation upon the nature of the substituents which can be introduced into the 2-aryl group and (possibly more important) into the *o*-phenylene radical. To overcome this difficulty, we have in our later work devised an alternative synthesis of these *iso*arsindolines (I). When phenyldimethylarsine is added to an equimolecular quantity of *o*-xylylene dibromide, quaternary salt formation readily occurs, and when the product is heated under reduced pressure methyl bromide is lost and ultimately crude 2-phenyl*iso*arsindoline (I; R = Ph) distils in *ca.* 60% yield. The precise course of this reaction is uncertain. The initial product is a mixture of arsonium bromides, of which we have been able to identify only *o*-xylylene bis(phenyldimethylarsonium bromide) (VIII) in the form of its *dipicrate*, although phenyl-*o*-bromomethylbenzyldimethylarsonium bromide (IX) is probably also present. The residue after the distillation



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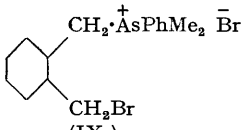

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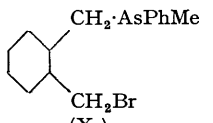

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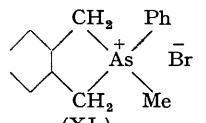


(XI.)

contains the more stable phenyltrimethylarsonium bromide, $PhMe_3AsBr$. It is clear therefore that a number of reactions occur during the heating. The compound (VIII) may dissociate, regenerating phenyldimethylarsine and forming (IX), which can then lose methyl bromide to give either the tertiary arsine (X) or 2-phenyl-2-methyl*iso*arsindolinium bromide (XI), either of which by subsequent further loss of methyl bromide would produce 2-phenyl*iso*arsindoline (I; R = Ph). Alternatively, it is possible that (VIII) decomposes with initial loss of methyl bromide and then phenyldimethylarsine, forming ultimately phenyltrimethylarsonium bromide and the *iso*arsindolinium bromide (XI), which then gives the *iso*arsindoline.

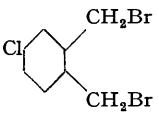
This new synthetic route is probably susceptible to wide development. In addition to allowing the introduction of groups which would be affected by metallic sodium, it does not require the prolonged precautions against arsine oxidation that the sodium condensation method demands, it is much shorter than this method, and its yields are considerably higher. Furthermore, it is probable that the initial use of trimethylarsine instead of phenyldimethylarsine would similarly afford 2-methyl*iso*arsindoline (I; R = Me).

The therapeutic activities of the three 2-aryl*iso*arsindolines (I; R = *p*-C_6H_4Me, *p*-C_6H_4Cl,

p-C_6H_4·OMe), in the form of their dihydroxides or oxides, have been tested by Dr. D. G. Davy in the Biological Laboratories of Imperial Chemical Industries Ltd., Blackley, Manchester; these compounds prove to have activities against *T. congolense* not appreciably higher than that of 2-phenyl*iso*arsindoline dihydroxide itself. It would appear therefore that the introduction of other groups more reactive chemically (such as OH, OAc, NH_2, NHAc) into the 2-aryl or the *o*-phenylene radicals may be necessary before this activity is increased. The introduction of such groups may now be possible by our second preparative method. It is noteworthy that the presence of the *o*-phenylene radical appears to be essential for this therapeutic activity, since phenyldimethylarsine oxide showed no activity against *T. congolense*; furthermore, the presence of the 2-aryl group would also appear to be necessary, for the arsonic acid (VII) also proved to be similarly inactive.

We have attempted to prepare 2-phenyl*iso*stibindoline by the interaction of *o*-xylylene dibromide, phenyldichlorostibine, and sodium in boiling ether, with the usual addition of ethyl acetate as a catalyst (Lyon and Mann, *loc. cit.*), but the only antimony derivative isolated was triphenylstibine, which had evidently been formed by dismutation of the dichlorostibine. We are now attempting to prepare the *iso*stibindoline by a method parallel to our second synthesis of the *iso*arsindolines.

We have also investigated the synthesis of a spirocyclic bis*iso*arsindolium salt which, by virtue of the presence of suitable substituents in the *o*-phenylene groups and the tetrahedral disposition of the arsonium ion, would show molecular dissymmetry and therefore be susceptible to optical resolution. For this purpose 4-chloro-*o*-xylene was brominated to 4-*chloro*-o-*xylylene*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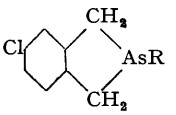
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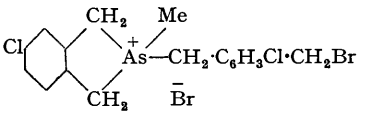
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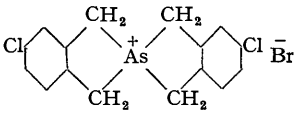
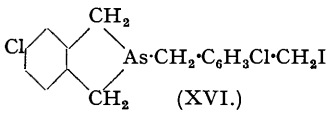

(XV.)

dibromide (XII), which was converted into 5-*chloro*-2-*phenyl*iso*arsindoline* (XIII; R = Ph) by both the above methods, *i.e.*, by heating with phenyldichloroarsine and sodium in ether, and by combination with phenyldimethylarsine and subsequent thermal decomposition. The phenylarsine was then treated with hydriodic acid to form 5-*chloro*-2-*iodo*iso*arsindoline* (XIII; R = I), which reacted with methylmagnesium iodide to give 5-*chloro*-2-*methyl*iso*arsindoline* (XIII, R = Me). This methylarsindoline was prepared by this circuitous route rather than by, for example, the direct action of methyldichloroarsine and sodium on the dibromide (XII) because previous experience (Lyon and Mann, *loc. cit.*) indicated that a higher overall yield of the final product would thus be obtained. The methyl*iso*arsindoline was then combined with the dibromide (XII) to form 5-*chloro*-2[4-(or 5)-*chloro*-2-*bromomethylbenzyl*]-2-*methyl*iso*arsindolinium bromide* (XIV), which when heated at 160—170°/15 mm. very readily furnished the highly crystalline As-spiro-*bis*-5-*chloro*iso*arsindolinium bromide* (XV).

This bromide was converted into the corresponding d-*bromocamphorsulphonate*, crops of which, after fractional crystallisation from methyl and ethyl alcohol under various conditions, showed values for $[M]_D$ which ranged from + 278° to + 318°. When, however, these crops were converted by the action of calcium or sodium iodide in cold solution into the *arsindolinium iodide*, the latter was inactive. The d-*camphorsulphonate*, when submitted to similar fractional crystallisation, gave various crops whose rotations never differed appreciably from that required for the sulphonate ion alone, and which also gave in turn the inactive *iodide*.


(XVI.)

In view of these results it was judged inadvisable in subsequent experiments to isolate the spirocyclic arsonium ion as the iodide after attempted resolution, since there was a possibility that one of the heterocyclic rings in the iodide might undergo fission to give the isomeric tertiary arsine (XVI) with consequent immediate racemisation, although no evidence of such fission could be detected.

In order to obtain a salt entirely different in type from the above sulphonates, the racemic arsonium bromide was treated with silver *l-N*-1-phenylethylphthalamate (Mann and Watson, this vol., p. 505), and thus converted into the spiro-*arsindolinium* l-N-1-*phenylethylphthalamate*, $[(C_8H_7Cl)_2As]$·O_2C·C_6H_4·CO·NH·CHPhMe. This salt separated from aqueous alcohol initially as fine crystals of the *monohydrate*, which melted indefinitely between 60° and 100° and therefore appeared to be a diastereoisomeric mixture. After one crystallisation from aqueous alcohol, the monohydrate had m. p. 144—145° (unchanged by dehydration) and was inactive in alcoholic solution. Two more recrystallisations left the m. p. unchanged, but the salt now had $[\alpha]_D$ + 2·7°

in alcoholic solution: this rotation was unchanged for two days, but the solution when then evaporated in a desiccator at room temperature deposited the phthalamate having m. p. 110—125°. When this feebly dextro-rotatory phthalamate was treated in ice-cold alcoholic solution with sodium thiocyanate, the crystalline inactive *arsindolinium thiocyanate* was deposited. The preparation of the *l*-phthalamate was repeated and the initial crop of this salt had m. p. 68—115°, increased to 137—139° and to 144—145° by two further recrystallisations. The final product had no detectable activity in alcoholic solution, and when treated with picric acid in cold concentrated alcoholic solution deposited the inactive *arsindolinium picrate*. That racemisation of the phthalamate ion (intrinsically very improbable) had not occurred was shown by the fact that the mother-liquors from the precipitation of the picrate—which must have contained the phthalamic acid—were markedly lævo-rotatory.

No fully satisfactory explanation of these data can be suggested. The inactivity (or very weak dextro-rotation) of the arsonium *l*-phthalamate would indicate that the recrystallisation had caused the resolution to proceed until the arsonium ion had a dextro-rotation almost equal to the lævo-rotation of the phthalamate ion. This would imply an almost instantaneous racemisation of the arsonium ion when it was subsequently precipitated as the thiocyanate or picrate. There is no obvious mechanism for racemisation of the arsonium ion, other than the opening of one ring described above, and such a reaction would be improbable for the thiocyanate and exceedingly improbable for the picrate. Furthermore, the homologous active *As-spiro*-bis-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium ion (Holliman and Mann, *J.*, 1945, 45) gave no indication of racemisation in solution. In view of these results, and of the small supply of material, these attempts at resolution were abandoned.

Experimental.

All compounds, unless otherwise stated, were colourless. Solvents used for recrystallisation are given in parenthesis after the compounds concerned. All rotations were determined in a 4-dcm. tube, the source of light being the sodium D line (λ 5893). The m. p.'s of many of the hydroxynitrates were dependent on the rate of heating, and the recorded values are those obtained when the material was placed in a bath at about 10° below the m. p., and the temperature then increased.

*2-Aryliso**arsindolines and Derivatives*.—(I) *2-Phenyliso**arsindoline* (I; R = Ph). The preparation by the sodium method has been described (Lyon and Mann, *loc. cit.*). The first two of the following three experiments were performed to indicate the nature of the intermediate products in the arsonium bromide method, and the third on a larger scale to determine the yield of the *iso*arsindoline. The phenyldimethylarsine was prepared in 90% yield by the action of methylmagnesium iodide on phenyldichloroarsine (Winmill, *J.*, 1912, **101**, 722), and was characterised by reaction with potassium palladochloride, whereby *dichlorobis(phenyldimethylarsine)palladium*, orange leaflets from alcohol, m. p. 170—173° (Found: C, 35·5; H, 4·2. $C_{16}H_{22}Cl_2As_2Pd$ requires C, 35·45; H, 4·1%), was obtained.

(i) A solution of *o*-xylylene dibromide (0·94 g.) in benzene (5 c.c.) was added to phenyldimethylarsine (0·65 g., 1 mol.) in a flask filled with carbon dioxide. The mixture was refluxed for 1 hour in a stream of carbon dioxide and the benzene then removed. The residue formed a very deliquescent glass which could not be crystallised. It was therefore dissolved in water and treated with sodium picrate, whereby *o-xylylene bis(phenyldimethylarsonium picrate)* (as VIII) was obtained, yellow crystals, m. p. 163·5—164·5°, after two recrystallisations (alcohol–acetone) (Found: C, 46·5; H, 3·35; N, 9·2. $C_{36}H_{34}O_{14}N_6As_2$ requires C, 46·7; H, 3·7; N, 9·1%).

(ii) Phenyldimethylarsine (0·36 g.) was run slowly into a solution of the dibromide (0·52 g., 1 mol.) in benzene, which was then slowly distilled in a current of carbon dioxide. The resulting glass was extracted with water, leaving a residue of unchanged dibromide (0·15 g., 30%). The aqueous extract gave the above picrate (0·4 g., 22%), m. p. 163·5—164·5° after recrystallisation, unchanged by admixture with the previous sample.

(iii) The dibromide (36·1 g.) was carefully added to a solution of phenyldimethylarsine (25·1 g.) in chloroform (40 c.c.) in a distilling flask through which a stream of carbon dioxide was passed. The chloroform was removed by distillation, and the residue then heated at 17 mm. pressure. Considerable foaming ensued as methyl bromide was evolved. Ultimately the product was heated at 180°/17 mm. for 2 hours, during which period a small amount of the unchanged dibromide distilled over, and colourless crystals separated in the residual product. The latter was then heated at 0·5 mm., and the crude 2-phenyl*iso*arsindoline (20·9 g., 59% yield based on the arsine) was obtained as the main fraction, b. p. 140—155°. The distillate when set aside formed two layers. The top layer (7·3 g.) on oxidation gave 2-phenyl*iso*arsindoline hydroxynitrate (crude, 9·0 g.; recrystallised, 4·4 g.; m. p. 147—148° (effer.); the lower layer (13·6 g.) also gave the hydroxynitrate (crude, 14·1 g.; recrystallised, 4·3 g.). The *iso*arsindoline was further characterised by conversion into the methiodide and methopicrate, both identical with products prepared by Lyon and Mann (*loc. cit.*).

The residue after the distillation, when recrystallised (alcohol), furnished phenyltrimethylarsonium bromide (3·3 g.), m. p. 281° (decomp.) (Found: C, 39·2; H, 5·1. Calc. for $C_9H_{14}BrAs$: C, 39·0; H, 5·05%), giving the picrate, yellow needles, m. p. 140—141·5° (Found: C, 42·4; H, 4·1; N, 10·0. Calc. for $C_{15}H_{16}O_7N_3As$: C, 42·3; H, 3·8; N, 9·9%). Steinkopf and Schwen (*Ber.*, 1921, **54**, 1437) give m. p. 284° (decomp.) and 145° respectively.

A repetition of the above experiment, in which the phenyldimethylarsine was now added to the dibromide, gave a similar result; yield of pure hydroxynitrate, 20%.

(2) 2-p-*Tolyl*iso*arsindoline* (I; R = *p*-C_6H_4Me). A solution of *p*-tolyldichloroarsine (47·4 g.) in dry ether (200 c.c.) was slowly added with cooling to a solution of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing fine sodium wire (40 g.), the apparatus employed being that already described (Lyon and Mann, *loc. cit.*). Cautious addition of the dichloroarsine was particularly necessary in this series, because the arsine reacts very vigorously and rapidly with the sodium. Ethyl acetate (5 c.c.) was then added and the mixture gently refluxed for 9 hours, further quantities of ethyl acetate (2 c.c. and 3 c.c.) being added after 4 and 6·5 hours' heating. After filtration of the solution under pressure followed by distillation of the ether in a nitrogen atmosphere as previously described, the sticky black residue on fractionation gave the crude arsine, b. p. 132—137°/0·05 mm.; 10 g., 19%.

For purification, the arsine (10 g.) was slowly added with stirring to concentrated nitric acid (*ca.* 50 c.c.) chilled in ice–water. When oxidation was complete, the *hydroxynitrate* (II; R = *p*-C_6H_4Me, X = NO_3) was precipitated by the addition of water, collected, and recrystallised (dilute nitric acid); m. p. 146—146·5° (effer. with preliminary softening) (Found: C, 51·6; H, 4·7; N, 4·2. $C_{15}H_{16}O_4NAs$ requires C, 51·6; N, 4·6; N, 4·0%); 9 g. (13%). This compound readily gave the *hydroxypicrate*, light feathery yellow crystals (alcohol), m. p. 147° (Found: C, 48·8; H, 3·6; N, 8·45. $C_{21}H_{18}O_8N_3As$ requires C, 48·9; H, 3·5; N, 8·2%).

The above hydroxynitrate (8 g.) was shaken with excess of 5% aqueous sodium hydroxide and extracted with chloroform. The dried chloroform layer on evaporation gave the viscous oily *arsine oxide* (III; R = *p*-C_6H_4Me) which solidified in a vacuum over phosphoric anhydride and then, being very hygroscopic, was rapidly crystallised (xylene); m. p. 134—136° (Found: C, 62·65; H, 5·6. $C_{15}H_{15}OAs$ requires C, 62·9; H, 5·3%). The oxide on exposure to air rapidly absorbed water, liquefied, and subsequently resolidified to the non-hygroscopic *arsine dihydroxide hemihydrate* (II; R = *p*-C_6H_4Me, X = OH): m. p. 53—54° (Found: C, 57·4; H, 5·8. $C_{15}H_{17}O_2As,\frac{1}{2}H_2O$ requires C, 57·5; H, 5·8%).

To obtain the pure arsine, the hydroxynitrate (10 g.) was shaken as before with dilute sodium hydroxide solution and chloroform, and the latter (*ca.* 100 c.c.) then separated, mixed with dilute hydrochloric acid (1 : 10 by vol., 150 c.c.) containing potassium iodide (0·1 g.), and saturated with sulphur dioxide for 2 hours. Distillation then gave the pure 2-p-*tolyl*iso*arsindoline* (I; R = *p*-C_6H_4Me), b. p. 138—139°/0·3 mm. (Found: C, 67·0; H, 6·0. $C_{15}H_{15}As$ requires C, 66·7; H, 5·6%); 7 g. When a mixture of this arsine and methyl iodide was refluxed for 30 minutes and then set aside in an open dish, large crystals of 2-p-*tolyl*-2-*methyl*iso*arsindolinium iodide* ultimately formed, m. p. 156° after recrystallisation (alcohol) (Found: C, 46·7; H, 4·6; I, 31·2. $C_{16}H_{18}IAs$ requires C, 46·6, H, 4·4; I, 30·8%). This salt formed the corresponding *picrate*, yellow needles (alcohol), m. p. 134—135° (Found: C, 51·6; H, 4·2; N, 8·4. $C_{28}H_{20}O_7N_3As$ requires C, 51·45; H, 3·9; N, 8·2%).

(3) 2-p-*Chlorophenyl*iso*arsindoline* (I; R = *p*-C_6H_4Cl). *p*-Chlorophenyldichloroarsine was prepared from the arsonic acid (Hunt and Turner, *J.*, 1925, **127**, 2671) and obtained as a colourless liquid, b. p. 110—115°/0·1 mm.

A solution of the dichloroarsine (51·5 g.) in ether (100 c.c.) was added to one of *o*-xylylene dibromide (52·8 g., 1 mol.) containing sodium wire (23 g.), and the mixture refluxed for 14 hours with additions of ethyl acetate (5 c.c.) every 4 hours. The usual treatment then gave a black oil which on distillation furnished three fractions: (*a*) b. p. 106—168°/0·1 mm., (*b*) b. p. 168—175°/0·05 mm., (*c*) b. p. 175—187°/0·05 mm. (5·8 g.). Fraction (*c*) contained the crude arsine, fractions (*a*) and (*b*) only by-products.

The crude arsine was oxidised as usual with nitric acid, but the crude sticky *hydroxynitrate* (II; R = *p*-C_6H_4Cl, X = NO_3) which separated on the addition of water had to be kneaded repeatedly with ether before it formed a clean white solid; recrystallisation (dilute nitric acid) then gave the pure salt, m. p. 144—145° (effer.) dependent on rate of heating (Found: C, 45·4; H, 3·4; N, 3·9; Cl, 9·45. $C_{14}H_{13}O_4NClAs$ requires C, 45·5; H, 3·5; N, 3·8; Cl, 9·6%). This salt gave the *hydroxypicrate*, yellow crystals (alcohol), m. p. 147—148° with preliminary softening (Found: C, 45·1; H, 2·6; N, 7·9. $C_{20}H_{15}O_8N_3ClAs$ requires C, 44·8; H, 2·8; N, 7·85%).

The usual treatment of the hydroxynitrate with sodium hydroxide solution and chloroform gave the oily *oxide* (III; R = *p*-C_6H_4Cl) which readily solidified and was then recrystallised (ethyl carbonate); m. p. 145—146° dependent on rate of heating (Found: C, 54·4; H, 3·84; Cl, 11·4. $C_{14}H_{12}OClAs$ requires C, 54·8; H, 3·95; Cl, 11·6%). The oxide although slightly hygroscopic was not very soluble in cold water; recrystallisation from hot water gave the *dihydroxide hemihydrate* (II; R = *p*-C_6H_4Cl, X = OH), m. p. 77—78° with preliminary softening (Found: C, 50·0; H, 4·7. $C_{14}H_{14}O_2ClAs,\frac{1}{2}H_2O$ requires C, 50·4; H, 4·5%). The dihydroxide was readily converted into the oxide in a vacuum desiccator.

The pure 2-p-*chlorophenyl*iso*arsindoline*, prepared in the usual way from the pure hydroxynitrate, was obtained as a colourless liquid, b. p. 153—154°/0·05 mm., which readily solidified and after crystallisation (alcohol) had m. p. 63—64° (Found: C, 57·7; H, 4·0; Cl, 11·9. $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·2; Cl, 12·2%). This arsine formed a *methiodide*, needles (alcohol), m. p. 204° (Found: C, 41·3; H, 3·4. $C_{15}H_{15}ClIAs$ requires C, 41·6; H, 3·5%), which in turn afforded a *methopicrate*, long yellow needles (water), m. p. 162° (Found: C, 47·6; H, 3·4. $C_{21}H_{17}O_7N_3ClAs$ requires C, 47·2; H, 3·2%).

(4) 2-p-*Anisyl*iso*arsindoline* (I; R = *p*-C_6H_4·OMe). Although the preparation of *p*-anisylarsonic acid has been previously described (Michaelis and Weitz., *Ber.*, 1887, **20**, 48; Schmidt, *Annalen*, 1920, **421**, 169; Adams *et al.*, *J. Amer. Chem. Soc.*, 1922, **44**, 1371; 1923, **45**, 1312), the following modifications improve the preparation. A solution of *p*-anisidine (184 g., 2 mols.) in a mixture of water (1·5 l.) and concentrated hydrochloric acid (375 c.c., 5 mols.) was diazotised at 0° by slow addition of sodium nitrite (104 g., 2 mols.) in water (200 c.c.). Meanwhile a mixture of arsenious oxide (178 g., 1·2 mols.), anhydrous sodium carbonate (330 g., *ca.* 4 mols.), hydrated copper sulphate (20 g.), and water (750 c.c.) was heated to boiling (it remained turbid) and then cooled to 17°. The diazo-solution was then added slowly to the well-stirred arsenite solution, benzene being occasionally added to prevent frothing. The complete mixture was then stirred for 6 hours, set aside overnight, filtered, cooled to 0°, and acidified by running in dilute hydrochloric acid with vigorous stirring; provided this operation was performed slowly the crude arsonic acid (222 g., 64%) separated with very little tar, could be readily collected on a filter, and was pure enough for the next stage.

Sulphur dioxide was passed into a mixture of the arsonic acid (100 g.), concentrated hydrochloric acid (200 c.c.), and potassium iodide at 0° for 1 hour. During the reduction benzene was added to dissolve the considerable amount of solid matter that was precipitated. Ultimately the benzene layer was separated, dried (Na_2SO_4), and distilled, *p*-anisyldichloroarsine being obtained as a pale pink oil, b. p. 138·5—139°/0·5 mm. which readily solidified and then had m. p. 47—48°; 75 g. (69%) (*cf.* Michaelis and Weitz, *loc. cit.*; Blicke *et al.*, *J. Amer. Chem. Soc.*, 1929, **51**, 3480; 1937, **59**, 536). If the reduction is performed at 100°, anisole and arsenic tri-iodide result.

To prepare the arsindoline, solutions of the dichloroarsine (50·6 g.) in ether (200 c.c.) and of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing sodium (40 g.) were mixed and refluxed for 13 hours with the usual addition of ethyl acetate. Careful fractionation of the usual tarry residue then gave 2-p-*anisyl*iso*arsindoline* (I; R = *p*-C_6H_4·OMe) (7 g., 12%) as a colourless liquid, b. p. 167—168°/0·03 mm., which readily solidified in the receiver and when first recrystallised (alcohol) had m. p. 69—70°, but when subsequently recrystallised or prepared had always m. p. 91—92° (Found: C, 63·2; H, 5·4; *M*, cryoscopic in 0·99% benzene solution, 272; in 2·26% solution, 287. $C_{15}H_{15}OAs$ requires C, 62·9; H, 5·3; *M*, 286). The arsine readily formed a *methiodide*, thick heavy plates (alcohol), m. p. 148° with preliminary softening (Found: C, 45·3; H, 4·5; I, 29·9. $C_{16}H_{18}OIAs$ requires C, 44·9, H, 4·2; I, 29·7%), which gave a *methopicrate*, yellow needles (alcohol), m. p. 134° (Found: C, 49·9; H, 3·7; N, 8·1. $C_{22}H_{20}O_8N_3As$ requires C, 49·9; H, 3·8; N, 7·9%).

The arsine also gave a *hydroxynitrate* (II; R = *p*-C_6H_4·OMe; X = NO_3), m. p. 141° (effer., preliminary softening) after recrystallisation (dilute nitric acid) (Found: C, 49·4; H, 4·6; N, 3·8. $C_{15}H_{16}O_5NAs$ requires C, 49·3; H, 4·4; N, 3·8%); this salt in turn furnished a *hydroxypicrate*, hard yellow crystals (alcohol), m. p. 159° (preliminary softening) (Found: C, 47·7; H, 3·3; N, 7·8. $C_{21}H_{18}O_9N_3As$ requires C, 47·4; H, 3·4; N, 7·9%).

The hydroxynitrate was converted by the usual treatment into the *oxide* (III; R = *p*-C_6H_4·OMe), needles (ethyl carbonate), m. p. 150—151°, unchanged by confinement in a vacuum over sulphuric acid (Found: C, 59·4; H, 4·8. $C_{15}H_{15}O_3As$ requires C, 59·6; H, 5·0%). The oxide when exposed to air slowly formed a viscous syrup, from which no crystalline dihydroxide could be isolated.

p-*Nitrophenyldichloroarsine*.—Sulphur dioxide was passed for 30 minutes through a solution of *p*-nitrophenylarsonic acid (20 g.) in cold concentrated hydrochloric acid (75 c.c.) containing potassium iodide (0·1 g.). The resultant yellow oil, when collected, dried (Na_2SO_4), and distilled, gave the liquid *chloroarsine*, b. p. 189°/0·4 mm. (Found: Cl, 26·6. $C_6H_4O_2NCl_2As$ requires Cl, 26·5%). Blicke *et al.* (*loc. cit.*) mention this preparation, but do not cite b. p. or analyses for the compound.

Many attempts were made to condense this dichloroarsine with *o*-xylylene dibromide in the presence of sodium in the usual way, but distillation of the final ethereal solution gave a minute residue which charred extensively on attempted distillation.

2-*Iodo*iso*arsindoline* (V).—2-Phenyl*iso*arsindoline, prepared as above from the hydroxynitrate and isolated from the chloroform extract without distillation, was at once heated with hydriodic acid (50 c.c., constant b. p.) at 120—130° for 2 hours in a stream of carbon dioxide. Initially the arsine floated on the surface but towards the end of the reaction it sank; consequently repeated shaking of the reaction mixture was necessary. After cooling to 0°, the solid *iodo*-compound (V) was collected, rapidly drained (since the crude product darkens on exposure to air) and recrystallised (alcohol); pale yellow plates, m. p. 107—108°, unaffected by subsequent crystallisation from light petroleum (b. p. 80—100°) (Found: C, 31·8; H, 3·1; I, 41·6. C_8H_8IAs requires C, 31·4; H, 2·6; I, 41·5%): 7·5 g. Precisely similar results were obtained when the 2-*p*-anisylarsine was used.

When the crude powdered iodide was stirred with aqueous sodium carbonate solution for 1 hour, a white solid (presumably the hydroxy-arsine) was obtained, but could not be recrystallised. When concentrated hydrochloric acid was added to its hot alcoholic solution, cooling and scratching gave 2-*chloro*iso*arsindoline* (as V), which when recrystallised from alcohol containing hydrochloric acid formed white crystals, m. p. 73—74° (Found: C, 44·7; H, 3·8; Cl, 16·6. C_8H_8ClAs requires C, 44·8; H, 3·8; Cl, 16·5%).

When a mixture of the powdered iodide and 5% aqueous sodium hydroxide was boiled for a few minutes, cooled, and just acidified with sulphuric acid, a white precipitate (of the hydroxide) was again formed. This was dissolved in chloroform and saturated with hydrogen sulphide; filtration and evaporation then gave an oil which readily solidified, and when recrystallised (alcohol) furnished *bis*-2-iso*arsindolyl sulphide* (VI), magnificent white crystals, m. p. 146°, dependent on rate of heating (Found: C, 49·3; H, 4·3; S, 8·2. $C_{16}H_6SAs_2$ requires C, 49·2; H, 4·1; S, 8·2%).

o-*Xylylenearsinic Acid* (VII).—Concentrated nitric acid was added dropwise to a mixture of the powdered iodo-arsine (7·5 g.) and water (50 c.c.). The mixture was gently warmed to volatilise the liberated iodine, and the addition of the acid continued until this liberation ceased; finally the mixture was boiled to remove the last traces of iodine and then cooled, when the *arsinic acid nitrate*, $C_6H_4<[CH_2]_2>As(OH)_2NO_3$, separated as white crystals (4·5 g.) which when collected and washed with ether had m. p. 123—124° (effer., preliminary softening), unchanged by recrystallisation from acetone (Found: C, 35·4; H, 3·6; N, 5·4. $C_8H_{10}O_5NAs$ requires C, 34·9; H, 3·7; N, 5·1%).

A mixture of N-sodium hydroxide (16·3 c.c.), the nitrate (4·48 g., 1 equivalent), and water (50 c.c.) was heated until clear and then cooled; the fine needles of the *monohydrated arsinic acid* (VII) which separated were collected and recrystallised (water); m. p. 144° (decomp.) (Found: C, 41·8; H, 5·1. $C_8H_9O_3As,H_2O$ requires C, 41·7; H, 4·8%).

Attempted Preparation of 2-*Phenyl*iso*stibindoline*.—A solution of phenyldichlorostibine (54 g.) in ether (300 c.c.) was added to one of *o*-xylylene dibromide (52·8 g., 1 mol.) in ether (400 c.c.) containing sodium wire (40 g.) and the mixture refluxed for 12 hours in a nitrogen atmosphere with the usual periodic additions of ethyl acetate. The normal filtration and distillation then gave a main fraction, b. p. 200—260°/0·5 mm. (chiefly 240°) (10 g.). A portion of this oil was cautiously oxidised with cold concentrated nitric acid; dilution with water gave a sticky solid which when kneaded with ether formed a clear white powder. A solution of this material in a large volume of boiling water was filtered and nitric acid (0·5 c.c.) added. On cooling, crystals of *bis*(*triphenylstibine*) *oxide dinitrate*, $(Ph_3Sb)_2O(NO_3)_2$,

m. p. 226—227° (effer.), unchanged by two further recrystallisations, separated (Found: C, 51·1, 50·8; H, 3·4, 3·6; N, 3·4. $C_{36}H_{30}O_7N_2Sb_2$ requires C, 51·1; H, 3·6; N, 3·3%). The duplicate analyses are of the products of two different experiments and are given to indicate the consistent composition of our product, since Morgan, Micklethwait, and Whitby (*J.*, 1910, **97**, 36) assert that triphenylstibine hydroxynitrate (which requires C, 50·2; H, 3·7; N, 3·3%) softens at 220° and melts at 224—225° (decomp.).

When concentrated hydrochloric acid was added to a hot alcoholic solution of the oxide-dinitrate, triphenylstibine dichloride separated in long needles, which after recrystallisation (alcohol containing a few drops of concentrated hydrochloric acid) had m. p. 141·5—142·5° (Found: C, 51·1; H, 3·6. Calc. for $C_{18}H_{15}Cl_2Sb$: C, 51·0; H, 3·6%). Michaelis and Reece (*Ber.*, 1882, **15**, 2876; *Annalen*, 1886, **233**, 39) give m. p. 143°.

4-Chloro-o-xylene.—This compound has previously been obtained only by direct chlorination (Kruger and Claus, *Ber.*, 1885, **18**, 1755; Baeyer, *Annalen*, 1893, **274**, 305). A solution of 4-amino-*o*-xylene (121 g.) in a warm mixture of concentrated hydrochloric acid (227 c.c.) and water (227 c.c.) was rapidly cooled so that fine crystals of the hydrochloride separated. Crushed ice (200 g.) was then added, and the temperature kept below 10° whilst a solution of sodium nitrite (77·2 g.) in water (182 c.c.) was slowly added with stirring. Meanwhile, a solution of sodium bisulphite (63·5 g.) in water (115 c.c.) was added to a solution of hydrated copper sulphate (127 g.) and sodium chloride (43 g.) in water (550 c.c.) at 60°. The mixture was cooled and the cuprous chloride collected, washed with water, and quickly transferred to a 2-l. flask containing concentrated hydrochloric acid (91 c.c.) and water (91 c.c.), and fitted with a reflux condenser and dropping funnel. The flask was heated on a boiling water-bath whilst a fine stream of the diazo-solution was run in with occasional shaking. The final product was steam-distilled, and the distillate basified and extracted with ether. The extract was shaken with aqueous sodium hydroxide solution, dried, and distilled. The fraction b. p. 190—200° on redistillation gave pure 4-chloro-*o*-xylene, b. p. 193—197°; 75 g. (53%).

4-Chloro-o-xylylene Dibromide (XII).—Bromine (107·6 c.c., 2 mols.) was slowly added to 4-chloro-*o*-xylene (150 g.) by means of a delivery tube which dipped below the surface of the xylene; the latter meanwhile was maintained at 125—130°. Addition of the bromine was necessarily slow (*ca.* 6 hours) because otherwise much unchanged bromine would have escaped with the hydrogen bromide evolved. When the addition was complete, heating was continued at atmospheric pressure for 1 hour, and then at *ca.* 15 mm. to remove readily volatile products. Slow distillation then gave the fractions: (i) b. p. 80—85°/0·1 mm., (ii) b. p. 85—112°/0·1 mm., (iii) b. p. 112°/0·1 mm.—130°/0·2 mm. (*ca.* 200 g.), (iv) b. p. 130—138°/0·2 mm. Fraction (iii) when distilled through a 30 cm. column gave the fractions: (*a*) b. p. 100—111°/0·1 mm., (*b*) b. p. 111—127°/0·1 mm. Fraction (*b*) (129 g., 40%) slowly solidified and when recrystallised (alcohol) afforded the *dibromide* (XII), m. p. 46—47° (Found: C, 31·9; H, 2·2. $C_8H_7ClBr_2$ requires C, 32·2; H, 2·4%).

Fraction (i) also solidified, and when recrystallised (alcohol) gave 3(or 4)-*chloro*-o-*xylyl bromide*, m. p. 37—38° (Found: C, 43·7; H, 3·7. C_8H_8ClBr requires C, 43·75; H, 3·7%). This compound liquefied when mixed with the dibromide (XII).

*5-Chloro-2-phenyl*iso*arsindoline* (XIII; R = Ph).—(1) *By the sodium reaction.* A solution of phenyldichloroarsine (50 g., 1·2 mols.) in ether (200 c.c.) was added to one of the dibromide (XI) (55 g., 1 mol.) in ether (400 c.c.) containing sodium wire (22 g.), and the mixture refluxed for 10 hours in a nitrogen atmosphere with the usual periodic additions of ethyl acetate. Filtration and distillation at 0·2 mm. then gave the fractions: (i) b. p. 80—110°, (ii) b. p. 110—150°; (iii) b. p. 150—180°. Fraction (i) was unchanged dichloroarsine, (iii) was the crude arsindoline (20 g.) boiling mainly at 155—165°/0·2 mm., and fraction (ii) was of negligible quantity.

The arsindoline (20 g.) was purified by the usual conversion into the hydroxynitrate, which, after precipitation by the addition of water, was collected, thoroughly washed with ether, and dissolved in boiling water (400—500 c.c.); concentrated nitric acid (20 c.c.) was added to the filtered solution, which was immediately cooled in ice-water. The pure *hydroxynitrate* (11 g.) which separated was washed with alcohol and ether; m. p. 143·5° (effer.) unchanged by crystallisation (alcohol) (Found: C, 45·3; H, 3·6; N, 3·7; Cl, 9·8. $C_{14}H_{13}O_4NClAs$ requires C, 45·5; H, 3·55; N, 3·8; Cl, 9·6%). This salt formed a *hydroxypicrate*, pale yellow crystals (alcohol), m. p. 154—155° with preliminary softening (Found: C, 45·0; H, 2·7; N, 7·8. $C_{20}H_{15}O_{11}N_3ClAs$ requires C, 44·8; H, 2·8; N, 7·85%).

The hydroxynitrate was treated as usual with aqueous sodium hydroxide and chloroform, and the latter then saturated with sulphur dioxide to reduce the arsine oxide. Distillation of the dried chloroform left the pure iso*arsindoline* (XIII; R = Ph) as a colourless liquid which did not solidify even after prolonged confinement in a desiccator (Found: C, 58·0; H, 4·6. $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·2%).

(2) *By the arsonium salt reaction.* The first of the following experiments indicates the nature of the intermediate product, and the second the formation of the required *iso*arsindoline. (i) The chloro-dibromide (XII) (0·74 g.) was added to phenyldimethylarsine (0·57 g., 1 mol.) in a flask filled with carbon dioxide, and the mixture warmed until it became homogeneous; it then rapidly formed a glass. This was cooled, well washed with ether, dissolved in water, and treated with sodium picrate. *4-Chloro-o-xylylene bis(phenyldimethyl arsonium picrate)* was obtained, yellow crystals (0·5 g.) after crystallisation (alcohol–acetone), m. p. 151—152° (Found: C, 45·3; H, 3·8; N, 8·8. $C_{36}H_{33}O_{14}N_6ClAs_2$ requires C, 45·1; H, 3·4; N, 8·8%).

(ii) Phenyldimethylarsine (9 g.) was slowly added to a solution of the chloro-dibromide (14·7 g., 1 mol.) in warm benzene (30 c.c.) in a flask through which carbon dioxide was passed. The benzene was distilled off, and the arsonium salt heated at 18 mm. until evolution of methyl bromide subsided. The product, heated at 0·2 mm., gave a main fraction of the crude *iso*arsindoline (XIII; R = Ph), b. p. 155—160°; 9·1 g. (63% based on arsine used). Oxidation gave the hydroxynitrate [crude, 10 g. (55%); recrystallised, 5·6 g. (31%)], m. p. 143—143·5° (mixed and unmixed). The residue in the flask after recrystallisation afforded phenyltrimethylarsonium bromide (0·85 g.), identified as before.

5-Chloro-2-iodo-iso*arsindoline* (XIII; R = I).—This was prepared precisely as the former iodo-arsine (V), and after recrystallisation (alcohol) had m. p. 121° (Found: C, 27·7; H, 2·1; I, 38·0. C_8H_7ClIAs requires C, 28·2; H, 2·1; I, 37·3%); yield, 42% based on hydroxynitrate used.

*5-Chloro-2-methyl*iso*arsindoline* (XIII; R = Me).—The powdered iodoarsine (6·8 g.) mixed with ether (150 c.c.) was slowly added to a well-stirred ice-cold Grignard reagent prepared from methyl iodide (11·2 g.), magnesium (2 g.), and ether (60 c.c.) under a nitrogen atmosphere. The complete mixture was refluxed for 30 minutes, cooled in ice–salt, and hydrolysed by the cautious addition of ice-cold dilute sulphuric acid (10 c.c. concentrated acid, 140 c.c. water), nitrogen being passed over the product throughout these operations. The ethereal layer was rapidly separated in a funnel previously filled with carbon dioxide, the aqueous layer was also extracted with ether, and the united ethereal extracts were dried with sodium sulphate containing anhydrous sodium carbonate to remove traces of hydrogen iodide. Distillation of the filtered extract ultimately gave the *methyl*iso*arsindoline* (XIII; R = Me) as a colourless liquid, b. p. 81°/0·1 mm. (Found: C, 46·8; H, 4·5. $C_9H_{10}ClAs$ requires C, 47·3; H, 4·4%); 3·5 g.

This arsine was characterised as its *methiodide* which was readily formed and after recrystallisation (alcohol) had m. p. 202—204°, dependent on rate of heating (Found: C, 32·2; H, 3·9; I, 34·9. $C_{10}H_{13}ClIAs$ requires C, 32·4; H, 3·5; I, 34·3%). This in turn formed the *methopicrate*, fine yellow needles (alcohol), m. p. *ca.* 270° (decomp.) (Found: C, 40·4; H, 3·35; N, 8·9. $C_{16}H_{15}O_7N_3ClAs$ requires C, 40·7; H, 3·2; N, 8·9%).

*5-Chloro-2-[4(or 5)-chloro-2-bromomethylbenzyl]-2-methyl*iso*arsindolinium Bromide* (XIV).—Powdered 4-chloro-*o*-xylylene dibromide (7·2 g.) was added to the above methylarsine (5·5 g., 1 mol.); the mixture, when gently warmed in a small stoppered flask, almost immediately formed a hard glass which readily fractured on cooling. For identification, a portion was powdered, thoroughly washed with ether, and dried (Found: C, 37·8; H, 3·5. $C_{17}H_{17}Cl_2Br_2As$ requires C, 38·7; H, 3·25%).

As-spiro-*Bis-5-chloro*iso*arsindolinium Bromide* (XV).—The crude bromide (XIV) (12·7 g.) was heated to 160° at 15 mm. for 30 minutes and then at 160—170°/15 mm. for 1·5 hours. Initially the bromide fused (*ca.* 110°) with gentle effervescence which steadily increased. After *ca.* 1 hour's heating the product began to crystallise, and finally only a pale brown solid remained. This was cooled, powdered under alcohol, and then washed on the filter with alcohol and then with much ether; yield, 8·5 g. The crude bromide was now dissolved in boiling water (*ca.* 1200 c.c.), and the hot solution filtered to remove a trace of insoluble lachrymatory impurity, diluted with hydrobromic acid of constant b. p. (50 c.c.), and then cooled and stirred. Crystallisation was slow and continued for several days. The *bromide* (XV) was then collected, washed with alcohol and ether, and dried; 6·5 g. (63% based on methylarsine used). A portion, recrystallised again, had m. p. 244—246° (decomp.) [Found: C, 44·4; H, 3·3; 2Cl + Br, 35·3; Br (ionic), 19·0. $C_{16}H_{14}Cl_2BrAs$ requires C, 44·45; H, 3·3; 2Cl + Br, 34·9; Br (ionic), 18·5%].

The spiro-*arsindolinium* d-*bromocamphorsulphonate*. Hot aqueous solutions of equimolecular quantities of the bromide (XV) and of silver *d*-bromocamphorsulphonate were mixed, gently boiled, filtered, concentrated to small bulk at 15 mm. pressure, and finally taken to dryness in a vacuum desiccator. The residual solid, when recrystallised from ethyl acetate, gave the d-*bromocamphorsulphonate monohydrate*, which on heating began to soften at *ca.* 130° becoming completely molten at *ca.* 150° (Found: C, 46·3; H, 4·9; S, 4·7. $C_{36}H_{28}O_4Cl_2BrSAs,H_2O$ requires C, 45·9; H, 4·45; S, 4·7%). A sample (4·25 g.) was recrystallised 6 times from ethyl alcohol; the product (1·8 g.) had m. p. 143—147° (effer.) without preliminary softening. A 0·345% solution in ethyl alcohol had α + 0·57°, [*M*] + 281° (for monohydrate).

Another sample was recrystallised 4 times from methyl alcohol; the product, which was still the monohydrate (Found: C, 46·3; H, 4·6%), on heating softened at 135° and became completely molten at 152° (effer.); a 0·338% solution in ethyl alcohol had α + 0·56°, [*M*] + 282°.

The mother-liquors from these 4 recrystallisations had deposited magnificent crystals after several days; the mother-liquors were carefully decanted, and the crystals rapidly washed with a small quantity of methyl alcohol, rapidly drained, dried, and investigated. The crystals from the first mother-liquor were still the monohydrate (Found: C, 45·6; H, 4·8%): a 0·404% solution in ethyl alcohol had α + 0·74°, [*M*] + 311°. Those from third mother-liquor had, in 0·374% solution in alcohol, α + 0·69°, [*M*] +313°. Those from the second and fourth mother-liquors were united, and in 0·389% solution in alcohol had α + 0·73°, [*M*] + 318°.

Since a slow crystallisation appeared to give the sulphonate of high rotation, a portion of the salt which had been recrystallised 6 times from ethyl alcohol and had [*M*] + 281° was dissolved in methyl alcohol so that the solution was almost saturated at room temperature. After several days, clumps of heavy crystals had separated which were quite distinct in appearance from those previously growing in cold methyl alcohol; a 0·353% solution of these heavy crystals in ethyl alcohol had α + 0·62°, [*M*] + 298°. The experiment was repeated with a second portion of the salt, and the cold methyl alcoholic solution seeded with the crystals having [*M*] + 313°; however, a crop of very fine needles resulted, and a 0·361% solution of these needles in ethyl alcohol had α + 0·59°, [*M*] + 278°.

These inconsistent values for the rotation indicated that the crops of high rotation which separated from the original methyl alcohol mother-liquors may have been partly or wholly resolved. To test this possibility, the salt having [*M*] + 318° was dissolved in a minimum amount of cold acetone containing methyl alcohol, and treated with a concentrated acetone solution of calcium iodide. The microcrystalline *arsindolinium iodide* rapidly separated, and when collected and washed in turn with acetone, water, and acetone, was colourless (Found: C, 39·8; H, 3·2. $C_{16}H_{14}Cl_2IAs$ requires C, 40·1; H, 2·9%); m. p. 258—262°. The iodide was almost insoluble in all the usual solvents except formamide; a 0·501% solution in formamide was inactive. To confirm this result, the salt having [*M*] + 313° was dissolved in cold methyl alcohol and treated with a cold concentrated sodium iodide solution also in methyl alcohol; the colourless arsindolinium iodide which separated was again inactive in 0·534% formamide solution. The insolubility of the iodide in all the common solvents affords strong evidence that it had retained the spirocyclic structure (as XV), because these physical properties, although not unexpected for such an arsonium salt, would be most improbable for the tertiary arsine (XVI).

The spiro-*arsindolinium* d-*camphorsulphonate*. A solution of silver *d*-camphorsulphonate (3·432 g.) in hot water (30 c.c.) was added to one of the above iodide (4·848 g., 1 mol.) in boiling aqueous alcohol

(450 c.c.; 3 vols. water–1 vol. alcohol), and the mixture quickly boiled, filtered, cooled, and stirred. Fine needles of the *arsindolinium* d-*camphorsulphonate monohydrate* separated. These were recrystallised from the aqueous alcohol (*ca.* 500 c.c.). The crop (2·95 g.) so obtained had m. p. 290°, and a 1·441% solution in pure chloroform had α + 0·97°, [*M*] + 101°. Another crystallisation gave needles, m. p. 290° (Found : C, 51·45; H, 5·0. $C_{26}H_{29}O_4Cl_2SAs,H_2O$ requires C, 51·9; H, 5·2; Cl, 11·8%); a 1·345% solution in chloroform had α + 0·96°, [*M*] + 107°. Since Holliman and Mann (*J.*, 1943, 554) have shown that the camphorsulphonate ion alone has [*M*] 111° in chloroform solution, no resolution was apparent.

Consequently, the camphorsulphonate was now recrystallised from methyl alcohol, from which it separated in fine woolly crystals; these after one and two recrystallisations had m. p. 298—302° and 302—303° respectively. The final material was still the monohydrate (Found : C, 52·3; H, 5·4; Cl, 12·0%); a 0·701% solution in chloroform had α + 0·49°, [*M*] + 105°. The chloroform solution on evaporation deposited the unchanged material, m. p. 295—296°. In view of these results the sulphonate was recovered and recrystallised 4 times from ethyl alcohol. It now separated as the *anhydrous* salt, m. p. 300° (Found : C, 53·7; H, 5·3. $C_{26}H_{29}O_4Cl_2SAs$ requires C, 53·5; H, 5·0%), and was too slightly soluble in chloroform for its rotation to be determined. It was therefore dissolved in a minimum amount of warm methyl alcohol, and treated with a concentrated methyl alcoholic solution of sodium iodide; the arsindolinium iodide which rapidly separated, when collected, washed with methyl alcohol and water, and dried, was inactive.

The spiro-*arsindolinium* l-N-1-*phenylethylphthalamate.* Solutions of the above iodide (1·957 g.) in hot aqueous alcohol (*ca.* 200 c.c.; 3 vols. water–1 vol. alcohol) and silver *l*-*N*-1-phenylethylphthalamate (1·535 g., 1 mol.) in hot 50% alcohol (120 c.c.) were mixed, briefly boiled, filtered, and cooled. As no crystals separated, the solution was concentrated first by gentle heating at *ca.* 30 mm. pressure and then by confinement in a vacuum desiccator. Magnificent rosettes of the *phthalamate monohydrate* (1·85 g., theoretical 2·53 g.), m. p. indefinite at 60—100°, separated. These were recrystallised by dissolving in warm alcohol and adding cold water until an emulsion was about to form; slow cooling and stirring gave the salt as fine crystals (1·5 g.), m. p. 145—146° on slow heating (Found : C, 59·8; H, 5·1; N, 2·3. $C_{32}H_{28}O_3NCl_2As,H_2O$ requires C, 60·1; H, 4·7; N, 2·2%). A portion when heated at 80°/0·1 mm. gave the *anhydrous* salt (Found : C, 61·8; H, 4·6. $C_{32}H_{28}O_3NCl_2As$ requires C, 61·9; H, 4·55%). A 0·652% solution of the monohydrate in alcohol was inactive. A second similar crystallisation gave the monohydrate (1·1 g.), a 0·660% solution of which in alcohol had α + 0·07°, [α] 2·7°, [*M*] + 17°, unchanged after 40 hours at room temperature; when, however, the alcohol was evaporated in a vacuum desiccator, the residual salt had m. p. 110—125°. Cold concentrated methyl-alcoholic solutions of this twice recrystallised salt and of sodium thiocyanate were mixed, whereupon the *arsindolinium thiocyanate* separated rapidly as white crystals, m. p. 223° (decomp.), which were collected and washed with water and alcohol (Found : C, 49·7; H, 3·5; N, 3·5. $C_{17}H_{14}NCl_2SAs$ requires C, 49·75; H, 3·4; N, 3·4%). A 0·713% solution in formamide was inactive.

A second similar preparation gave an initial crop of the phthalamate monohydrate which began to soften at 68° and ultimately melted at 80—115° (effer.) : a 0·663% solution in alcohol had α — 0·05°. A second crystallisation gave material which shrank slightly at 120° and then melted at 137—139°; a third crystallisation gave material, m. p. 144—145° on slow heating. A 0·511% solution in alcohol was inactive. When alcoholic picric acid solution was added dropwise to a cold alcoholic solution of this last crop (*ca.* 0·3 g.), the yellow *arsindolinium picrate*, m. p. 108—112° (decomp.), was deposited (Found : N, 7·5. $C_{23}H_{16}O_7N_3Cl_2As$ requires N, 7·2%). It was collected, washed with water, and dried, but a 0·480% solution in alcohol containing 6% of acetone was inactive. The alcoholic mother-liquor from the precipitation of the picrate had α — 0·50°.

If in the above recrystallisations of the phthalamate hot water (instead of cold) was added to the hot alcoholic solution, the phthalamate separated as usual, but the m. p. [*e.g.*, 63—110° (effer.)] was now almost identical with that of the initial crop.

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