

THE SYNTHESIS AND STEREOCHEMISTRY
OF HETEROCYCLIC DERIVATIVES OF
ARSENIC

A Thesis submitted in Candidature for the
Degree of Doctor of Philosophy at the
University of Cape Town

by

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August, 1958.

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PREFACE

The work described in this thesis was carried out between February, 1956 and September, 1957 in the Department of Chemistry, University of Cape Town; and from October, 1957 to September, 1958, in the University Chemical Laboratory, Cambridge.

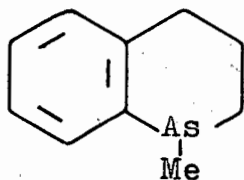
I wish to record my indebtedness to my supervisor, Professor F.G. Holliman, Mally Professor of Organic Chemistry in the University of Cape Town; and to Dr. F.G. Mann, F.R.S., Reader in Organic Chemistry, University of Cambridge, for their advice and helpfulness in many matters pertaining to this problem. During the former period, the author held the post of Junior Lecturer in the Department of Chemistry, University of Cape Town, and thereafter was awarded a research grant by British Celanese Limited, both of which are

gratefully acknowledged. My thanks are also due to the technical staffs of both laboratories for their kind assistance. In particular, I wish to thank Mr. R. von Holdt, B. Sc., (of the Department of Chemistry, Cape Town,), and Mr. R. Maxim, Miss J. Barrance and Miss M. Day (of the Chemical Laboratory, Cambridge) for carrying out most of the microanalyses.

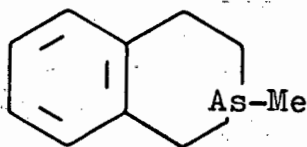
David Thomson.

NOTE ON NOMENCLATURE

Many of the names given to heterocyclic derivatives of arsenic are self-explanatory in that they are adaptations of the names commonly used for the corresponding nitrogen compounds. For example, the compounds (I) and (II) are named as 1-methyl-1:2:3:4-tetrahydroarsinoline and 2-methyl-1:2:3:4-tetrahydroisoarsinoline respectively, by analogy with the corresponding nitrogen-containing compounds, 1-methyl-1:2:3:4-tetrahydroquinoline and 2-methyl-1:2:3:4-tetrahydroisoquinoline.



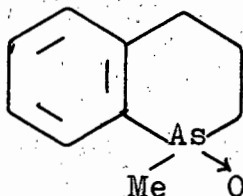
(I)



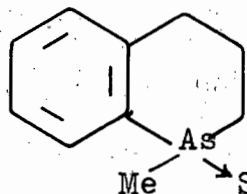
(II)

The naming of simple alkyl derivatives

hydroarsinoline oxide (VIII), and 1-methyl-1:2:3:4-tetrahydroarsinoline sulphide (IX), respectively.



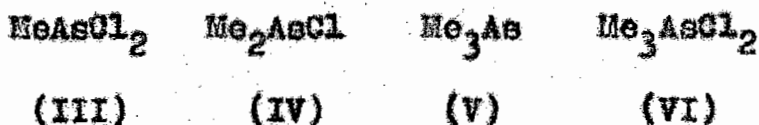
(VIII)



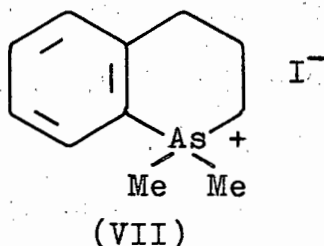
(IX)

Some chemists prefer to employ an adaptation of the generally-accepted trivial name for the analogous carbon, oxygen or nitrogen containing system, when naming heterocyclic derivatives of arsenic. In these cases, the prefix "arsa-" is generally employed, indicating that a carbon, oxygen or nitrogen atom has been replaced by an arsenic atom. Thus, the arsinoline (I) could be named as arsakairolin on the basis that kairolin is the trivial name for 1-methyl-1:2:3:4-tetrahydroquinoline, the nitrogen analogue. Similarly, the compound (X) is normally referred to as 9-methyl-9-arsafluorene by analogy with the corresponding hydrocarbon, fluorene.

of arsenic is also usually a straightforward matter. Thus the compounds (III), (IV), (V) and (VI) are named as methyldichloroarsine, dimethyl(mono)chloroarsine, trimethylarsine and trimethylarsine dichloride respectively.

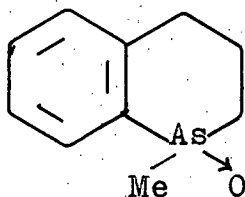


Quaternary salts of arsenic are named in similar fashion to the corresponding quaternary ammonium salts. Thus, the methiodide of the arsinoline (I) is correctly named as 1:1-dimethyl-1:2:3:4-tetrahydroarsinolinium iodide (VII), or as 1-methyl-1:2:3:4-tetrahydroarsinoline methiodide.

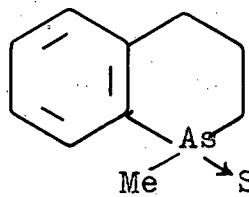


The oxide and sulphide of the arsinoline (I) are simply named as 1-methyl-1:2:3:4-tetra-

hydroarsinoline oxide (VIII), and 1-methyl-1:2:3:4-tetrahydroarsinoline sulphide (IX), respectively.

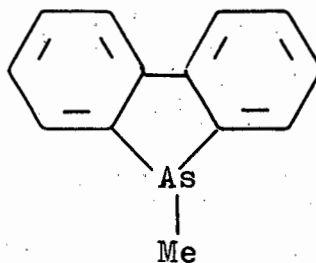


(VIII)



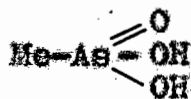
(IX)

Some chemists prefer to employ an adaptation of the generally-accepted trivial name for the analogous carbon, oxygen or nitrogen containing system, when naming heterocyclic derivatives of arsenic. In these cases, the prefix "arsa-" is generally employed, indicating that a carbon, oxygen or nitrogen atom has been replaced by an arsenic atom. Thus, the arsinoline (I) could be named as arsakairolin on the basis that kairolin is the trivial name for 1-methyl-1:2:3:4-tetrahydroquinoline, the nitrogen analogue. Similarly, the compound (X) is normally referred to as 9-methyl-9-arsafluorene by analogy with the corresponding hydrocarbon, fluorene.



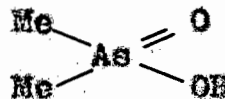
(X)

The acids derived from arsenic present a far greater problem. Unfortunately, two systems are at present in use for naming these compounds. The American system has been recommended for use by F.G. Mann¹ as being the more logical system, and has been adopted in this thesis. This system is illustrated by the following examples, whilst the British system names are given below in parenthesis:



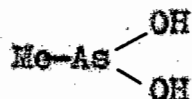
methylarsonic acid

(methylarsonic acid)



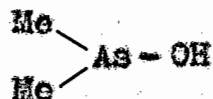
dimethylarsinic acid

(dimethylarsonous acid)



methyarsinous acid

(methyarsinic acid)



dimethylarsinous acid

(dimethylarsinous acid)

It would obviously be of great advantage if general agreement could be reached on a system for naming all possible types of organic compounds of arsenic so that confusion in this rapidly growing field of chemistry may be avoided.

INTRODUCTION

INTRODUCTION

A large amount of work has been carried out on the attempted resolution of quaternary salts of phosphorus and arsenic possessing atoms of these elements as the asymmetric centre. On the basis of a tetrahedral configuration for the atoms of the Group Vb elements when 4-covalent, three classes of optically-active organic compounds containing these elements are possible. These are the oxide (or sulphide) of the tertiary amine, phosphine or arsine of type $abcQO$ (or $abcQS$), ($Q = N, P$ or As); a quaternary salt of type $abcdQ^+X^-$; and a spirocyclic salt possessing molecular dissymmetry.

Up to the present time (August, 1958), a tertiary amine oxide has been resolved by

Meisenheimer² who has also resolved a phosphine oxide successfully³. A quaternary ammonium salt has been resolved by Pope and Peachey⁴ and more recently a quaternary phosphonium and a quaternary arsonium salt by Holliman and Mann^{5,6}. Spiro-cyclic salts of all these elements (except antimony and bismuth) have now successfully been resolved^{7,8,9}. Finally, the resolution of a tertiary phosphine sulphide has been accomplished by Davies and Mann¹⁰ and an arsine sulphide by Mills and Raper¹¹. Tertiary amine sulphides are apparently unknown, whilst the consistent failure of attempts to resolve a tertiary arsine oxide have been explained as possibly due to the conversion $[abcAsOH]X \longrightarrow abcAsO$ through the transient dihydroxide $abcAs(OH)_2$ which may possess a plane of symmetry, this conversion occurring after removal of the resolving agent. No quaternary stibonium salts have apparently been resolved. The stereochemistry of heterocyclic derivatives of the Group Vb elements has thus been placed on

a firm footing and the successful resolution of the above-mentioned types of derivative has meant that considerable support to other physical and chemical evidence which indicates a tetrahedral configuration for the 4-covalent atoms of these elements has been given.

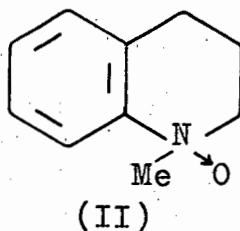
Among the earliest attempts made at the preparation and resolution of quaternary arsonium salts where it was hoped optical activity would be shown to be due to an asymmetric arsenic atom was the work of Winmill¹³ in 1912. Several chemists had previously investigated the resolution of quaternary ammonium salts possessing an asymmetric nitrogen atom. Thus Pope and Peachey⁴ had in 1899 successfully accomplished the resolution of allylbenzyl-methylphenylammonium iodide (I).



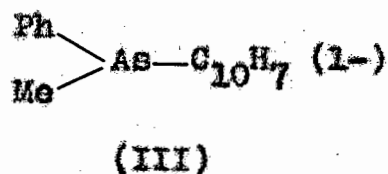
(I)

Winmill prepared the arsenic analogue

of (I) but attempted resolution via the (+)-camphorsulphonate and (+)-bromocamphorsulphonate failed. Many attempted resolutions of similar arsonium and phosphonium salts carried out at this time had resulted in failure and some chemists seemed on the verge of concluding that arsenic and phosphorus do not function as centres of optical activity in quaternary salts. Fortunately, Burrows and Turner¹⁴ saw the necessity for testing different types of asymmetric arsenic compounds. In view of Meisenheimer's successful resolution of kairiline oxide (II)¹⁵, Burrows and Turner prepared the

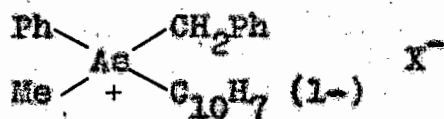


solid arsine, methyl-1-naphthylphenylarsine (III), but attempted resolution of the oxide via the (+)-bromocamphorsulphonate was not successful.

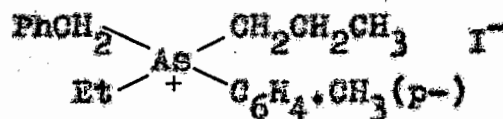


Ultimately, a quaternary arsonium salt, benzylmethyl-1-naphthylphenylarsonium bromide (IV, X = Br), was prepared, and, recrystallisation of the (+)-bromocamphorsulphonate followed by conversion to the iodide gave a product with a fleeting rotation, the highest recorded value being $[M]_D +12^\circ$.

Kamail¹⁶ prepared the quaternary arsonium salt, benzylethyl-n-propyl-p-tolylarsonium iodide (V). Crystallisation of the (+)-bromocamphorsulphonate gave three fractions, two of which were optically inactive, the third undergoing rapid racemisation (as experienced by Burrows and Turner). The highest molecular rotation observed here was $[M]_D +45^\circ$.



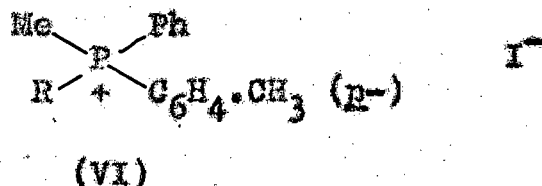
(IV)



(V)

At this stage, the failure of Pope and Gibson¹⁷ to resolve the quaternary phosphonium

salts, benzylmethylphenyl-*p*-tolylphosphonium iodide (VI, R = -CH₂Ph), and allylmethylphenyl-*p*-tolylphosphonium iodide (VI, R = -CH₂CH=CH₂), must be mentioned. In the first case,



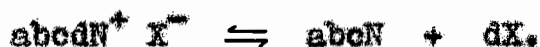
crystallisation of three different optically-active salts could not be effected, and in the second case, crystallisation of the (+)-bromocamphorsulphonate gave three fractions of identical molecular rotation.

Before 1943, no quaternary phosphonium salt of type $\text{abcdP}^+ \text{X}^-$ had been resolved and in the case of quaternary arsonium salts (IV, X = I) and (V), rapid racemisation had in each case taken place. An explanation of the racemisation and hence optical instability of these quaternary arsonium salts was sought.

Comparable difficulties had not been encountered in the resolution of quaternary

ammonium salts. However, it was generally accepted that the quaternary ammonium sulphates and nitrates containing asymmetric nitrogen atoms were more optically stable than the corresponding iodides and that the latter were particularly subject to racemisation in chloroform solution.

Pope and Harvey¹⁸ found that when the (+)-isomer of the ammonium iodide (I) was dissolved in chloroform, it underwent rapid racemisation. They suggested that this might be due to the operation of a dissociation equilibrium of the type



On decomposition of the salt, benzyl iodide is produced so that the dissociation equilibrium could be represented as

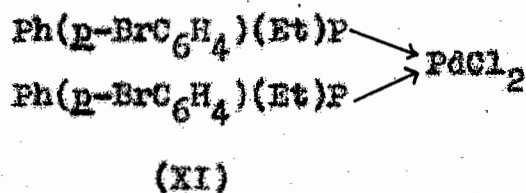
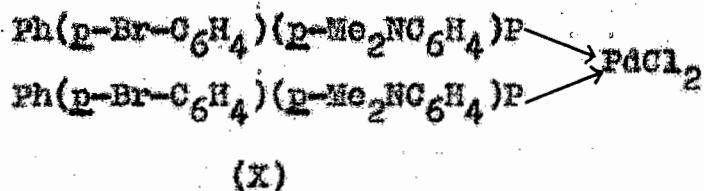
$PhCH_2 \cdot N(Ph)(C_3H_5)(CH_3)I \rightleftharpoons CH_3N(Ph)(C_3H_5) + PhCH_2I.$
Wedekind and von Halban^{19, 20, 21, 22} have subsequently confirmed this view.

It is noteworthy that of the six quaternary ammonium, phosphonium and arsonium salts mentioned, whose resolution has been

attempted, five contained a benzyl group attached to the central atom, and the remaining one an allyl group. Snyder and Speck²³ have shown that, under the influence of heat, benzyldimethylphenylammonium thiocyanate dissociates to dimethylaniline and benzyl thiocyanate. Similarly, on investigation of other quaternary ammonium salts, the fact emerged that benzyl groups were always preferentially eliminated on rearrangement and that allyl groups were the next readily cleaved, due to the fact that benzyl and allyl groups are both capable of giving a stabilised carbenium ion and hence are readily eliminated as such. Furthermore, they were able to show that cleavage of these groups is facilitated by the presence of an aromatic group attached to the nitrogen atom. These observations lent considerable support to those of Wedekind and von Halban and Pope and Harvey mentioned above.

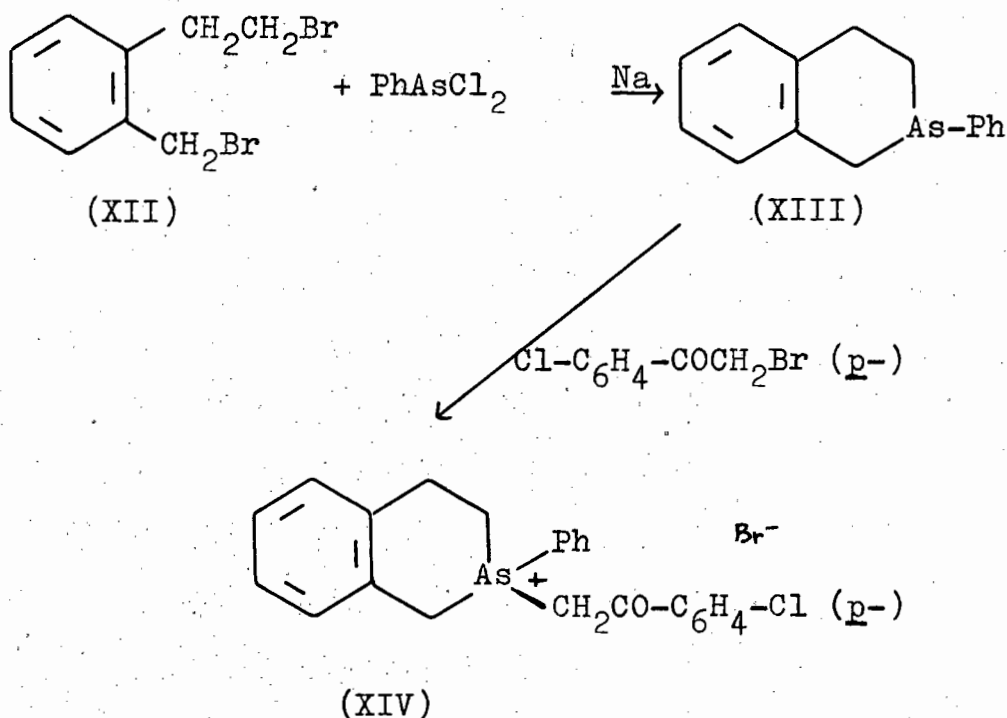
The successful separation of ethylene-1:2-bis(n-butylmethylphenylarsonium picrate) (VII), and ethylene-1:2-bis(n-butylphenylarsine)-dichloropalladium (IX), by Chatt and Mann^{24, 25}

In their investigation of similar phosphorus compounds, Davies and Mann¹⁰ prepared the compounds, dichlorobis(p-bromophenyl-p-dimethylaminophenylphenylphosphine)-palladium (X) and dichlorobis(p-bromophenylethylphenylphosphine)palladium (XI), each of which undoubtedly possesses the trans configuration and contains two similar asymmetric 4-covalent phosphorus atoms and should therefore exist in the meso and racemic forms as found with the compound (IX). Unfortunately, the compound (X) proved too insoluble for fractional crystallisation and repeated crystallisation of (XI) gave no indication of the existence of these two forms.



In order to avoid the setting up of the dissociation equilibrium which was thought to have been responsible for the rapid racemisation of the only two quaternary arsonium salts (IV, X = I) and (V), which had shown any signs of optical activity, Holliman and Mann⁶ attempted the preparation of 2-p-chlorophenacyl-2-phenyl-1:2:3:4-tetrahydroisoarsinolinium bromide (XIV). This compound was chosen on the grounds that the 1:2:3:4-tetrahydroiso-arsinoline system possesses high stability, further, that p-chlorophenacyl compounds also possess marked stability (greater than that of the corresponding phenacyl compounds, c. f. Crowther and Mann²⁶). For the preparation of 2-substituted-1:2:3:4-tetrahydroisoarsinolines, o-2-bromoethylbenzyl bromide (XII) has been made readily available due to an improved synthesis by Holliman and Mann²⁷ and recently further modified by Anderson and Holliman²⁸. This compound was condensed in ethereal solution with phenyldichloroarsine in the presence of sodium (Michaelis reaction) to give 2-phenyl-

1:2:3:4-tetrahydroisoevarinoline (XIII), which, on addition of *p*-chlorophenacyl bromide in benzene solution, yielded the desired quaternary salt:



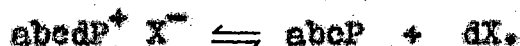
Resolution of the salt (XIV) was now readily accomplished via the bromocamphorsulphonate, the optically-pure (+)- and (-)-picrates having $[\alpha]_D +457$, -450° respectively. This represented the first completely successful resolution of a quaternary arsenium salt into the optically-

stable enantiomorphous forms, and lent still further evidence for the validity of the dissociation equilibrium theory.

The failure of Pope and Gibson to obtain evidence of optical activity in the case of the quaternary phosphonium salts, (VI, $R = -CH_2CH=CH_2$) and (VI, $R = -CH_2Ph$) has already been mentioned. Because of the success which attended their resolution of the arsonium salt (XIV), Helliman and Mann²⁹ attempted to prepare the phosphorus and antimony analogues by a similar procedure, employing phenyldichlorophosphine and phenyldiiodostibine respectively in the Michaelis condensation reaction with o-2-bromoethylbenzyl bromide. Various catalysts and solvents were used but only a very small yield of the impure phosphinoline (characterized as its methiodide) resulted and none of the stibinoline was obtained. The failure of these attempts is not surprising in view of the observation by Michaelis, Gleichmann and Reese³⁰ that in general, the formation of phosphines by the Michaelis reaction proceeds very much more slowly than the formation of arsines by

the same method. Furthermore, the work of Davies and Lewis³¹ has shown that the conversion of phosphines into quaternary phosphonium salts proceeds very much more rapidly than the similar formation of quaternary arsonium salts.

Davies and Mann¹⁰ have also pointed out that a quaternary phosphonium salt having four aryl groups attached to the phosphorus atom would be unlikely to undergo dissociation of the type



Combining this feature with the expected inherent stability of the tetrahydroisophosphinoline system (the stability of this system should be comparable with that of the analogous isocarsinoline), the resolution of 2:2-diaryl-1:2:3:4-tetrahydroisophosphinolinium salts should probably be readily accomplished.

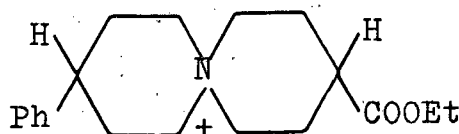
With this object in view, Holliman and Mann⁵ therefore sought a route to salts of this type. The spirocyclic salts, As-spiro-bis-isocarsindolinium bromide (XXI) and

(\pm)-As-spiro-bis-1:2:3:4-tetrahydroisoarsinolinium bromide (XXII), (see below), had been successfully prepared by a synthesis involving the pyrolytic elimination of methyl bromide from a quaternary salt carrying a methyl group. The application of this reaction to the preparation of the required isophosphinolinium salts was therefore investigated. However, Meisenheimer, Zimmerman and von Kummer³² have shown that the ethyl radicle is more readily removed from quaternary phosphonium chlorides than the methyl radicle. The reason for this is probably because (as is now known), the mechanism in the two cases differs. Ethyl bromide is removed from a quaternary phosphonium bromide as ethylene and hydrogen bromide, whereas from an arsonium bromide, it is removed as such. With this fact in mind, Holliman and Mann prepared o-(2-bromoethyl)benzylethyl-phenyl-p-tolylphosphonium bromide (XV, R = Et), but pyrolysis failed to effect removal of the ethyl group, nor could methyl bromide be removed from the corresponding methyl compound,

2-p-Bromophenyl-2-phenyl-1:2:3:4-tetrahydro-
isophospholinium bromide (XVI, Ar = Ph;
Ar' = $p\text{-C}_6\text{H}_4\text{Br}$) was thus prepared but crystal-
lisation of various of its optically active
salts could not be effected. It was thought
that the introduction of an hydroxyl group
into one of the aryl groups might facilitate
crystallisation and the corresponding p-hydroxy-
phenyl compound was accordingly prepared by
the above general synthesis. The (+)-bromo-
camphorsulphonate now readily crystallised,
but recrystallisation from various solvents
gave no evidence that resolution was proceeding.
Ultimately, the (+)-bromide, $[\alpha]_D = +32.9^\circ$ in
aqueous ethanol, was obtained via the (+)-
camphorsulphonate, but attempts at separation
of the optically-pure (-)-bromide failed, nor
could the resolution be repeated due to the
formation of a partial racemate. This represented
the first successful resolution of a quaternary
phosphonium salt into one of its optically-
active forms.

Mills and Warren⁷, in attempting to

obtain chemical evidence for the tetrahedral configuration of the nitrogen atom when 4-covalent, prepared the compound, 4-phenyl-4'-carbethoxy-bis-piperidinium-1:1'-spiran bromide (XVII) and showed that, on the basis of a



(XVII)

pyramidal configuration for 4-covalent nitrogen, this compound would have a plane of symmetry, whereas, on the basis of a tetrahedral disposition of groups about the nitrogen atom, molecular dissymmetry results and evidence of optical activity should be obtained. Their successful resolution of the compound into the (+)- and (-)-bromides having $[\alpha]_{5461} +50.5^\circ$ and -50.8° respectively, provided direct chemical evidence for the tetrahedral configuration of the quaternary ammonium ion.

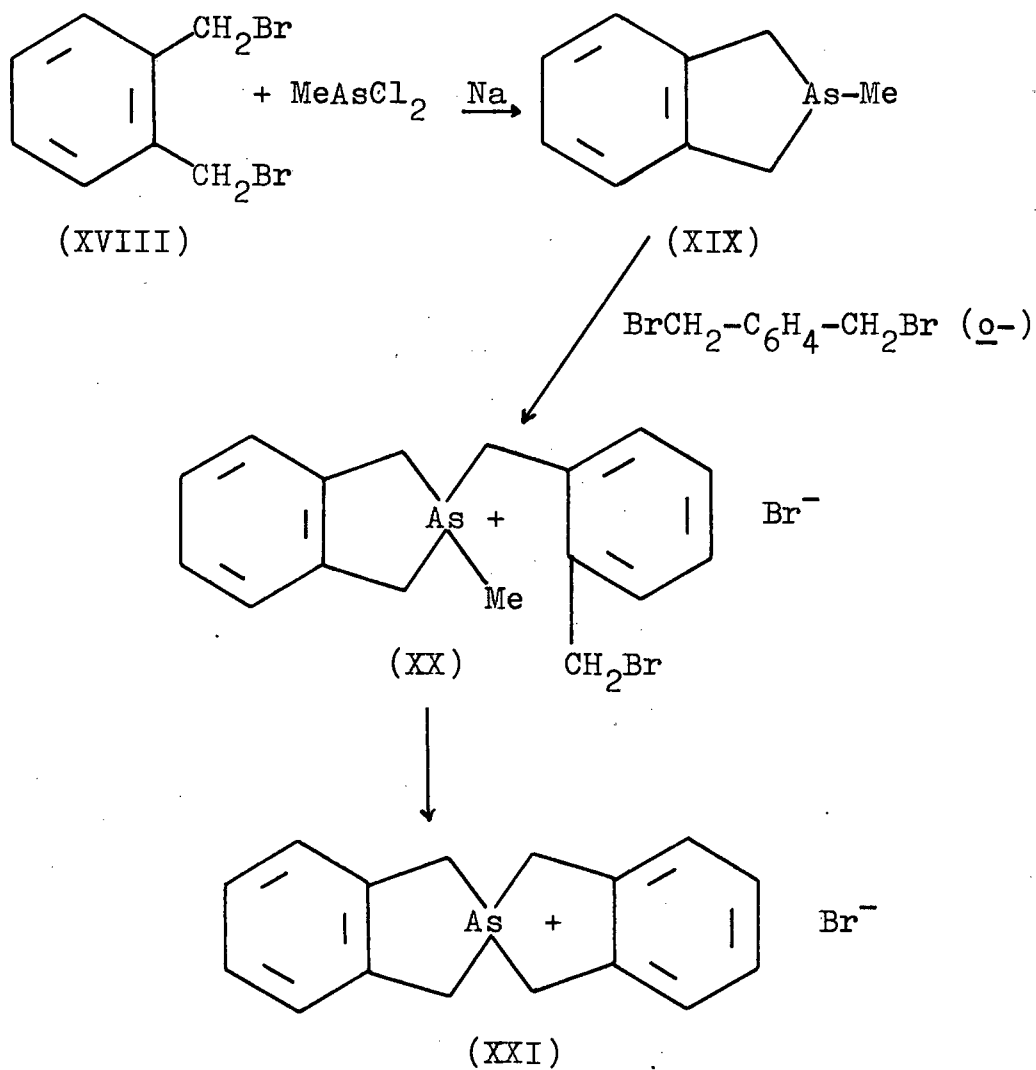
Prior to Holliman and Mann's successful resolution of the quaternary arsonium bromide (XIV) in 1943, no successful resolution of a

similar quaternary arsonium salt of type $\text{abcdAs}^+ \text{X}^-$ had been accomplished so that chemical evidence for the tetrahedral configuration of 4-covalent arsenic had not been forthcoming. As has already been shown, the difficulties experienced in the resolution of such quaternary arsonium salts are readily explained by the operation of a dissociation equilibrium.

The successful resolution of the arsonium salt just mentioned, lends support to, but does not prove the fact that 4-covalent arsenic possesses the tetrahedral configuration. It shows in fact that the groups attached to arsenic are not co-planar with the arsenic atom. Unambiguous evidence on this point was finally obtained by Mann, Purdie and Wells³³ who have demonstrated that triethylarsine combines with cuprous iodide to form the complex, tetrakis(monoiidotriethylarsine copper), $[\text{Et}_3\text{As} \rightarrow \text{CuI}]_4$, and the complete structural determination of this compound has shown that the arsenic atom lies at the centre of a tetra-

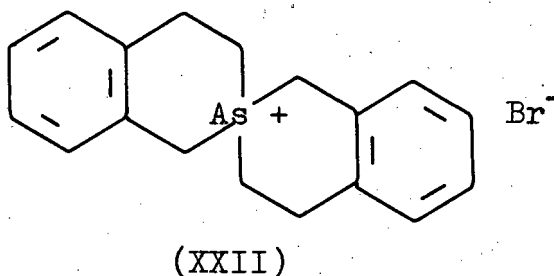
hedron with one cuprous and three carbon atoms at its apices. Corresponding phosphorus compounds are isomorphous with the arsenic analogues and it is therefore clear that the 4-covalent phosphorus atom also has the tetrahedral configuration. X-Ray elucidation of the structure of the bridge compound, dibromobis(trimethylarsine)-p-dibromodipalladium, $[(\text{Me}_3\text{As})\text{BrPdBr}_2\text{PdBr}(\text{Me}_3\text{As})]$ by Mann and Wells³⁴ has further provided conclusive evidence that the tetrahedral structure for arsenic is correct.

The preparation by Lyon and Mann³⁵ of the spirocyclic arsonium salt, As-spiro-bis-isoarsindolinium bromide (XXI) was accomplished by condensation of p-xylylene dibromide (XVIII) with methylchloroarsine in the presence of sodium to yield 2-methylisoarsindoline (XIX). Condensation with a further molecule of the dibromide gave the quaternary salt (XX) which underwent loss of methyl bromide on pyrolysis to form the spiro salt by cyclisation:



Holliman and Mann⁹ suggested that the general features of this synthesis might be applied to other heterocyclic arsonium salts possessing a suitable degree of stability. Previous work had shown the 1:2:3:4-tetrahydro-

isoarsinoline nucleus to possess a high degree of stability and condensation of 2-methyltetrahydroisoarsinoline with o-2-bromoethylbenzyl bromide yielded the quaternary salt corresponding with (XX), which, on pyrolysis, lost methyl bromide to give the spiro salt, (\pm)-As-spiro-bis-1:2:3:4-tetrahydroisoarsinolinium bromide (XXII).



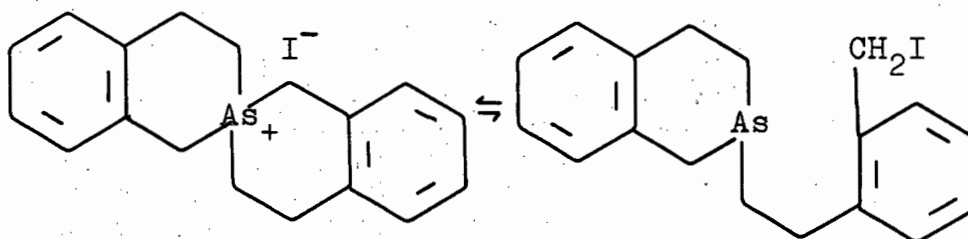
The physical and chemical evidence cited above for the tetrahedral configuration of 4-covalent arsenic implies that the salt (XXII) should exhibit molecular dissymmetry and thus be resolvable into optically-active isomerides. On the other hand, assumption of a pyramidal configuration for the arsenic atom in the cation implies that it should exhibit geometric isomerism and thus be separable into the cis- and trans-forms. Of these forms, the cis would

possess a plane of symmetry, so that only the trans-form would exhibit optical activity.

Holliman and Mann obtained no evidence for the existence of geometric isomers, but successfully resolved the salt into the (+)- and (-)-iodides, $[\text{M}]_D +342^\circ$ and -344° in chloroform solution, via the bromocamphorsulphonate. The tetrahydro-isocarsinoline system possesses high stability and in the spiro salt, the heterocyclic rings cannot be subjected to any strain, since the (+)- and (-)-iodides exhibit remarkable stability.

Jones³⁶ had to abandon the use of chloroform as solvent in the investigation of the optical rotation of the (+)-iodide of benzylethylmethylphenylammonium iodide because of the racemisation which this isomer underwent in this solvent. Jones and Hill^{37, 38} have further shown that (+)-allyl-*p*-bromophenylmethyl-*n*-propylammonium iodide undergoes autoracemisation in chloroform solution and that the velocity of racemisation in this solvent varies with different quaternary ammonium iodides. As has been mentioned, chloroform generally

promotes dissociation of most quaternary salts of this type, so that the high degree of optical stability shown by the spirocyclic salt obtained by Holliman and Mann was clearly demonstrated by the fact that the chloroform solutions of the (+)- and (-)-iodides underwent no change in molecular rotation whatsoever over four weeks and remained unaffected on crystallisation from hot ethanol. No dissociation of the type:

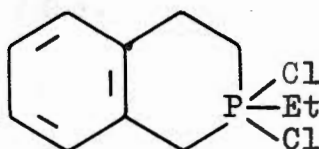


therefore occurs.

The successful preparation of a spirocyclic phosphonium salt by Hart and Mann⁸ was attended by difficulties not experienced with the spiro ammonium and arsonium salts which have thus far been mentioned.

The failure to remove, by heating, methyl or ethyl bromide from certain quaternary phosphonium salts has been mentioned. It is not surprising then, that attempted preparation of the phosphorus analogue of the spirocyclic salt (XIII) by a similar method, failed. Condensation of 2-ethyl-1:2:3:4-tetrahydroiso-phosphinoline with g-2-bromoethylbenzyl bromide occurred readily, affording the salt (XIII), but, the action of heat on this compound failed to effect removal of ethyl bromide. It is possible that the substituted benzyl group was more readily removed. That this group is more readily removed from quaternary phosphonium salts than the ethyl group has been established 18, 19, 23. Furthermore, attempted thermal decomposition of the salt (XIV) again failed although, in the case of this compound, the benzyl group has been ^{re-}placed by a 2-phenylethyl group.

Hart and Mann realised that if the phosphorus analogue of (XXVII) could be obtained, the required spiro salt might be prepared via the Grignard reaction. 2-Ethyl-tetrahydroisosphosphinoline was readily converted into the dichloroethyl compound (XXVIII), but, heating of this compound failed to yield the desired chlorophosphine.



(XXVIII)

Because of these synthetic difficulties, the attempted preparation of the phosphorus analogue of (XIII) was abandoned in favour of an attempt to prepare the salt (XXIII) which was in fact successful at last. This salt differs from that whose preparation was initially attempted in that the phosphorus atom is now linked to two phenyl groups directly. Thus a synthetic route involving the thermal decomposition of a quaternary salt carrying only one non-cyclic alkyl group attached to the phosphorus atom

could be evolved.

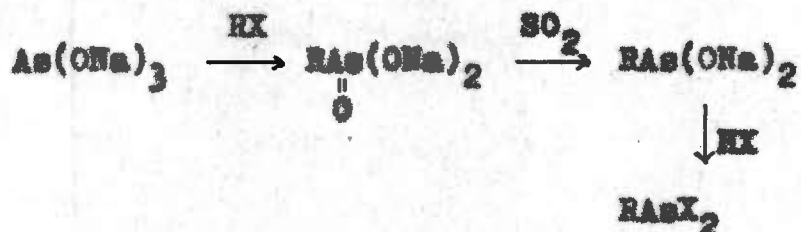
o-Bromo-3-phenylpropyl methyl ether (XXIX) was converted into the lithio compound with n-butyllithium which underwent condensation with ethyldichlorophosphine to yield ethyldi-(o-3-methoxypropylphenyl)phosphine (XXX). This was converted by the action of hydrobromic acid into the corresponding dibromo compound which cyclised to (XXXI, R = Br). In order to protect the 3-bromopropylphenyl group from cleavage on heating, the methyl ether (XXXI, R = OMe) was prepared. Pyrolysis of this compound resulted in the successful removal of ethylene and hydrogen bromide to form the phosphine (XXXII, R = Br) which underwent cyclisation to the spirocyclic bromide, (+)-P-spiro-bis-1:2:3:4-tetrahydrophosphinolinium bromide (XXXIII).

After the attempted crystallisation of several of its optically-active salts, resolution via the (-)-menthoxyacetate was eventually effected. The (+)- and (-)-bromides were converted into the corresponding iodides

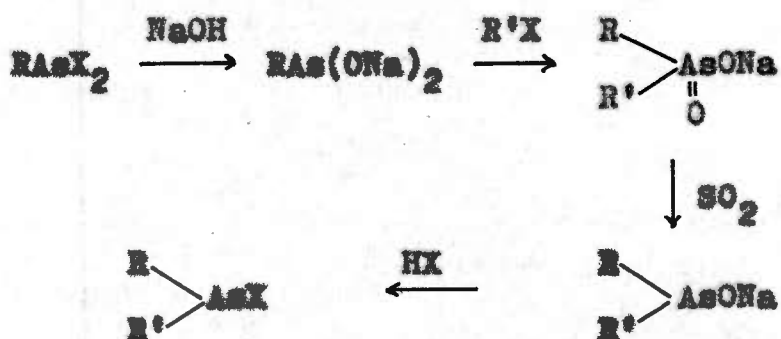
which had $[\alpha]_D +66^\circ$, -65° respectively in chloroform solution. The optical stability exhibited by the iodides is comparable with that found in the case of the spirocyclic arsonium salt. This is the first example of both the synthesis and resolution of a spirocyclic phosphonium salt.

It will have been noticed that many of the compounds whose syntheses have been described in this section have required for their preparation certain lower alkylhalogeno phosphines and arsines. In fact compounds of this type are invaluable for the preparation of more complex quaternary phosphonium and arsonium salts. It is therefore necessary to discuss here the methods available for their preparation.

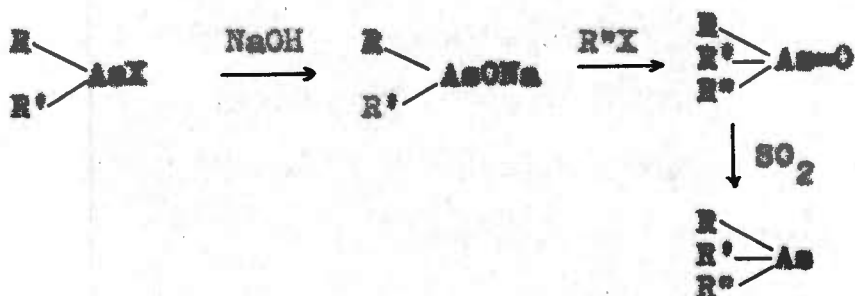
The reaction developed by Meyer and now commonly known as the Meyer reaction has been widely employed for the synthesis of dihalogenomonoalkyl, monohalogenodialkyl and trialkyl arsines. The general stepwise procedure, starting from sodium arsenite, Na_3AsO_3 , is outlined below:



The monoalkyldihalogenearsine thus obtained can now be resubmitted to the Meyer reaction to obtain a dialkylmonohalogenearsine:

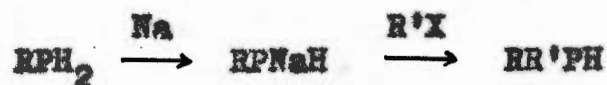


If desired, the trialkylarsine may now be obtained by a further repetition of the process:



Thus the Meyer reaction can be readily adapted to the synthesis of almost any possible alkyl-

or halogenoalkylarsine. This synthetic route has no parallel in the phosphorus series. Trialkyl phosphines can often be obtained however, by reaction of a primary phosphine with one equivalent of sodium in liquid ammonia, followed by treatment of the sodio derivative thus obtained with the appropriate alkyl halide:

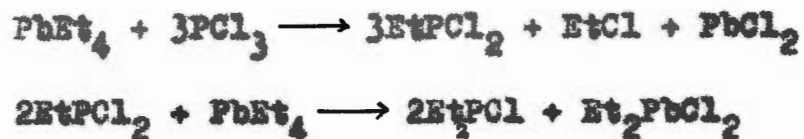


The secondary phosphine, on similar treatment, yields a trialkylphosphine:



A new route to the synthesis of ethyldichlorophosphine and diethylmonochlorophosphine has recently been developed by Jensen, Kharasch and Weinhouse³⁹. This method involves treatment of phosphorus trichloride with lead tetraethyl to give ethyldichlorophosphine in

high yield. Subsequent treatment of this compound with lead tetraethyl in excess then furnishes diethylmonochlorophosphine:



When arsenic trichloride or antimony trichloride is employed in place of the phosphorus halide, high yields of ethyldichloroarsine and ethyldichlorostibine are obtained for the first stage of the reaction. The application of the second stage of the reaction to these compounds does not appear to have been investigated.

Finally, another recent approach to the synthesis of alkylphosphines has recently been made available by the reduction of benzylphosphonium halides with lithium aluminium hydride by Bailey and Buckler⁴⁰.

Thus, certain of these lower alkyl phosphines and stibines, which were formerly available only by difficult procedures (usually involving thermal decomposition of the tertiary

phosphine or stibine dihalides and often giving rise to a mixture of the monohalogenodialkyl and dihalogenomonoalkyl compounds) can now be readily synthesised. The greatest advantage of these recently developed methods of synthesis is that handling of these very readily oxidised and sometimes spontaneously inflammable compounds is reduced to a minimum.

Alkyl- and halogenoalkylarsines, however, are in the highly favoured position of being less readily oxidised than their phosphorus and antimony analogues and can usually be easily obtained by the unique Meyer reaction. These factors (combined with the important Bart reaction for the synthesis of arylarsonic acids and certain arylstibonic acids) have played a large part in determining the rapid growth of the organic chemistry of arsenic compared with that of the other elements (other than nitrogen) in Group Vb of the Periodic System.

Some remarks concerning the correlation of optical rotatory power and molecular structure are now necessary since it was primarily for

the purpose of obtaining further data for such a correlation to be drawn that the work described in this thesis was undertaken.

A considerable quantity of work has been carried out by several chemists to determine in what way the degree of optical activity varies within an homologous series of compounds. For example, Pickard and Kenyon⁴¹ have, as part of a most interesting series of papers, prepared and resolved a series of methylalkylcarbinols where the chain length of the straight chain alkyl group has been progressively increased one methylene group at a time from ethyl to n-undecyl. The molecular rotations of successive members of this series of alcohols were found in general to increase with the chain length of the alkyl group but the increment apparently becomes smaller as the series progresses. A similar relationship was found to obtain for the ethylalkylcarbinols⁴² (see Tables). Pickard and Kenyon⁴³ have also resolved a series of esters. Here, as the length of the alkyl group or the acyl group increases, the

$[\text{M}]_{\text{D}}^{20}$ of MeCHOHR (n-) compounds

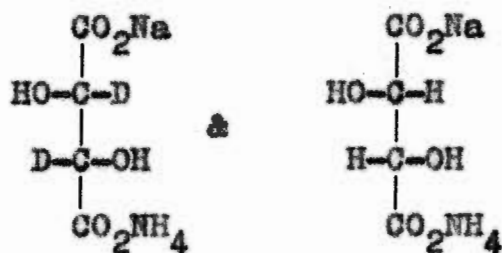
Methylethylcarbinol	10.30
Methyl- <u>n</u> -propylcarbinol	12.10
Methyl- <u>n</u> -butylcarbinol	11.80
Methyl- <u>n</u> -amylcarbinol	12.00
Methyl- <u>n</u> -hexylcarbinol	12.70
Methyl- <u>n</u> -heptylcarbinol	12.90
Methyl- <u>n</u> -octylcarbinol	13.70
Methyl- <u>n</u> -nonylcarbinol	14.00
Methyl- <u>n</u> -decylcarbinol	14.50
Methyl- <u>n</u> -undecylcarbinol	14.40

$[\text{M}]_{\text{D}}^{20}$ of EtCHOHR (n-) compounds

Ethyl- <u>n</u> -propylcarbinol	2.01
Ethyl- <u>n</u> -butylcarbinol	9.43
Ethyl- <u>n</u> -amylcarbinol	10.69
Ethyl- <u>n</u> -hexylcarbinol	10.63
Ethyl- <u>n</u> -heptylcarbinol	10.58
Ethyl- <u>n</u> -octylcarbinol	10.74
Ethyl- <u>n</u> -nonylcarbinol	11.09
Ethyl- <u>n</u> -decylcarbinol	12.44
Ethyl- <u>n</u> -undecylcarbinol	12.56

molecular rotation of successive members again approaches a limiting value.

The replacement of hydrogen by deuterium in an optically active compound has been found to cause a slight change in optical rotatory power. In the case of the compounds



it has been shown by Erlenmeyer and Bitterlin⁴⁴ that the specific and molecular rotations of the former compound are lower than those of the latter, $[\alpha]_D^{20} +60.8^\circ$ and 62.7° respectively.

Whilst it is extremely valuable to have such data made available, it is clear from such results that no deductions concerning the molecular rotation of a molecule can be drawn from a knowledge of its structure.

Very little is known of the relationship between the molecular rotations of

successive members of an eutropic series of optically active compounds (i.e. a series of optically active compounds successive members of which differ only in that they contain atoms of consecutive elements of any one sub-group of the Periodic Classification, these atoms being the centre of asymmetry).

The essential difference between such a relationship and that given by the data of Pickard and Kenyon and Erlenmeyer and Bitterlin is that in an eutropic series it is the actual centre of the asymmetry that is altered, whereas in an homologous series, it is the nature of the groups attached to the same asymmetric centre (in the above cases, the carbon atom) which is changed between successive members.

Naturally, it is in general both more difficult and a more lengthy procedure to synthesise and resolve an eutropic series of optically active compounds than an homologous series. Furthermore the number of members of an eutropic series that can theoretically be

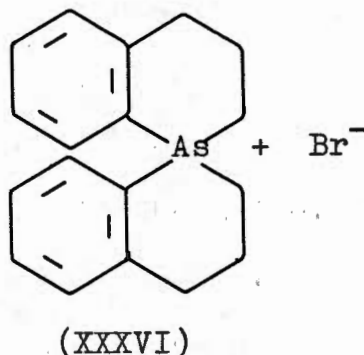
prepared is restricted. It is restricted to five such members in the case of the Group Vb elements and it is likely that the antimony and bismuth compounds would provide great synthetic difficulties. Probably for these reasons, only two such series of optically-active compounds have previously been prepared and resolved (see below), one such series containing the Group VIa elements, sulphur, selenium and tellurium and the other containing two of the Group Vb elements, arsenic and antimony. Data for a third series of two of the Group Vb elements has now been made available by the work described in this thesis.

Holliman and Mann⁴⁵ prepared the 2-p-chlorophenacylthio-, seleno, and telluro-isochromanium picrates (XXIV, $X = C_6H_2O_7N_3$, $Q = S, Se \text{ and } Te$), the (+)- and (-)-picrates being obtained via the (+)-bromocamphorsulphonates. They suggested that if the optical stability of these compounds was found to be low, this might be due to the operation of a dissociation equilibrium of the type:

The results of Campbell and Poller also showed that the optical stability of the compounds diminishes on going from arsenic to antimony, as it does with increasing molecular weight in the thio-, seleno- and telluroisochromanium salts. One difference between these two series of compounds ought to be mentioned as it may be of some importance. In the series of isochromanium salts, the hetero atoms were in their higher covalent states, whilst in the Group Vb series, these atoms were in their lower covalent states. As it happens, in both cases the covalency is three.

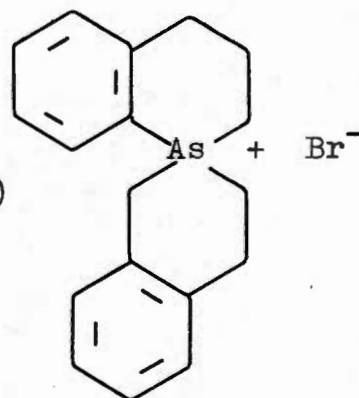
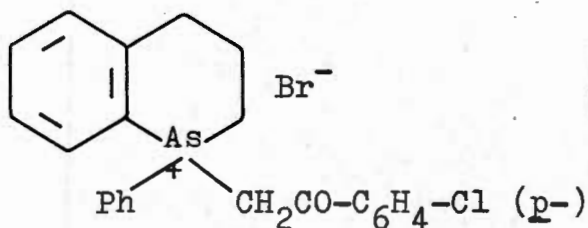
The synthesis and resolution of the spirocyclic arsonium salt (XXXVI) has now been achieved although its preparation was attended by greater difficulties than that of any other spirocyclic salts mentioned. For this reason, the scope of this work unfortunately became rather limited. Nevertheless, the molecular rotation of this compound has been found to be greater than that of the analogous

phosphonium salt.



One further point may be mentioned here. No comparison has previously been drawn between the molecular rotations of a series of isomeric compounds which possess, as the hetero atom, an atom of the same element, but differ only in the position of that atom in the heterocyclic system. The data necessary for drawing such a comparison is at present lacking. In an attempt to bridge this gap, the synthesis of the arsonium salt (XXIVII) and of the spirocyclic salt (XXVIII) have been attempted by the author. The molecular rotation of the former compound could then be compared with that of the salt (XIV, page 12) whilst that of the latter compound could be compared with the rotations of the spiro salts (XXVI) and (XXII, page 22). Unfortunately, whilst

the salt (XXXVII) was readily synthesised, attempted resolution proved unsuccessful; and the synthesis of the spiro salt (XXXVIII) could not be accomplished.



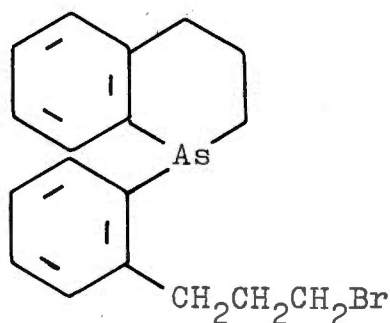
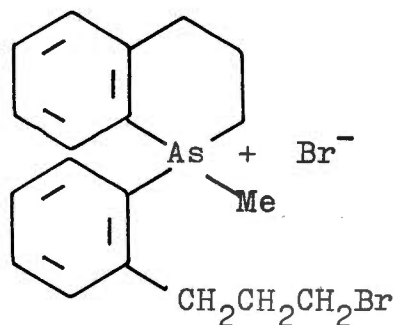
A discussion of the results obtained from these attempts is to be found in the following section.

DISCUSSION

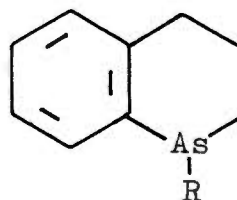
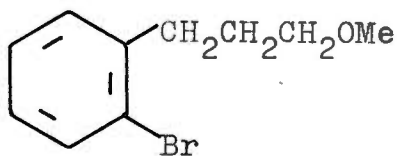
DISCUSSION

Holliman and Mann⁹ prepared the spirocyclic salt, (I)-As-spiro-bis-1:2:3:4-tetrahydro-isoarsinolinium bromide (XXII, page 22) with great ease, by quaternisation of 2-methyl-1:2:3:4-tetrahydroisoarsinoline with o-2-bromoethylbenzyl bromide followed by thermal decomposition of the product. A similar procedure for obtaining the spirocyclic salt (XXXVI, page 43) required by the author, yields, as one possibility, the thermal decomposition of the quaternary salt (I), but this compound could be obtained only by quaternisation of the tertiary arsine (II) with methyl bromide and this compound (II) would in all probability undergo intramolecular quaternisation

thus spontaneously cyclising to the desired spiro salt.



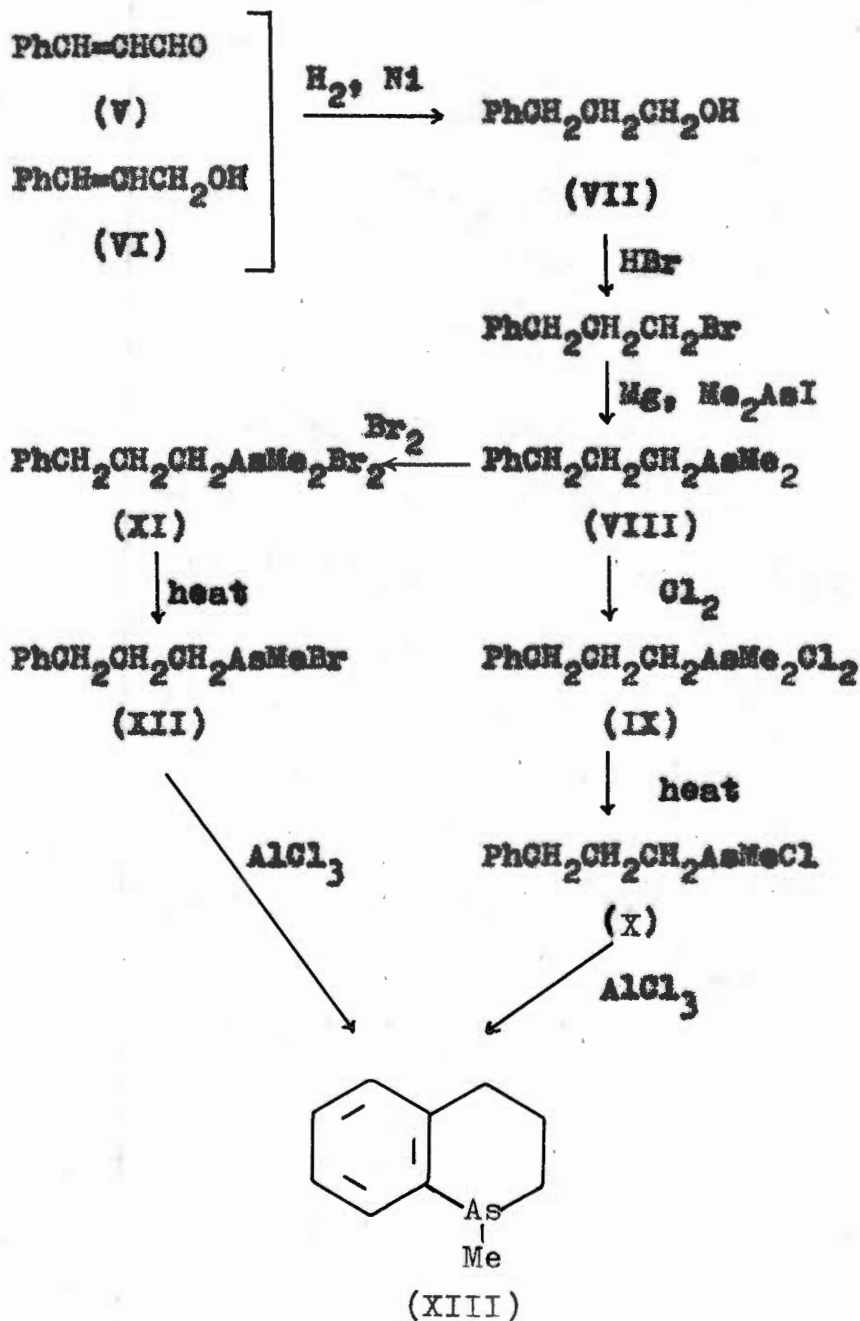
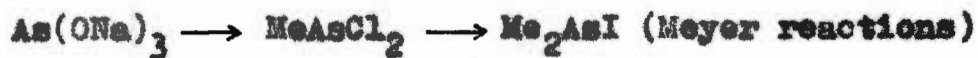
The thermal decomposition method is thus not favourable to the synthesis of a spiro salt of the type required. The obvious alternative is to attempt the synthesis of the arsinoline (II). A possible route to this compound appeared to be reaction of the Grignard or lithio derivative of *o*-bromo-3-phenylpropyl methyl ether (III) with 1-chloro-1:2:3:4-tetrahydroarsinoline (IV, R = Cl). The former com-



pound has been prepared by Beeby and Mann⁴⁷, and the latter by Roberts, Turner and Bury⁴⁸. The preparation of the chloroarsinoline involves a lengthy synthesis of ten stages of which the first eight, leading to the corresponding 1-methyl compound (IV, R = Me) have been described by Burrows and Turner¹⁴. The reactions involved in this synthesis with the modifications adopted by the author, are set out on the following page.

Burrows and Turner had prepared dimethyliodoarsine by a double Meyer reaction from sodium arsenite, using methyldiiodoarsine as intermediate, but it has been found to be economically more practicable to use methyldichloroarsine as intermediate in this synthesis. This compound, purified by distillation, was converted into the disodium salt of methylarsonous acid, MeAs(ONa)_2 , with sodium hydroxide and yielded dimethyliodoarsine on being resubmitted to the Meyer reaction.

Although most of the dimethyliodoarsine used in this work was prepared by the above procedure, dimethylarsinic acid (cacodylic acid), $\text{Me}_2\text{As:O(OH)}_2$, is now commercially available



(but rather expensive) and is readily converted by treatment with hydriodic acid, followed by sulphur dioxide reduction, into dimethyldiarsine in one step in 85% yield. The optimum overall yield via the former method is 47%. The method employing cacodylic acid has the further advantage that the highly poisonous and obnoxious methyl-dichloroarsine is avoided.

A method for the reduction of cinnamaldehyde (V) to hydrocinnamyl alcohol (3-phenylpropan-1-ol) (VII) with Raney Nickel catalyst has been described by Covert and Adams⁴⁹ but the time required for the completion of the reduction is not mentioned. The author found that when a starting pressure of 100 atmospheres of hydrogen is employed, the pressure being raised once during the course of the reaction, 24 hours are required to give an 83% yield of the alcohol, whilst, at a starting pressure of 80 atmospheres, the pressure again being raised during the course of the reaction, 42 hours were required to give an equivalent yield. The hydrogen was absorbed rapidly at first, then very slowly, due, no doubt, to the initial ready

reduction of the double bond followed by the slow reduction of the carbonyl group. This apparent ready reduction of the double bond led to an attempt to reduce the now commercially-available cinnamyl alcohol (VI). No record of this reduction could be traced in the literature, but Holliman (private communication) has found that, with Adams' catalyst, the alcohol was obtained in good yield. In this work, a yield of 94% was obtained after five hours at a starting pressure of 2.3 atmospheres. Increasing the starting pressure to 50 atmospheres with the same catalyst did not substantially reduce the time required, whereas the yield was slightly lowered. With Raney nickel as catalyst, the remarkably short time of ten minutes sufficed for the reduction when a starting pressure of 57 atmospheres was employed, giving the reduced alcohol in 96% yield. No significant temperature rise (which would have caused a momentary pressure increase) was observed during the course of the reduction. Hydrocinnamyl alcohol, which has recently become commercially available, has previously been prepared by the

reaction of benzyl magnesium bromide with ethylene oxide or by the Bouveault-Blanc reduction of ethyl 2-phenylpropionate, both of which are less convenient procedures and give lower yields of the product.

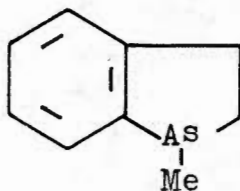
Hydrocinnamyl alcohol was readily converted into 3-phenylpropyl bromide by Hydrobromic acid in the presence of sulphuric acid. The Grignard derivative of this bromide, on treatment with dimethyliodoarsine, afforded, on hydrolysis, 3-phenylpropyldimethylarsine (VIII) in 88% yield. Treatment of this product with one molar proportion of chlorine in carbon tetrachloride gave the dichloride (IX) as a viscous oil which underwent thermal decomposition to yield two fractions: a low-boiling liquid, and the product (X) in 46% yield. In case the first fraction should have been the unreacted dimethylarsine (VIII), it was again treated with chlorine in carbon tetrachloride. A substantial quantity was taken up before the yellow colour of free chlorine developed in the solution, but thermal decomposition of the product gave only a low-boiling liquid. The original first fraction

was thus clearly not the unchanged arsine (VIII). The dimethylarsine (VIII), when similarly treated with bromine in carbon tetrachloride, yielded the arsine dibromide (XI) which lost methyl bromide smoothly on heating to yield the methylbromoarsine (XII) in 56% yield again accompanied by a low-boiling first fraction. This first fraction, on redistillation gave five fractions, the last of which was a further small quantity of the methylbromoarsine (XII). The major fraction gave no product on reaction with methyl iodide, and the by-product thus remained unidentified. The preparation of the bromoarsine (XII) is more satisfactory than that of the chloroarsine (X) since the bromine solution is more readily prepared than that of chlorine and the yield of (XII) is greater than that of (X).

Both the methylchloro- and methylbromoarsines, in benzene solution, readily underwent cyclisation in the presence of aluminium chloride to yield 1-methyl-1:2:3:4-tetrahydroarsinoline (XIII).

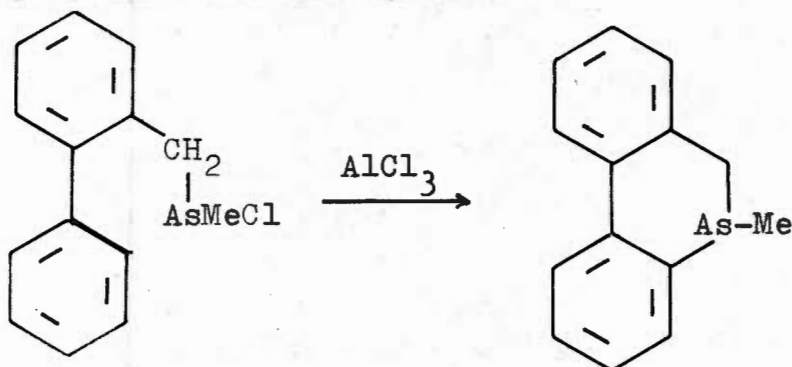
Due to the lengthy series of reactions involved in preparing this arsinoline, other, simpler methods were sought for its synthesis.

Burrows and Turner's above procedure is based on the Friedel-Crafts cyclisation of a chloroarsine. This was the earliest method employed for the synthesis of heterocyclic arsines and was also used for the preparation of 1-methyl-arsindoline (XIV), the above arsinoline's lower homologue, by Turner and Bury⁵⁰.

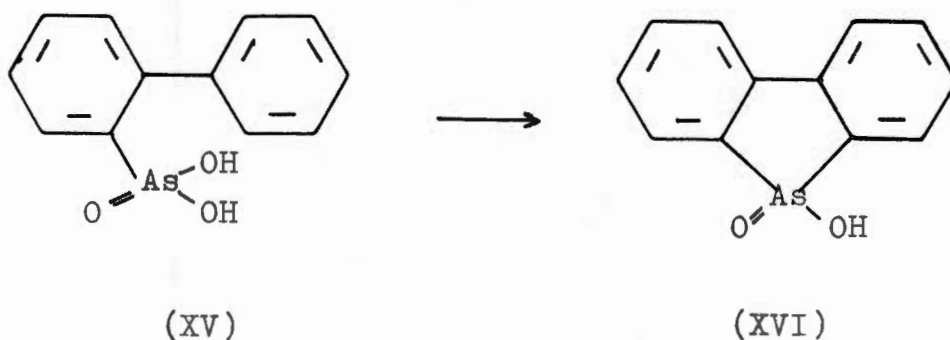


(XIV)

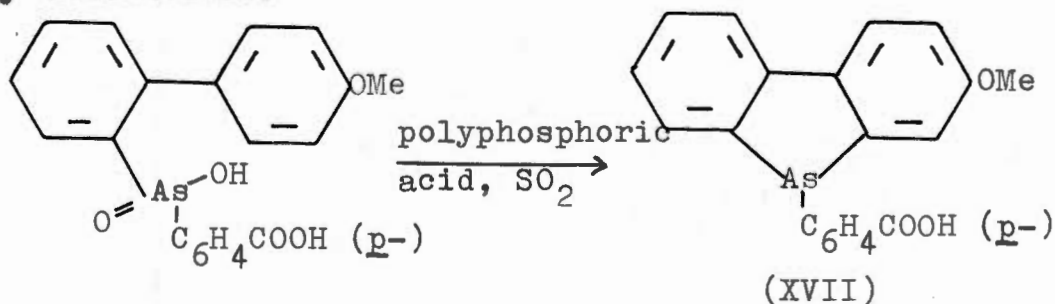
More recently, the method has been used by Cookson and Mann⁵¹ for obtaining the 9:10-dihydroarsanthridine system:



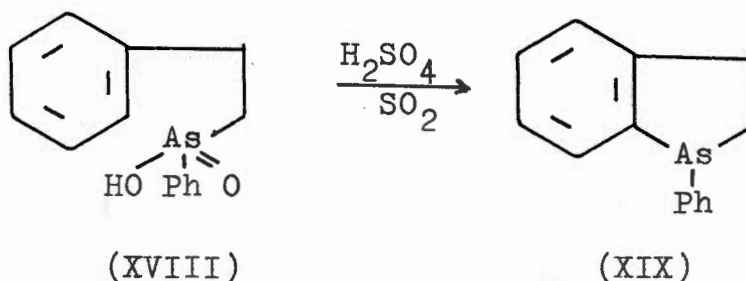
Another method which has been successfully applied to the synthesis of cyclic arsines and stibines is cyclisation by dehydration of arsonic and stibonic acids. Thus, diphenyl-2-arsonic acid (XV) readily undergoes cyclisation with hot sulphuric acid to yield arsafluorinic acid (XVI)⁵².



A variation of this method is the similar cyclisation of arsinic and stibinic acids. Thus Campbell and Poller⁴⁶ have prepared 9-p-carboxyphenyl-2-methoxy-9-arsafluorene (XVII), whose stereochemical interest has been mentioned in the Introduction, by this method:



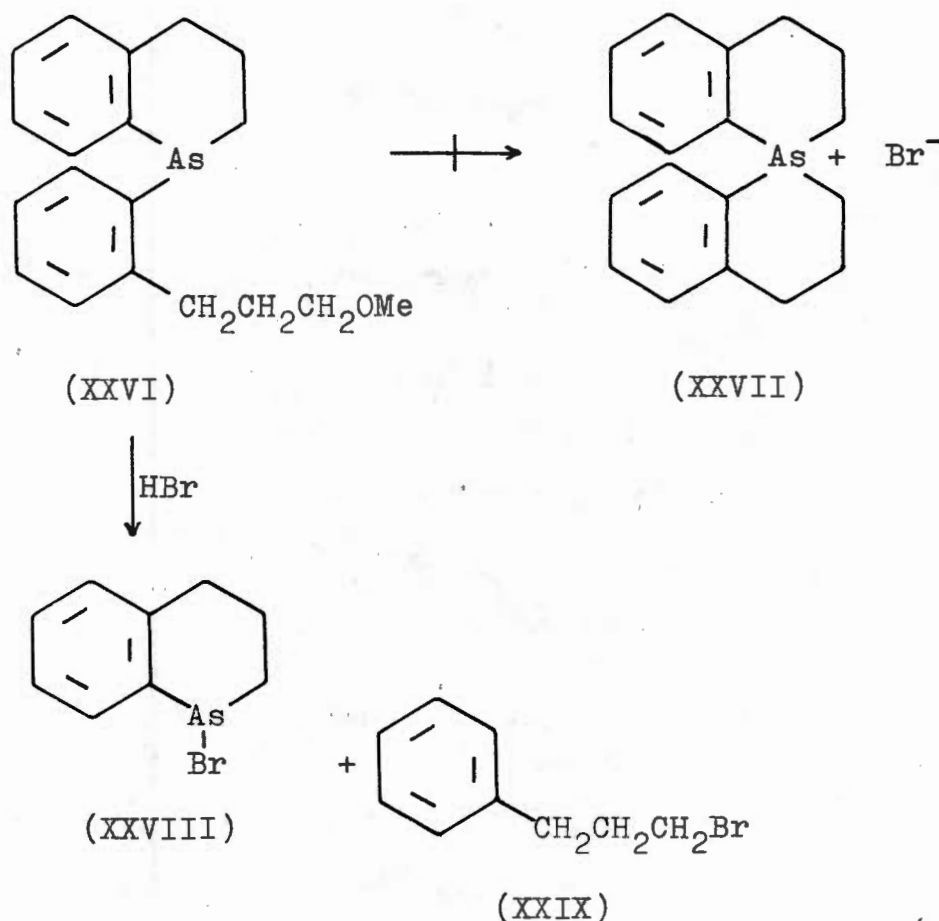
Very recently, Jones and Mann⁵³ have found that phenyl-2-phenylethylarsinic acid (XVIII) (prepared by the Meyer reaction of 2-phenylethyl bromide with the disodium salt of phenylarsonous acid) readily underwent cyclisation with hot sulphuric acid. Reduction of the arsine oxide thus obtained gave 1-phenylarsindoline (XIX) in 76% yield. The author has



applied this method successfully, but in low yield, to the synthesis of the homologous 1-phenyl-1:2:3:4-tetrahydroarsindoline. This is discussed more fully later. A similar method, employing the disodium salt of methylarsonous acid (X), yielded what was probably methyl-3-phenylpropylarsinic acid (XXI) but which could not be obtained crystalline. Treatment of the viscous product with sulphuric acid,

Before attempting such a synthesis, it was obviously advisable to determine whether the methobromide (XXIV) would undergo thermal decomposition to yield the required tetrahydroarsinoline (XXV). A sample of this methobromide was therefore prepared from an authentic sample of the arsinoine (XXV) prepared by Burrows and Turner's method, and underwent decomposition smoothly when heated at its melting point to give the methylarsinoine in 95% yield. This was characterized by reconversion to the methobromide (XXIV). *o*-Bromo-3-phenylpropyl methyl ether (XXII) was converted into the Grignard derivative by the entrainment method with activated magnesium and reacted smoothly with dimethyldiarsine to produce the arsine (XXIII) in good yield, characterized as its methopicate, but when the arsine was treated with hydrobromic acid no ether-insoluble product was obtained. In view of the author's failure (mentioned in detail later) to convert the arsinoine (XXVI) into the spiro salt (XXVII), also by treatment with hydrobromic acid, this failure is not

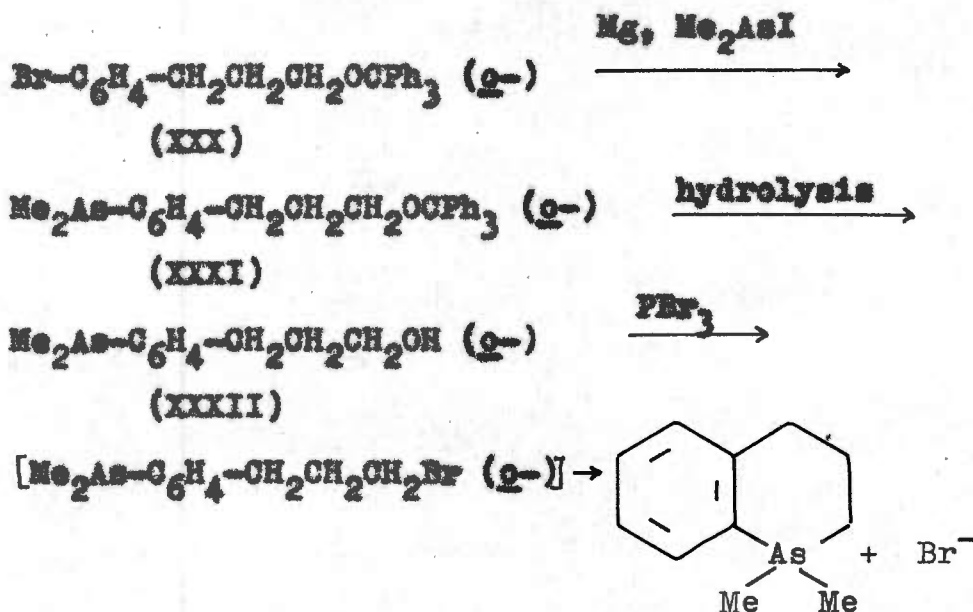
surprising. It was shown in the latter case that 3-phenylpropyl bromide (XXIX) was one of the products of the reaction, the other almost certainly being 1-bromo-1:2:3:4-tetrahydroarsinoline (XXVIII). That a similar reaction had occurred in the case of the arsine (XXIII) is almost undoubtedly true.



As is discussed in detail later, phenyl groups directly attached to arsenic readily undergo replacement by a bromine atom on treatment with hydrobromic acid. It is not unreasonable to suppose that a substituted phenyl group would exhibit a similar tendency.

If the triphenylmethyl (trityl) ether (XXXI) could be prepared, it would probably be readily hydrolysed with acetic acid to the alcohol (XXXII) which, on treatment with phosphorus tribromide would in all probability yield the required methobromide. In this way the use of hydrobromic acid would be avoided. Such a scheme proved in a later synthesis to be highly successful and the use of the trityl group as an alternative to the methoxyl group is discussed in detail at that point.

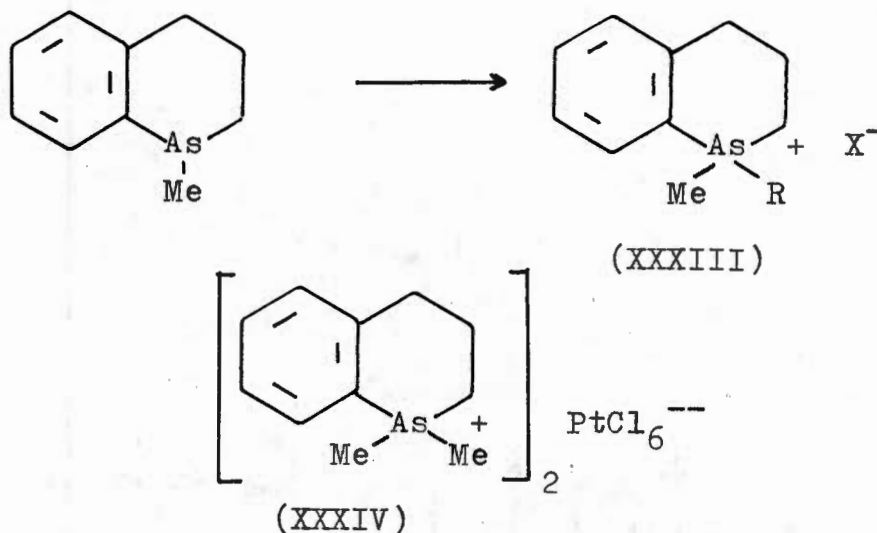
The trityl ether (XXX) was thus converted into the Grignard derivative and treated with dimethyliodarsine, a viscous gum being obtained after hydrolysis. No attempt was made to purify this product as previous ex-



perience had shown that attempted distillation of such compounds leads to partial decomposition. Furthermore, hydrolysis with acetic acid yielded another gum which failed to distil under high vacuum even with a bath temperature of 300° . Treatment of the residue with phosphorus tribromide gave an ether-insoluble and highly crystalline solid which was however free from halogen. Analysis indicated that it might possibly be a sample of dimethyltritylarsine oxide, $\text{Ph}_3\text{C-As(O)Me}_2$. This compound could possibly have resulted by cleavage at the arsenic-phenyl bond (at some stage during the above procedure) followed by reaction of the arsenic-containing fragment with

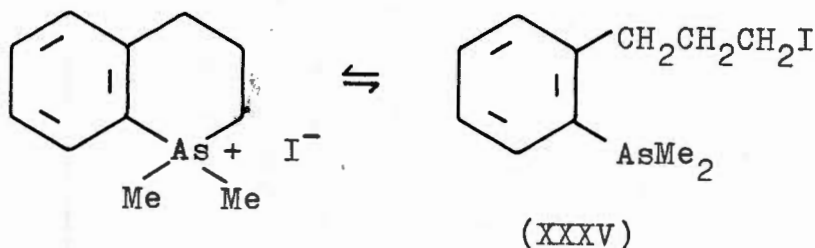
the triphenylcarbinol formed during the hydrolysis of the trityl ether group. In view of these results, further attempts to facilitate the preparation of 1-methyl-1:2:3:4-tetrahydroarsinoline were abandoned.

1-Methyl-1:2:3:4-tetrahydroarsinoline is a colourless, readily-oxidised liquid with a typical arsine odour. Burrows and Turner have prepared for the identification of the arsine, the methiodide (XXXIII, $R = \text{Me}$, $X = \text{I}$). They



have stated that when this methiodide was warmed with ethanol, the solution assumed a yellow colour and again became colourless on cooling. Also, they state that a rapid volumetric estimation of ionic iodine gave a figure 7% lower than that

required for the methiodide, and have used these observations in support of the possibility that in solution there exists a dissociation equilibrium between the cyclic methiodide and the open-chain arsine (XXXV):



If this is so, it may indicate that other quaternary derivatives containing the tetrahydroarsinoline ring system would possibly be chemically unstable, and any attempt to prepare an optically-active spirocyclic salt or any other optically-active quaternary salt containing this system might prove unsuccessful. For this reason, the methyltetrahydroarsinoline was converted into a variety of quaternary derivatives, all of which showed no evidence of chemical instability.

The arsinoline readily formed a methobromide (XXXIII, R = Me, X = Br) on being mixed with methyl bromide and allowed to stand in the

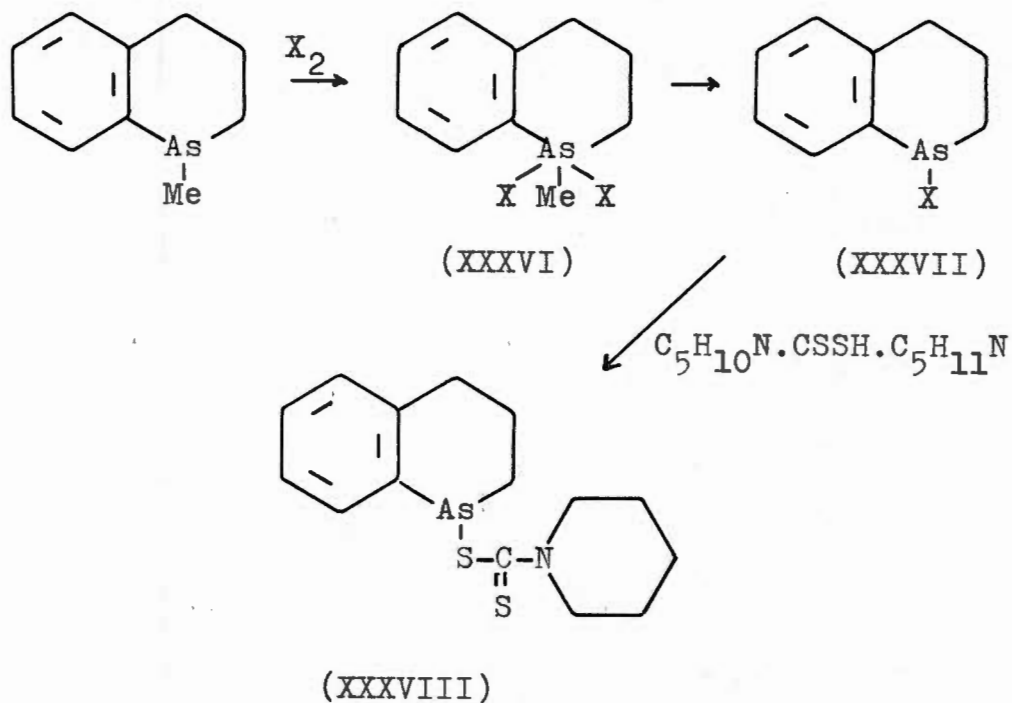
cold for some time. This methobromide, when heated, underwent decomposition only at its melting point, being (as has been mentioned) reconverted into the parent arsinoline in 95% yield. The methobromide, in ethanolic solution, was treated with an aqueous solution of potassium iodide, yielding the corresponding methiodide (XXXIII, $R = \text{Me}$, $X = \text{I}$). This compound, in turn, when treated with aqueous sodium picrate, yielded the corresponding methopicrate (XXXIII, $X = \text{C}_6\text{H}_2\text{O}_7\text{N}_3$, $R = \text{Me}$). The hydroxy-nitrate (XXXIII, $R = \text{OH}$, $X = \text{NO}_3$), formed by direct oxidation of the arsine with nitric acid, could not be obtained crystalline, but, after neutralisation, gave what must have been the dihydroxide (XXXIII, $R = \text{OH}$, $X = \text{OH}$) since, when allowed to react with picric acid, the crystalline hydroxy-picrate (XXXIII, $R = \text{OH}$, $X = \text{C}_6\text{H}_2\text{O}_7\text{N}_3$) was readily obtained. The methobromide, moreover, gave, with an aqueous solution of chloroplatinic acid, the stable, crystalline salt, bis(1:1-dimethyl-1:2:3:4-tetrahydroarsinolinium)chloroplatinate (XXXIV).

Finally, the observation by Burrows and Turner that an ethanolic solution of the methiodide became yellow on warming and colourless on cooling, could not be substantiated by the author; whilst a rapid volumetric estimation of ionic bromine in the methobromide (using automatic titration apparatus to ensure speed of determination) gave a figure in excellent agreement with that theoretically required. On these grounds, it appears that Burrows and Turner's observation was more probably due to photochemical decomposition of the methiodide than to the existence of a dissociation equilibrium in solution, and for this reason, it was considered worthwhile to continue with attempts at the synthesis of the required spirocyclic salt.

For the preparation of this spiro salt, the above arsinoline had to be converted into the corresponding 1-halogeno compound (XXXVII, X = Cl, Br or I).

The 1-chloro compound (XXXVII, X = Cl) has previously been prepared by Roberts, Turner and Bury⁴⁸ by chlorination of the corresponding

methyltetrahydroarsinoline, followed by thermal decomposition of the dichloro-methyl compound (XXXVI, X = Cl) thus obtained. The final product

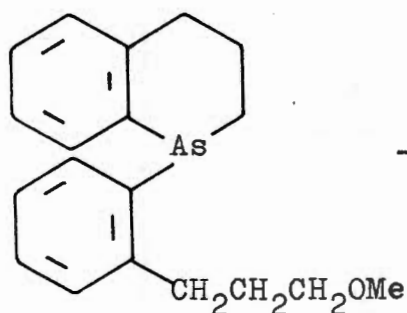
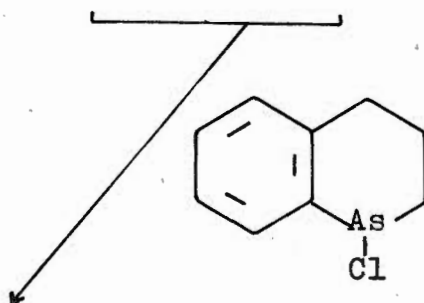
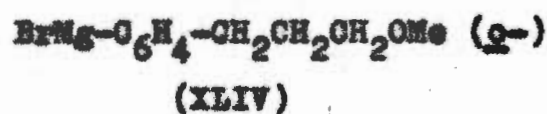
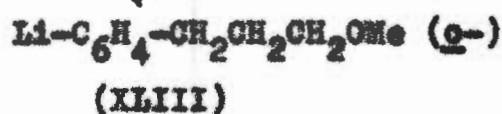
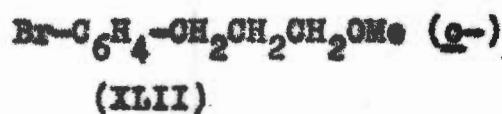
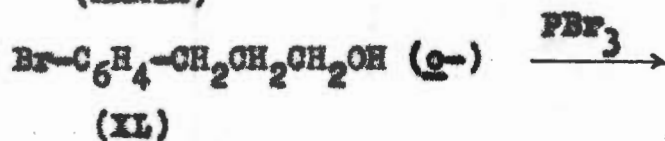
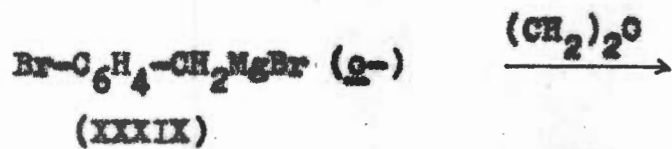


is obtained in excellent yield (87% over the two stages). From the point of view of convenience, bromination of the methyltetrahydroarsinoline would be preferable. Addition of one molar equivalent of bromine in carbon tetrachloride to the arsinoline was found to yield readily the insoluble dibromomethyl compound (XXXVI, X = Br) which, on

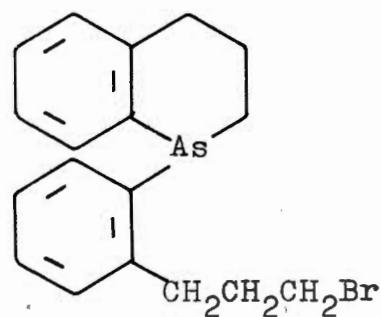
being heated under reduced pressure, very readily lost methyl bromide to furnish 1-bromo-1:2:3:4-tetrahydroarsinoline (XXXVII, X = Br) in 68% yield. Piperidine N-pentamethylenedithiocarbamate serves as an excellent reagent for the characterisation of halogenoarsines (c.f. Blicke and Oakland⁵⁴) and gave on reaction with 1-bromo-1:2:3:4-tetrahydroarsinoline, the crystalline N-pentamethylene-S-1-(1:2:3:4-tetrahydroarsinoline)-dithiocarbamate (XXXVIII).

Both the 1-chloro and 1-bromotetrahydroarsinolines served well for purposes of condensation with lithio derivatives and Grignard reagents.

o-Bromotoluene was converted into o-bromobenzyl bromide, which on treatment with one equivalent of magnesium formed chiefly the mono-Grignard derivative (XXXIX). This gave, on reaction with ethylene oxide, o-bromo-3-phenylpropan-1-ol (XL) in 49% yield. The alcohol, when treated with phosphorus tribromide and then sodium methoxide, gave the bromide (XLI) and the methyl ether (XLII) respectively. The methyl ether was converted with n-butyllithium into the lithio derivative (XLIII) and, with magnesium, also

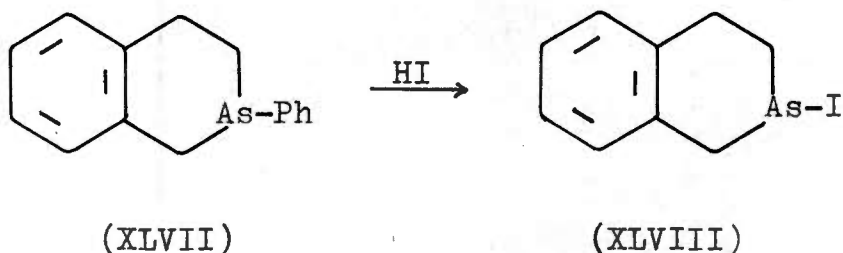


(XLV)

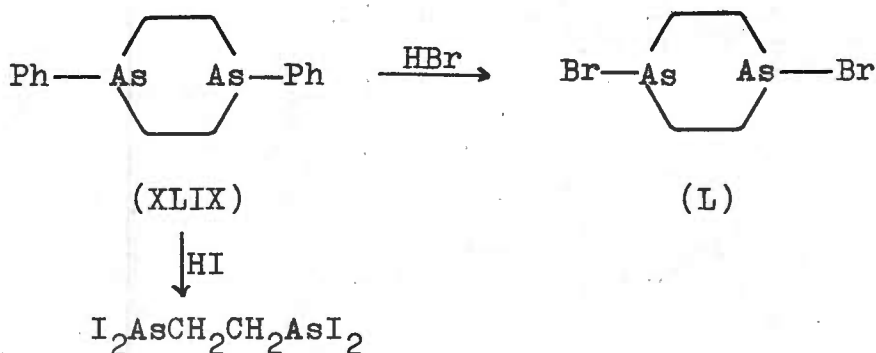


(XLVI)

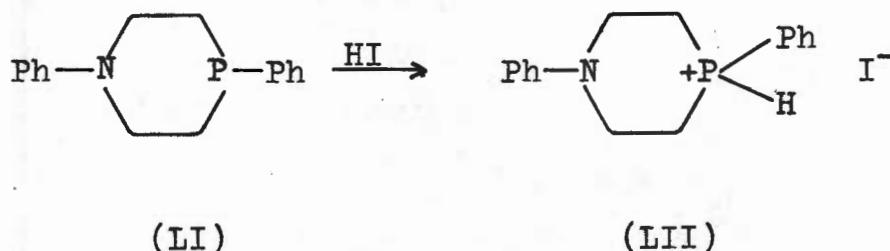
tetrahydroisarsinoline with hydriodic acid to yield the corresponding 2-iodo compound (XLVIII), which, although not isolated in a pure state, was characterised as its *N*-pentamethylenedithiocarbamate derivative. Also, Jones and Mann⁵⁶ have found that



treatment of the cyclic diarsine (XLIX) with hydrobromic acid gave the corresponding dibromodiarsine (L). Hydriodic acid however, under similar conditions, caused rupture of the molecule:



Such substitution of a phenyl group by a halogen atom is apparently not found to occur with P-phenyl cyclic phosphines. For example, treatment of hexahydro-1:4-diphenyl-1:4-azaphosphine (LI) with hydriodic acid gave only the monohydriodide (LII) (c.f. Mann and Miller⁵⁷).



The result of the treatment of the arsinoline (XLV) with hydrobromic acid appears to be the first recorded example of a substituted phenyl group undergoing such replacement.

It was thought that the use of hydrobromic acid could be avoided by employing a more readily hydrolysed protective group than the methoxyl group for use in the Grignard reaction. Various possibilities for readily-cleaved ethers were therefore considered.

Cleavage of ethers has been accomplished with acidic reagents; with nucleophilic reagents

in the absence of acids; with alkali metals; and by reactions involving heterogeneous catalysts. Most of the reactions of the first three types can be explained in terms of bimolecular nucleophilic substitution (S_N2) reactions and carbonium ion (S_N1) reactions. (For an excellent review on this topic see Burwell: "Cleavage of Ethers"⁵⁸).

Cleavage of the carbon-oxygen bond in an ether often occurs as readily as (and sometimes more readily than) that in alcohols. This is illustrated by the fact that for the carbon-oxygen bond in an ether to be cleaved by a nucleophilic reagent alone, a reagent such as a very strong base is required; such a reagent would remove a proton from an alcohol, making the resulting negatively-charged alkoxide ion less susceptible to nucleophilic attack. Many ether-cleavage reactions proceed through an oxonium salt intermediate such as R_2OH^+ . The assumption of a positive charge by the oxygen atom in the oxonium salt renders one of the R groups liable to departure as a carbonium ion. Furthermore, the formation of the oxonium salt intermediate increases the rate of attack of an ether by a nucleophilic reagent. This has been

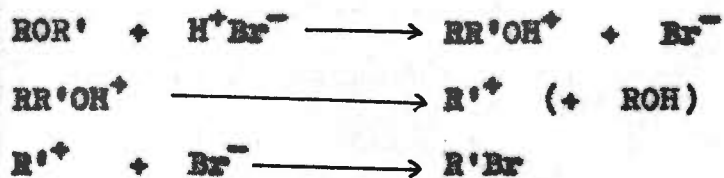
demonstrated experimentally by considering the behaviour of an oxonium salt towards displacing anions of varying nucleophilic potential. For example, if triethyloxonium tetrafluoroborate, $\text{Et}_3\text{O}^+ \text{BF}_6^-$, is allowed to react in a 2M aqueous solution of NaA , where A is the displacing anion, ethyl ether and ethyl A are formed. The percentage of ethyl A formed where A is various anions with varying nucleophilic potential is: $\text{A} = \text{F}^-$, trace; $\text{A} = \text{Cl}^-$, 12%; $\text{A} = \text{Br}^-$, 23%; $\text{A} = \text{I}^-$, 53%; and $\text{A} = \text{CNS}^-$, 64%. This is in order of increasing nucleophilic reactivity of A.

Solutions of ethers in strong acids form oxonium salts which are the conjugate acids of the ether. For example, diethyl ether in 100% sulphuric acid shows a lowering of the freezing point indicative of the presence of two particles per molecule of ether. Undoubtedly the oxonium salt, Et_2OH^+ is formed along with HSO_4^- . In the presence of a strong acid therefore, it would be expected that an ether would be reactive towards a nucleophilic reagent. The reaction of ethers with acids such as hydriodic and hydrobromic acids

is probably the method that has found greatest application for their cleavage. Experiments have shown that in an ether, ROR' (where R and R' are both primary alkyls or R is primary and R' is secondary alkyl) reaction with hydrobromic acid involves an $\text{S}_{\text{N}}2$ mechanism: probably reaction occurs between the dialkylhydronium ion and the bromide ion:



But when R' is tertiary, the bond between the tertiary alkyl group and oxygen is broken to give R'Br and ROH and cleavage of tertiary ethers occurs far more readily than that of primary or secondary alkyl containing ethers. The reaction is now of the $\text{S}_{\text{N}}1$ type involving a carbonium ion intermediate:



Cleavage of ethers has also been accomplished by the action of hydrogen halides in organic acids, particularly by hydrogen bromide in glacial acetic acid. The alkyl bromide and an alcohol are initially formed; the alcohol is then esterified and the ester reacts further with hydrogen bromide forming the alkyl bromide. Tronov and Ladigina⁵⁹ have measured the rates of reaction of a number of ethers in glacial acetic acid containing hydrobromic acid. The relative rate constants (second order) for anisole, allyl phenyl ether, benzyl phenyl ether and ethyl tert-butyl ether are respectively 9.42, 156, 8140 and 68600. This indicates the ease of cleavage to be $-\text{OMe} < -\text{OCH}_2\text{CH}=\text{CH}_2 < -\text{OCH}_2\text{Ph} < -\text{OC}(\text{CH}_3)_3$.

Organic carboxylic acids on their own are in general ineffective for the cleavage of ethers. Thus, anisole is not cleaved by formic, acetic or even trichloroacetic acids. However, very reactive ethers, such as trityl ethers, are cleaved by aqueous acetic acid. The trityl group has been used to a large extent for the protection of hydroxyl groups during reactions of sugars. Its use is limited however by its extremely ready

cleavage in even slightly acidic media, and it appears to have been little used for the protection of hydroxyl groups other than in carbohydrate chemistry for this reason.

For use in the Grignard reaction, undoubtedly the best method for the protection of the alcoholic group would be by conversion to an ether of some type. The methoxyl group having proved unsatisfactory in the compound (XLV, page 68), because of the subsequent cleavage at the arsenic-phenyl bond when treated with hydrobromic acid, an ether group was now sought, whose cleavage could readily be accomplished by some reagent which would not affect or be affected by the tertiary arsine. Of the four types of method available for the cleavage of ethers, treatment with nucleophilic reagents such as strong bases would undoubtedly result in attack at the arsenic atom in a compound containing the tertiary arsine group, resulting in the formation of the dihydroxide of the arsine; the action of alkali metals may be harmful towards the tertiary arsine; and reactions involving heterogeneous catalysts, such as the hydrogenolysis of a benzyl ether to the corresponding alcohol in the

presence of Raney nickel would undoubtedly result in poisoning of the catalyst by the arsenic; in fact, in previous cases where the hydrogenation of an olefinic group attached to an arsenic atom has been attempted, such poisoning of the catalyst has occurred and the original arsine was recovered unchanged from the reaction mixture.

There remains only the cleavage by means of acidic reagents and here the acid employed would have to be sufficiently mild so as not to cleave the arsenic-phenyl bond in a compound of type (XLV). The benzyl, tert-butyl and trityl ethers are probably all suitable in this respect, but the trityl ether has the advantage that it is very readily prepared simply by treatment of the corresponding alcohol with trityl chloride and is furthermore readily hydrolysed under mild conditions (i.e. by boiling with dilute aqueous acetic acid for about 30 minutes). For these reasons, the trityl ether corresponding with (XLV) seemed a suitable possibility as an alternative intermediate to the required spiro salt.

o-Bromo-3-phenylpropyl trityl ether (LIII) was therefore prepared by interaction between the

allisation, was found, by mixed melting point and analysis, to be triphenylcarbinol. The distillate thus consisted almost certainly of triphenylcarbinol itself. This could have been formed by hydrolysis of the trityl ether (LIV) on treatment of the product from the Grignard reaction with ammonium chloride solution, or, by dissociation of the trityl ether on attempted distillation.

The residue from the attempted distillation had evidently undergone extensive oxidation, since, when ground to a powder and hydrolysed by boiling with dilute acetic acid, it gave, on treatment with thionyl chloride, the unstable hydroxy-chloride (LVI). This furnished in turn, with dilute nitric acid, the corresponding stable and crystalline hydroxy-nitrate (LVII). Furthermore, the hydroxy-chloride (LVI) yielded, after reduction with sulphur dioxide, the 3-chloropropylphenylarsinoline (LVIII) which underwent spontaneous cyclisation to the spirocyclic chloride (LIX). Since purification of this chloride would have proved wasteful, it was not isolated in a pure condition, but was converted directly into the corresponding spiro iodide by reaction with sodium iodide in aqueous ethanol.

The arsine oxide (LX), when reduced with sulphur dioxide, gave the alcohol (LXI). This compound was once again not a solid and proved to have an extremely high boiling point. Rapid distillation from a flask having a short distillation path proved possible, but the alcohol underwent some decomposition during this process, and was obtained as a brown, viscous gum. However, when treated with phosphorus tribromide, the spirocyclic bromide was readily formed and gave with sodium iodide, the spirocyclic iodide (LXII), having the same melting point as the iodide obtained by the former method, both alone and in admixture.

In all subsequent preparations of the spiro iodide, no attempt was made to distil either the trityl ether (LIV) or the alcohol (LXI) because of the oxidation and partial decomposition attending this procedure, but the residual gum obtained after hydrolysis was treated in chloroform solution with sulphur dioxide to reduce any arsine oxide there might be present, the residue, after removal of the chloroform, then being treated directly with phosphorus tribromide. The resulting spiro bromide, in ethanol, on reaction with an aqueous

initially attempted via the (+)-bromocamphorsulphonate. This optically active derivative was readily obtained crystalline. Successive recrystallisations from diethyl carbonate failed to change the melting point significantly; furthermore, the thrice recrystallised material gave an inactive iodide. Recrystallisation from diethyl ketone gave material of m. p. practically the same as that obtained from diethyl carbonate. This material had $[\alpha]_D +286^\circ$ and was too insoluble for further recrystallisation from diethyl ketone. Recrystallisation from ethyl methyl ketone failed to alter the m. p. or the molecular rotation significantly. This twice recrystallised material was now too insoluble for further recrystallisation from ethyl methyl ketone. Recrystallisation from acetone gave a product of unchanged m. p., $[\alpha]_D +284^\circ$. It was clear that resolution was not proceeding, ($[\alpha]_D$ for (+)-bromocamphorsulphonic acid in methanol, $+274^\circ$) but to confirm this point, the thrice recrystallised material was converted into the picrate which was inactive and identical with an authentic sample of the racemic picrate.

Hart and Mann's analogous spiro phosphonium salt had been successfully resolved via the (-)-menthoxyacetate and this optically-active derivative fortunately proved suitable for the resolution of the arsenic analogue.

The (-)-menthoxyacetate was readily obtained crystalline from diethyl ketone, m. p. 85-90°, not significantly changed after five further recrystallisations from the same solvent, when it had become constant. The menthoxyacetate analysed as the dihydrate after being dried at room temperature and as the (hygroscopic) anhydrous salt when dried at 40°. In order to test whether resolution was proceeding, the above six-times recrystallised material which was undoubtedly optically pure, was converted into the picrate which proved to be the (-)-picrate, m. p. 95-97°, $[\alpha]_D -132^\circ$.

Another sample of the (-)-menthoxyacetate was prepared and recrystallised four times from diethyl ketone, the m. p. remaining unchanged between the final two recrystallisations. This material was analytically pure and had $[\alpha]_D -48.6^\circ$. A fifth recrystallisation failed to alter the

m. p. or the rotation, $[\alpha]_D -48.0^\circ$. These figures indicated that resolution was complete.

Addition of ethanolic sodium iodide to an ethanolic solution of the optically pure (-)-menthoxyacetate failed to precipitate the (-)-iodide which was subsequently found to be highly soluble in cold ethanol (in contrast with the highly insoluble racemic iodide). Evaporation of the ethanolic solution gave a residue of the (-)-iodide and sodium iodide which was taken up in hot water. The aqueous solution readily deposited on cooling, the chemically and optically pure (-)-iodide, m. p. $223-223.5^\circ$ (m. p. of the racemic iodide, $277-278^\circ$). A 0.5933% solution in A.R. chloroform (4 dm. tube) had $\alpha_D^{22.5} -0.712^\circ$; $[\alpha]_D^{22.5} -30.0^\circ$; $[\eta]_D^{22.5} -131.5^\circ$; these values were completely unchanged after the solution had remained in the dark for 24 hours.

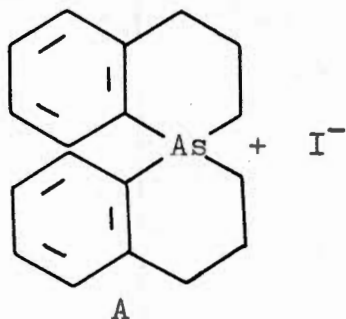
The observation that the (-)-iodide was soluble in cold ethanol but could be recrystallised from water, led to the following procedure being employed for the isolation of the (+)-iodide.

The solvent was distilled under reduced pressure from a portion of the diethyl ketone mother liquors from the first crystallisation of the (-)-menthoxyacetate, leaving a dark-coloured gum. This was taken up in ethanol, boiled with charcoal and filtered. The colourless filtrate was warmed and treated with a warm ethanolic solution of sodium iodide containing a trace of water. Cooling and scratching gave the crude racemic iodide which, after three recrystallisations from ethanol, was analytically pure and had m. p. 276-277°. The m. p. indicated that this was the racemic iodide, this point being confirmed by a mixed m. p.

The mother liquors from this racemic iodide, which were now rich with respect to the (+)-iodide were evaporated to dryness and the solid residue (consisting of the (-)-iodide and sodium iodide) taken up in hot water. Cooling now gave the crystalline (+)-iodide contaminated with some gummy material. The crystalline material was separated and recrystallised twice from water, the m. p. being identical with that of the (-)-iodide, whilst a mixture of the (+)- and (-)-

0.00442 mgm./ml. in 95% aqueous ethanol was therefore investigated. There was no appreciable absorption between 4000 and 2900 Å, but an intense band was found to occur at 2595 Å, $\epsilon = 0.0008894$, $\log \epsilon = 4.95$, preceded by a point of inflexion at 2670 Å, $\epsilon = 0.0008527$, $\log \epsilon = 4.93$.

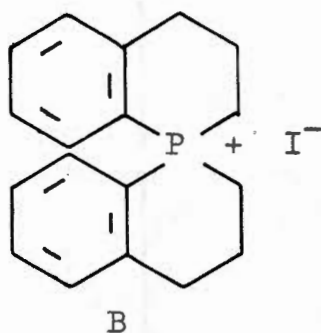
It is of interest to compare the rotation data for the four compounds, A, B, C and D.



$$[\alpha]_D +133^\circ, -131^\circ$$

$$\lambda_0 = 2992 \text{ Å}$$

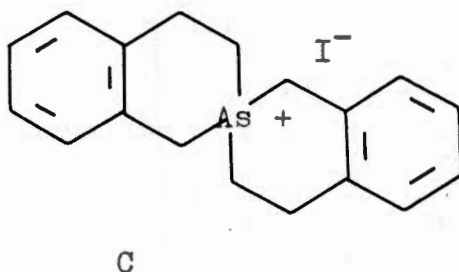
Absorption maximum: 2595 Å



$$[\alpha]_D +66^\circ, -65^\circ$$

$$\lambda_0 = 2032 \text{ Å}$$

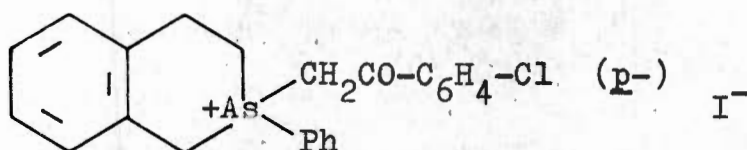
Absorption spectrum not taken



$$[\alpha]_D +342^\circ, -344^\circ$$

$$\lambda_0 = 2316 \text{ Å}$$

Absorption maximum: 2635 Å



$$[\alpha]_D -354^\circ$$

$$\lambda_0 = 2443 \text{ \AA}$$

Absorption maxima:

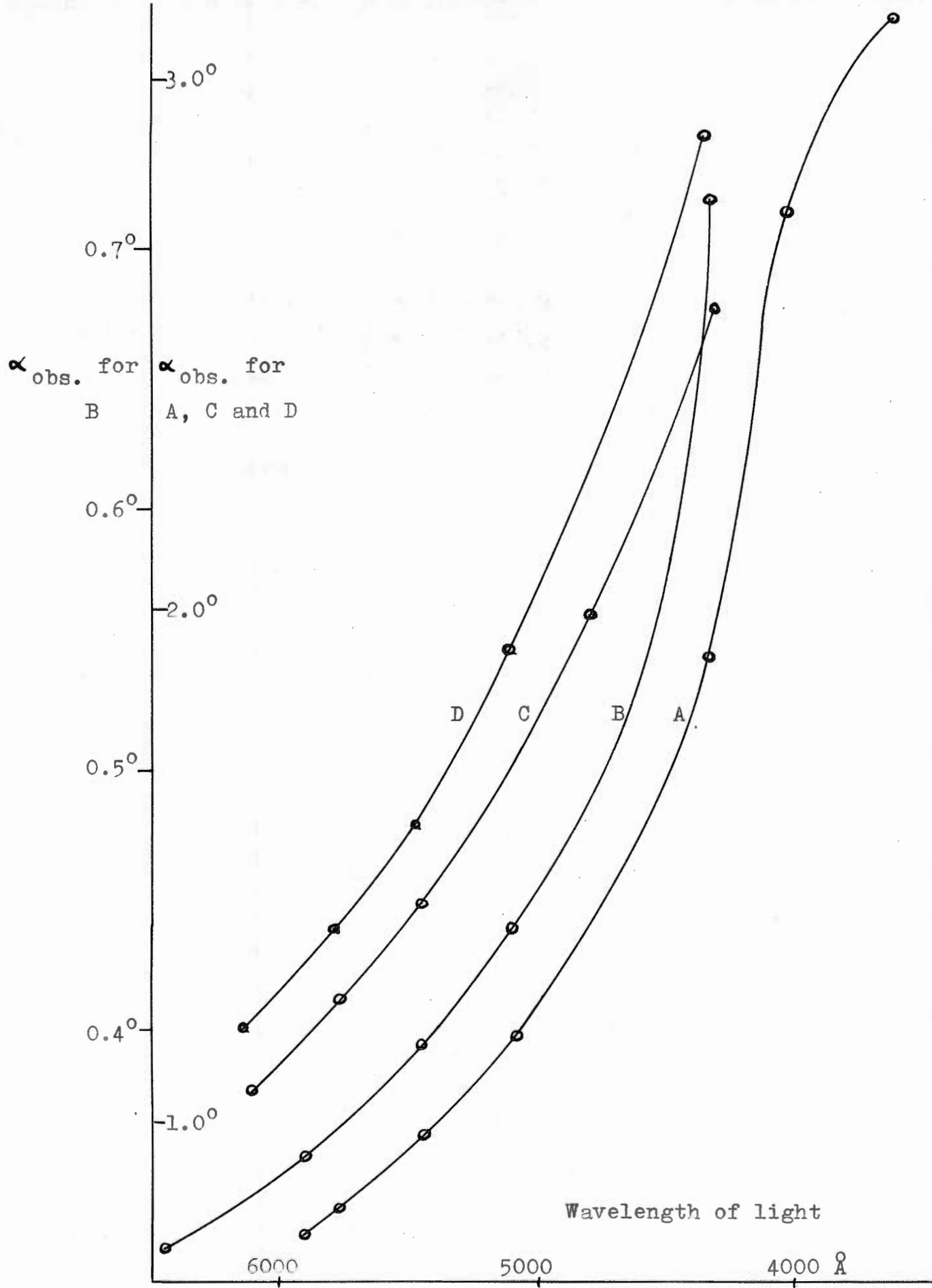
3115 \AA (p-chlorophenacyl group); 2635 \AA (o-phenylene group); 2300 \AA

Fortunately, in all these cases, the rotatory dispersion has been investigated. It is important to note however, that for a comparison between the rotatory dispersion data for a series of compounds to be made, several factors (all of which influence the rotation exhibited by a solution of an optically-active compound) should be maintained as nearly constant as possible within the series of compounds considered. The solvent employed should in all cases be identical as change of solvent often has a marked effect on rotation; secondly, the concentrations of the solutions should not

Rotatory dispersion of (+)-As-spiro-bis-1:2:3:4-tetrahydroarsinolinium
iodide

Source	Na	Hg	Hg	Cd	Hg	Hg	Hg
$\lambda(\text{\AA})$	5893	5780	5461	5086	4358	4047	3650
$\lambda^2 (\text{\AA})^2 \times 10^{-8}$	0.3472	0.3341	0.2982	0.2587	0.1900	0.1639	0.1332
$\alpha(\text{obs.})^\circ$	0.796	0.861	0.995	1.185	1.924	2.758	3.145
$[\alpha]^\circ$	30.38	32.86	37.97	45.24	73.43	105.3	120.0
$[\text{M}]^\circ$	133.1	144.0	166.4	198.3	321.8	461.3	526.0
$\alpha(\text{calc.})^\circ$	0.796	0.839	0.983	1.213	2.042	2.758	4.698
$\alpha(\text{obs.}) - \alpha(\text{calc.})^\circ$	0.000	+0.022	+0.012	-0.028	-0.118	0.000	-1.553

The rotations have been calculated from the simple Drude equation, $\alpha = k/(\lambda^2 - \lambda_0^2)$, using as reference values, the observed rotations for $\lambda = 5893$ and 4047 \AA . Solution of the simultaneous equations gives the rotation constant, $k = 0.2051$; and the dispersion constant, $\lambda_0^2 = 0.08954$. Hence $\lambda_0 = 2992 \text{ \AA}$.



appreciably vary (preferably they should be equimolecular); thirdly, if the concentrations are similar, the tube length should be identical in all cases; and lastly, the temperature at which observations were recorded should not vary significantly. Fortunately, for the four compounds considered, measurements were taken at very nearly the same temperature, whilst the concentrations of the solutions varied only very slightly. The tube length was 4 dm. and the solvent chloroform in all cases.

It must be emphasised that the deductions given in the following few pages are only tentative. More decisive conclusions can be drawn only when further data on similar series of compounds is made available.

It is in general found that simple saturated aliphatic compounds possessing no strongly chromophoric group, exhibit simple dispersion, and the value of the dispersion constant, λ_0^2 , lies between 0.020 and 0.025, so that λ_0 has a value in the far ultra-violet. This is in agreement with the fact that substances of this type

have absorption bands in the far ultra-violet. The introduction of an unsaturated, or other, chromophoric group, such as a phenyl group, into the molecule causes an increase in the value of λ_0 which accords with the fact that the absorption band is now shifted nearer to the visible region. It is important to note however, that the introduction of a chromophoric group into an optically-active molecule does not necessarily imply that the absorption band will make a contribution to the total rotation (c.f. Tschugaeff⁶⁰). For example, nicotine has an absorption band at 2650 Å and the corresponding chromophore is active since $\lambda_0 = 2550$ Å. The introduction of a carbonyl group in methyl-nicotone gives an absorption band at 2950 Å which is expected for a keto group, but the dispersion remains simple and $\lambda_0 = 2668$ Å. The new chromophore thus makes no contribution to the optical activity (c.f. Lowry and Gore⁶¹). A highly similar case is represented by the compounds C and D. In C, $\lambda_0 = 2316$ Å and the absorption maximum occurs at 2635 Å. This band

is undoubtedly due to the o-phenylene groups since it is also present in the spectrum of D, where one o-phenylene group prevails and the arsenic atom is in the same position relative to this o-phenylene group. Furthermore the chromophoric o-phenylene groups in C are active since the values for the absorption maximum and λ_0 differ by 319 Å. But D contains also the chromophoric p-chlorophenacyl group which gives rise to an absorption band at 3115 Å, i.e. nearer to the visible region. This has little influence on the value of λ_0 (2443 Å) whilst the dispersion remains simple. Furthermore the molecular rotations of C and D are closely similar (-344° and -354° respectively). Hence the p-chlorophenacyl group is inactive and makes very little contribution to the optical activity.

Allsep⁶ has suggested that the optical anisotropy of the (-)-iodide of D is centred in an electron of the asymmetric arsenic atom. In this it would differ from optically-active carbon compounds in which the anisotropy is often found to be largely confined to a weakly absorbing

chromophoric substituent. It is only when the electronic oscillator (i.e. if Allsop's suggestion is correct, an electron of the arsenic atom) is able to couple with the active electrons in the chromophoric substituent(s) that such a group influences the nature of the dispersion. The probability of such coupling often depends on the proximity of the chromophoric group to the asymmetric centre; the inducing action of the asymmetric centre on the chromophoric group is known as its vicinal action^{62, 63}. Here proximity is not the only factor influencing vicinal action however, the nature of the groups present also being important. In this connection, it is apparent from the comparisons drawn between the data for compounds C and D in the previous paragraph, that the arsenic atom has very little, if any, vicinal action on the chromophoric p-chlorophenacyl group.

In this connection, a comparison between the isomeric spirocyclic arsonium salts A and C is of great interest. In these compounds, the chromophoric q-phenylene group is present in each, whilst the proximity of both q-phenylene groups

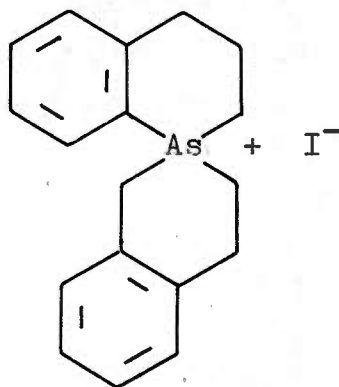
to the arsenic atom is increased in passing from C to A. It would be expected therefore that any vicinal action which the arsenic atom in C might have on the o-phenylene group would make its effect more apparent in A. The effect of the increased proximity of the o-phenylene group in A is in fact made evident in three different ways. Firstly, the rotatory dispersion is now complex whereas in C it was simple; secondly, the value of λ_0 is now markedly different (by 400 Å) from the wavelength of the absorption maximum; and finally the molecular rotation of A is much lower than that of C or D. Lowry has suggested that the coupling of a strongly chromophoric group to an asymmetric complex might result in the production of induced asymmetry in the former. In general, the new centre of activity produced in this way (induced anisotropy) would have the effect of causing a rotation opposite to that of the remainder of the molecule, so that anomalous dispersion would result. The fact that, in passing from C to A, the molecular rotation is considerably decreased and the dispersion

altered from simple to anomalous would seem therefore to be in excellent agreement with Lowry's suggestion. This is in marked contrast with the case of C and D where the chromophoric p-chlorophenacyl group in D had little effect on the value of λ_0 and none on the nature of the dispersion. Here, the p-chlorophenacyl group is clearly not coupled with the electronic oscillator of the arsenic atom.

In D, the nearest portion of the p-chlorophenacyl group to the arsenic atom which would contribute to the chromophore as a whole (viz. the carbonyl group), is separated from the arsenic atom by one methylene group. Similarly in C, the chromophoric o-phenylene groups are each one methylene group removed from the arsenic atom. In the former compound, the chromophores are (as has been suggested) apparently inactive; in the latter they are not. The fact that mere proximity of the chromophoric groups is not the only factor influencing vicinal action is therefore clearly illustrated by these two cases.

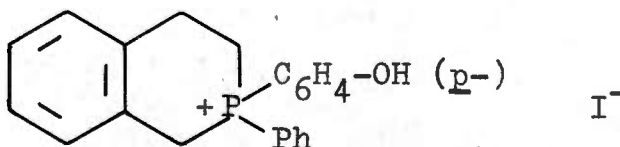
If the views stated in the preceding pages are correct, one would expect that the

value of the molecular rotation of the spiro salt E would lie between those for the isomeric salts A and C, since the presence of the adjacent o-phenylene group in the tetrahydroarsainoline ring would be expected to lower the molecular rotation below the value for C but not to the same extent as in A.



E

Unfortunately, the data required for a legitimate comparison between the phosphonium salts, B and F, are lacking.



F

Firstly, F was, after resolution, converted into the bromide (whereas in all other cases considered, the anion was the iodide); secondly, the ultra-violet spectrum has not been recorded; and thirdly, the rotation of the bromide was taken in aqueous ethanol, not in chloroform. Furthermore, change of solvent was found to have a marked effect on the value of the rotation: $[M]_D$ in aqueous ethanol, $+32.9^\circ$, in methanol, $+5^\circ$ (this was proved not to be due to racemisation in the latter solvent). For these reasons, it is impossible to suggest what the molecular rotation of the iodide in chloroform would have been.

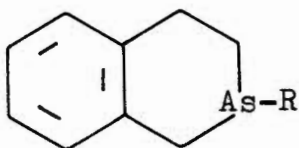
Finally, a comparison between the molecular rotations of the eutropic salts A and B, will be considered. Here the significance of any difference between the molecular rotations will be greatest, since the molecules are (except for the hetero atom) identical. In neither case is the dispersion simple whilst the trends of the rotatory dispersion curves (see graph) are practically identical. It is reasonable to expect (and this is supported by the identical

trends of the two curves) that any effect on the rotation caused by the chromophoric *p*-phenylene groups in the one compound would be repeated in the other. If this is so, the increase in molecular rotation in passing from the phosphorus to the arsenic compound is due solely to the change in the hetero atom which is also the centre of asymmetry in the molecule. This is the most significant and fundamental observation that can be drawn from this work and furthermore is a precisely similar relationship to that found to hold for the only two series of eutropic compounds which have previously been resolved (see Introduction). Unfortunately, a more detailed comparison between individual members of the latter two series of compounds cannot be drawn since the data for the rotatory dispersions and ultra-violet spectra of these compounds is not available.

Previous to the preparation of the spiro arsonium salt A, only two such optically-active salts containing phosphorus and arsenic had been prepared. To the author's knowledge,

only three other spirocyclic salts containing these elements have been synthesised. These are Lyon and Mann's spiro arsonium salt (see Introduction, page 20) and a derivative of this compound suitably substituted in order to introduce an element of asymmetry but which could not be resolved; also a di-spirocyclic salt of arsenic prepared by Jones and Mann⁶⁴ but which is not relevant to the present discussion. The optically-active salts are Hart and Mann's compound, B, and Holliman and Mann's arsonium salt, C. These can be seen to contain respectively two condensed phosphinoline ring systems and two condensed isoparsinoline ring systems. No spirocyclic salt of a Group Vb element containing a condensed "normal" and "iso" ring system has been reported. For this reason and also because of its stereochemical interest, an attempt was made to prepare such a salt containing arsenic as the hetero atom, viz., ($\frac{1}{2}$)-As-spiro-(1:2:3:4-tetrahydroarsinoline)-1:2:3:4-tetrahydroiso-arsinolinium bromide (LXIII).

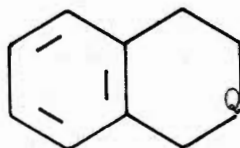
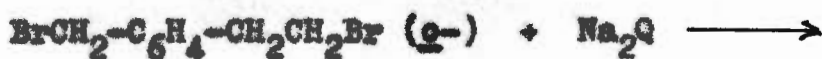
This tedious process and low yield prevented a study of its application to the synthesis of such heterocyclic compounds of the iso series being made until Holliman and Mann²⁷ worked out a successful five-stage synthesis also from o-toluidine with an overall yield of 8%. Holliman and Mann^{27, 65} have applied this dibromide to the synthesis of 2-substituted tetrahydroisoquinolines and to the synthesis of the previously unknown 2-methyl- and 2-phenyltetrahydroisocarolinolines²⁹ (LXIV, R = Me, Ph).



(LXIV)

von Braun and Zobel had moreover used this compound for the preparation of thioiso-chroman (LXV, Q = S) by its interaction with sodium sulphide, whilst Holliman and Mann⁴⁵ have prepared in addition, the previously unknown

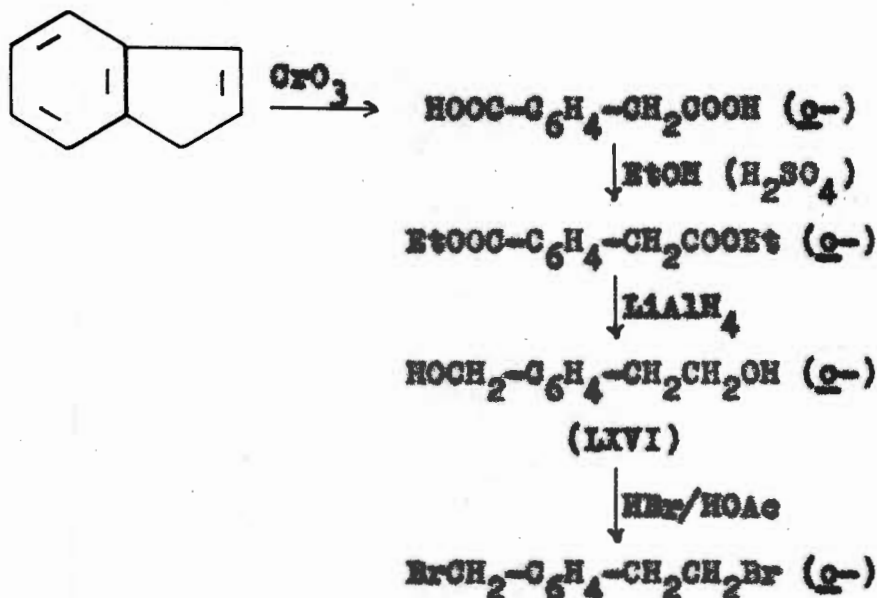
selenoisochroman (LXV, Q = Se) and telluroiso-chroman (LXV, Q = Te) using sodium selenide and sodium telluride respectively. The stereochemical interest of these compounds has been mentioned in the introduction.



(LXV)

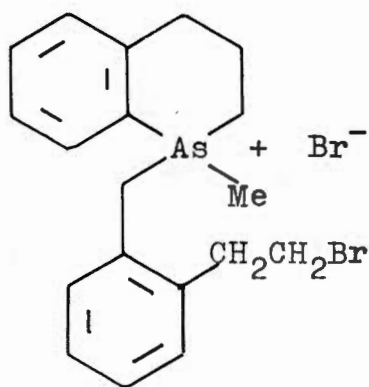
Recently, Anderson and Hellman²⁸ have improved the synthesis of the dibromide to a four-stage process commencing with indene, with an overall yield of 30%. Indene is oxidised to homophthalic acid with chromium trioxide; the acid, after esterification and reduction of the ester with lithium aluminium hydride, yields g-2-hydroxyethylbenzyl alcohol (LXVI). The alcohol, when allowed to react with hydrogen bromide in glacial acetic acid in a sealed tube at 100°, furnishes the dibromide in high yield. This method was employed without modification

for the preparation of the dibromide required in this work.



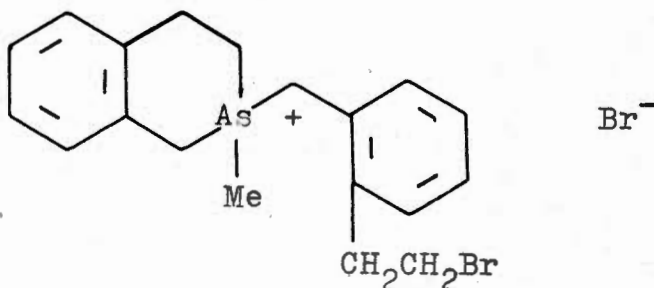
For the synthesis of the "normal-iso" spiro salt (LXIII, page 101), 1-methyl-1:2:3:4-tetrahydroarsinoline was quaternised with o-2-bromoethylbenzyl bromide to yield the quaternary salt (LXVII). This compound was originally prepared by Holliman (unpublished), but exhaustive attempts by both him and the author to thermally decompose the salt have failed to yield a crystalline derivative. A variety of conditions were employed for its attempted thermal

decomposition and on all occasions effervescence occurred with the evolution of a gas which gave a precipitate of silver bromide when passed through an aqueous solution of silver nitrate, but the residue appeared in each case to be a complex mixture which defied attempted purification. This contrasts strongly with the ease with which Holliman and Mann obtained the "iso-iso" spiro salt in 38% yield by thermal decomposition of (LXVIII), but recalls the difficulty



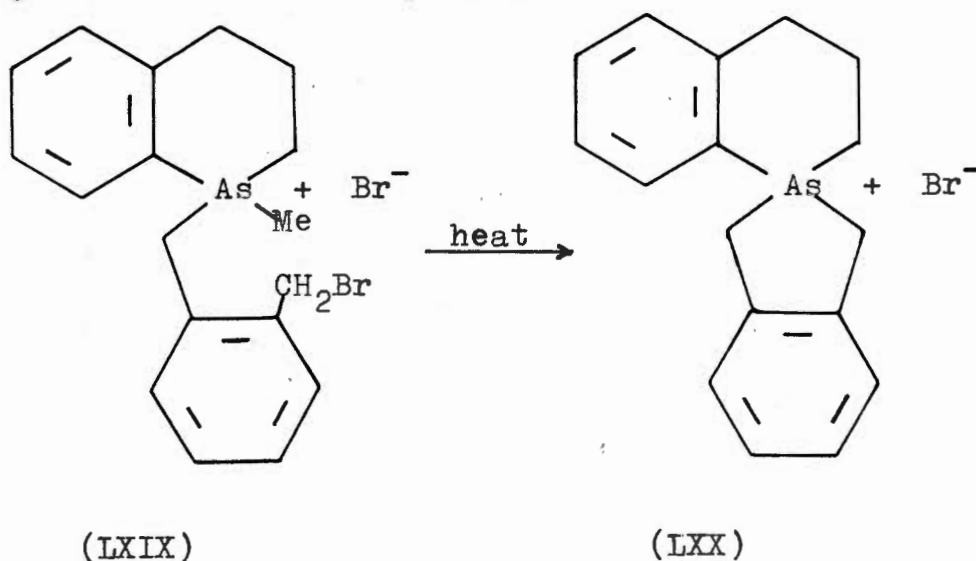
(LXVII)

encountered in the attempted thermal decomposition of the similar phosphonium salt by Hart and Mann (see Introduction, page 25).



One essential difference between the quaternary salts (LXVII) and (LXVIII) is that whereas in the latter compound, the arsenic atom is linked on either side to methylene groups, the former compound contains an arsenic atom linked directly to a benzene ring and the instability of such compounds to hydrobromic acid and hydriodic acid has already been noted. The question now arose as to whether such a salt would also exhibit instability when submitted to thermal decomposition. In order to test this point, 1-methyl-1:2:3:4-tetrahydroarsinoline was condensed with

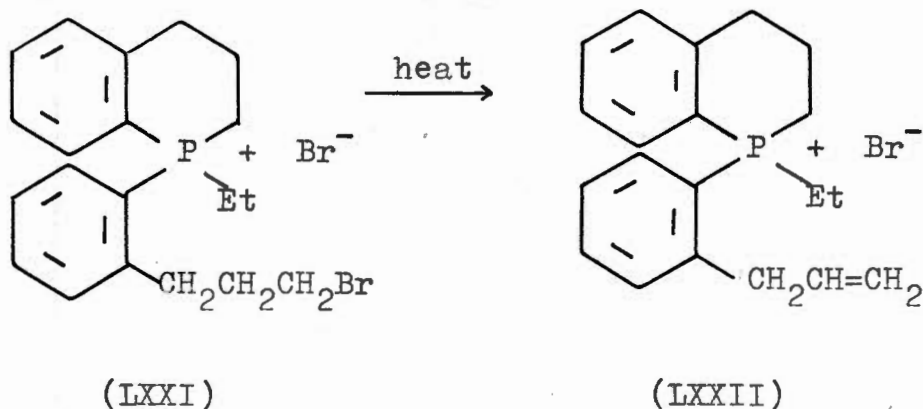
o-xylylene dibromide to yield the quaternary salt (LXIX) which, without isolation, now underwent thermal decomposition smoothly to yield As-spiro-isoparsindoline-1:2:3:4-tetrahydro-arsinolinium bromide (LXX) which was converted directly into the iodide and further characterised by conversion to the picrate:



This spirocyclic salt thus formed readily and very little side reaction could have occurred. Other than Jones and Mann's di-spiro salt of arsenic (mentioned earlier), this is the only other example of a spirocyclic salt of a Group Vb element (other than nitrogen) containing a 5- and a 6-membered ring adjacent to the hetero

evolution of methyl bromide. Alternatively, a mixture of the two possible products may be obtained.

Loss of hydrogen bromide has been found to occur from the bromopropyl group in the quaternary salt (LXXI) when it was submitted to thermal decomposition⁸, the corresponding allyl compound (LXXII) resulting:



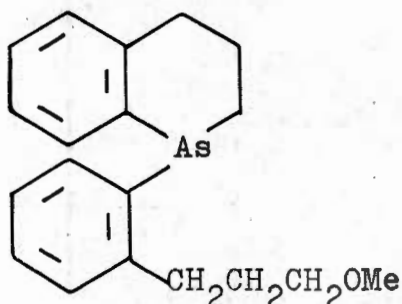
In this particular case, loss of hydrogen bromide from the side chain occurred more readily than removal of the ethyl group from the quaternary phosphonium ion. It frequently happens that thermal decomposition of quaternary phosphonium salts carrying an ethyl group attached to the phosphorus atom occurs with greater difficulty

than the corresponding removal of a methyl group from an arsonium salt. The reason for this difference (as has been mentioned in the Introduction) may be due to the fact that the mechanism in the two cases differs. If, in the case of the arsonium salt (LXVII), partial loss of hydrogen bromide from the 2-bromoethyl group had occurred, the reaction product might well comprise a mixture from which no crystalline derivative could be isolated. Furthermore, fission at the arsenic-benzyl bond may occur, although this now seems unlikely in view of the readiness with which the spirocyclic salt (LXX) is formed.

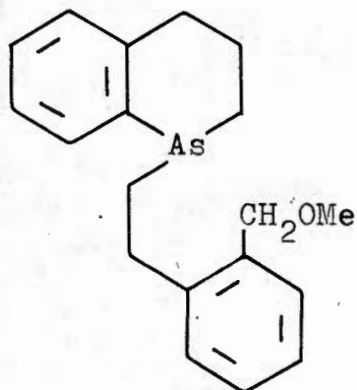
An interesting point in connection with the formation of allyl or vinyl groups on thermal decomposition, is that the position of the hetero atom in the cyclic ring may possibly determine the probability of such reaction occurring. Holliman and Mann found that thermal decomposition of the salt (LXVIII) proceeded sufficiently smoothly to isolate the spiro bromide in reasonable yield; in fact, the reaction mixture itself crystallised even

at the high temperature employed (200°). In this case the arsenic atom is not directly linked to a phenyl group. In the case of Hart and Mann's salt (LXXI) and in the author's case (LXVII), the hetero atom is so attached. It may well be that in such cases, the probability that loss of hydrogen bromide from the side chain attached to the phenyl group will occur, is increased.

The thermal decomposition method having failed, a route via a Grignard condensation was now sought. It has been suggested that when the compound (LXXIII) was treated with hydrobromic acid, one of the products was probably 1-bromo-1:2:3:4-tetrahydroarsinoline. If this is so, the tetrahydroarsinoline ring itself is stable to this reagent while the other free arsenic-aryl link is not. This suggested that if the compound (LXXIV) could be prepared, the tetrahydroarsinoline ring would once again prove stable towards hydrobromic acid, whilst the free arsenic-aryl link now having been replaced by an arsenic-alkyl link, this might also prove stable towards the reagent.

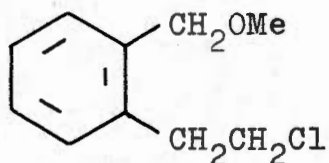


(LXXIII)



(LXXIV)

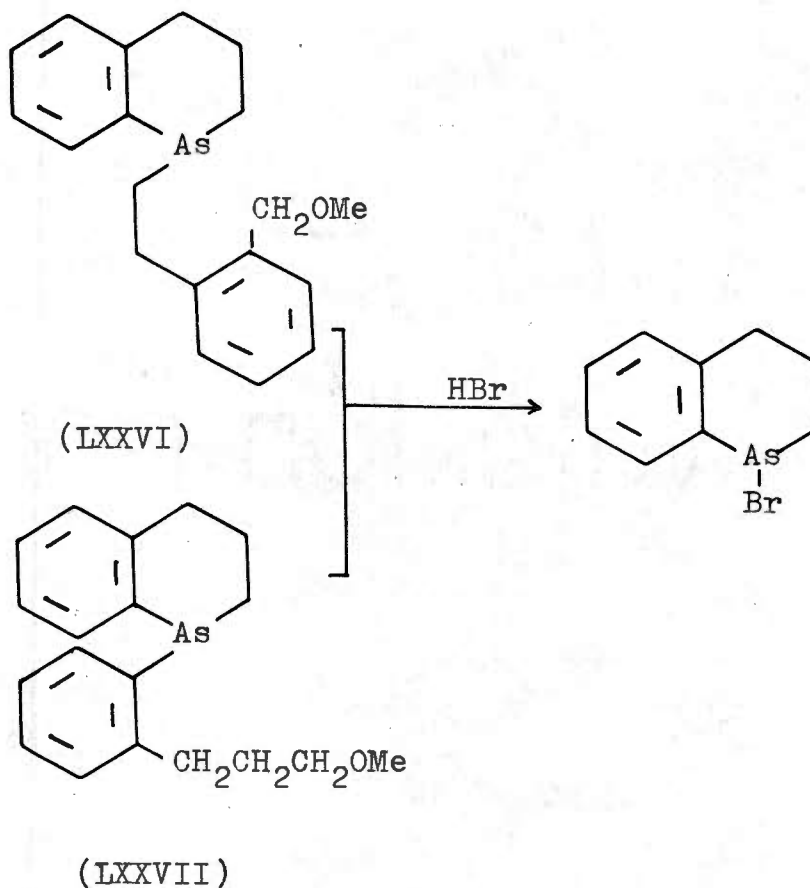
o-2-Chloroethylbenzyl methyl ether (LXXIV), required for the preparation of the arsinoline (LXXIV) was readily synthesised by the method recorded by Holliman and Mann⁵.



(LXXV)

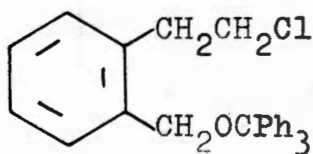
The Grignard derivative of this compound readily underwent condensation with the 1-chlorotetrahydroarsinoline which has proved so successful in the synthesis of the bigarsinolinium spiro salt. The arsinoline thus obtained (LXXVI)

(characterized as its methiodide) was treated with hydrobromic acid in glacial acetic acid but gave only an ether-soluble liquid which, after redistillation and analysis appeared to be an impure sample of 1-bromo-1:2:3:4-tetrahydroarsinoline. If this is so, hydrobromic acid has here caused fission at the arsenic-alkyl link, as had been found to occur at the arsenic-aryl link in the case of the arsinoline (LXXVII).

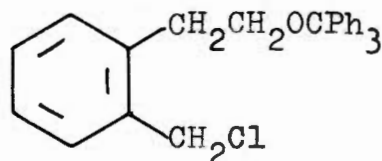


Since this method held out little hope of success, it was abandoned in favour of a procedure similar to that which had proved successful for the preparation of the bis-arsinolinium spiro salt.

It was thought that if the compounds (LXXVIII) or (LXXIX) could be obtained, they could be converted into the Grignard derivative and condensed with 1-bromo-1:2:3:4-tetrahydroarsinoline to yield the arsine (LXXX) or (LXXXI) respectively which would, on hydrolysis to the alcohol, followed by treatment with thionyl chloride or phosphorus tribromide, probably yield the spirocyclic chloride or bromide.

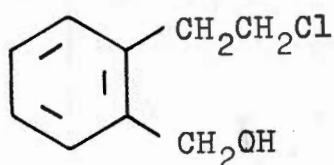


(LXXVIII)

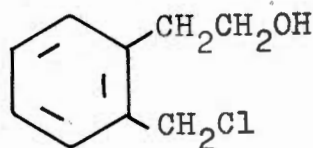


(LXXIX)

In order to prepare the trityl ethers (LXXVIII) or (LXXIX), the corresponding alcohols should preferably be initially obtained and

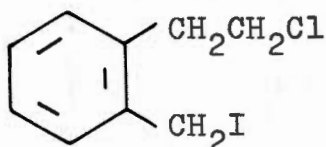


(LXXXII)

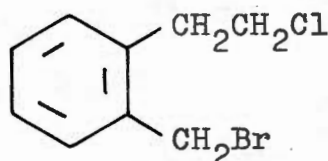


(LXXXIII)

difficulties which belie their apparently simple nature. A sample of *o*-2-chloroethylbenzyl methyl ether (LXXIV) was available and attempts were therefore made to hydrolyse this compound to the corresponding alcohol (LXXXII) but without success. Treatment with either hydriodic acid or one equivalent of hydrobromic acid gave what were almost certainly the corresponding benzyl halides (LXXXIV) and (LXXXV), since they were intense lachrymators. They had further the most unpleasant effect in that they



(LXXXIV)

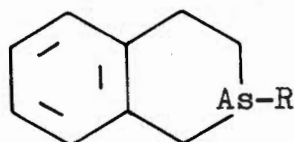


(LXXXV)

gave rise to blisters on the hands and face which took several days to disappear. No attempts were therefore made to characterize

these compounds. The author always experienced similar discomfit whilst working with other o-2-halogenoethylbenzyl halides such as o-2-bromoethylbenzyl bromide.

One way of avoiding the use of either of the trityl ethers (LXXVIII) or (LXXIX) would be to start the synthesis with the isoarsinoline ring system complete. 2-Iodo-1:2:3:4-tetrahydro-isoarsinoline (LXXXVI, R = I) has previously been prepared by Beeby, Cookson and Mann⁵⁵ by interaction of the corresponding 2-phenyl compound (LXXXVI, R = Ph) with hydriodic acid.



(LXXXVI)

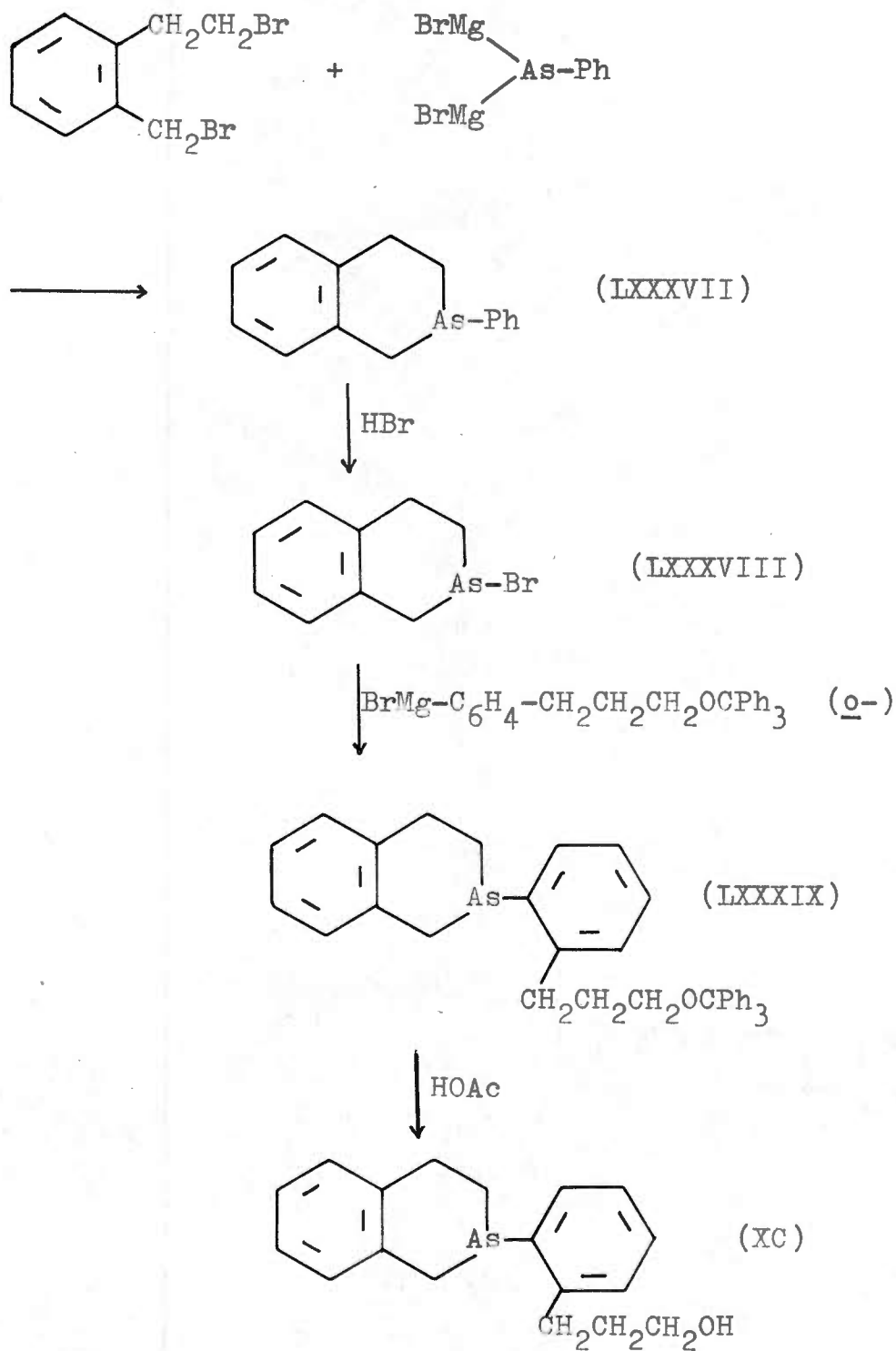
This compound has not been isolated in a pure state but was shown to be present by conversion to the N-pentamethylenedithiocarbamate derivative. Furthermore, Holliman and Mann⁶ have prepared the 2-chloro analogue (LXXXVI, R = Cl) by thermal decomposition of the 2-dichloromethyl compound

(LXXXVI, R = MeCl_2) obtained in turn by reaction of the 2-methyl compound (LXXXVI, R = Me) with chlorine. No yields are reported for either of the procedures leading to the iodo and chloro compounds. The 2-methylisoarsinoline (LXXXVI, R = Me) is obtained in 16% yield by the Michaelis reaction, whilst the 2-phenyl compound (LXXXVI, R = Ph) has been obtained in 32% yield by an analogous procedure employing phenyldichloroarsine in place of methyldichloroarsine in this reaction. However, a 60% yield of the 2-phenyl compound is obtained by interaction between o-2-bromoethylbenzyl bromide and phenylarsinebis(magnesium bromide)⁵⁵. Obviously, the latter method is more satisfactory. Furthermore, the 2-bromoisoarsinoline would in all probability be more stable than the 2-iodo analogue and hence would prove more suitable for the Grignard condensation reaction. The phenylisoarsinoline was therefore heated under reflux with hydrobromic acid when it readily afforded the corresponding bromoisoarsinoline in 36% yield, characterised as its

N-pentamethylenedithiocarbamate derivative.

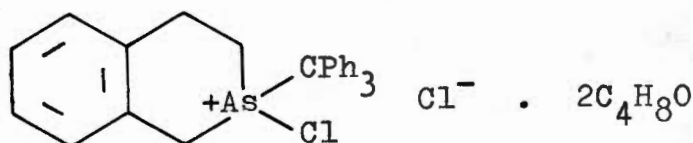
Thus the series of three halogenoisoarsinoline is now known.

Condensation of the 2-bromoisoarsinoline with the Grignard derivative of o-bromo-3-phenyl-propyl trityl ether afforded what was presumably the isoarsinoline (LXXXIX). No attempt was made to purify or isolate this compound because of the decomposition which had attended the attempted distillation of the previously prepared isomeric arsinoline. Instead, it was hydrolysed by boiling with dilute acetic acid and the product divided into two parts. In case this was the alcohol (XC), it was treated with phosphorus tribromide, but no crystalline material could be obtained from the reaction product nor could it be converted into a solid iodide or picrate. Treatment of the other portion with thionyl chloride, on the other hand, produced a colourless highly-crystalline derivative which was ether-insoluble and contained ionic chlorine. Although three different portions of this material gave good analytical agreement, no suitable structural formula could at first be found to agree with these

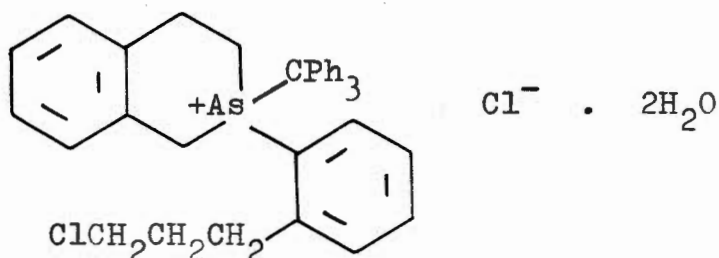


figures.

It was subsequently found that the compound contained molecular chlorine in addition to the ionic chloride, and that the total chlorine in the molecule was precisely double the ionic chloride content. Furthermore, it was suspected that the triphenylcarbinol produced during the hydrolysis of the trityl ether (LXXXIX) (and which would subsequently have been converted into trityl chloride during the reaction with thionyl chloride) might have interfered with the reaction. Possibly the very reactive trityl chloride had quaternised with the arsenic atom, although this did not apparently occur in the case of the analogous preparation of the isomeric big-arsinolinium spiro salt. Ethyl methyl ketone had been used for recrystallisation of the product and the structure



accorded with the analytical figures (if it could be assumed that one of the two chlorine atoms was covalently, the other ionically linked). But this structure was ruled out by the infra-red absorption spectrum which lacked a band at the position expected for a carbonyl group. However the infra-red data did indicate a large proportion of monosubstituted benzene in the molecule which is in agreement with the presence of a trityl group. The following structure:

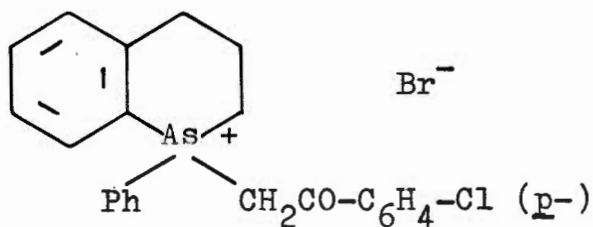


is in accord with all the information available, but when the compound was dried even at 105° under high vacuum, the analytical figures remained unchanged and the water in the dihydrate must

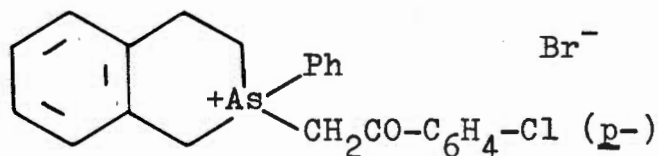
therefore be very firmly bound. Attempts are now being made to repeat the above preparation of the spiro salt. On this occasion it is hoped that the triphenylcarbinol formed during the reaction can be removed either by high-vacuum distillation, or by oxidation of the arsinoline (XC) followed by ether-extraction of the triphenylcarbinol. The residual oxide could then be reduced with sulphur dioxide and the treatment with thionyl chloride repeated. Unfortunately, steam distillation cannot be employed to effect a separation, since triphenylcarbinol is not steam-volatile.

For the purpose of obtaining data for drawing a comparison between the molecular rotations of a series of isomeric compounds which possess, as the hetero atom, an atom of the same element, but differ only in the position of that atom in the heterocyclic system, the preparation and resolution of (\pm)-1-*p*-chloro-phenacyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium bromide (XCI) was next attempted, the isomeric "iso" compound (XCII) having previously been

synthesised by Holliman and Mann⁶ (by quaternisation of 2-phenyl-1:2:3:4-tetrahydroisoarsinoline with p-chlorophenacyl bromide) and resolved via the bromocamphorsulphonate.



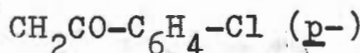
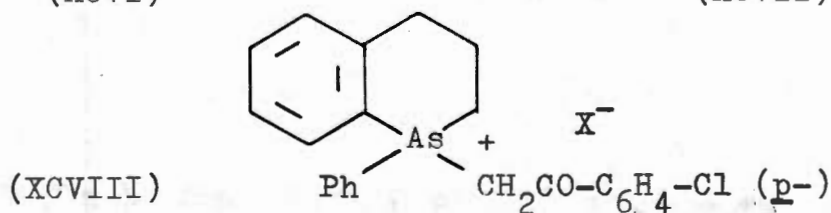
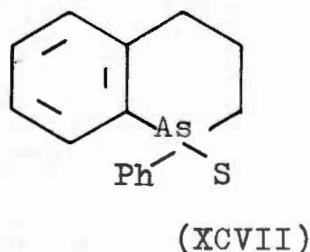
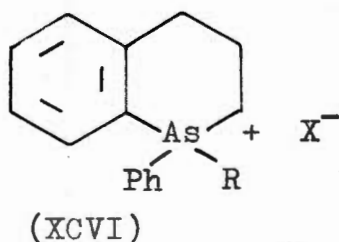
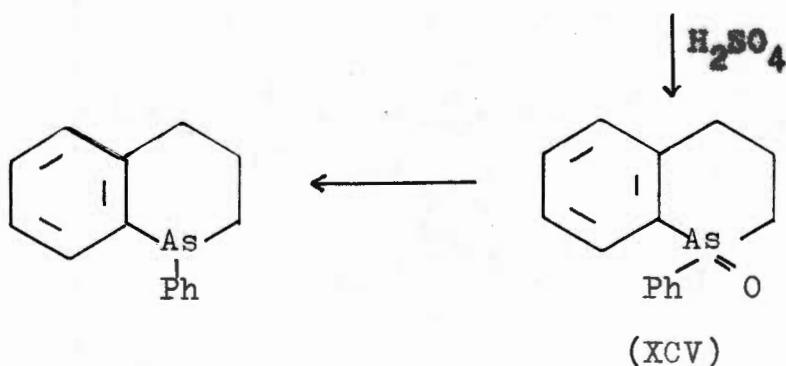
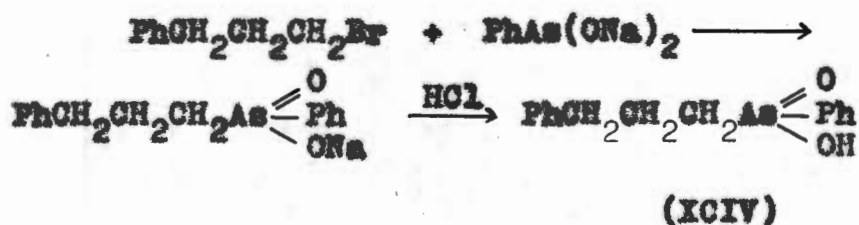
(XCI)



(XCII)

Initial attempts at the preparation of the unknown 1-phenyltetrahydroarsinoline (XCIII) were made by condensation of phenyl magnesium bromide with 1-chloro-1:2:3:4-tetrahydroarsinoline. This was highly successful, the arsinoline (XCIII) being obtained as a colourless liquid which crystallised on standing,

this oil did contain the arsinic acid (XCIV) was shown by the fact that it underwent cyclisation with hot, concentrated sulphuric acid to yield the arsine oxide (XCV) which was then reduced with sulphur dioxide to yield the required arsinoline:



The overall yield however, was only 6% as found from the weight of quaternary salt which was formed by interaction of the product with *p*-chlorophenacyl bromide. In spite of the low yield, this 5-step procedure (starting with cinnamyl alcohol) is more advantageous than the 9-step procedure employing the 1-chloroarsinoline, for which the overall yield is lower.

The phenylarsinoline readily formed a variety of quaternary derivatives in common with the isomeric 2-phenylisarsinoline. It gave a methiodide (XCVI, R = Me, X = I) which, with sodium picrate, furnished the methopicate (XCVI, R = Me, X = $C_6H_2O_7N_3$). The hydroxy-nitrate (XCVI, R = OH, X = NO_3) formed by oxidation of the arsinoline, could not be obtained crystalline. Treatment of the arsinoline with one mole of bromine in chloroform, yielded the dibromide which, without isolation, afforded the hydroxy-picrate (XCVI, R = OH, X = $C_6H_2O_7N_3$) with picric acid. The dibromide also furnished, on reaction with hydrogen sulphide, the arsinoline sulphide

(XCVII), obtained initially as a gum, which, after standing under ethanol in an open tube for six weeks, finally crystallised.

Condensation of the arsinoline with *p*-chlorophenacyl bromide in dry benzene, readily afforded the quaternary bromide (XCVIII, X = Br) required for resolution. This compound further yielded with sodium picrate, the *p*-chlorophenacyl picrate (XCVIII, X = $C_6H_2O_7N_3$) which, with potassium iodide, gave the corresponding iodide (XCVIII, X = I).

The resolution of the bromide (XCVIII, X = Br) was next attempted. The (+)-camphor-sulphonate was readily obtained crystalline, but after successive recrystallisations from aqueous ethanol, the melting point and the specific rotation were not significantly changed. It was apparent that resolution was not proceeding, but, to confirm this, the four-times recrystallised material was converted into the picrate which was inactive. The (+)-bromocamphorsulphonate was also readily obtained crystalline and at first appeared very promising since, after four recrystallisations from

ethanol, the melting point had been raised from $182-185^{\circ}$ to 261° and the molecular rotation from $+321^{\circ}$ to $+690^{\circ}$. After the fifth recrystallisation however, the melting point fell to $188-191^{\circ}$ and the molecular rotation to $+404^{\circ}$. When attempts were made to repeat the resolution starting with a fresh sample of the (+)-bromocamphorsulphonate, material of low melting point was obtained and this was not significantly changed after nine recrystallisations from ethanol when it was $184.5-185^{\circ}$. It was evident that the salt was now being deposited from solution as a partial racemate and that it was therefore pointless to proceed with attempted resolution via the bromocamphorsulphonate. Attempts were next made to prepare the (-)-mentheryacetate, but these were unsuccessful. On each occasion, only a very small quantity of crystalline material was obtained, the major portion of the material apparently undergoing considerable decomposition to an ether-soluble oil. The small quantity of crystalline material gave analysis figures which were consistent over three different preparations,

but were not those required for the (-)-menthoxy-acetate or for the solvated product. Finally, the (-)-1-N-phenylethylphthalamate was prepared, but it was obtained as a gum which could not be induced to crystallise. Lack of time prevented further attempted resolution of the arsonium salt.

EXPERIMENTAL

SECTION I: SYNTHESIS OF 1-METHYL-1:2:3:4-TETRA-
HYDROARSINOLINE

1. Methyldichloroarsine

Modified from Holliman and Mann, J. Chem., Soc., 1943, 549.

To a hot solution of sodium hydroxide (256 gm.) in water (750 ml.), arsenious oxide (168 gm.) was added with stirring to give a clear solution of sodium arsenite. The solution was cooled to 10° in a three-necked flask fitted with sealed stirrer, dropping funnel, reflux condenser and thermometer. Dimethyl sulphate (267 gm., 2.5 mols.) was slowly added to the cooled, stirred solution over 2.5 hours. The mixture was allowed to stand at room temperature overnight and then heated under reflux on a water bath at 80° for 2 hours. After cooling, sulphur dioxide was passed through the mixture until the contents of the flask had become solid with precipitate (about 5 hours is required). Concentrated hydrochloric acid (1 litre) was added and the vapour from 2 litres boiling hydrochloric acid passed through the solution for 6 hours after which it was "steam distilled" in the vapour from boiling hydrochloric acid until no further oily droplets passed over with

the distillate (about 7 hours). The dense, colourless oil was separated, dried over anhydrous sodium sulphate and distilled, the fraction boiling at $129-133^{\circ}/754$ mm. being the required product. Yield: 171 gm., 62%.

2. Dimethyliodoarsine (from methyldichloroarsine)

Modified from Burrows and Turner,
J. Chem. Soc., 1921, 426.

Methyldichloroarsine (522 gm., 1 mol.) in 96% ethanol (2270 ml.) was placed in a 5-litre, 3-necked flask fitted with sealed stirrer, reflux condenser and dropping funnel. Whilst the solution was thoroughly chilled in an ice-bath, an ice-cold solution of sodium hydroxide (555 gm.) in water (800 ml.) was slowly added with vigorous stirring over 1.5 hours. A white solid separated, the mixture becoming quite viscous towards the end of the addition. After thoroughly chilling in ice, methyl iodide (400 gm., 1.13 mols.) was slowly added over 2 hours with vigorous stirring. After stirring for a further 6 hours, the mixture was set aside at room temperature for 33 hours. The alcohol was distilled off at atmospheric pressure, the contents of the flask being stirred to prevent bumping. After thoroughly chilling in ice, cold water (2430 ml.) followed by hydriodic acid (1335 gm., 780 ml., S.G. 1.7, 3.24 mols.) was slowly added over 45 minutes with stirring.

from time to time with shaking. A pale-yellow, dense oil separated slowly. Whenever the solution faded to a pale yellow colour, the gas was passed for further 10 minute periods until eventually the precipitation of sulphur occurred. The lower layer of the arsine was separated, dried over anhydrous calcium chloride and finally distilled at atmospheric pressure, the fraction boiling at $155-158^{\circ}/750$ mm. being collected. Yield: 144.4 gm. (85%).

4. 3-Phenylpropan-1-ol (from cinnamaldehyde)

c.f. Covert and Adams, J. Amer. Chem. Soc., 1932, 54, 4116.

200 Gm. dried and redistilled cinnamaldehyde (b.p. $128-132^{\circ}/18$ mm.) in absolute ethanol (200 ml.) were hydrogenated in the presence of 22 ml. settled Raney nickel catalyst (containing 1.2 gm./ml.) also in ethanol, at a starting pressure of 80 atmospheres, the pressure being raised twice during the course of the reduction to 77 atmospheres and occupying 42 hours. The catalyst was filtered off and the ethanol removed by distillation, yielding 184 gm. of the alcohol, b. p. $124-126^{\circ}/15$ mm. (89%). The product gave a negative test for unsaturation with a solution of bromine in chloroform.

In another preparation, 166 gm. of the

aldehyde in 250 ml. ethanol were hydrogenated in the presence of 15 ml. of the settled catalyst at a starting pressure of 100 atmospheres, the pressure being raised once during the course of the reduction to 87 atmospheres, 24 hours being required for completion of the reaction. Yield: 141 gm., 83%.

5. 3-Phenylpropan-1-ol (from cinnamyl alcohol with Adams' catalyst)

0.3 Gm. Adams' catalyst was reduced to platinum black by shaking with 50 ml. 96% ethanol for 20 minutes in hydrogen at 2.3 atmospheres pressure. 42 Gm. cinnamyl alcohol in 100 ml. 96% ethanol were then added to the reaction bottle and shaken at a starting pressure of 2.3 atmospheres, the time required for constant pressure to be attained being 5 hours. The alcohol was distilled off at atmospheric pressure and the residue fractionated under reduced pressure, collecting the fraction distilling at 126-129°/14 mm. Yield: 39.5 gm., 94%.

In another preparation, 175 gm. cinnamyl alcohol in 400 ml. 96% ethanol were hydrogenated in the presence of 0.5 gm. Adams' catalyst at a starting pressure of 40 atmospheres hydrogen. The resulting solution, on being worked up as before, yielded 147 gm. hydrocinnamyl alcohol distilling at 132-137°/17 mm. (85%).

6. 3-Phenylpropan-1-ol (from cinnamyl alcohol with Raney nickel).

A solution of cinnamyl alcohol (139 gm.) in absolute ethanol (400 ml.) was placed in an autoclave together with approximately 15 gm. Raney nickel in ethanol and the hydrogen pressure raised to 57 atmospheres. The stirrer was set in operation and after 10 minutes at room temperature, the pressure had dropped to a stationary value of 37 atmospheres. On raising the pressure to 67 atmospheres, no further drop occurred. The catalyst was filtered off, the alcohol distilled at atmospheric pressure and the residue fractionated under reduced pressure, the whole distilling at 124-126°/15 mm. Yield: 135 gm., 96%.

7. 3-Phenylpropyl bromide

Ice-cold concentrated sulphuric acid (161 ml.) was slowly added with stirring to chilled constant boiling (48%) hydrobromic acid (530 ml.) over 45 minutes. 3-Phenylpropan-1-ol (225 gm.) followed by 106 ml. cold concentrated sulphuric acid were then added with stirring over periods of 25 minutes and 15 minutes respectively, after which the mixture was boiled under reflux with stirring for 3.5 hours. When cool, the upper layer was diluted with ether, washed with water, 5% aqueous sodium hydroxide, and then 3 times with water, finally being dried over anhydrous calcium chloride. The ether was distil-

led off at atmospheric pressure and the product fractionated under reduced pressure, collecting the fraction distilling at 116-118°/16 mm.

Yield: 267 gm., 81%.

8. 3-Phenylpropyldimethylarsine

c.f. Burrows and Turner, J. Chem. Soc., 1921, 426.

Ether-washed and dried magnesium turnings (17 gm., 1.08 atoms) in a three-necked flask fitted with sealed stirrer, dropping funnel and reflux condenser (CaCl₂ tubes) were covered with dry ether and 50 ml. of a solution of 3-phenylpropyl bromide (138 gm., 1.1 mols.) in dry ether (420 ml.) were added. On warming to reflux, the reaction commenced, the rest of the solution being added at such a rate that refluxing was maintained without external cooling, whilst the mixture was stirred in a nitrogen atmosphere. After the addition, the mixture was boiled under reflux for 2 hours. Ether (250 ml.) was distilled off in a stream of nitrogen and replaced with an equal volume of dry benzene. After thoroughly chilling in ice, a solution of dimethyliodarsine (146 gm., 1 mol.) in dry benzene (400 ml.) was slowly added and the mixture boiled under reflux for 2 hours. After again thoroughly chilling in ice, the product was hydrolysed by the addition of 500 ml. sulphuric acid (1 vol. acid : 9 vols. water). After stirring in ice for 30 minutes,

the benzene layer was separated, the aqueous layer extracted with benzene, the combined benzene solutions washed once with 10% aqueous sodium carbonate, twice with water and dried over anhydrous calcium chloride. The benzene was removed by distillation under nitrogen at atmospheric pressure and the residue distilled under reduced pressure employing a nitrogen leak. A small first fraction was followed by the product distilling at 124-130°/12.5 mm., 120 gm., 85%. In subsequent preparations, the following boiling points were recorded: 127-132°/18 mm., 134-136°/18 mm.

9. 3-Phenylpropyldimethylarsine dichloride

c.f. Burrows and Turner, J. Chem. Soc., 1921, 426.

A steady stream of chlorine was passed through concentrated sulphuric acid and then led through 900 ml. previously dried and redistilled carbon tetrachloride. A 5 m. aliquot of this solution was made up to 100 ml. with dry carbon tetrachloride in a volumetric flask and a 25 ml. aliquot of this diluted solution was pipetted into a 250 ml. volumetric flask, followed by the addition of 20 ml. 20% aqueous potassium iodide, the liberated iodine being titrated against a standard solution of sodium thiosulphate with constant shaking, using starch as indicator. The concentration of the chlorine solution was thus determined.

This preparation was conducted throughout in a stream of dry nitrogen. 3-Phenylpropyl-dimethylarsine (207 gm., 1 mol.) was dissolved in dry carbon tetrachloride (350 ml.) in the usual Grignard-type apparatus under anhydrous conditions. 540 ml. of a solution of chlorine in carbon tetrachloride containing 134.2 gm./litre (i.e. 67.5 gm. chlorine, 1 mol.) were slowly added with stirring to the arsine whilst the flask was cooled in an ice bath. As the last few ml. of the chlorine solution entered the flask, the reaction mixture became yellow due to the presence of free chlorine. The carbon tetrachloride was distilled off from a mantle at atmospheric pressure, the last few drops being drawn off under reduced pressure with a nitrogen leak. The dichloride remained as a pale-yellow oil.

10. 3-Phenylpropylmethylchloroarsine

c.f. Burrows and Turner, J. Chem. Soc., 1921, 426.

The following preparation was conducted in an atmosphere of nitrogen throughout.

The oily dichloride from the previous preparation was heated under reflux at 160-175°/15 mm. in an oil bath for 1.75 hours. Effervescence commenced when the temperature had reached 145° and remained vigorous for 1 hour during the course of which the pressure rose due to the evolution

of methyl chloride and finally slowly returned to its original value. The residual viscous, red liquid was distilled under reduced pressure, the fraction distilling at $158-162^{\circ}/14$ mm. being the required arsine; a large low-boiling fraction was also obtained, which, on refractionation, yielded a further small quantity of the arsine. The total yield was 104 gm. of a colourless liquid (46%); in a subsequent preparation, a b. p. of $156-162^{\circ}/13.5$ mm. was recorded. It appears that the more concentrated the chlorine solution employed, the higher is the yield of the chloroarsine.

Rechlorination of the low-boiling fraction was attempted in case it should contain any of the unchanged dimethylarsine. Approximately 100 ml. of the chlorine solution was taken up before the yellow colour of free chlorine appeared, but after distilling off the carbon tetrachloride, and heating under reduced pressure as before, no further quantity of the arsine could be obtained, the only product being a colourless liquid distilling at $96-100^{\circ}/11.5$ mm.

11. 3-Phenylpropyldimethylarsine dibromide

c.f. Burrows and Turner, J. Chem. Soc.,
1921, 426.

385 ml. of a solution of bromine in carbon tetrachloride containing 225.4 gm./litre were slowly added to 3-phenylpropyldimethylarsine

14. 1-Methyl-1:2:3:4-tetrahydroarsinoline (from 3-phenylpropylmethylbromarsine)

Modified from Burrows and Turner, J. Chem. Soc., 1921, 426.

When 47.7 gm. (1.19 mols.) anhydrous aluminium chloride in 500 ml. dry benzene was treated with 86 gm. (1 mol.) 3-phenylpropylmethylbromarsine in exactly the same manner as described in the previous preparation, two fractions were obtained on distillation of the product. The second and main fraction (b.p. 136-166°/12 mm., 54 gm., 73%) was the required arsine in a crude condition. On redistillation with a fractionating column, it yielded the product as a colourless liquid, b. p. 139-144°/12 mm., 30.3 gm., 50%.

15. 1:1-Dimethyl-1:2:3:4-tetrahydroarsinolinium bromide

When 3.0 gm. 1-methyl-1:2:3:4-tetrahydroarsinoline and 12 ml. (20.8 gm., 14.8 mols.) methyl bromide were allowed to stand in a stoppered flask at 5° for 25 hours, the mixture set to a solid cake as the methobromide was formed. Ether was added and the excess methyl bromide boiled off as the flask returned to room temperature. After filtering off the product, and washing with ether, 3.6 gm. of the methobromide were obtained, m. p. 246-247° with effervescence. (83%). After three recrystallisations from absolute ethanol, the dried product had m. p.

250–251° with effervescence.

Analysis: Found: C, 43.6; H, 5.2; Br (ionic), 26.8%.
 $C_{11}H_{16}AsBr$ requires: C, 43.6; H, 5.3; Br, 26.4%.

16. 1:1-Dimethyl-1:2:3:4-tetrahydroarsinolinium iodide

The above methobromide, in aqueous solution, when treated with a saturated aqueous solution of potassium iodide, rapidly deposited the crystalline arsinoline methiodide, which was filtered off, washed with ethanol and dried, m. p. 231–233°. (Burrows and Turner, J. Chem. Soc., 1921, 426, record m. p. 235°). On being warmed, an ethanolic solution of the methiodide underwent no change in colour.

17. 1:1-Dimethyl-1:2:3:4-tetrahydroarsinolinium picrate

A saturated aqueous solution of sodium picrate was added in excess to an aqueous solution of the above methobromide, an oil being immediately precipitated which rapidly crystallised. The methopicrate was filtered off and recrystallised five times from ethanol to yield glistening plates of m. p. 119–120° after drying.

Analysis: Found: C, 45.0; H, 4.0; N, 9.2%.
 $C_{17}H_{18}O_7N_3As$ requires: C, 45.2; H, 4.0; N, 9.3%.

Similarly, the methopicate was obtained from the methiodide, on reaction with sodium picrate. After recrystallisation from ethanol, it had m. p. 118-119.5° alone and 119-121° in admixture with the above analysed sample.

18. 1-Hydroxy-1-Methyl-1:2:3:4-tetrahydro-arsinolinium picrate

1-Methyl-1:2:3:4-tetrahydroarsinoline (1 gm.) was just covered with water and 2.5 ml. concentrated nitric acid added dropwise with stirring and chilling in ice. Much heat was evolved along with nitrous fumes. The oily hydroxy-nitrate thus obtained could not be caused to crystallise and was thus converted directly into the corresponding hydroxy-picrate. The solution of the hydroxy-nitrate was brought to pH 3 (test paper) by the addition of dilute sodium hydroxide solution drop by drop (i.e. just before precipitation of the arsine dihydroxide commenced). A saturated aqueous solution of picric acid was added and after standing at room temperature for 36 hours, the precipitated hydroxy-picrate was filtered at the pump. After two recrystallisations from ethanol, followed by drying, the crystalline product had m. p. 151-152°.

Analysis: Found: C, 42.8; H, 3.4; N, 9.4%.

$C_{16}H_{16}N_3O_8As$ requires: C, 42.4; H, 3.6; N, 9.3%.

19. Bis(1:1-dimethyl-1:2:3:4-tetrahydroarsino-
linium) chloroplatinate

The methobromide (part 15) in cold aqueous solution, when treated with a cold aqueous solution of chloroplatinic acid, rapidly deposited the bisarsonium chloroplatinate. This was filtered off and recrystallised three times from water in which it was sparingly soluble. After drying, the deep-orange crystalline material melted at 218-219° with effervescence.

Analysis: Found: C, 30.9; H, 3.8; Pt, 23.2%.

$C_{22}H_{32}As_2PtCl_6$ requires: C, 30.9; H, 3.8; Pt, 22.8%.

SECTION II: FIRST ATTEMPTED NEW SYNTHESIS OF
1-METHYL-1:2:3:4-TETRAHYDROARSINOLINE

1. o-Bromobenzyl bromide

c.f. Kenner and Wilson, J. Chem. Soc.,
1927, 1110; Holliman and Mann, ibid.,
1942, 739.

In a flask fitted with a dropping funnel and reflux condenser closed with calcium chloride tubes, were placed 200 gm. (1.17 mols.) o-bromotoluene. Whilst the temperature was maintained at 135° by heating in a silicone bath, 160 gm. (1 mol., 85% of the theoretical quantity) bromine was added dropwise without agitation over 3 hours. A vigorous evolution of hydrogen bromide occurred during the addition. The crude product was fractionated under reduced pressure, the first fraction distilling at 78-85°/14 mm. being mainly unchanged o-bromotoluene. This fraction was re-distilled at atmospheric pressure, collecting the fraction of b. p. 180-186°/759 mm. and finally under reduced pressure once more, the pure o-bromotoluene distilling at 66-68°/14.5 mm., 50 gm. The second fraction was the product, distilling at 131-134°/14 mm., yielding 187 gm. of a colourless oil which, on cooling, deposited a colourless, crystalline mass. Yield: 85%, allowing for the recovered o-bromotoluene.

2. o-Bromo-3-phenylpropan-1-ol

c.f. Beeby and Mann, J. Chem. Soc.,
1951, 413.

This preparation was conducted throughout in an atmosphere of nitrogen. Magnesium turnings (32 gm., 1.03 mols.) were covered with dry ether in the usual Grignard apparatus. 20 ml. of a solution of o-bromobenzyl bromide (320 gm., 1 mol.) in dry ether (1 litre) were added and the reaction started by adding a crystal of iodine and gentle warming, after which the remainder of the bromide solution was slowly added with stirring at room temperature over 3.5 hours (i.e. at such a rate as to prevent refluxing of the ether without external cooling). The reaction was completed by stirring for three hours at room temperature. The flask was chilled in ice and ethylene oxide (130 ml., 113 gm., 2 mols.) in ether (250 ml.), chilled to 0° was slowly added with vigorous stirring over 2.5 hours, observing all the usual precautions against loss of the reagent. After the addition was complete, a sticky solid had separated and the reaction mixture was set aside at room temperature overnight in an atmosphere of nitrogen. The mixture was hydrolysed with sulphuric acid (750 ml., 1 vol. acid : 9 vols. water), the ether layer separated, the aqueous layer extracted twice with ether, the combined ethereal solutions washed once with 10% aqueous sodium carbonate and then twice with water before

drying over anhydrous calcium chloride. The ether was distilled off at atmospheric pressure and the residue fractionated, firstly under water-pump vacuum and finally under high vacuum, employing a nitrogen leak. Three fractions were collected:

fraction 1, (ethylene bromohydrin), b. p. 62-70°/
14 mm., (149 gm.);

fraction 2, b. p. 92-106°/0.4 mm., (15 gm.);

fraction 3, b. p. 106-108°/0.4 mm.

The third fraction was the product, a viscous, colourless liquid. Yield: 133 gm. (49%); reported yield, 47%. The residue amounted to approximately 60 ml. of semi-solid material reported to contain 2:2'-dibromodibenzyl and 2:2'-di-(2-hydroxyethyl)di-benzyl.

3. o-Bromo-3-phenylpropyl bromide

c.f. Beeby and Mann, J. Chem. Soc.,
1951, 414.

Phosphorus tribromide (9.3 ml., 26.5 gm., 0.33 mol.) was slowly added with vigorous stirring to o-bromo-3-phenylpropan-1-ol (56.5 gm., 1 mol.) under reflux and anhydrous conditions over 1 hour. Without agitation, the temperature was slowly raised to 100°, where it was maintained for 1 hour. After cooling in ice, dry ether (125 ml.) was added and the solution washed three times with water; the ethereal layer was separated and dried over anhydrous calcium chloride. The

ether was removed at atmospheric pressure and the residue distilled under high vacuum, employing a nitrogen leak. Practically the whole distilled at $94^{\circ}/0.8$ mm., yielding 55.6 gm. of a colourless liquid (74%).

4. o-Bromo-3-phenylpropyl methyl ether

c.f. Beeby and Mann, J. Chem. Soc.,
1951, 414.

Sodium (8 gm., 1.73 atoms), in the form of wire, was dissolved in 180 ml. dry methanol and the resulting solution chilled with stirring in an ice-bath. o-Bromo-3-phenylpropyl bromide (55.6 gm., 1 mol.) was now slowly added to the chilled solution with stirring under reflux and anhydrous conditions, after which the mixture was slowly brought to the boil and boiled under reflux with stirring for 1 hour. The methanol was distilled off with vigorous stirring to prevent serious bumping and 250 ml. water were added to the cold residue; the aqueous solution was extracted three times with ether and the ethereal solution washed twice with water and then dried over anhydrous calcium chloride. The ether was distilled off and the residue fractionated under reduced pressure, collecting the fraction distilling at $127-130^{\circ}/15$ mm. Yield: 39.2 gm. of a colourless liquid. (86%).

5. Dimethyl(o-3-methoxypropylphenyl)arsine

A solution of o-bromo-3-phenylpropyl methyl ether (12.1 gm., 1 mol.) and ethyl bromide (2.9 gm., 0.5 mol.) in dry ether (40 ml.) was slowly added to magnesium turnings (2.05 gm., 1.58 atoms) previously activated with iodine and then covered with dry ether (10 ml.) in the usual Grignard apparatus equipped with a nitrogen inlet tube. A stream of nitrogen was led through the flask whilst a few ml. of the solution of the bromides was added, the reaction being started with gentle warming. The remainder of the solution was added over 25 minutes, i.e. at such a rate as to cause gentle refluxing of the ether without external cooling. After boiling under reflux for 3 hours with stirring, the solution was cooled and stirred whilst a solution of dimethyl-iodoarsine (14.7 gm., 1.2 mols.) in sodium-dried benzene (40 ml.) was slowly added, the mixture being refluxed again for 2 hours. When cool, the reaction product was hydrolysed with 200 ml. sulphuric acid (1 vol. acid : 9 vols. water). The foul-smelling benzene layer was separated and the aqueous layer extracted three times with benzene. The combined benzene extracts were washed once with water before being dried over anhydrous calcium chloride in an atmosphere of nitrogen. The benzene was distilled off at atmospheric pressure in a stream of nitrogen and the residue distilled under reduced pressure

with a nitrogen leak. A small forerun was followed by the product distilling at 142-146°/18 mm., yielding 8.8 gm. of a colourless liquid. (66%).

Analysis: Found: C, 56.3; H, 6.4%. $C_{12}H_{19}OAs$ requires: C, 56.7; H, 7.5%.

6. Trimethyl(o-3-methoxypropylphenyl)arsonium picrate

The above arsine (0.8 gm.) was warmed under reflux with excess methyl iodide in an atmosphere of nitrogen for one hour. The methyl iodide was allowed to evaporate spontaneously and the gummy residue dried in vacuo. The residue was triturated with dry ether several times but gave no crystalline material on this treatment or on being taken up in various solvents. The gummy methiodide was therefore taken up in ethanol and to this solution, a hot, saturated ethanolic solution of sodium picrate was added. On cooling, the solution deposited the yellow, crystalline methopicrate either on standing for 24 hours, or immediately, on dilution with water and scratching. After three recrystallisations from ethanol and drying, the product melted at 108.5-110°.

Analysis: Found: C, 45.9; H, 4.9; N, 8.5%. $C_{19}H_{24}N_3O_8As$ requires: C, 45.9; H, 4.9; N, 8.5%.

7. Attempted preparation of 1:1-dimethyl-1:2:3:4-tetrahydroarsinolinium bromide

Dimethyl(o-3-methoxypropylphenyl)arsine (3.9 gm.) and a mixture of glacial acetic acid (100 ml.) and constant boiling hydrobromic acid (100 ml.) were heated under reflux at 120° for 3.5 hours whilst a stream of dry hydrogen bromide generated by combination of elementary hydrogen and bromine and freed from bromine by passage over copper gauze was passed through the reaction mixture. After cooling, the solvent was distilled off under nitrogen, the residue extracted twice with chloroform, washed with water, 10% aqueous sodium carbonate, once again with water and the extract dried over anhydrous calcium chloride. The chloroform was distilled off under nitrogen leaving a mobile, ether-soluble liquid from which no solid material could be obtained. Distillation under nitrogen yielded about 1 ml. of a golden oil, b. p. 141-145°/17 mm. which gave no ether-insoluble product after being refluxed with methyl iodide under nitrogen for 50 minutes. Although the liquid distillate had an odour resembling that of 3-phenylpropyl bromide, no solid derivative could be obtained on interaction with ammonium dithiocarbamate.

SECTION III: SECOND ATTEMPTED NEW SYNTHESIS
OF 1-METHYL-1:2:3:4-TETRAHYDRO-
ARSINOLINE

1. o-Bromo-3-phenylpropyl trityl ether

Triphenylchloromethane (60 gm.) was dissolved in dry pyridine (100 ml.). The suspension was warmed on the water bath to obtain a clear solution, whilst o-bromo-3-phenylpropan-1-ol (46 gm., 1 mol.) was slowly added dropwise from a dropping funnel to the stirred solution, the reaction being conducted under reflux and under anhydrous conditions. After about half of the alcohol had been added, precipitation of the product commenced. The suspension was then heated for 2 hours on the boiling water bath and whilst still warm, was poured into 400 ml. water. The product was precipitated as an oil which solidified on being cooled with stirring. It was filtered, washed with water, dried at the pump and recrystallised from ethanol (about 500 ml. are required). Yield: 80.0 gm., m. p. 84-86°, (82%). A sample of this material, after five recrystallisations from ethanol, followed by drying, had m. p. 89-91°.

Analysis: Found: C, 73.35; H, 5.7%. $C_{28}H_{25}OBr$
 requires: C, 73.5 ; H, 5.5%.

2. 1-Methyl-1:2:3:4-tetrahydroarsinoline (by thermal decomposition of 1:1-dimethyl-1:2:3:4-tetrahydroarsinolinium bromide)

1:1-Dimethyl-1:2:3:4-tetrahydroarsinolinium bromide (4.0 gm.) was placed in a small distilling flask having a short distillation path. The flask was heated under reduced pressure (23 mm.) the temperature being raised very cautiously, whilst a nitrogen leak was used. When the external temperature had reached 260° , the methobromide commenced to melt, accompanied by vigorous effervescence. The pressure rose a little due to the evolved methyl bromide. The bath temperature was maintained at $260-270^{\circ}$ for 15 minutes, during which time a colourless liquid distilled slowly into the receiver (b. p. $156-159^{\circ}/26$ mm.). At the end of the decomposition, no residue remained in the distilling flask, whilst the distillate smelled strongly of 1-methyl-1:2:3:4-tetrahydroarsinoline. Yield: 2.5 gm., 95%.

The whole of the above product, on being allowed to stand in a stoppered flask at 5° in the presence of methyl bromide (10 ml., 17.3 gm., 15.2 mols.) for several days, was reconverted into the methobromide, yielding in all, 2.3 gm. of the original methobromide. This represents a yield of 64% and shows that the above distillate must have consisted of practically pure 1-methyl-1:2:3:4-tetrahydroarsinoline. The crude material

had m. p. 248-250°; mixed m. p. with an authentic sample of the methobromide (of m. p. 250-251°), 247-249°.

3. Attempted preparation of 1:1-dimethyl-1:2:3:4-tetrahydroarsinolinium bromide

The following reaction was conducted throughout in an atmosphere of nitrogen.

A few ml. of a solution of *o*-bromo-3-phenylpropyl trityl ether (15.0 gm., 1 mol.) and ethyl bromide (1.79 gm., 0.5 mol.) in dry ether (120 ml.) were added to activated magnesium powder (1.26 gm., 1.58 atoms) covered with dry ether in the usual Grignard apparatus. The reaction was started with gentle warming and the remainder of the solution of the bromides added with stirring at such a rate that the ether boiled gently under reflux without external cooling. The mixture was boiled under reflux with stirring for 2.75 hours, then cooled and stirred whilst dimethyliodarsine (9.2 gm., 1.2 mols.) in dry benzene (50 ml.) was added. After boiling under reflux for 2 hours, the mixture was cooled and stirred whilst a saturated aqueous solution of ammonium chloride was slowly added. The benzene layer was separated, washed twice with water and dried over anhydrous magnesium sulphate. The benzene was removed by distillation at atmospheric pressure, leaving 13.3 gm. of a viscous residue.

The whole of the residue was mixed with 35% aqueous acetic acid and boiled under reflux

for 20 minutes, cooled, diluted with water and extracted with chloroform. The chloroform solution was washed twice with water and dried over anhydrous magnesium sulphate. The solvent was removed by distillation at atmospheric pressure and an attempt made to distil the residue under high vacuum, but only 4 drops of a liquid, distilling over the range $138-200^{\circ}/0.1$ mm. were obtained. This distillate crystallised in the receiver and consisted undoubtedly of triphenylcarbinol.

The residual gum (10 gm.) which could not be obtained crystalline, was treated with phosphorus tribromide (3.75 gm., 1.4 ml.) added slowly under nitrogen, the flask being kept chilled in ice. The residue was covered with water, stirred and heated on the water bath for 1.5 hours which caused it to crystallise as a pale-cream, ether-insoluble solid. The suspension was filtered, yielding 1.2 gm. of solid material, a further 1.8 gm. being deposited from the filtrate on standing. The combined solid material was recrystallised twice from diethyl carbonate when it had m. p. $255-267^{\circ}$ with previous softening. After five recrystallisations from diethyl carbonate, the m. p. was raised to $268-270^{\circ}$.

Analysis: Found: C, 69.4; H, 5.6%. 1:1-Dimethyl-1:2:3:4-tetrahydroarsinolinium bromide, $C_{11}H_{16}BrAs$ requires: C, 43.6; H, 5.3%.

The Beilstein test showed halogen to be absent. The compound, dimethyltritylarsine oxide, $Ph_3C-As(O)Me_2$, $C_{21}H_{21}OAs$, requires: C, 69.2; H, 5.8% and is thus

consistent with the above results. This product was not further investigated.

2. Attempted preparation of 1-methyl-1:2:3:4-tetrahydroarsinoline

In case the above oil should contain methyl-3-phenylpropylarsinic acid, the whole of it (74 gm.) was mixed with concentrated sulphuric acid (200 ml.) and heated to 100° on a water bath for 15 minutes. When cool, the reaction mixture was poured into water, the solution being cooled and neutralised with 30% aqueous sodium hydroxide. An oil was deposited which was extracted with chloroform, the chloroform extract washed with water, covered with a solution of 300 ml. water containing 0.5 gm. potassium iodide and 300 ml. concentrated hydrochloric acid, and sulphur dioxide passed through the cooled mixture for 2 hours. After allowing to stand for 8 hours, the chloroform extract was separated, washed once with water, rapidly with 7% aqueous sodium hydroxide and twice with water before being dried over calcium chloride in an atmosphere of nitrogen. When the chloroform had been removed in a stream of nitrogen, only about 0.5 gm. of residue remained from which no methiodide could be obtained.

SECTION V: ATTEMPTED SYNTHESIS OF (\pm)-As-SPIRO-
bis-1:2:3:4-TETRAHYDROARSINOLINIUM
BROMIDE

1. 1-Methyl-1:2:3:4-tetrahydroarsinoline dichloride

c.f. Roberts, Turner and Bury, J. Chem. Soc.,
1926, 1443.

A solution of chlorine in carbon tetrachloride was prepared and standardised as described in the preparation of 3-phenylpropyldimethylarsine dichloride (section 1, part 9). 1-Methyl-1:2:3:4-tetrahydroarsinoline (19 gm., 1 mol.) was dissolved in 60 ml. dry carbon tetrachloride in a 3-necked flask fitted as for a Grignard reaction with a nitrogen inlet tube. Whilst this solution was chilled in ice, 82 ml. of a solution of chlorine in carbon tetrachloride containing 114 gm./litre (i.e. 9.35 gm. chlorine, 1.4 mols.) was slowly added under nitrogen with stirring over a period of 1 hour. The carbon tetrachloride was distilled off at atmospheric pressure, leaving a white, crystalline residue of the hygroscopic product.

2. 1-Chloro-1:2:3:4-tetrahydroarsinoline

c.f. Roberts, Turner and Bury, J. Chem. Soc., 1926, 1443.

The product from the above preparation

was heated under reflux under reduced pressure in an atmosphere of nitrogen. The bath temperature was gradually raised to 145° during which time effervescence occurred and the pressure rose due to the evolution of methyl chloride. After 10 minutes at this temperature, the pressure had returned to its former value and the solid had been converted into a chocolate-brown liquid which, after cooling, was transferred to a distilling flask and fractionated under reduced pressure employing a nitrogen leak. Only one fraction was obtained, distilling at $160-165^{\circ}/15$ mm., yielding 18.2 gm. of a pale-yellow oil which solidified on standing. (87%). In subsequent preparations, the following boiling points were recorded: $168-171^{\circ}/18.5$ mm., $165-169^{\circ}/17$ mm., $155-158^{\circ}/13$ mm. As found in the preparation of 3-phenylpropylchloromethylarsine, it again appears that the more concentrated the chlorine solution employed, the higher is the yield of product.

3. n-Butyllithium

c.f. Adams (Ed.): Organic Reactions, VIII, page 285.

Sodium dried ether (150 ml.) was placed in a 500 ml. 4-necked flask fitted with a low-temperature thermometer, double-surface reflux condenser, nitrogen inlet, sealed stirrer

and dropping funnel, the condenser and dropping funnel being closed with calcium chloride tubes. The flask was swept through with a stream of nitrogen washed free from oxygen by passage through an alkaline solution of pyrogallol (15 gm. pyrogallol in 100 ml. 50% aqueous sodium hydroxide) and dried by passage through two wash bottles containing concentrated sulphuric acid, the gas finally being passed through glass wool. Seventeen pieces of freshly-pressed lithium wire, each 20 cm. in length and weighing 0.2365 gm. per length (total: 4.3 gm., 1.25 atoms) were cut into small pieces and allowed to fall directly into the flask. The contents were stirred vigorously whilst 30 drops of a solution of freshly-dried and redistilled *n*-butyl bromide (35 gm., 0.50 mol.) in dry ether (500 ml.) were added. The contents of the flask were cooled to -10° in a solid carbon dioxide bath. After ten minutes, bright spots appeared on the lithium indicating that the reaction had commenced. The bromide solution was allowed to run in slowly, the temperature being controlled at -10° when necessary by adding acetone to the solid carbon dioxide. The addition occupied 1.5 hours. After the addition, stirring was continued for 2 hours whilst the temperature was slowly raised to 10° . The excess lithium was filtered off through glass wool in a stream of dry nitrogen, the filtrate passing directly into a measuring cylinder which was swept out with dry nitrogen, stoppered and kept at -10° until required.

Part of the solution of n-butyllithium was poured into a burette and 2 ml. aliquots rapidly run off into conical flasks, one containing a solution of 1 ml. freshly dried and redistilled benzyl chloride in 10 ml. dry ether, and the other, 10 ml. water, both flasks being swept out with nitrogen and immediately stoppered. After allowing to stand for 1 minute, 10 ml. water were added to the first flask and the contents of both flasks titrated against a standard (approximately 0.1N) solution of hydrochloric acid using phenolphthalein as indicator, the flask being thoroughly shaken throughout the titration. The first titre represents the alkali due to compounds other than n-butyllithium, the second, the total alkali; the difference thus representing the alkali due to n-butyllithium. Determined in this way, the solution was found to be 1.005N after standing for 48 hours at -10° . The volume obtained (180 ml.) thus represents a yield of 11.6 gm. (70%) after 48 hours.

4. 1-(o-3-methoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline (first method)

This reaction was carried out in the usual Grignard apparatus fitted with nitrogen inlet and thermometer.

n-Butyllithium (125 ml., 0.75N solution, 5.5 gm., 1 mol.) was slowly added with stirring to a solution of o-bromo-3-phenylpropyl methyl ether (20 gm., 1 mol.) in 90 ml. dry ether over

a period of 40 minutes in an atmosphere of dry nitrogen, the temperature being maintained between 5° and 10° with external cooling. Dry ether (20 ml.) was added to dissolve some of the precipitated solid, after which the contents were boiled under reflux with stirring for 1.5 hours. After cooling, dry ether (85 ml.) was added, followed by the slow addition, with stirring, of a solution of 1-chloro-1:2:3:4-tetrahydroarsinoline (17.5 gm., 1 mol.) in dry ether (85 ml.), the contents then being boiled under reflux for 1 hour. The mixture was allowed to cool to room temperature and hydrolysed with 350 ml. sulphuric acid (1 vol. acid: 9 vols. water) and 250 gm. crushed ice. The ethereal layer was separated and the aqueous layer extracted three times with ether. The combined ethereal solution was washed once with 10% aqueous sodium carbonate and finally with water before being dried over anhydrous calcium chloride in an atmosphere of nitrogen. The ether was removed by distillation under nitrogen at atmospheric pressure and the residue fractionated under high vacuum employing a nitrogen leak. A small preliminary fraction was followed by the product distilling at $192-194^{\circ}/1$ mm., other boiling points recorded in subsequent preparations being $197-201^{\circ}/1.5$ mm., $171-173^{\circ}/0.3$ mm. Yield: 14.4 gm., 55%.

Analysis: Found: C, 66.5; H, 6.95%. $C_{19}H_{23}OAs$
requires: C, 66.7; H, 6.8%.

5. 1-(o-3-methoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline (second method)

Magnesium powder which had been activated by heating with iodine (1.47 gm., 1.58 atoms) was just covered with dry ether in the usual Grignard apparatus fitted with a nitrogen inlet. 3 ml. of a solution of freshly dried and re-distilled ethyl bromide (2.06 gm., 0.5 mol.) and o-bromo-3-phenylpropyl methyl ether (8.64 gm., 1 mol.) in dry ether (30 ml.) was added to the magnesium and after gentle warming, the formation of the Grignard reagent commenced. The remainder of the solution of the bromides was added over 45 minutes in an atmosphere of nitrogen and the mixture refluxed with stirring for 3 hours. After cooling, a solution of 1-chloro-1:2:3:4-tetrahydroarsinoline (9.5 gm., 1.1 mols.) in dry ether (50 ml.) was slowly added with stirring over 45 minutes after which the mixture was refluxed with stirring under nitrogen for 3 hours. When cool, hydrolysis was accomplished with 250 ml. sulphuric acid (1 vol. acid : 9 vols. water), the ethereal solution separated, the aqueous layer extracted twice with ether and the combined ethereal solutions washed once with 10% aqueous sodium carbonate and once with water before being dried over anhydrous calcium chloride in an atmosphere of nitrogen. The ether was distilled off at atmospheric pressure in a current of nitrogen and the residue fractionated under high vacuum employing a nitrogen leak.

50% hydrobromic acid in glacial acetic acid and first heated in a sealed tube at 100° for 4 hours and finally, for a further 21 hours, but in both cases, on removal of the solvent by distillation under reduced pressure, the mobile liquid residue gave almost no turbidity on addition of ether. Similarly, treatment of the arsinoline with constant-boiling aqueous hydrobromic acid (48%) under reflux in an atmosphere of nitrogen for 2 hours yielded an ether-soluble residue on removal of the solvent.

On repeating the experiment with 4 gm. of the arsinoline in 20 ml. of 50% (w/v) hydrobromic acid in glacial acetic acid, the mixture being heated at 120° under reflux for 3.5 hours whilst a stream of hydrogen bromide (generated by the addition of bromine to tetralin and freed from traces of bromine by passage through dry tetralin) was passed through, again a mobile liquid was obtained as the residue after removal of the solvent. In case this should be the uncyclised bromoarsinoline corresponding with the above methoxyarsinoline, the residue was heated at 150° under reduced pressure under nitrogen for 1.5 hours and allowed to stand for 10 days under nitrogen. After this period, addition of ether caused the deposition of a small quantity of hygroscopic material having no definite melting point, and from which a small quantity of crystalline material was obtained from ethyl acetate. On attempted recrystallisation from ethyl acetate however,

this material became increasingly contaminated with an oil into which it appeared that the solid material was dissociating. No solid iodide was obtained on the addition of a hot, concentrated aqueous solution of potassium iodide to an aqueous solution of the amorphous solid material. The ethereal filtrate from this solid material was filtered into a microdistillation apparatus, the ether distilled off in a stream of nitrogen at atmospheric pressure and the dark-coloured residue distilled under high vacuum employing a nitrogen leak. Three fractions were obtained:

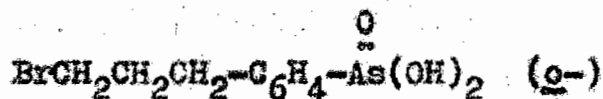
fraction 1, b. p. $58-90^{\circ}/0.20$ mm., 0.54 gm.;
fraction 2, b. p. $90-115^{\circ}/0.19$ mm., 0.50 gm.;
fraction 3, b. p. $118-120^{\circ}/0.19$ mm., 1.84 gm.

Fraction 3 gave a positive result on being tested for bromine and arsenic but gave no crystalline methiodide on reaction with methyl iodide. This fraction was treated in the cold with concentrated nitric acid after being just covered with water. A fairly vigorous reaction ensued, accompanied by the evolution of heat and nitrous fumes. After stirring and cooling for a few minutes, a dark brown solution remained which, on dilution with water, deposited a mass of colourless, glistening plates. After three recrystallisations from dilute nitric acid, washing with water and drying in a vacuum desiccator, the melting point remained constant at $134-135^{\circ}$. Attempted drying of small portions

in a pistol over phosphorus pentoxide at 77° for 3 hours under reduced pressure always resulted in a lowering of the m. p., the product then melting over a range of 8° .

Analysis: Found: C, 33.6; H, 3.6; Br, 22.7%.
N, absent.

This crystalline derivative was insoluble in ether and soluble in hot water from which it was reprecipitated on cooling. The aqueous solution had pH 6. It was soluble in cold sodium hydroxide solution which, when acidified with hydrochloric acid, caused reprecipitation of the original material. Treatment of an aqueous solution with aqueous silver nitrate gave no precipitate of silver halide. The solid dissolved in 10% aqueous sodium carbonate without the liberation of carbon dioxide and was again precipitated on acidification with hydrochloric acid. Treatment of an aqueous solution with a dilute alkaline solution of potassium permanganate or treatment of a chloroform solution with a dilute solution of bromine in chloroform, caused no decolourisation. These tests indicate that the material is almost certainly an arsenic acid and this evidence, in conjunction with the above analytical figures, indicates the possibility of the structure,



for this compound. $C_9H_{12}O_3BrAs$ requires:
C, 33.4; H, 3.7; Br, 24.7%.

Due to lack of material, the above treatment of the arsinoline with hydrobromic acid was repeated, the heating and passage of hydrogen bromide being continued for 2.5 hours. On removal of the solvent as before, the residue gave almost no solid material on treatment with dry ether. On distillation of the residue under high vacuum with a nitrogen leak, the following fractions were collected:
fraction 1, b. p. 72-132°/0.8 mm., very small;
fraction 2, b. p. 134-142°/0.8 mm., 1.87 gm.
None of the formerly-obtained crystalline material was obtained from an ethyl acetate solution of the residue. Fraction 2, on analysis, gave the following figures: Found: C, 33.8; H, 3.75%. The remainder of this fraction was redistilled under high vacuum employing a nitrogen leak, after which the following analysis was obtained: Found: C, 35.3; H, 3.85; Br, 10.9%. No feasible structure could be found which would correspond with these figures. On heating a portion of fraction 2 under reflux in an atmosphere of nitrogen for 45 minutes, no crystalline material separated after cooling, or on seeding the solution with a small quantity of the crystalline material obtained from ethyl acetate in the previous preparation.

(11) Action of a mixture of constant-boiling aqueous hydrobromic acid and acetic acid on 1-(o-3-methoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline

The arsinoline (7.4 gm.) was mixed with constant-boiling (48%) aqueous hydrobromic acid (150 ml.) and glacial acetic acid (150 ml.) and the solution heated at 120° for 5.5 hours whilst a stream of anhydrous hydrogen bromide (generated by combination of elementary bromine and hydrogen and freed from traces of bromine by passage over copper gauze) was passed through the mixture. An insoluble liquid slowly settled at the bottom of the flask. On attempted removal of the solvent by distillation under reduced pressure in a stream of nitrogen, this liquid proved steam-volatile and was therefore extracted with chloroform. The chloroform extract was washed twice with water, once with 10% aqueous sodium carbonate and once again with water, finally being dried over calcium chloride. The chloroform was removed by distillation at atmospheric pressure under nitrogen and the residue distilled under high vacuum employing a nitrogen leak. Three fractions were collected, the last two representing a negligible amount of material: fraction 1, b. p. 52-62°/0.25 mm., 2.3 gm.; fraction 2, b. p. 94-136°/0.25 mm.; fraction 3, b. p. 136-140°/0.25 mm. No crystalline material could be obtained from the small residue. The above fraction 1, which

smelt strongly of 3-phenylpropyl bromide, gave a positive test for bromine but a negative test for arsenic by both the Lassaigne sodium fusion and sodium peroxide-sodium carbonate oxidative fusion methods. Difficulty was experienced in obtaining an oxidation product of this fraction by boiling with potassium permanganate under reflux, and it was therefore characterised by conversion into 3-phenylpropyldithiocarbamate, (see below).

8. 3-Phenylpropyldithiocarbamate

(1) Ammonium dithiocarbamate

c.f. Alles, Icke and Redemann,
Organic Syntheses: Coll. Vol. III,
page 763 (Wiley, New York, 1955).

Gaseous ammonia was passed into 96% ethanol (250 ml.) contained in a tared flask in an ice-bath until the gain in weight was 39 gm. (2.3 mols.). To this solution, still chilled in ice, a well-cooled solution of carbon disulphide (76 gm., 1 mol.) in ether (200 ml.) was added. The flask was loosely stoppered and allowed to remain in the ice-bath for 3 hours and then at room temperature overnight. Sheaves of lemon-yellow needles of the unstable ammonium dithiocarbamate slowly separated. These were filtered at the pump, washed with ether and immediately employed for the following preparation.

(ii) 3-Phenylpropyldithiocarbamate

c.f. von Braun, Berichte, 1912, 1565.

The fraction of b. p. 52-62°/0.25 mm. (1.5 gm.) from the above treatment of 1-(o-3-methoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline with hydrobromic acid was mixed with 10 ml. ethanol, 5 ml. water were added, followed by 0.8 gm. (1 mol.) ammonium dithiocarbamate. No reaction appeared to take place in the cold, but after warming on the water bath for 30 minutes and subsequent dilution with water, an oil was precipitated which, on being cooled and stirred, rapidly solidified. This solid material was filtered off and dried in vacuo. After two recrystallisations (once from petrol ether-ether and once from cyclohexane), and drying in vacuo, the crystalline material melted at 70-71°, also when mixed with an authentic sample prepared from 3-phenylpropyl bromide as above and having the same m. p.

2. 1-Bromo-1:2:3:4-tetrahydroarsinoline

The solid material from the above experiment was heated under reflux at reduced pressure in an atmosphere of nitrogen. As the temperature of the bath reached 60° , the pressure rose due to the evolution of methyl bromide and when a temperature of 100° was reached, effervescence which had been very vigorous, ceased, leaving a pale-yellow liquid. This was allowed to cool, and, after standing overnight, was fractionated, employing a 10 cm. fractionating column, under reduced pressure in an atmosphere of nitrogen. A small forerun was followed by the product, b. p. $174-180^{\circ}/11$ mm., 13.4 gm., 68%; a pale yellow-liquid which crystallised on standing. A sample of b. p. $176^{\circ}/11$ mm. analysed as follows:

Analysis: Found: C, 41.1; H, 4.0%. $C_9H_{10}AsBr$
requires: C, 39.6; H, 3.7%.

This compound was characterised as described in part 4 below.

3. Piperidine N-pentamethylenedithiocarbamate

c.f. Blicke and Oakland, J. Amer. Chem. Soc., 1932, 54, 2994.

Dry piperidine (5.1 ml., 4.3 gm., 2 mols.) was added dropwise with shaking to carbon disulphide

(1.6 ml., 2 gm., 1 mol.) in dry ether (15 ml.), the tube being kept chilled in an ice bath in order to moderate the extremely vigorous reaction. After stirring for some time, the product was filtered and washed with dry ether, after which it sublimed at 174-175°. This salt is very much more stable than ammonium dithiocarbamate (see Section V, part 8 (i)) and may safely be used after being kept at 5° for several weeks. Yield: 5.0 gm., 78%.

4. N-Pentamethylene-S-1-(1:2:3:4-tetrahydroarsinoline)dithiocarbamate

Piperidine N-pentamethylenedithiocarbamate (0.36 gm.) in dry benzene was added with stirring to 1-bromo-1:2:3:4-tetrahydroarsinoline (0.40 gm., 1 mol.) also in dry benzene. The contents were allowed to stand in a stoppered tube for 8 hours at room temperature. The benzene was allowed to evaporate on a boiling water bath and the reddish-brown residue dried in vacuo. After washing with water to remove piperidine hydrobromide, and again drying, the product was recrystallised three times from acetone and dried when it had m. p. 159-160°.

Analysis: Found: C, 51.0; H, 5.75%. $C_{15}H_{20}NS_2As$ requires: C, 51.0; H, 5.7%.

5. 1-(o-3-triphenylmethoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline

Attempted distillation of the above residue under high vacuum yielded only a small quantity of distillate, b. p. 81-200°/0.08 mm. The residue which was a hard glass, could not be obtained crystalline, nor did vacuum sublimation assist in its purification. On attempted distillation at 10^{-3} mm., approximately 4 gm. of a viscous, pale-yellow syrup were obtained, b. p. 205-209°/ 10^{-3} mm., followed by a second fraction, b. p. 237-270°/ 10^{-3} mm. A portion of the first fraction when heated in a sealed tube with methyl iodide for one hour at 100°, yielded no methiodide. Another portion of this fraction was just covered with water, followed by the addition of nitric acid. When stirred and cooled, little reaction appeared to occur. It was therefore warmed, when nitrous fumes were evolved. Cooling and stirring now produced a crystalline precipitate which was washed with water and dried, m. p. 143-153°. After three recrystallisations from aqueous ethanol, the m. p. was raised to 155.5-156.5°. After drying, analysis showed this material to be triphenylcarbinol.

Analysis: Found: C, 87.8; H, 5.9%. $C_{19}H_{16}O$
requires: C, 87.7; H, 6.2%.

Another portion of fraction 1, when boiled with an aqueous-acetone solution of hydrobromic acid, yielded a crystalline solid which, after three recrystallisations from aqueous ethanol and being dried, had m. p. 155.5-157°.

The product was also triphenylcarbinol, since a mixture of this material with the product of m. p. 155.5-156.5° obtained with nitric acid, had m. p. 155.5-157.5°. Furthermore, when mixed with an authentic sample of triphenylcarbinol (of m. p. 156-159°), the m. p. was 156-159°. Finally, a Beilstein test showed the absence of halogen.

6. 1-(o-3-hydroxypropylphenyl)-1:2:3:4-tetrahydroarsinoline

A portion of the glassy residue remaining from the above attempted distillation (4 gm.) was boiled under reflux with 50 ml. 35% (v/v) aqueous acetic acid for 20 minutes under nitrogen. After cooling, the aqueous layer was poured off from the hard glass which was washed with water. This glass could not be obtained crystalline and it was therefore taken up in ether, the ethereal solution was washed with water, 10% aqueous sodium carbonate and again with water before being dried over anhydrous sodium sulphate. After filtering, the ether was distilled off under nitrogen at atmospheric pressure when a viscous gum remained which, on attempted distillation under nitrogen, first with a silicone bath and then with a free flame, yielded no distillate. This was almost certainly the arsinoline oxide, since it gave after sulphur dioxide-reduction a distillable gum which, on treatment with phosphorus tribromide, yielded the spirocyclic bromide (see below).

The residue from the preparation above was extracted with chloroform (30 ml.), covered with 20 ml. 5N hydrochloric acid containing 0.05 gm. potassium iodide and chilled in ice whilst sulphur dioxide was passed through the mixture for 1.5 hours. The chloroform layer was separated, washed once with water and dried over anhydrous sodium sulphate. The solvent was removed by distillation under nitrogen at atmospheric pressure, leaving a dark-coloured, viscous syrup. Distillation of this syrup now proved possible, but only if rapidly distilled with a free flame under high vacuum in a stream of nitrogen, yielding ca. 1 gm. of a dark, viscous gum. Due to lack of material, no attempt was made to characterise the distillate. That it contained the alcohol was shown by the fact that with phosphorus tribromide, it yielded the spirocyclic bromide (see below).

In all subsequent preparations, the residue from the preparation of the trityl ether which no attempt had been made to distil (see part 5 above) was hydrolysed to the alcohol as follows.

The residue (13.3 gm.) was boiled under reflux in an atmosphere of nitrogen with 50 ml. 35% (v/v) aqueous acetic acid for 50 minutes. After cooling, the aqueous layer was decanted and the residual gum extracted with chloroform, washed once with water, covered with 100 ml. 5N hydrochloric acid containing 0.2 gm. potassium iodide and chilled in ice whilst sulphur dioxide

was passed through the mixture for 2.5 hours. The chloroform layer was separated, washed once with water and dried over anhydrous sodium sulphate. The chloroform was removed by distillation under nitrogen at atmospheric pressure, the last traces being removed by warming under reduced pressure. The gummy residue weighed 12.7 gm. and contained also the triphenylcarbinol resulting from hydrolysis of the trityl group.

7. 1-(o-3-chloropropylphenyl)-1-hydroxy-1:2:3:4-tetrahydroarsinolinium chloride

A portion of the powdered residue from the attempted distillation of 1-(o-3-triphenylmethoxypropylphenyl)-1:2:3:4-tetrahydroarsinoline (3 gm., see part 5 above) was treated under nitrogen with thionyl chloride (3.4 ml., 5.54 gm., ca. 5 mols.) slowly added from a burette under anhydrous conditions over 20 minutes with ice-cooling. The mixture was heated on a boiling water bath for 3 hours in order to complete the reaction. The condenser was set for distillation and the flask heated at 100° under reduced pressure in order to remove the excess of thionyl chloride. On cooling, a viscous gum remained which readily crystallised on being rubbed with ethyl acetate. After washing with ether, 1.2 gm. of a cream-coloured solid were obtained, m. p. 147-158°. After four recrystallisations from ethyl acetate, the product had m. p. 158-161°. When dried in a pistol at 85°, the melting point was lowered

and it was evident that some decomposition had occurred. Therefore another portion of the product was recrystallised three times from ethyl acetate. On this occasion, the compound was dried at room temperature under reduced pressure, when the following analysis was obtained:

Analysis: Found: C, 55.9; H, 4.5%.

For some time the identity of this compound remained a mystery. The Beilstein test showed the presence of halogen and addition of aqueous silver nitrate to an aqueous solution containing nitric acid gave a white precipitate of silver chloride. Furthermore, an aqueous solution liberated picric acid from sodium picrate. This evidence led to the pH of the aqueous solution being tested when it was found to have a pH of 3. An hydroxy-chloride was now suspected on these grounds and because hydroxy-chlorides of arsines often exhibit instability. 1-(o-3-chloropropylphenyl)-1-hydroxy-1:2:3:4-tetrahydroarsinolinium chloride, $C_{18}H_{21}OCl_2As$, requires: C, 54.2; H, 5.3%. This was finally confirmed by conversion into the corresponding highly-crystalline and stable hydroxy-nitrate (see below) which, by the Beilstein test, still showed the presence of halogen indicative of the chloropropyl group but gave no precipitate of silver halide with silver nitrate, showing that the chloride ion had been replaced by a halogen-free anion.

8. 1-Hydroxy-1-(o-3-chloropropylphenyl)-1:2:3:4-tetrahydroarsinolinium nitrate

The above hydroxy-chloride (20 mgm.) which had been recrystallised from ethyl acetate three times, in aqueous solution, when treated with dilute nitric acid, immediately deposited the crystalline and stable hydroxy-nitrate, which, after two recrystallisations from water, a drop of dilute nitric acid being added on each occasion to induce crystallisation, was washed with water and dried, m. p. 128.5-129°. The Beilstein test showed the presence of halogen but this was no longer ionic since an aqueous solution yielded no precipitate with aqueous silver nitrate.

Analysis: Found: C, 50.6; H, 5.1%. $C_{18}H_{21}O_4ClNaS$ requires: C, 50.8; H, 5.0%.

9. (±)-As-spiro-bis-1:2:3:4-tetrahydroarsinolinium iodide (via the chloride)

A portion of the residue (3.7 gm., powdered) from the attempted distillation of the trityl ether (see part 5 above) was treated with thionyl chloride (6.83 gm., ca. 5 mols.) as described in part 7 above, but, after removal of the excess of thionyl chloride, the residue was extracted with chloroform (25 ml.), covered with 5N hydrochloric acid (20 ml.) containing potassium iodide (approximately 0.1 gm.) and chilled in ice whilst sulphur dioxide was passed

through the mixture for 2 hours. The chloroform layer was separated and the aqueous layer extracted once with chloroform. The chloroform was removed by distillation leaving a viscous gum which could not be obtained crystalline. That this was the spirocyclic chloride was shown by the fact that after trituration with ether, the residual gum was taken up in hot acetone, excess of aqueous sodium iodide was added and the solution boiled with charcoal and filtered. On cooling, no crystalline material could be obtained from the filtrate which was therefore again boiled with charcoal and filtered. Cautious addition of water to the filtrate now gave a solid which was collected and dried in vacuo. After recrystallisation from ethanol, this gave rise to a crystalline product, m. p. 267-270° with slight darkening. After three recrystallisations from ethanol, the iodide was obtained as glistening cream-coloured plates of m. p. 277-278°. After being dried it analysed as follows:

Analysis: Found: C, 48.9; H, 4.7; I (ionic), 28.8%.
 $C_{18}H_{20}IAS$ requires: C, 49.3; H, 4.6; I, 29.0%.

10. (\pm)-As-spiro-bis-1:2:3:4-tetrahydroarsinolinium
 bromide and iodide

The product (1 gm.) obtained from the distillation of 1-(*o*-3-hydroxypropylphenyl)-1:2:3:4-tetrahydroarsinoline (see part 6 above) was treated under nitrogen and anhydrous conditions

with ice-cooling, with phosphorus tribromide (0.10 ml., 0.28 gm., 0.33 mol.) added slowly from a burette and then heated under reflux on a boiling water bath for 1.5 hours in order to complete the reaction. The product was allowed to cool and triturated several times with ether. The residue was taken up in hot ethanol, excess of an aqueous ethanolic solution of sodium iodide added and more ethanol added to give a clear solution which was then boiled with charcoal and filtered. After cooling, the filtrate deposited the crystalline iodide. This was filtered off, washed with water and dried. After two recrystallisations from ethanol, the m. p. was $276-277^{\circ}$ with darkening. On admixture with the above (analysed) sample of the iodide (of m. p. $277-278^{\circ}$) the m. p. was $276-277.5^{\circ}$.

In subsequent preparations, the residue from the preparation of the alcohol (24 gm.) was treated as described above with phosphorus tribromide (4.5 ml.) added from a burette over 20 minutes. After heating on the water bath for 1 hour to complete the reaction, the residue was triturated with ether, dissolved in ethanol and allowed to cool slowly. The crystalline bromide separated on scratching. This was filtered off, when it yielded 4.32 gm. of colourless crystals. The filtrate, on treatment with aqueous-ethanolic sodium iodide, yielded a further 1.78 gm. of the iodide. A

portion of the bromide, after three recrystallisations from ethanol, gave the bromide dihydrate, m. p. 253-254° when dried at room temperature.

Analysis: Found: C, 50.1; H, 5.0%. $C_{18}H_{20}AsBr \cdot 2H_2O$
requires: C, 50.6; H, 5.7%.

When the spirocyclic bromide was dried at a slightly higher temperature (25°), the bromide hemihydrate was obtained, m. p. 270-271°.

Analysis: Found: C, 53.9; H, 5.2%. $C_{18}H_{20}AsBr \cdot \frac{1}{2}H_2O$
requires: C, 54.0; H, 5.3%.

Finally, when dried at 80°, the anhydrous bromide was obtained, m. p. 270-271°.

Analysis: Found: C, 54.8; H, 5.5%. $C_{18}H_{20}AsBr$
requires: C, 55.3; H, 5.15%.

11. (±)-As-spiro-bis-1:2:3:4-tetrahydroarsinolinium
picrate

The above bromide dihydrate in ethanolic solution, was treated with excess of a saturated ethanolic solution of sodium picrate, the solution brought to the boil and water added dropwise to the point of incipient turbidity. After cooling and stirring, the precipitated picrate was collected and recrystallised four times from ethanol. After being dried, the

m. p. was 102-103°.

Analysis: Found: C, 53.4; H, 4.4; N, 8.0%.

$C_{24}H_{22}O_7N_3As$ requires: C, 53.4; H, 4.1; N, 7.8%.

SECTION VII: OPTICAL RESOLUTION OF (+)-AS-SPIRO-
BIS-1:2:3:4-TETRAHYDROARSINOLINIUM
IODIDE

1. Silver (+)-3-bromocamphor-8-sulphonate

Ammonium (+)-3-bromocamphor-8-sulphonate (commercial product, 20 gm.) was treated with 80 ml. (i.e. 20 ml. in excess) 0.9930N hydrochloric acid. The solution was brought to the boil and silver oxide (17 gm., i.e. 10 gm. in excess) was added and the mixture boiled for 25 minutes. After filtering whilst hot, the filtrate was evaporated down to 40 ml. and again filtered. The filtrate was just acidified with dilute nitric acid and cooled, when it gave a deposit of the crystalline silver salt. Two further successive filtrations and evaporations of the mother liquors yielded a further quantity of the product, m. p. 136-137°, dec. after one recrystallisation from water. Yield: 16 gm. (63%).

2. Attempted resolution of the spirocyclic salt
via the (+)-3-bromocamphor-8-sulphonate

The spirocyclic iodide (0.56 gm.) and silver (+)-3-bromocamphor-8-sulphonate (0.534 gm., 1 mol.) in ethanol (50 ml.) containing a trace of water were boiled together under reflux for 5 minutes. The precipitated silver iodide

was filtered off from the hot suspension and the alcohol distilled from the filtrate under reduced pressure. The residual gum was dried in vacuo when it partially crystallised. On being rubbed with either ethyl acetate or ether, the crystalline bromocamphorsulphonate (0.42 gm.) was readily obtained, m. p. 166-183° with slight previous softening. After one recrystallisation from diethyl carbonate, the m.p. was 191-192° and after the second and third recrystallisations, 191-192.5° and 191.5-193° respectively.

Analysis: Found: C, 53.8; H, 5.8%. $C_{28}H_{34}O_4BrSAs$ requires: C, 54.1; H, 5.5%.

Treatment of an ethanolic solution of the (+)-bromocamphorsulphonate with an aqueous ethanolic solution of sodium iodide caused precipitation of the iodide which was recrystallised once from ethanol. A 0.132% solution in A.R. chloroform (4 dm. tube) gave no rotation.

In another preparation, the spirocyclic bromide dihydrate (2.45 gm.) and silver (+)-3-bromocamphor-8-sulphonate (2.394 gm., 1 mol.) in ethanol (50 ml.) were boiled together under reflux for 15 minutes and the suspension filtered whilst hot. The filtered silver bromide was extracted with boiling ethanol and refiltered. The solvent was removed from the combined filtrates by distillation under reduced pressure with gentle warming and the residual gum was triturated.

with ether, yielding 2.85 gm. (84%) of the crude (+)-bromocamphorsulphonate.

After recrystallisation from diethyl ketone, the m. p. was 188-193° (2.03 gm.). A 0.493% solution in A.R. methanol (4 dm. tube) had $\alpha_D^{16} +0.91^\circ$, $[\alpha]_D^{16} +46.1^\circ$, $[M]_D^{16} +286^\circ$. This material now proved too insoluble for further recrystallisation from diethyl ketone. It was therefore recrystallised from ethyl methyl ketone containing a trace of ethanol, m. p. 191-194° (0.93 gm.). A 0.508% solution in A.R. methanol (4 dm. tube) had $\alpha_D^{18} +0.96^\circ$, $[\alpha]_D^{18} +45.0^\circ$, $[M]_D^{18} +280^\circ$. A third recrystallisation from acetone gave 0.29 gm. of material, m. p. 191-193°. A 0.487% solution in A.R. methanol (4 dm. tube) had $\alpha_D^{19} +0.89^\circ$, $[\alpha]_D^{19} +45.7^\circ$, $[M]_D^{19} +284^\circ$. (Walden, Monatshefte, 1932, 53, 30; records $[M]_D$ for (+)-3-bromocamphor-8-sulphonic acid in methanol as +274°.).

Conversion to the picrate

The thrice recrystallised (+)-bromocamphorsulphonate in ethanol was treated with a saturated ethanolic solution of sodium picrate. The solution was warmed whilst water was cautiously added to the point of incipient turbidity. Slow cooling, followed by scratching, gave the crude picrate, m. p. 102-106° (0.177 gm.). After recrystallisation from ethanol, this had m. p. 102-103° (0.117 gm.) and mixed m. p. with an authentic sample of the (+)-picrate, 101-103°.

A 0.379% solution in A.R. chloroform (4 dm. tube) had $\alpha_D^{18} +0.02^\circ$, the picrate thus being considered inactive.

Recovery of the racemic iodide

The mother liquors and polarimeter-tube solutions from the above work were combined, evaporated to dryness and the residue taken up in ethanol. To this solution, aqueous ethanolic sodium iodide was added. The precipitated iodide was collected, washed with ethanol and dried, when it weighed 1.49 gm.

3. (-)-Menthoxycetic acid

c.f. Leffler and Calkins, Organic Syntheses, Coll. Vol. III, page 544 (Wiley, New York, 1955).

Sodium wire (17.5 gm., 1.19 atoms) was added to a solution of natural (-)-menthol (100 gm.) in sodium-dried toluene (250 ml.) in the usual Grignard-type apparatus. The mixture was heated on a mantle until the toluene began to boil under reflux. When the sodium had melted, it was powdered by vigorous stirring in the boiling toluene for 15 hours. After cooling, the excess sodium was rapidly filtered off, the filtrate returned to the apparatus and warmed to 90° (internal temperature). Monochloroacetic acid (24 gm., 0.397 mol.) in warm, dry toluene (200 ml.)

was slowly added with stirring, when sodium chloroacetate commenced to separate. The glutinous suspension was boiled under reflux for 48 hours with vigorous stirring, the solid which adhered to the sides of the flask being detached from time to time. During this period, toluene was occasionally added to maintain the volume constant. After cooling, the mixture was transferred to a separating funnel and extracted with three 250 ml. portions of water. Acidification of the aqueous extract with 5N hydrochloric acid gave an oil which was extracted with three 50 ml. portions of benzene. The benzene was removed by distillation and the residue distilled under high vacuum. The first fraction consisted chiefly of (-)-menthol (b. p. 72-144°/0.5 mm.) which crystallised in the receiver. The second fraction (b. p. 146-149°/0.5 mm.) was the acid, obtained as a treacly oil, 30 gm., 44%.

4. Silver (-)-menthoxyacetate

c.f. Mann and Watson, J. Chem. Soc.,
1947, 511.

Aqueous sodium hydroxide (46 ml., 1.015N, 1 equiv.) was added with stirring to (-)-menthoxyacetic acid (10.0 gm.). A.R. silver nitrate (7.93 gm., 1 mol.) in water (75 ml.) was added, causing immediate precipitation of the silver salt. After stirring vigorously, the suspension was filtered, and the salt dried overnight in a vacuum oven at 60°. 15 Gm. (100%) of the dried

product were obtained as a white powder which darkens on exposure to light.

A 1.019% solution of the silver salt in A.R. chloroform (4 dm. tube) had $\alpha_D^{20} -2.25^\circ$, $[\alpha]_D^{20} -50.7^\circ$, $[M]_D^{20} -163^\circ$. The specific rotation of the silver salt has not previously been recorded. After standing in the dark for 2 hours, a silver mirror was deposited on the walls of the polarimeter tube.

5. Resolution of the spirocyclic salt via the (-)-menthoxyacetate

Initially, attempts were made to prepare the (-)-menthoxyacetate by boiling together equimolecular quantities of the spiro iodide and silver (-)-menthoxyacetate in ethanol or aqueous ethanol, but, on these occasions, the yield of the optically-active salt was always low and the product was contaminated with dark-coloured impurities, presumably caused by decomposition of the silver salt. In subsequent preparations, acetone was found to be far more satisfactory as a solvent.

The spirocyclic bromide dihydrate (5.00 gm.) and silver (-)-menthoxyacetate (3.759 gm., 1 mol.) in acetone (125 ml.) were boiled together under reflux for 30 minutes. The hot solution was filtered and the insoluble residue extracted with two 20 ml. portions of boiling acetone. After removal of the solvents from the combined filtrates by gentle warming under reduced pressure, a gum remained. Trituration with ether caused

it to crystallise. The crystalline menthoxyacetate was filtered off and recrystallised from diethyl ketone, when it had m. p. $85-90^{\circ}$. The yield of the optically-active salt over several such preparations varied from 1.0 to 2.3 gm.

In order to test whether resolution was proceeding and whether an active product could be obtained, a portion of the (-)-menthoxyacetate was recrystallised six times from diethyl ketone (i.e. to constant m. p.). This material was converted into the picrate as follows. The solid menthoxyacetate was covered with aqueous sodium picrate, the mixture warmed and ethanolic sodium picrate added to give a clear solution. Water was cautiously added dropwise to the warm solution to the point of incipient turbidity, and the solution allowed to cool slowly. The crystalline picrate was collected and recrystallised once from aqueous ethanol, m. p. $95-97^{\circ}$.

Analysis: Found: C, 53.7; H, 4.2%. $C_{22}H_{24}N_3O_7As$ requires: C, 53.4; H, 4.1%.

A 0.757% solution in A.R. chloroform (4 dm. tube) had $\alpha_D^{20} -0.74^{\circ}$, $[\alpha]_D^{20} -24.4^{\circ}$, $[\eta]_D^{20} -131.8^{\circ}$.

Another portion of the (-)-menthoxyacetate gave, after successive recrystallisations from diethyl ketone, the following yields and melting points:

once recrystallised, 3.8 gm., m. p. 85-90°;
 twice recrystallised, 2.5 gm., m. p. 87.5-90°;
 thrice recrystallised, 2.3 gm., m. p. 87-89°;
 four times recrystallised, 2.0 gm., m. p. 87-89°.
 This material analysed as the dihydrate when dried
 at room temperature:

Analysis: Found: C, 63.95; H, 7.8%. $C_{30}H_{41}O_3As \cdot 2H_2O$
 requires: C, 64.3; H, 8.1%.

When dried at 40°, the highly hygroscopic anhydrous
 (-)-menthoxyacetate was obtained, m. p. 88.5-90°.

Analysis: Found: C, 68.4; H, 8.3%. $C_{30}H_{41}O_3As$
 requires: C, 68.7; H, 7.9%.

A 0.484% solution of the four times recrystallised
 (-)-menthoxyacetate dihydrate in A.R. chloroform
 (4 dm. tube) had α_D^{20} -0.941°, $[\alpha]_D^{20}$ -48.6°.

After a fifth recrystallisation from
 diethyl ketone, the m. p. remained unchanged. A
 0.480% solution of the dihydrate in A.R. chloroform
 (4 dm. tube) had α_D^{20} -0.921°, $[\alpha]_D^{20}$ -48.0°.
 These figures indicate that resolution was complete
 after the fourth recrystallisation.

The (-)-iodide

The five times recrystallised (-)-menthoxy-
 acetate (0.41 gm.) was dissolved in ethanol and
 excess of an aqueous ethanolic solution of sodium

iodide was added. Only a very small quantity of solid material was deposited from the solution after chilling in ice. This is in marked contrast to the (+)-iodide which was only sparingly soluble in cold ethanol. Evaporation of the solution gave a solid residue which consisted of the (-)-arsonium iodide and sodium iodide. When the residue was dissolved in boiling water and filtered, the (-)-iodide was deposited from the cooled solution as fine, colourless needles. When dry, the iodide weighed 0.18 gm. and had m. p. 223-223.5°.

Analysis: Found: C, 49.5; H, 4.9%. $C_{18}H_{20}IAs$ requires: C, 49.3; H, 4.6%.

A 0.5933% solution of the iodide in A.R. chloroform (4 dm. tube) had $\alpha_D^{22.5} -0.712^\circ$, $[\alpha]_D^{22.5} -30.0^\circ$, $[M]_D^{22.5} -131.5^\circ$. After standing in the dark for 24 hours, this solution had $\alpha_D^{22} -0.712^\circ$ and was thus completely unchanged.

The (+)-iodide

A portion of the diethyl ketone mother liquors from the first crystallisation of the (-)-menthoxyacetate was evaporated under reduced pressure with gentle warming. The dark-coloured residual gum was taken up in ethanol, boiled with charcoal and filtered. The warm, colourless

filtrate, when treated with an ethanolic solution of sodium iodide containing a trace of water, deposited when cooled and scratched, some colourless crystalline material of m. p. $270-277^{\circ}$, (0.6 gm.). After three recrystallisations from ethanol, the m. p. was raised to $276-277^{\circ}$.

Analysis: Found: C, 49.4; H, 4.8%. $C_{18}H_{20}IAS$
requires: C, 49.3; H, 4.6%.

When mixed with an authentic sample of the (+)-iodide (of m. p. $277-278^{\circ}$) the m. p. was $274-278^{\circ}$. This material was therefore the racemic iodide.

The solution from which this racemic iodide had crystallised was now rich with respect to the (+)-iodide. After evaporation, the solid residue was taken up in boiling water and filtered. Slow cooling of the filtrate caused some crystalline material to separate, accompanied by the deposition of a gum. The crystals were filtered off, leaving the gum on the walls of the tube. After two recrystallisations from water (one with charcoal) the product was dried and had m. p. $223-223.5^{\circ}$ alone (0.20 gm.) and $220-274^{\circ}$ when mixed with the (-)-iodide also of m. p. $223-223.5^{\circ}$.

Analysis: Found: C, 48.75; H, 4.9%. $C_{18}H_{20}IAS$
requires: C, 49.3; H, 4.6%.

A 0.655% solution in A.R. chloroform (4 dm. tube) had $\alpha_D^{21} +0.796^{\circ}$, $[\alpha]_D^{21} +30.4^{\circ}$, $[\eta]_D^{21} +131.1^{\circ}$.

NOTE: Where values for the observed rotation in the above section are given to 0.001° , measurements were taken with a Rudolph Photoelectric Polarimeter; in all other cases, a visual instrument was used.

SECTION VIII: SYNTHESIS OF AS-SPIRO-(ISOARSINDOLINE)-
1:2:3:4-TETRAHYDROARSINOLINIUM IODIDE

1. As-spiro-(isoarsindoline)-1:2:3:4-tetrahydro-
arsinolinium iodide

2.0 Gm. 1-methyl-1:2:3:4-tetrahydro-arsindoline and 2.54 gm. (1 mol.) *o*-xylylene dibromide were stirred together in a flask. Some heat was evolved and on warming the mixture set to a hard glass. This was undoubtedly 1-methyl-1-(*o*-bromoethylbenzyl)-1:2:3:4-tetrahydroarsinolinium bromide although it was not crystallised or purified for characterisation. This quaternary salt was heated under nitrogen under reduced pressure (13 mm.) under reflux. On slowly raising the bath temperature, effervescence commenced at 60°, becoming more rapid as the temperature rose to 160°. The temperature was maintained at 190-200° for 1.25 hours, when effervescence had ceased. After cooling, the contents had set to a hard glass which was freely soluble in hot ethanol or hot acetone, from neither of which it was redeposited on cooling. Addition of ether or water to an ethanolic or acetone solution of this glass produced a cloudiness and on cooling, the bromide was deposited as a gum. A portion was triturated several times with dry ether and, all attempts at obtaining the resulting glass crystalline having failed, it

was converted directly into the iodide by adding a saturated ethanolic solution of sodium iodide to an ethanolic solution of the bromide. The pale-yellow crystalline iodide which was immediately precipitated, was filtered off, washed with ethanol and dried at the pump, when it melted at $246-252^{\circ}$ with previous darkening from 237° . Yield: 2.0 gm., 49%. After four recrystallisations from ethanol, the pale-yellow crystalline iodide had m. p. $241-243^{\circ}$ with darkening. After drying, it gave the following analysis figures:

Analysis: Found: C, 48.2; H, 4.6%. $C_{17}H_{18}IAs$
requires: C, 48.1; H, 4.3%.

2. As-spiro-(isocarsindoline)-1:2:3:4-tetrahydro-arsinolinium picrate

To a hot ethanolic solution of the bromide (as a glass) was added excess of a hot, saturated ethanolic solution of sodium picrate. On cooling, the crystalline picrate was slowly deposited. This was filtered at the pump and after five recrystallisations from ethanol and drying, had m. p. $163-164^{\circ}$.

Analysis: Found: C, 52.7; H, 4.15; N, 7.85%.
 $C_{23}H_{20}O_7N_3As$ requires: C, 52.6; H, 3.8; N, 8.0%.

SECTION IX: FIRST ATTEMPTED SYNTHESIS OF
(\pm)-As-SPIRO-(1:2:3:4-TETRAHYDRO-
ARSINOLINE)-1:2:3:4-TETRAHYDROISO-
ARSINOLINIUM BROMIDE

1. Homophthalic acid

c.f. Fieser and Pechot, J. Amer. Chem. Soc.,
1946, 2577.

Chromium trioxide (300 gm.) in 1150 ml. water was placed in a 5-litre flask fitted with dropping funnel, sealed stirrer and reflux condenser. The solution was thoroughly chilled in an ice-bath whilst indene (100 gm.) was slowly added with vigorous stirring over 40 minutes. The flask was now immersed in ice up to the neck, whilst concentrated sulphuric acid (750 ml.) was slowly added over 2.5 hours with vigorous stirring. The mixture was boiled under reflux for 2 hours and then immediately filtered as rapidly as possible through glass wool. After allowing to stand overnight (not longer, otherwise chromium salts begin to separate), the crystalline product was filtered at the pump and recrystallised from hot water with decolourising charcoal, yielding 87 gm. colourless crystals, m. p. 174-176° (625).

over 1.5 hours so that the ether boiled gently without external cooling. A precipitate formed during the last stages of the addition. After boiling under reflux for 1.5 hours, the mixture was allowed to stand overnight. The supernatant liquid which was originally red, had now become yellow. Water (100 ml.) was cautiously added with stirring to the contents which were then stirred for 30 minutes. The cream-coloured suspension was poured into water (1 litre) and ice-cold sulphuric acid (500 ml., 1 vol. acid : 9 vols. water) was added with stirring. The ether layer was separated and the aqueous layer continuously extracted with ether for 8 hours. The combined ether layer and extracts were washed once with 10% aqueous sodium carbonate and once with water. After being dried overnight over anhydrous potassium carbonate, the ether was removed by distillation at atmospheric pressure and the residue fractionated under reduced pressure, yielding 20 gm. of a cloudy distillate, b. p. 180-186°/15 mm. (50%).

4. o-2-Bromoethylbenzyl bromide (from o-2-hydroxyethylbenzyl alcohol)

c.f. Anderson and Holliman, J. Chem. Soc., 1950, 1037.

o-2-Hydroxyethylbenzyl alcohol (13 gm.)
and 50% (w/v) hydrogen bromide in glacial acetic

6. 1-(o-2-bromoethylbenzyl)-1-methyl-1:2:3:4-tetrahydroarsinolinium bromide

Holliman, private communication

A solution of 1-methyl-1:2:3:4-tetrahydroarsinoline (2 gm.) and o-2-bromoethylbenzyl bromide (2.66 gm., 1 mol.) in A.R. acetone (25 ml.) was boiled under reflux in an atmosphere of nitrogen for 4 hours. The acetone was allowed to evaporate and the residual gum was dried in vacuo. This was deposited as the crystalline bromide from acetone. The dried product had m. p. 154-156° (reported m. p. 155.5-156.5°), 2.8 gm., 60%.

7. Attempted preparation of (±)-As-spiro-(1:2:3:4-tetrahydroarsinoline)-1:2:3:4-tetrahydroisoarsinolinium bromide

The above bromide was heated in an atmosphere of nitrogen under a variety of conditions ranging from atmospheric pressure to high vacuum and from 160° to 220°. In all cases, effervescence occurred, leaving a residual gum which could not on any occasion be obtained crystalline; nor could a crystalline iodide or picrate be obtained from the residue.

SECTION X: SECOND ATTEMPTED SYNTHESIS OF
(±)-As-SPIRO-(1:2:3:4-TETRAHYDRO-
ARSINOLINE)-1:2:3:4-TETRAHYDROISO-
ARSINOLINIUM BROMIDE

1. o-Bromobenzyl methyl ether

c.f. Holliman and Mann, J. Chem. Soc.,
1947, 1639.

o-Bromobenzyl bromide (160 gm.) was cautiously added to a chilled solution of sodium (16 gm., 1.08 atoms) in absolute methanol (450 ml.). The mixture was boiled under reflux with vigorous stirring over 45 minutes. The alcohol was distilled off at atmospheric pressure, a rapid stream of air being drawn through the mixture to prevent serious bumping. The sodium bromide which had separated was dissolved by the addition of water (300 ml.), when a pale-yellow oil separated. This was removed and the aqueous layer extracted three times with small quantities of ether. The combined ether extracts and the oil were washed once with water and dried over anhydrous calcium chloride. The ether was distilled off at atmospheric pressure and the residual golden oil fractionated under reduced pressure. Almost the whole distilled at 105-110°/15.5 mm. The residue and the preliminary fraction were combined and refractionated when a further 8 gm. distilling over the same range of temperature

were obtained. Yield: 110 gm., (85.5%).

2. o-2-Hydroxyethylbenzyl methyl ether

c.f. Holliman and Mann, J. Chem. Soc.,
1947, 1639.

A solution of o-bromobenzyl methyl ether (145 gm.) and ethyl bromide (26 gm., 0.33 mol.) in sodium-dried ether (300 ml.) was slowly added to activated magnesium (35 gm., 2.02 atoms) under dry ether (100 ml.), the rate of addition being adjusted so that gentle refluxing was maintained without external cooling. After being boiled under reflux for 2 hours, the ethereal solution was chilled in an ice-salt freezing mixture whilst ethylene oxide (100 gm., 3.15 mols.) in dry ether (600 ml.) was added with stirring over a period of 4 hours. The stock solution was kept chilled throughout and added to the dropping funnel in small portions at a time. The contents of the flask were stirred for 30 minutes and allowed to stand overnight at room temperature. Hydrolysis was accomplished by the addition of dilute sulphuric acid (850 ml., 1 vol. acid : 9 vols. water). The ethereal layer was separated and the aqueous layer extracted twice with ether. The combined ether layer and extracts were washed three times with water and dried over anhydrous sodium sulphate. The ether was removed by distillation at atmospheric

pressure and the residue fractionated under reduced pressure. A forerun of 2-bromoethyl alcohol was followed by the product, b. p. 159-164°/19 mm., 64 gm., (53%).

3. o-2-Chloroethylbenzyl methyl ether

c.f. Holliman and Mann, J. Chem. Soc., 1947, 1640.

A solution of o-2-hydroxyethylbenzyl methyl ether (32 gm.) in dry pyridine (16 gm., 1 mol.) and dry chloroform (40 ml.) was chilled in an ice-bath whilst thionyl chloride (23 gm., 1 mol.) was added with stirring over 2 hours. The mixture was boiled under reflux for 2.5 hours. Initially, an oil separated and sulphur dioxide was evolved, but after 45 minutes, the solution had become clear. After cooling, the chloroform solution was washed four times with water, once with 1% aqueous sodium hydroxide and finally with water before being dried over anhydrous calcium chloride. The solvent was removed by distillation at atmospheric pressure and the residue fractionated under reduced pressure. A fraction boiling at 126-148°/21 mm., of which most distilled at 139-141°/21 mm., was collected. This, on refractionation, yielded the product, b. p. 137-141°/22 mm. as a colourless liquid, 20.5 gm., 60%.

4. 1-(o-methoxybenzylethyl)-1:2:3:4-tetrahydro-
arsinoline

o-2-Chloroethylbenzyl methyl ether (8.7 gm.) and ethyl bromide (2.6 gm., 0.5 mol.) in dry ether (40 ml.) were slowly added to magnesium turnings (1.7 gm., 1.5 atoms) under ether (20 ml.) in the usual Grignard apparatus. A crystal of iodine was added and the flask gently warmed to initiate the reaction, the rate of addition of the solution being adjusted so that gentle refluxing was maintained without external cooling. The mixture was boiled under reflux with stirring for 2.5 hours, then cooled and stirred whilst 1-chloro-1:2:3:4-tetrahydro-arsinoline (11.8 gm., 1.1 mols.) in dry ether (60 ml.) was slowly added. After boiling under reflux for 2.5 hours, the mixture was cooled and hydrolysed by the addition with stirring of sulphuric acid (200 ml., 1 vol. acid : 9 vols. water). The ethereal layer was separated and the aqueous layer extracted three times with ether, the ethereal solution finally being washed once with 10% aqueous sodium carbonate and once with water before being dried over anhydrous calcium chloride. The ether was removed by distillation at atmospheric pressure and the residue fractionated under reduced pressure employing a nitrogen leak. A small preliminary fraction was followed by the product, b. p., 176-179°/0.19 mm., 9.5 gm. of a pale-yellow oil (59%).

5. 1-(o-methoxybenzylethyl)-1-methyl-1:2:3:4-tetrahydroarsinolinium iodide

The above arsinoline (1 gm.) was boiled under reflux for 1 hour with excess of methyl iodide in an atmosphere of nitrogen. The excess of methyl iodide was allowed to evaporate and the residual gum triturated with dry ether, when it hardened to a glass. This was taken up in hot acetone from which it crystallised as colourless needles. The product was recrystallised four times from acetone and dried when it had m. p. 114-116°.

Analysis: Found: C, 49.4; H, 5.55; I, 26.4%.

$C_{20}H_{26}OIAS$ requires: C, 49.6; H, 5.4; I, 26.2%.

6. Attempted preparation of (\pm)-As-spiro-(1:2:3:4-tetrahydroarsinoline)-1:2:3:4-tetrahydroisoarsinolinium bromide

1-(o-methoxybenzylethyl)-1:2:3:4-tetrahydroarsinoline (4 gm.) and 50% (w/v) hydrogen bromide in glacial acetic acid (20 ml.) were heated at 120° under nitrogen for 4 hours whilst a steady stream of hydrogen bromide prepared by the action of bromine on dry tetralin (and freed from traces of bromine by passage through dry tetralin) was passed through the solution. After 3.5 hours, two layers had separated. The solvent was removed by distillation under reduced pressure

SECTION XI: THIRD ATTEMPTED SYNTHESIS OF
(⁺)-As-SPIRO-(1:2:3:4-TETRAHYDRO-
ARSINOLINE)-1:2:3:4-TETRAHYDROISO-
ARSINOLINIUM BROMIDE

1. 2-Phenyl-1:2:3:4-tetrahydroisocarsinoline

c.f. Beeby, Cookson and Mann, J. Chem. Soc., 1950, 1921.

The following reaction was carried out in an atmosphere of nitrogen using the usual Grignard-type apparatus.

A few ml. of a solution of dried and redistilled bromobenzene (29.0 gm., 2.2 mols.) in dry ether (50 ml.) were added to magnesium turnings (4.7 gm., 2.3 atoms) covered with dry ether. The reaction was started by the addition of a crystal of iodine and gentle warming, the bromide solution then being added with stirring at such a rate that gentle refluxing of the ether was maintained without external cooling. The ethereal solution was boiled under reflux for 20 minutes, cooled in ice and a solution of phenylarsine (13.0 gm.) in dry benzene (70 ml.) added over 10 minutes, heat being evolved during the addition. The mixture was boiled under reflux for 30 minutes and then cooled in an ice-bath.

To the solution of phenylarsinebis-

(magnesium bromide) thus obtained (1 mol.), a solution of *o*-2-bromoethylbenzyl bromide (23.5 gm., 1 mol.) in dry benzene (100 ml.) was slowly added with stirring, heat being evolved during the addition. The complete mixture was boiled under reflux for 1.5 hours, cooled and hydrolysed by the addition of a saturated aqueous solution of ammonium chloride (500 ml.). The benzene layer was separated under nitrogen, the aqueous layer extracted once with benzene and the combined benzene extracts washed once with water and dried over anhydrous calcium chloride. The benzene was removed by distillation and the residue distilled under high vacuum in a stream of nitrogen employing a 10 cm. fractionating column. A forerun of *o*-2-bromoethyltoluene was followed by the product, b. p. 151-154°/0.6 mm., obtained as a cloudy liquid, 12.6 gm, 55%.

2. 2-Bromo-1:2:3:4-tetrahydroisoarsinoline

2-Phenyl-1:2:3:4-tetrahydroisoarsinoline (12.6 gm.) and constant-boiling (48% w/v) aqueous hydrobromic acid (190 ml.) were boiled together under nitrogen under reflux for 3.5 hours. The mixture was cooled, diluted with water and extracted twice with ether. The ethereal solution was washed rapidly twice with water and dried over anhydrous sodium sulphate. The ether was removed by distillation at atmospheric pressure and the residue distilled under reduced pressure in an atmosphere of nitrogen. The

bromoisoarsinoline was obtained as the only fraction, a colourless oil, b. p. 173-176°/12 mm., 4.5 gm., 36%. It was characterised as described below.

3. N-Pentamethylene-S-2-(1:2:3:4-tetrahydroisoarsinoline)dithiocarbamate

2-Bromo-1:2:3:4-tetrahydroisoarsinoline and piperidine N-pentamethylenedithiocarbamate in ethanol were boiled together for 10 minutes under reflux in an atmosphere of nitrogen. After slow cooling, scratching gave a crystalline solid which was filtered and washed with ethanol, m. p. 127-129°. Three recrystallisations from acetone raised the m. p. to 132-133°. Beeby, Cookson and Mann, J. Chem. Soc., 1950, 1921, have prepared this compound from the corresponding 2-iodoisoarsinoline and report the m. p. as 121.5-122°.

Analysis: Found: C, 50.7; H, 5.6; N, 4.1%.

$C_{15}H_{20}NS_2As$ requires: C, 51.0; H, 5.7; N, 4.0%.

4. Attempted preparation of (±)-As-spiro-(1:2:3:4-tetrahydroarsinoline)-1:2:3:4-tetrahydroisoarsinolinium bromide and chloride

The following reaction was carried out under nitrogen in the usual Grignard-type apparatus.

A solution of o-bromo-3-phenylpropyl trityl ether (8.0 gm., 1 mol.) and dried and redistilled ethyl bromide (0.95 gm., 0.65 ml., 0.5 mol.) in dry ether (70 ml.) was slowly added to activated magnesium powder (0.66 gm., 1.6 atoms) covered with dry ether (5 ml.). The reaction was started with gentle warming and the rate of addition of the solution of the bromides adjusted so that the ether boiled gently without external cooling. The mixture was boiled under reflux for 2.75 hours, then cooled and stirred whilst a solution of 2-bromo-1:2:3:4-tetrahydroisocarsinoline (4.5 gm., 1 mol.) in dry benzene (50 ml.) was slowly added. After boiling under reflux for 2.75 hours, the solution was cooled and stirred whilst a saturated aqueous solution of ammonium chloride (150 ml.) was slowly added. The benzene layer was separated, the aqueous layer extracted with benzene, the combined benzene extracts washed twice with water and dried over anhydrous sodium sulphate. The benzene was removed by distillation at atmospheric pressure, leaving a viscous residue (ca. 10 gm.).

The residue was hydrolysed and reduced exactly as described for the isomeric compound in Section VI, part 6.

5.7 Gm. of the residue from the hydrolysis were treated under nitrogen with phosphorus tribromide (0.57 ml., 1.6 gm.) as described in Section VI, part 10. The residue from this treatment was insoluble in ether but could not be

obtained crystalline from any of the common solvents, nor did it give a solid product with sodium iodide or sodium picrate.

The remainder of the residue from the hydrolysis (3.9 gm.) was treated with thionyl chloride (4.3 ml., 7.1 gm.) as described in Section VI, part 9. The product obtained was an ether-insoluble gum which solidified on trituration with ether. After three recrystallisations from ethyl methyl ketone, it had m. p. 176-177°. An aqueous ethanolic solution gave a white precipitate of silver chloride on treatment with silver nitrate.

Analysis: Found: C, 67.8; H, 6.2%.

The spirocyclic chloride, $C_{18}H_{20}ClAs$ requires: C, 62.4; H, 5.8%.

Another sample, recrystallised four times from ethyl methyl ketone, had m. p. 179-180°.

Analysis: Found: C, 67.5; H, 6.1; ionic Cl^- , 5.55, 5.6%; total Cl, 11.0%.

A further sample, also recrystallised four times from ethyl methyl ketone, had m. p. 179.5-180°.

Analysis: Found: C, 66.7; H, 5.8; total Cl, 10.95%.

After being dried at 105° , these figures were not significantly altered.

Analysis: Found: C, 66.3; H, 5.8%.

The infra-red absorption spectrum showed significant bands at 1600, 1283, 1199, 1176, 1160, 1153, 1117, 1089, 1033, 1020, 968, 955, 934, 921, 896, 829, 863, 785 cm^{-1} (Nujol mull); and at 3330, 3060, 2955, 2760, 1490, 1477, 1450, 1437, 1415, 1399, 1343, 1297, 762, 724, and 702 cm^{-1} (hexachlorobutadiene mull).

Dr. N. Sheppard interprets the data as indicating the presence in the molecule of benzene rings, monosubstituted benzene (probably the trityl group) and possibly the group $-\text{OH}$ or water. There was no peak in the 1700 cm^{-1} region, indicative of the presence of a carbonyl group.

Suggestions as to the probable structure of this compound will be found in the Discussion.

SECTION XII: SYNTHESIS OF (+)-1-p-CHLOROPHEN-
ACYL-1-PHENYL-1:2:3:4-TETRAHYDRO-
ARSINOLINIUM BROMIDE

1. Phenyl-3-phenylpropylarsinic acid

Phenyldichloroarsine (147 gm., 90 ml.) was slowly added with stirring to a warm solution of sodium hydroxide (118 gm., 4.5 mols.) in water (500 ml.). 3-Phenylpropyl bromide (146 gm., 1.1 mols.) prepared as described in Section I, part 7, was slowly added and the mixture boiled under reflux with stirring for 6 hours. When cool, the mixture had formed two layers. Ether was added and after shaking, there appeared three immiscible layers. These were the sodium salt of the arsinic acid (insoluble in the aqueous layer due to the common-ion effect), the aqueous layer and the ethereal layer. After two extractions with ether, the lower and middle layers were diluted with water when they formed a single layer which was acidified to Congo Red with concentrated hydrochloric acid. An oil was deposited which was separated by decantation and washed several times with water before being dried in vacuo. The dried oil could not be obtained crystalline, (140 gm.).

2. 1-Phenyl-1:2:3:4-tetrahydroarsinoline (first method)

The above oily residue (140 gm.) was added to concentrated sulphuric acid (400 ml.) and the mixture heated on a boiling water bath for 30 minutes. When cool, the mixture was poured cautiously into water (2 litres) and after again being cooled, was cautiously neutralised with 30% aqueous sodium hydroxide when the volume had become approximately 5 litres. After extraction with four 500 ml. portions of chloroform, the extract was washed once with water and covered with 500 ml. concentrated hydrochloric acid and 500 ml. water containing 1.0 gm. potassium iodide, sulphur dioxide then being passed for 2 hours through the chilled mixture. After standing aside overnight, the chloroform layer was separated, washed rapidly with dilute sodium hydroxide solution, then with water and finally dried over anhydrous calcium chloride in an atmosphere of nitrogen overnight. The chloroform was distilled off at atmospheric pressure in a current of nitrogen, when about 80 ml. of a glutinous, light red gum remained. Much frothing occurred on distillation of the residue under high vacuum employing a nitrogen leak, but this trouble was largely avoided by using a free flame in place of a bath during the distillation. Redistillation gave the following two fractions:

fraction 1, b. p. 136-141°/0.17 mm., 18.5 gm.;

fraction 2, b. p. 143-185°/0.17 mm., 8 gm.

Most of the second fraction distilled

at 182-185°/0.17 mm., and a very small residue remained. When the whole of fraction 1 was treated with p-chlorophenacyl bromide as described in this section, part 10, only 50% of the theoretical quantity of 1-p-chlorophenacyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium bromide was obtained and since this product is formed in almost quantitative yield from a pure sample of 1-phenyl-1:2:3:4-tetrahydroarsinoline, the actual yield of the pure arsinoline must have been ca. 10 gm., representing an overall yield (based on phenyl-dichloroarsine) of 6%.

Investigation of the by-products

In a previous preparation of the phenylarsinoline by the above method (using one-sixth of the above quantities), the three layers obtained on the addition of ether after the period of reflux in the preparation of phenyl-3-phenylpropylarsinic acid (15 hours in this case) were investigated separately.

(1) The ethereal layer, after being washed with water several times, was dried over calcium chloride, the ether distilled off and the residue distilled under reduced pressure. Only one fraction was obtained, b. p. 120-124°/10 mm., undoubtedly unchanged 3-phenylpropyl bromide. The quantity obtained (4.0 gm.) represented one-sixth of the bromide used in the reaction, but,

allowing for transfer losses, etc., the actual fraction is probably somewhat higher than this. A residue remained in the distilling flask which failed to distil even with a bath temperature of 300° at 10 mm. This residue, when treated with concentrated nitric acid, evolved heat and nitrous fumes, liberating an oil which could not be obtained crystalline, but gave, after neutralisation with sodium hydroxide solution and treatment with a saturated aqueous solution of picric acid, a crystalline derivative which, after four recrystallisations from ethanol and drying, had m. p. 163° . This was evidently not yet analytically pure, since the same picrate was obtained as follows and had a somewhat higher m. p. The solvent was removed from a portion of the chloroform solution of the material obtained after the sulphuric acid cyclisation but before reduction with sulphur dioxide. This material gave, with ethanolic picric acid, a picrate, which, after two recrystallisations from ethanol had m. p. $167-168^{\circ}$ and $158-162^{\circ}$ when mixed with the picrate mentioned above.

Analysis: Found: C, 56.7; H, 4.0; N, 7.6%.

This is evidently a sample of 1:1-diphenyl-1:2:3:4-tetrahydroarsinolinium picrate, probably arising from the presence of diphenylmonochloroarsine as an impurity in the phenyldichloroarsine. ($C_{27}H_{22}O_7N_3As$ requires: C, 56.35; H, 3.85; N, 7.3%).

(ii) The lower (aqueous) layer was acidified with concentrated hydrochloric acid when a white, amorphous solid was precipitated. The mixture was chilled in ice and the solid material filtered off and dried at the pump, when it weighed 5.6 gm. This was completely insoluble in all the common solvents and did not melt, so was evidently silicic acid formed by the action of the concentrated sodium hydroxide solution on the glass apparatus used. That it did in fact contain some of the arsenic acid was shown by the fact that, on treatment with concentrated sulphuric acid and sulphur dioxide exactly in the manner described above, it yielded 0.7 gm. of a liquid distilling at $130-136^{\circ}/1.0$ mm., almost certainly the phenyltetrahydroarsinoline.

(iii) The middle layer contained the whole of the sodium salt of the arsenic acid, since on acidification with hydrochloric acid, an oil was deposited which, on being treated with concentrated sulphuric acid and sulphur dioxide as described in the above large-scale preparation, yielded eventually 3.1 gm. of a pale-yellow oil, b. p. $158-164^{\circ}/1.5$ mm., leaving a residue (as obtained above) of some material which underwent decomposition without distilling. This distillate gave, on quaternisation with p-chlorophenacyl bromide, the quaternary salt, m. p. $210-211^{\circ}$ and $211-212^{\circ}$ when mixed with an authentic sample

of 1-p-chlorophenacyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium bromide.

3. 1-Phenyl-1:2:3:4-tetrahydroarsinoline (second method)

A solution of dried and redistilled bromobenzene (13.8 gm., 1.5 mols.) in sodium-dried ether (50 ml.) was added slowly under nitrogen to magnesium turnings (2.2 gm., 1.1 atoms) with stirring in the usual Grignard apparatus fitted with a nitrogen inlet. The reaction was started by adding a crystal of iodine and gently warming the flask and the rate of addition of the bromide adjusted so that the ether boiled gently without external cooling. The contents were boiled under reflux for 1.5 hours to complete the formation of phenyl-magnesium bromide. The ethereal solution was decanted from the unreacted magnesium into a clean flask which was immediately attached to the apparatus used for the preparation of the Grignard reagent. The flask was cooled in ice whilst a solution of 1-chloro-1:2:3:4-tetrahydroarsinoline (8.7 gm., 1 mol.) in dry ether (50 ml.) was slowly added with stirring over 50 minutes, the contents then being boiled under reflux for 3 hours. The mixture was cooled in an ice-bath and then cautiously hydrolysed with 200 ml. dilute sulphuric acid (1 vol. acid : 9 vols. water) and 100 gm. crushed ice. After dilution

with ether, the ethereal layer was separated, the aqueous layer extracted three times with small portions of ether and the combined ethereal solutions washed once with 10% aqueous sodium carbonate and once with water before being dried over anhydrous calcium chloride in an atmosphere of nitrogen. Throughout the extraction and washings, a stream of nitrogen was allowed to impinge on the surface of the ethereal solution to minimise oxidation of the product. The ether was distilled off in a stream of nitrogen at atmospheric pressure and the solid residue submitted to high vacuum fractionation employing a nitrogen leak. Except for a small forerun, almost the whole distilled at $140-144^{\circ}/0.4$ mm., yielding a colourless oil, which, on standing, crystallised, 7.7 gm., 75%. The same yield was obtained when the reaction was carried out on thrice the above quantities (76%), b. p. $148-151^{\circ}/0.95$ mm.

4. 1-Methyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium iodide

1-Phenyl-1:2:3:4-tetrahydroarsinoline was heated under reflux with excess of methyl iodide under nitrogen for 30 minutes and the excess of methyl iodide allowed to evaporate spontaneously by running the water out of the reflux condenser. The residual yellow oil

was triturated with dry ether. After some difficulty, the product was eventually obtained crystalline from ethanol. After three recrystallisations from ethanol, the colourless crystalline product was dried and then had m. p. 165-166°.

Analysis: Found: C, 46.6; H, 4.4; I, 30.9%.

$C_{16}H_{18}IAs$ requires: C, 46.6; H, 4.4; I, 30.8%.

5. 1-Methyl-1-phenyl-1:2:3:4-tetrahydroarsinolin-
ium picrate

An alcoholic solution of the above methiodide was brought to the boil and excess of a hot, saturated ethanolic solution of sodium picrate was added. After being set aside at room temperature for 48 hours, an oil had separated from the solution. Water was added to cause further precipitation of the oil which, 24 hours later, had crystallised as fine, yellow needles. The methopicate was recrystallised from ethanol four times and dried, after which it had m. p. 105.5-107°.

Analysis: Found: C, 51.45; H, 4.2; N, 8.4%.

$C_{22}H_{20}O_7N_3As$ requires: C, 51.5; H, 3.9; N, 8.2%.

6. 1-Hydroxy-1-phenyl-1:2:3:4-tetrahydroarsinolin-
ium picrate

A well-chilled solution of 1-phenyl-

1:2:3:4-tetrahydroarsinoline (1 gm.) in dry chloroform (25 ml.) was treated with a solution of bromine in dry chloroform (6.4 ml. of a solution containing 9.58 gm. bromine/100 ml. of solution, 1 mol.). The bromine was at once absorbed. The solution was shaken with excess of a dilute solution of ammonia after which the chloroform solution was evaporated to dryness over a water bath, leaving a brown, gummy residue which was dried in vacuo. A portion of the gum, which contained the dihydroxide of the arsinoline, was taken up in hot dilute nitric acid in an attempt to form the hydroxy-nitrate of the arsinoline but crystallisation could not be effected, nor could the hydroxy-nitrate be obtained by the usual method of addition of concentrated nitric acid to the moistened arsinoline, in each case an oil or gum being obtained which could not be induced to crystallise. The remainder of the gummy residue was taken up in hot water and a saturated aqueous solution of picric acid added. This produced an emulsion from which the hydroxy-picrate gradually separated as crystalline, yellow plates. After two recrystallisations from ethanol, the product had m. p. 113.5-115°.

Analysis: Found: C, 49.5; H, 3.6; N, 8.2%.

$C_{21}H_{18}O_6N_3As$ requires: C, 48.9; H, 3.5; N, 8.2%.

7. 1-Phenyl-1:2:3:4-tetrahydroarsinoline sulphide

A cooled solution of 1-phenyl-1:2:3:4-tetrahydroarsinoline (1 gm.) in dry chloroform (22 ml.) was treated dropwise with a solution of bromine in chloroform (5.8 ml. of a solution containing 10.52 gm. bromine/100 ml. of solution, 1 mol.). The bromine was at once absorbed with the formation of the arsinoline dibromide. A stream of dry hydrogen sulphide was passed into the chilled solution for 35 minutes after which the solution was filtered to remove traces of sulphur, the filtrate then being evaporated on the water bath. The residual oil, after being dried was taken up in various solvents from none of which any crystalline material could be obtained. The ethanolic solution had, after standing in an open tube for some time, deposited some gummy material which, after six weeks at room temperature yielded a small quantity of crystalline material. The above preparation was repeated and the whole of the oil obtained taken up in ethanol. This solution gave the crystalline sulphide only after being seeded with a crystal from the former preparation. After four recrystallisations from ethanol, the colourless crystalline product was dried and had m. p. 103.5-105°.

Analysis: Found: C, 59.2; H, 5.2; S, 11.5%.
 $C_{15}H_{15}SAs$ requires: C, 59.6; H, 5.0; S, 10.6%.

8. p-Chloroacetophenone

c.f. Judofind and Reid, J. Amer. Chem. Soc.,
1920, 42, 1043.

In a two litre, 3-necked flask fitted as usual for a Friedel-Crafts reaction, was placed dried and redistilled chlorobenzene (102 ml., 112 gm., 1 mol.), dried and redistilled carbon disulphide (400 ml.) and powdered anhydrous aluminium chloride (300 gm.). The mixture was stirred and heated on the water bath until refluxing of the contents commenced. Redistilled acetic anhydride (95 ml., 102 gm., 1 mol.) was then slowly added with stirring over 1 hour. Gentle refluxing of the contents was maintained during the addition of the anhydride and the mixture was boiled under reflux for one hour thereafter. Most of the carbon disulphide was distilled off with stirring and, whilst still warm, the reaction mixture was poured cautiously onto a mixture of 1 kgm. ice and 600 ml. concentrated hydrochloric acid. The residue in the flask was decomposed with ice and concentrated hydrochloric acid and added to the main product. The mixture was extracted with benzene (700 ml.) in three portions, the benzene layer was washed once with water, once with 10% aqueous sodium hydroxide and twice again with water before being dried over anhydrous calcium chloride. The benzene was distilled off at atmospheric pressure and the

residue distilled under reduced pressure. A very small forerun was followed by the product, b. p. 114-116°/12 mm., yielding 120 gm. of a colourless liquid (78%).

9. p-Chlorophenacyl bromide

c.f. Judofind and Reid, J. Amer. Chem. Soc., 1920, 42, 1043.

A solution of p-chloroacetophenone (118 gm.) in glacial acetic acid (240 ml.) was treated (with stirring and under anhydrous conditions) with bromine (30 ml., 96 gm., 0.8 mol.) added over one hour, the internal temperature being kept below 20°. The p-chlorophenacyl bromide commenced to separate during the addition. The flask was allowed to stand at room temperature for 4 hours, then cooled in ice. The product was filtered at the pump and washed with 50% aqueous ethanol. After being dried, the product was recrystallised from ethanol and dried, yielding 81.7 gm. of colourless crystals. The mother liquors furnished a further 4 gm. The total yield was 48%, m. p. 96-97° (reported m. p. 96.5°).

10. (±)-1-p-Chlorophenacyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium bromide

A solution of 1-phenyl-1:2:3:4-tetrahydroarsinoline (2 gm., 1 mol.) and p-chlorophenacyl bromide (1.73 gm., 1 mol.) in dry benzene (10 ml.)

was boiled under reflux for one hour in an atmosphere of nitrogen. The mixture had separated into two layers after two minutes. On cooling, the lower layer solidified to a glass. The benzene was decanted and the remainder removed by drying in vacuo. The glass was crystallised as transparent plates from ethanol. In subsequent preparations, the product was obtained crystalline from the reaction mixture. The yield is quantitative. After two recrystallisations from ethanol and being dried, the bromide had m. p. 210-211°.

Analysis: Found: C, 54.9; H, 3.9; Br, 16.4%.
 $C_{23}H_{21}OClBrAs$ requires: C, 54.8; H, 4.2; Br, 15.9%.

Rapid volumetric analysis of ionic bromide (two different samples): Found: Br, 15.9; 15.95%.

11. 1-p-Chlorophenacyl-1-phenyl-1:2:3:4-tetrahydroarsinolinium iodide

A solution of the above bromide (0.5 gm.) in chloroform (20 ml.) was shaken nine times with 20 ml. portions of a saturated aqueous solution of sodium picrate. The aqueous layer became turbid after the second extraction, but no solid material separated from this layer. After standing for 5 days, no solid material had separated from the combined sodium picrate extracts. The chloroform was evaporated from

the combined chloroform solutions when a yellow-red gummy residue remained. This was thoroughly dried in vacuo when it crystallised. A portion of this picrate was recrystallised from ethanol and then taken up in hot acetone. To this solution, an aqueous acetone solution of potassium iodide was added. After standing at room temperature for 15 minutes, some fine, yellow needles had been deposited from the solution. These appeared to be the unchanged picrate. After a further 20 hours, large plates of colourless crystals had also separated from the solution. The mixture of crystals was filtered off at the pump and after being dried, the two types of crystal were separated by handpicking. The colourless plates, after two recrystallisations from ethanol, followed by washing to remove the picrate on each occasion, were dried and then had m. p. 160-162°.

Analysis: Found: C, 50.8; H, 4.0; I, 22.5%.

$C_{23}H_{21}OClIAS$ requires: C, 50.2; H, 3.8; I, 23.0%.

SECTION XIII: ATTEMPTED OPTICAL RESOLUTION OF
(±)-1-p-CHLOROPHENACYL-1-PHENYL-
1:2:3:4-TETRAHYDROARSINOLIUM
BROMIDE

1. Attempted resolution via the (+)-camphor-
10-sulphonate

The bromide (3.0 gm.) and silver (+)-camphor-10-sulphonate (2.02 gm., 1 mol.) in aqueous ethanol (4 vols. ethanol : 1 vol. water; 50 ml.) were boiled together under reflux for 15 minutes, the suspension filtered whilst hot and the filtrate reduced in volume by evaporation on the water bath, the last traces of solvent being removed in vacuo at room temperature. The (+)-camphor-10-sulphonate formed a crystalline mass, m. p. 172-184° contaminated with a small quantity of gummy material, 2.5 gm., 64%.

This material was recrystallised from aqueous ethanol, the product, after successive recrystallisations, having the following m. p. and rotation figures:

first recrystallisation, $\alpha_D^{20} +0.32^\circ$, $[\alpha]_D^{20} +15.7^\circ$, $[\eta]_D^{20} +103^\circ$ (0.510% solution in ethanol, 4 dm. tube);

second recrystallisation, m. p. 175-178°, $\alpha_D^{19} +0.31^\circ$, $[\alpha]_D^{19} +15.3^\circ$, $[\eta]_D^{19} +100^\circ$ (0.505% solution in ethanol, 4 dm. tube);

third recrystallisation, m. p. 179-181°;

fourth recrystallisation, m. p. 178-180°;

$\alpha_D^{19} +0.31^\circ$, (0.510% solution in ethanol (4 dm. tube));

After a fifth recrystallisation from aqueous acetone, the m. p. was $181-183^\circ$.

Analysis: Found: C, 60.7; H, 5.4%. $C_{33}H_{36}O_5ClSAG$ requires: C, 60.5; H, 5.5%.

The four times recrystallised material (0.6 gm.) in hot water, was treated with excess of a saturated aqueous solution of sodium picrate. After one hour, the crystalline picrate was filtered off, washed with water and dried, m. p. $128-162^\circ$. A 0.514% solution in acetone had $\alpha_D^{20} +0.05^\circ$. After recrystallisation from ethanol, the picrate had m. p. $129-130^\circ$.

Analysis: Found: C, 53.2; H, 3.8; N, 6.4%. $C_{29}H_{23}O_8N_3ClAS$ requires: C, 53.4; H, 3.55; N, 6.45%.

A 0.508% solution in acetone (4 dm. tube) was completely inactive and the above compound was therefore the racemic picrate.

2. Attempted resolution via the (+)-3-bromocamphor-8-sulphonate

The arsinolinium bromide (1.00 gm.) and silver (+)-3-bromocamphor-8-sulphonate (0.81 gm., 1 mol.) in aqueous ethanol (4 vols. ethanol : 1 vol. water; 15 ml.) were boiled together under reflux for 15 minutes, the hot

solution filtered and the filtrate evaporated and finally dried in vacuo. The gummy residue was obtained crystalline from ethyl acetate, m. p. 182-195° with some previous softening. After successive recrystallisations from ethanol, the following m. p. and rotation figures were recorded:

first recrystallisation, m. p. 182-185° with previous softening; $\alpha_D^{16.5} +0.76^\circ$, $[\alpha]_D^{16.5} +43.75^\circ$, $[\eta]_D^{16.5} +321^\circ$, (0.3635% solution in A.R. methanol, 2 dm. tube);

second recrystallisation, m. p. 187-191° with slight previous softening; $\alpha_D^{16} +0.72^\circ$, $[\alpha]_D^{16} +46.6^\circ$, $[\eta]_D^{16} +342^\circ$, (0.7725% solution in A.R. methanol, 2 dm. tube);

fourth recrystallisation, m. p. 261° with effervescence; $\alpha_D^{20} +0.42^\circ$, $[\alpha]_D^{20} +94^\circ$, $[\eta]_D^{20} +690^\circ$, (0.4450% solution in A.R. methanol, 1 dm. tube).

After a fifth recrystallisation, the m. p. had fallen to 188-191° and the material was now evidently deposited as a partial racemate, $\alpha_D^{20} +0.56^\circ$, $[\alpha]_D^{20} +55^\circ$, $[\eta]_D^{20} +404^\circ$, (1.015% solution in A.R. methanol, 1 dm. tube). (Walden, Monatshefte, 1932, 53, 30, records $[\eta]_D$ for (+)-3-bromocamphor-8-sulphonic acid in methanol as +274°).

When an attempt was made to repeat the resolution from a freshly-prepared sample of the optically active salt, the m. p. was not significantly changed after successive recrystallisations from ethanol, the six-times recrystallised material having m. p. 184-185°. Difficulty

was experienced in obtaining an analytically pure sample of this material, probably because it now crystallised from ethanol only with difficulty after long standing as large, and therefore probably chemically-impure, crystals. The above six-times recrystallised material, after a further three recrystallisations from ethanol, had m. p. 184.5-185°.

Analysis: Found: C, 54.9; H, 4.3%. $C_{33}H_{35}O_5ClBrSAc$ requires: C, 54.0; H, 4.8%.

Attempts were made to find an alternative solvent for recrystallisation, but these met with no success. In view of these results, attempted resolution via the (+)-bromocamphorsulphonate was abandoned.

3. Attempted resolution via the (-)-menthoxy-acetate

The arsinolinium bromide (1.00 gm.) and silver (-)-menthoxyacetate (0.638 gm., 1 mol.) in a mixture of 25 ml. ethanol and 40 ml. water were boiled together under reflux for 20 minutes. The suspension was filtered whilst hot and the filtrate reduced in volume on the water bath and the residue finally dried in vacuo. The residue was triturated with ether; a small quantity of crystalline solid was obtained together with a larger quantity of dark-coloured, ether-soluble

oil. After one recrystallisation from aqueous ethanol, the crystalline material had m. p. 185-186°, raised to 187-187.5° after three further recrystallisations from aqueous ethanol.

Analysis: Found: C, 55.65; H, 4.9%. The (-)-menthoxyacetate, $C_{35}H_{42}O_4ClAs$, requires: C, 66.0; H, 6.6%.

The above preparation was repeated by boiling together 4.00 gm. of the bromide and 2.57 gm. of the silver salt in 250 ml. 95% ethanol for 30 minutes. After being worked up as before, the dark-coloured residue was taken up in diethyl ketone from which only 0.36 gm. of crystalline material was obtained, m. p. 181-183°. After three recrystallisations from ethanol, the m. p. was raised to 184.5-185°. Evaporation of the diethyl ketone from the filtrate from the first recrystallisation left an ether-soluble reddish oil as before.

Analysis: Found: C, 55.3; H, 4.35%.

This was evidently the same compound that was obtained in the former preparation, but not the required optically-active salt. The Beilstein test showed the presence of halogen.

Attempts were made to employ milder conditions in order to avoid the partial decomposition which had evidently accompanied the previous preparations. The bromide (0.50 gm.) and silver salt (0.319 gm., 1 mol.) in 30 ml.

50% aqueous acetone were shaken together at room temperature for 3.5 hours, then allowed to stand overnight, warmed and filtered. The solvent was removed by gentle warming under reduced pressure, a hard glass remaining. A solution of the glass in acetone gave, on standing, a deposit of crystalline material. This was filtered off, washed with acetone and dried, m. p. 187-188°. After three recrystallisations from aqueous ethanol, the m. p. was 188-190°.

Analysis: Found: C, 55.4; H, 4.5%.

These results, for which no explanation could be found, caused the attempted resolution via the (-)-menthoxyacetate to be abandoned.

4. Attempted resolution via the (-)-1-N-phenylethylphthalamate

The bromide (3.00 gm.) and silver (-)-1-N-phenylethylphthalamate (1.81 gm., 1 mol.) in 50% aqueous ethanol were boiled together for 15 minutes under reflux. The hot suspension was filtered and the solvent removed from the filtrate by distillation under reduced pressure. The residue, after drying in vacuo, was a clear ether-soluble gum which was very soluble in all the common polar solvents and could not be obtained crystalline.

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