Some Aspects of the Organic Chemistry of Phosphorus and Arsenic.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY, AT NEWCASTLE ON MARCH 17TH, 1944, AND AT LONDON ON MAY 18TH, 1944.

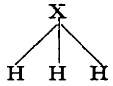
By F. G. MANN, Sc.D., D.Sc.

IT is probable that to the minds of most chemists the expression " The Organic Chemistry of Phosphorus and Arsenic " will recall most immediately the use of such compounds in chemotherapy. This applies, of course, primarily to the organic compounds of arsenic, which have two distinct applications : they are used as curative drugs for (in particular) various spirochætal infections, and also as offensive weapons in gas warfare, an application the chemical study of which may well be termed negative chemotherapy. Phosphorus differs strikingly from arsenic in that many organic compounds containing phosphorus occur naturally in animal and plant organisms, whereas apparently no organic derivatives of arsenic are of natural occurrence.* I do not, however, intend to discuss any of these subjects in this lecture. The chemotherapy of organic arsenic compounds has not of recent years undergone any striking development on the chemical side : on the physiological side, the precise mode of action of such compounds remains uncertain, and its discussion is the province of the physiologist himself. The use of organic arsenic compounds in warfare is a subject which it would be both unprofitable and undesirable to discuss at the present time. The naturally occurring organic compounds containing phosphorus are almost wholly esters of phosphoric acid, and are thus not true organic derivatives of phosphorus : to the organic chemist, therefore, the phosphorus unit in such compounds is the least interesting portion of the molecule.

I am therefore devoting this lecture to a discussion of the stereochemistry of the organic derivatives of phosphorus and arsenic, with some emphasis on the preparative methods which have been employed to obtain suitable compounds for the necessary investigations. In such a discussion the resolution of racemic compounds into their optically active forms must necessarily be prominent. There is a tendency among some chemists, more particularly those who have not kept in touch with modern chemical progress, to consider that the resolution of compounds into optically active forms is a subject which has been so exhaustively investigated in the past that it has now lost most of its theoretical significance and consequently most of its former vivid interest. It is true that no progressive organic chemist would at the present time resolve a compound with optically active forms merely to record one more optically active compound. Yet it must always be remembered that the optical activity of a compound is a physical property which throws much light on the configuration, structure, stability, and other physical and chemical properties of the compound itself. Consequently it is still actively studied, as other physical properties (for example, dipole moments, parachors, infra-red spectra, *X*-ray diffraction) are studied, for the valuable information it affords concerning the other properties of the molecule.

The organic derivatives of phosphorus and arsenic fall into two main classes, those in which these elements are in the 3-covalent condition, and those in which they are 4-covalent. Members of the first class can all be regarded as derivatives of phosphine (PH_3) and arsine (AsH_3), in which one, two, or three of the hydrogen atoms have been replaced by organic radicals : since, however, compounds having hydrogen directly linked to phosphorus or arsenic are unstable and, in particular, very readily oxidised, stereochemical work has been limited to the more stable tertiary compounds, of type PR_3 and AsR_3, where R represents an alkyl or aryl group. Members of the second class, in which the phosphorus or arsenic atom is 4-covalent, can be subdivided into three main groups. (*a*) True quaternary salts, of type $[PR_4]X$ and $[AsR_4]X$, where X is a univalent acid radical : (*b*) compounds obtained by the union of oxygen, sulphur, or selenium to the tertiary phosphine or arsine, and therefore of type $R_3P\rightarrow O$, $R_3P\rightarrow S$, $R_3P\rightarrow Se$: (*c*) compounds similarly obtained by the union of metallic salts (particularly the halides of the heavier metals) to tertiary phosphines or arsines, for example, $[R_3P\rightarrow AuCl]$. It should be noted, however, that in group (*b*), the oxygen members differ from the sulphur and selenium members in that the P—O and As—O links may have polar properties, and these compounds therefore often combine with strong acids to give salts, of type $[PR_3{\cdot}OH]Cl$ and $[AsR_3{\cdot}OH]Br$, which are akin to the true quaternary salts and thus fall systematically into group (*a*). The structure of these various types is discussed later.

In considering derivatives of 3-covalent phosphorus and arsenic, mention must be made of certain physical evidence for the configuration of these elements. Bradley (*Phil. Mag.*, 1924, **47**, 657) showed by an *X*-ray investigation that in crystalline arsenic each atom could be regarded as being situated at the apex of a tetrahedron, with its three valencies directed along the edges of the tetrahedron to join three other atoms situated at the remaining apices : from Bradley's results, the intervalency angle at the arsenic atom is 97°. It was therefore to be expected that both phosphine and arsine would have a pyramidal molecule (I, X = P or As), similar to that of ammonia. The structural constants of these molecules have been determined by Sutherland, Lee, and Wu (*Trans. Faraday Soc.*, 1939, **35**, 1373), using infra-red spectra. Their results, together with those for ammonia, are collected in Table I.



(I.)

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* Although such compounds can be obtained in the laboratory by the action of living organisms; *e.g.*, trimethylarsine from arsenious oxide by the action of *Penicillium brevicaule* (Challenger *et al.*, J., 1933, 95; *Biochem J.*, 1935, **29**, 1757).

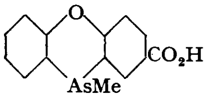
TABLE I.

	X—H length (A.).	H—X—H angle.	Height of pyramidal molecule (A.).	Frequency of inversion per second.
NH_3	1·02	111°	0·30	2×10^{10}
PH_3	1·46	99	0·67	5×10^{6}
AsH_3	1·56	97	0·75	16×10^{4}
PD_3				6×10^{3}
AsD_3				30

Their value for the intervalency angle of arsine confirms Bradley's result for elementary arsenic, and is closely similar to that for phosphine. Their values for the frequency of inversion of the molecules per second, *i.e.*, of the oscillation of the nitrogen, phosphorus, and arsenic atom about the mean plane of the three hydrogen atoms, are of particular interest to organic chemists. The very rapid inversion of ammonia shows clearly that attempts to resolve a dissymmetric tertiary amine must fail unless this frequency can be very substantially decreased. It is much less for phosphine, and still less for arsine, but still remains very high. Replacement of the hydrogen by deuterium has a remarkable effect, however, the frequency of inversion of phosphine being reduced to *ca.* one-thousandth of its original value by this replacement, and that of arsine being reduced to the comparatively slow rate of 30 per second. If these immense reductions are caused by mere doubling of the mass of the atoms attached to the phosphorus or arsenic, the use of heavy organic radicals might, as these authors suggest, so reduce the speed of inversion that the optical resolution of (in particular) a suitable dissymmetric tertiary arsine might become practicable under suitable conditions.

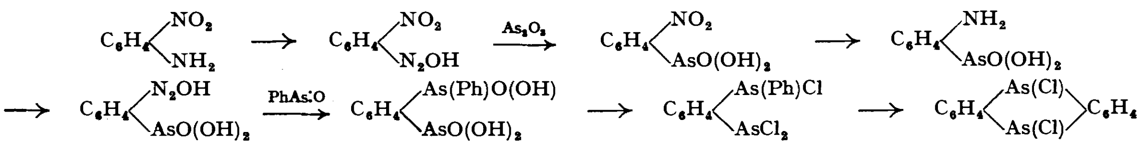
Other physical evidence, for example, the electron diffraction of trimethylarsine (Springall and Brockway, *J. Amer. Chem. Soc.*, 1938, **60**, 996), although not so precise as that quoted above, confirms the value of *ca.* 97° for the arsenic intervalency angle.

There is at present no organic evidence for the configuration of derivatives of 3-covalent phosphorus, but for similar arsenic derivatives there is evidence based both on optical and on geometric isomerism. It is significant, however, that this evidence has been obtained solely by the study of compounds in which the arsenic atom has been part of a ring system and in which the above inversion about this atom is almost certainly inhibited : all attempts to resolve a dissymmetric tertiary arsine abcAs, where a, b, and c are univalent groups, have failed (cf. Kamai, *J. Gen. Russ. Chem.*, 1940, **10**, 733), possibly owing to the nature of the groups employed.


(II.)

Lesslie and Turner (J., 1934, 1170; 1935, 1051, 1268; 1936, 730) have prepared and resolved 10-methylphenoxarsine-2-carboxylic acid (II) and its 10-ethyl and 10-phenyl homologues; all three acids showed high optical stability. This optical activity might be dependent on one of two possible properties of the molecule : (*a*) the three rings might be coplanar, with the methyl group projecting above or below this plane; the three rings could be coplanar, however, only if the intervalency angle at the arsenic atom within the central ring approached 120° (Campbell, Le Fèvre, Le Fèvre, and Turner, J., 1938, 404), and this entails a most improbable increase in the normal value of this angle : (*b*) the molecule might be folded about the O . . . As axis, in order to accommodate the normal intervalency arsenic angle; in this case the three valencies of the arsenic atom might conceivably be in one plane, although this is improbable. If this folding about the O . . . As axis occurred, however, the molecule would lack a plane of symmetry, irrespective of the position of the methyl group. Lesslie and Turner consider that (*b*) is the more probable condition of the molecule. It is significant that loss of activity occurred when the compound (II) was converted into the arsine ethiodide and when the 10-phenyl homologue was converted into the arsine oxide : in both these derivatives the arsenic has become 4-covalent and tetrahedral (see later) and the expansion of the intervalency angle at the arsenic atom might allow the three rings to become coplanar. On the other hand, if the explanation (*a*) were correct, the optical activity might well have been made even more stable by the conversion of the arsenic into the 4-covalent condition.

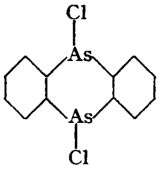
To avoid any possible complication in the above compounds due to the cyclic oxygen atom, Chatt and Mann (J., 1940, 1184) investigated derivatives of " arsanthren dichloride " (correctly named, 5 : 10-dichloro-5 : 10-dihydroarsanthren) (III), in which the ring system is identical with that of Lesslie and Turner's compounds except that the oxygen is now replaced by a second arsenic atom. Arsanthren dichloride had been synthesised from *o*-nitroaniline by Kalb (*Annalen*, 1921, **423**, 53), using the following reactions :



$$C_6H_4\left\langle\begin{matrix}NO_2\\NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}NO_2\\N_2OH\end{matrix}\right. \xrightarrow{As_2O_3} C_6H_4\left\langle\begin{matrix}NO_2\\AsO(OH)_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}NH_2\\AsO(OH)_2\end{matrix}\right.$$

$$\longrightarrow C_6H_4\left\langle\begin{matrix}N_2OH\\AsO(OH)_2\end{matrix}\right. \xrightarrow{PhAs:O} C_6H_4\left\langle\begin{matrix}As(Ph)O(OH)\\AsO(OH)_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}As(Ph)Cl\\AsCl_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}As(Cl)\\As(Cl)\end{matrix}\right\rangle C_6H_4$$

Quite apart from structural features, however, the arsanthren dichloride and its derivatives lend themselves readily to stereochemical investigation, owing to the ease and perfection with which they crystallise. If in the arsanthren molecule the intervalency arsenic atom remains *ca.* 97°, the molecule must be folded about the As . . . As axis, and the possibility of geometric isomerism immediately occurs. Chatt and Mann converted the 5 : 10-dichloro-compound (III) into the less reactive 5 : 10-di-*p*-tolyl compound (IV), which they subjected to fractional crystallisation. This compound, if folded about the above axis, should exist in a *cis*-form, shown in (IVA, T = *p*-tolyl), where the arsenic atoms and tolyl groups are in the plane of the paper, whereas the more prominent benzene ring projects towards, and the other ring away from, the observer: in this *cis*-form, the two tolyl groups are both within the angle subtended by the benzene rings. The compound should also exist in a *trans*-form (IVB), in which one tolyl group is now on the opposite side of the As . . . As axis to the other. A third form, in which the two tolyl groups are again in the *cis*-position, but both on the opposite side of the axis to the benzene rings (IVC), cannot be realised, because the position of the two tolyl groups becomes almost coincident, a fact which can be readily demonstrated by models. Chatt and Mann succeeded in isolating the two forms, which possessed remarkable stability and underwent no interconversion even when maintained in the molten conditions for 10 minutes. When, however, bromine was added to each arsenic atom and the tetrabromide then hydrolysed to the crystalline tetrahydroxide (V), the same product was obtained from both forms : this was in accordance with theoretical expectations, because in the tetrahydroxide the intervalency ring angle of the arsenic has now become *ca.* 120° (see later) and the arsanthren ring system in consequence has become planar. Hence the basis of the former geometric isomerism has disappeared.



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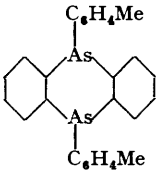

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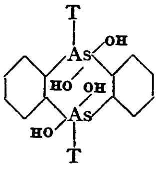

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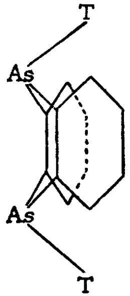
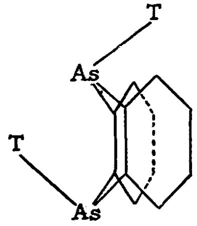
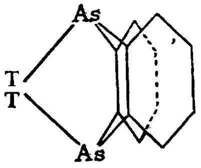


(IVA.)



(IVB.)



(IVC.)

In discussing the stereochemistry of organic derivatives of 4-covalent phosphorus and arsenic, it is advantageous to consider the arsenic derivatives first, because they have been more widely investigated and have yielded richer results than those of phosphorus. This position has arisen because the organic arsenic compounds have proved much more attractive to the practical chemist than the phosphorus compounds. The arsenic derivatives often crystallise readily and with great beauty, whereas the phosphorus analogues often show strong disinclination to crystallise. Furthermore, the Bart reaction for the synthesis of arylarsonic acids, and the ready reduction of many arsonic acids and tertiary arsine oxides to the corresponding arsenious compounds—reactions of the greatest synthetic value—have no counterpart in the chemistry of phosphorus derivatives, the preparation of which in consequence frequently proves of much greater difficulty.

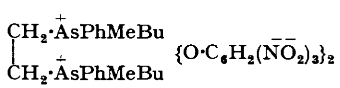
Summarising briefly the stereochemistry of 4-covalent nitrogen derivatives for comparison, it will be recalled that the first resolution of a quaternary salt containing an asymmetric nitrogen atom, phenylbenzylmethylallylammonium iodide, was accomplished in 1899 by Pope and Peachey (J., 1899, **75**, 1127), and that of a tertiary amine oxide, phenylmethylethylamine oxide, in 1908 by Meisenheimer (*Ber.*, 1908, **41**, 3966) : finally, chemical evidence for the tetrahedral configuration of the nitrogen atom in quaternary salts was obtained in 1925 by Mills and Warren (J., 1925, **127**, 2507) by the optical resolution of 4-phenyl-4′-carbethoxybispiperidinium-1 : 1′-spiran bromide. Pope and Peachey's work stimulated many chemists to attempt in particular the preparation and optical resolution of a similar quaternary arsonium salt, of type [abcdAs]X, since it was exceedingly unlikely that either phosphorus or arsenic compounds would possess a configuration essentially different from that of the corresponding types of nitrogen compounds. All attempts to isolate optically stable arsonium salts failed, however, although Burrows and Turner (J., 1921, **119**, 426) obtained phenyl-α-naphthylbenzylmethylarsonium iodide having a maximum experimental rotation α_D 0·1°, $[M]_D$ 12°, in alcoholic acetone, but the activity of the solution rapidly disappeared at room temperature. Similarly Kamai (*Ber.*, 1933, **66**, 1779; *J. Gen. Chem. Russia*, 1934, **4**, 184) obtained *p*-tolylbenzylethyl-*n*-propylarsonium iodide with an experimental rotation of $\alpha_D + 0{\cdot}22°$, and $[M]_D + 45°$, but this salt also rapidly lost this small rotation when in acetone solution at room temperature. The difference between the difficulty attending the resolution of such arsonium salts and the ease with which many similar ammonium salts had been resolved was striking, and at first difficult to explain. It was known, however, that several optically active quaternary ammonium nitrates and sulphates showed considerably stability in solution, whereas the corresponding halides, although usually optically stable in aqueous solution, often showed rapid racemisation in solvents such as chloroform. Pope and Harvey (J., **1901**, **79**, **831**) suggested that this racemisation was due to the formation of a "dissociation-equilibrium," of the type $[\mathrm{abcdN}]\mathrm{I} \rightleftarrows \mathrm{abcN} + \mathrm{dI}$, in solution, a suggestion for which considerable physical evidence was later forthcoming. This explained the optical stability of the nitrates and sulphates, which clearly could not undergo this facile dissociation.

Burrows and Turner (*loc. cit.*) suggested that the failure to obtain optically stable arsonium salts was due to the formation of a similar " dissociation-equilibrium " in solution. It is noteworthy that for synthetic reasons all arsonium salts whose resolution had been attempted had contained at least one alkyl group attached to the arsenic atom, an obviously necessary condition for the establishment of the dissociation-equilibrium. Burrows and Turner obtained some evidence for the formation of this equilibrium, for they showed that phenyldimethylarsine, when treated at room temperature with an excess of ethyl iodide, furnished the expected phenyldimethylethylarsonium iodide, but also afforded phenyltrimethylarsonium iodide. The formation of

$$\mathrm{PhMe_2As + EtI} \rightleftarrows \mathrm{[PhMe_2EtAs]I} \rightleftarrows \mathrm{PhMeEtAs + MeI} \qquad \mathrm{PhMe_2As + MeI} \rightleftarrows \mathrm{[PhMe_3As]I}$$

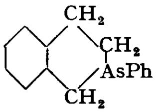
the latter salt can be reasonably explained only on the assumption that the former salt established an equilibrium both with the two original components and also with phenylmethylethylarsine and methyl iodide. The methyl iodide thus generated, however, then reacted also with the phenyldimethylarsine, furnishing the phenyltrimethylarsonium iodide. Burrows and Turner obtained several other examples of similar interchange of alkyl groups occurring at room temperature.

More recently, further evidence to confirm, if not to prove, the existence of these dissociation equilibria of arsonium salts has been obtained. Chatt and Mann (J., **1939**, **610**) prepared ethylene-αβ-bis(phenylmethyl-*n*-butylarsonium picrate) (VI), and by fractional crystallisation separated it into two isomeric forms, m. p. 113—115° and 139·5—140·5°. This salt contains two similar asymmetric arsonium atoms, and one of the two forms isolated must therefore have been the racemic and the other the *meso*-form, the type of isomerism being identical with that shown by the tartaric acids. The two forms of the picrate were highly stable and underwent no interconversion even in boiling alcohol. Such an interconversion, had it occurred, would have involved a change of configuration of one of the arsonium atoms. If such a change of configuration is dependent on the formation of a dissociation-equilibrium, the stability of the two forms is at once explained, because such a dissociation would have entailed the formation of the tertiary arsine and an alkyl picryl ether, which is obviously exceedingly unlikely to occur.



$$\begin{matrix}\mathrm{CH_2\cdot\overset{+}{A}sPhMeBu}\\ |\\ \mathrm{CH_2\cdot\overset{+}{A}sPhMeBu}\end{matrix}\ \{\mathrm{O\cdot C_6H_2(NO_2)_3}\}_2^{-}$$

(VI.)



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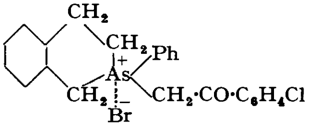
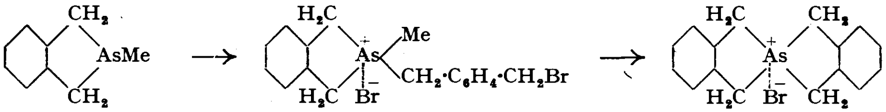


(VIII.)

Chemical evidence for the validity of the dissociation-equilibrium theory of optical instability of arsonium salts could be obtained by the resolution into optically stable forms of an arsonium salt which for structural reasons could not so dissociate in solution. The structural stability might be peculiar to the particular compound studied, or (a more general case) it could be obtained by preparing a dissymmetric arsonium salt [abcdAs]X, in which four unlike *aryl* groups were linked to the arsenic atom, so that dissociation almost certainly could not occur.

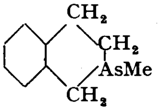
The former case has been realised by Holliman and Mann (J., **1943**, **551**), who showed that *o*-β-bromoethylbenzyl bromide, $\mathrm{C_6H_4(CH_2Br)(CH_2{\cdot}CH_2Br)}$, reacted with phenyldichloroarsine in the presence of sodium to give 2-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (VII), a compound in which the heterocyclic ring had very considerable stability and could only with difficulty be ruptured. This compound was combined with *p*-chlorophenacyl bromide to give 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium bromide (VIII). This particular arsonium salt was chosen because there was evidence that the *p*-chloro-group stabilised the phenacyl radical, and greatly strengthened its union to the arsenic atom. This salt was resolved through the corresponding bromocamphorsulphonates, and the *d*- and the *l*-arsonium picrate were isolated having $[M]_D$ + 457° and − 450° respectively : the *l*-iodide had moreover $[M]_D$ − 354° and remained optically unchanged in chloroform solution at room temperature over a period of five days. This optical activity, both in its order and in its stability, is in marked contrast to previous results, and is undoubtedly due, I consider, to the chemical stability of the iodide preventing the formation of a dissociation-equilibrium.

Striking evidence for the chemical stability of the heterocyclic ring in the 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines (such as VII) has recently been obtained in the Cambridge laboratories. Lyon and Mann (this vol., p. 30) had shown that *o*-xylylene dibromide reacts with methyldichloroarsine in the presence of sodium to form 2-methyl*iso*arsindoline (IX). This tertiary arsine united readily with a further molecule of *o*-xylylene dibromide to form the arsonium salt, 2-*o*-(bromomethyl)benzyl-2-methyl*iso*arsindolinium bromide (X), which when heated lost methyl bromide, forming *As*-*spiro*-bis*iso*arsindolinium bromide (XI), a highly crystalline water-soluble salt. This constitutes the first synthesis of an *As-spiro*cyclic salt having all the four arsenic valencies joined directly to carbon atoms. A precisely similar synthesis was therefore carried out by Holliman

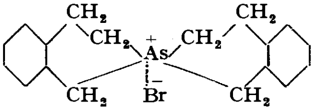


(IX.) (X.) (XI.)

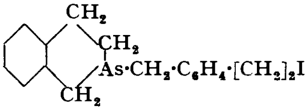
and Mann, who united 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline (XII) with *o*-β-bromoethylbenzyl bromide to give the arsonium salt (similar in type to X), which on heating also lost methyl bromide, furnishing *As-spiro*-bis-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium bromide (XIII). In this salt the arsenic atom is symmetric



(XII.)



(XIII.)



(XIV.)

(unlike that in VIII), but the tetrahedral disposition of the ring systems around the central arsenic atom causes the compound to possess molecular dissymmetry. This salt was also resolved through its bromocamphorsulphonates, and the *d*- and the *l*-arsonium iodide isolated, having $[M]_D$ + 342° and — 344° respectively in chloroform solution. These solutions underwent no change in rotation at room temperature during a period of one month, and the salts therefore possessed very high optical stability. Had any rupture of one of the heterocyclic rings occurred in solution, to give, for example, even a small proportion of the tertiary arsine (XIV) in equilibrium with the parent compound, racemisation must certainly have occurred, probably speedily.

For the synthesis of a dissymmetric tetra-arylarsonium salt, [abcdAs]X, the necessary triarylarsine, abcAs, can be readily prepared, the critical stage being the addition of a fourth aryl group to the arsenic atom to furnish the required arsonium ion, since simple addition of an aryl halide to the arsine is clearly impossible. For this purpose, however, two distinct reactions are available. Blicke and Monroe (*J. Amer. Chem. Soc.*, 1935, **57**, 720) have shown that triphenylarsine oxide, when treated with phenylmagnesium bromide and then with hydrobromic acid, yields tetraphenylarsonium bromide, $[Ph_4As]Br$: this reaction appears, however, to have limited application for the synthesis of tetra-aryl arsonium salts (Blicke and Cataline, *ibid.*, 1938, **60**, 423). Alternatively, Chatt and Mann (J., 1940, 1192) have shown that triphenylarsine, when heated with aluminium chloride and bromobenzene, also furnishes tetraphenylarsonium bromide. This reaction is of wide application, since the use of triaryl phosphines and stibines, in place of the arsine, similarly yields the corresponding tetra-aryl-phosphonium and -stibonium salts respectively. The mechanism of this reaction has been elucidated by Lyon and Mann (J., 1942, 666), who showed that triphenylarsine unites readily with aluminium chloride to give the very reactive trichlorotriphenylarsinealuminium, $[Ph_3As\rightarrow AlCl_3]$. The reactivity of the latter is shown by the fact that it undergoes ready atmospheric oxidation at room temperature, forming triphenylarsine oxide, a reaction which is not shown by pure triphenylarsine under these conditions. It also readily reacts with hot bromobenzene to give the salt, $[Ph_4\overset{+}{A}s][\overset{-}{AlCl_3Br}]$, which of course on subsequent treatment with hydrobromic acid furnishes tetraphenylarsonium bromide. This aluminium chloride reaction has recently been utilised by Mann and Watson to prepare a tetra-arylarsonium salt of the required type, the aryl groups being inserted in the following order :

$$PhAs{:}O \xrightarrow{p\text{-}C_6H_4Me\cdot N_2OH} Ph(p\text{-}C_6H_4\cdot Me)AsO(OH) \xrightarrow{SO_2 + HCl} Ph(p\text{-}C_6H_4Me)AsCl \xrightarrow{p\text{-}C_6H_4Cl\cdot MgI}$$

$$Ph(p\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As \xrightarrow[+ AlCl_3]{m\text{-}C_6H_4MeBr} [Ph(p\text{-}C_6H_4Me)(m\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As]Br$$

This salt furnished in turn the crystalline and less soluble arsonium iodide. Clearly the latter cannot dissociate in solution, and if our attempts to resolve it into optically stable forms prove successful, very strong evidence for the dissociation-equilibrium theory of optical instability will have been obtained.

Turning now to those compounds formed by the union of a tertiary arsine with a Group VI element, it is noteworthy that no success has attended various attempts to resolve a dissymmetric tertiary arsine oxide, of type abcAs→O, although by analogy with Meisenheimer's tertiary amine oxides, such a resolution should be practicable under suitable conditions. The structure of such arsine oxides and their derivatives presents some very interesting points, however, and will be discussed later with the analogous tertiary phosphine oxides.

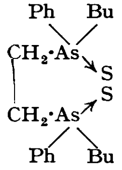
A sulphide of similar type, *p*-carboxyphenylmethylethylarsine sulphide (XV), was prepared by Mills and Raper (J., 1925, **127**, 2479), using the following reactions :

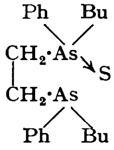
$$p\text{-}CH_3\cdot C_6H_4\cdot As{:}O \xrightarrow[+ SO_2]{MeI + NaOH} p\text{-}CH_3\cdot C_6H_4(Me)AsI \xrightarrow{EtMgI} p\text{-}CH_3\cdot C_6H_4(Me)(Et)As \xrightarrow{O}$$

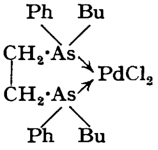
$$p\text{-}CO_2H\cdot C_6H_4(Me)(Et)As\rightarrow O \xrightarrow{H_2S} p\text{-}CO_2H\cdot C_6H_4(Me)(Et)As\rightarrow S \qquad \text{(XV.)}$$

The acid was resolved through its brucine and morphine salts, and obtained in *d*- and *l*-forms, having $[M]_{5780}$ + 51° and − 52° respectively in alcoholic solution. This acid had considerable optical stability : an aqueous solution of its sodium salt was optically unaffected by prolonged boiling.

This stability is in marked contrast to that shown by ethylene-αβ-bis(phenyl-*n*-butylarsine sulphide) (XVI), which Chatt and Mann (*loc. cit.*) prepared and separated into two isomerides, m. p. 113—116° and 121°, one of which must have been the racemic and the other the *meso*-form (cf. the metho-picrates, VI). In this diarsine-disulphide, however, the lower-melting form passed very readily (even in hot alcohol) into the higher-melting form, a process which must have involved a change of configuration of one of the 4-covalent arsenic atoms. It is difficult to suggest a probable mechanism for the racemisation of an arsine sulphide, other than by the formation once again of a dissociation-equilibrium, now of the type $\mathrm{abcAs}\rightarrow\mathrm{S} \rightleftharpoons \mathrm{abcAs} + \mathrm{S}$. The question at once arises as to the reason why Mills and Warren's compound should possess great optical stability, whilst one form of Chatt and Mann's diarsine-disulphide should possess so labile a configuration.


(XVI.)


(XVII.)


(XVIII.)

I think the probable explanation is that in the preparation of the diarsine-disulphide (XVI) by the direct addition of sulphur to the di-tertiary arsine, the first atom of sulphur unites readily and probably very firmly to the arsenic, to give the diarsine-monosulphide (XVII). The 4-covalent (upper) arsenic atom now acquires a positive charge, which, although much weaker than that on a true arsonium ion, is strong enough to exert an inductive effect through the methylene groups, and so to weaken the normal reactivity of the lone pair of electrons on the second (lower) arsenic atom. This reduced reactivity does not prevent this arsenic atom combining with the second sulphur atom to give the diarsine-disulphide (XVI), but does weaken its attachment, so that in solution the equilibrium, diarsine-disulphide $\rightleftharpoons$ diarsine-monosulphide + sulphur, occurs. This dissociation could not actually be detected by molecular weight determinations, but clearly the degree of dissociation need be only very small to cause a rapid change in configuration : in these circumstances the complete conversion of the less stable into the more stable form is to be expected.

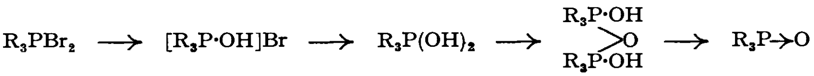
It is noteworthy that the palladochloride derivative (XVIII) of the diarsine (Chatt and Mann, J., 1939, 1622) was separated into two similar forms, m. p. 172—174° and 185—186°, which possessed great configurational stability, and each form could be maintained even in the molten condition without detectable conversion into the other. In this compound, however, the ring system is undoubtedly very stable, and is not ruptured by mere dissolution or fusion : consequently there is no mechanism by which change of configuration of the arsenic atoms can occur.

It may be added that arsenic can show a covalency of six and therefore apparently an octahedral configuration, for Rosenheim and Plato (*Ber.*, 1925, **58**, 2000) have obtained tripyrocatechylarsenic acid, $\mathrm{H[(C_6H_4O_2)_3As]}$, in optically active forms. In this and similar compounds, however, the arsenic is linked to oxygen and not directly to carbon, and their consideration is therefore outside the scope of this lecture.

Turning to the organic derivatives of 4-covalent phosphorus, it is a striking fact that in spite of many attempts to resolve a dissymetric phosphonium salt, of type [abcdP]X, no success has hitherto been achieved (cf. Michaelis, *Annalen*, 1901, **315**, 54; Pope and Gibson, J., 1912, **101**, 753; Wedekind, *Ber.*, 1912, **45**, 2933; Radcliffe and Brindley, *Chem. and Ind.*, 1923, **42**, 64; Meisenheimer *et al.*, *Annalen*, 1926, **449**, 224; Kamai, *J. Gen. Chem. Russ.*, 1932, **2**, 526). Although greater experimental difficulties have made this work more restricted, both in range and in application, than that on similar arsonium salts, I am convinced that the failure to resolve the phosphonium compounds has been caused by the same factor that underlies the arsonium compounds, namely, the formation of dissociation-equilibrium, $\mathrm{[abcdP]X} \rightleftharpoons \mathrm{abcP} + \mathrm{dX}$, in solution, although Wedekind (*loc. cit.*) has adduced some evidence to disprove the existence of such dissociation. It is, however, significant that all the phosphonium salts investigated by the above workers have possessed at least one alkyl group attached to the phosphorus atom, and dissociation should thereby have been favoured. The problem can be satisfactorily solved only by the means described above for similar arsonium salts, namely, by the synthesis and resolution of a dissymmetric phosphonium salt which, by virtue of its structure, cannot dissociate in solution.

Considerable interest attaches to the structure and properties of the tertiary phosphine oxides, of general formula $\mathrm{R_3P\rightarrow O}$, where R may be an alkyl or aryl group, and to their arsenic analogues : the aryl derivatives have been most intensively studied, since the triarylphosphines (unlike the alkyl analogues) are crystalline solids at room temperature, and their oxides are also stable crystalline compounds, usually devoid of the deliquescent properties of trialkylphosphine oxides. Whereas, however, the tertiary amine oxides, $\mathrm{R_3N\rightarrow O}$, contain a true co-ordinate link, *i.e.*, the link consists of two electrons both contributed by the nitrogen atom, in the phosphine oxides the P→O distance is intermediate between that required for a single and that for a double link : this link is probably therefore a resonance hybrid between a true co-ordinate link and a double bond.

[Chemists have no symbol for such a bond, and hence I am retaining a conventional $\rightarrow$ sign in these compounds.] This resonance link may retain sufficient polarity, however, for the tertiary phosphine oxides to unite with strong acids, *e.g.*, hydrobromic acid, forming salts such as $[R_3P{\cdot}OH]Br$, a class of compounds whose arsenic analogues, $[R_3As{\cdot}OH]Br$, are even more frequently encountered. The properties of these " hydroxybromides " show clearly that they are true salts, the bromine being present as ions, and the hydroxy-group being therefore covalently linked to the phosphorus (or arsenic). If, however, a tertiary phosphine is treated with one molecular equivalent of bromine, the tertiary phosphine bromide, R_3PBr_2, is formed : such compounds are reasonably stable in the absence of water, and can often be recrystallised unchanged. The stability of the bromine atoms is greatly affected by the nature of the organic groups R (Mann and Chaplin, J., **1937**, 527), but usually boiling water causes hydrolysis of one bromine atom to give the hydroxybromide, $R_3P(OH)Br$, whilst hot caustic alkaline solution causes complete hydrolysis to the dihydroxide, $R_3P(OH)_2$. The stability

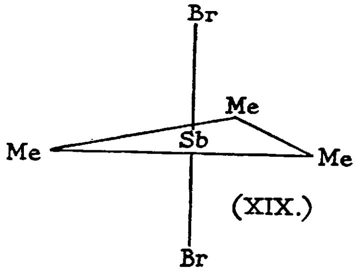


$$R_3PBr_2 \longrightarrow [R_3P{\cdot}OH]Br \longrightarrow R_3P(OH)_2 \longrightarrow \begin{matrix} R_3P{\cdot}OH \\ \quad >O \\ R_3P{\cdot}OH \end{matrix} \longrightarrow R_3P{\rightarrow}O$$

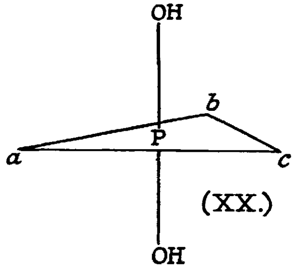
of the tertiary phosphine and arsine dihydroxides varies between wide limits, however, because it also is determined by the nature of the attached groups R. Some dihydroxides are exceedingly stable; others undergo dehydration to a definite crystalline intermediate " sesqui " stage, $(R_3P{\cdot}OH)_2O$; others may undergo such ready dehydration to the oxide, $R_3P{\rightarrow}O$, that the existence of the dihydroxide is difficult to prove. In view of this wide diversity of properties, it is unlikely that any one structure can be rigidly applied to all tertiary phosphine and arsine dihydroxides. Three possible structures can be briefly discussed :

(a) *The ionic structure.* In view of the above preparation of the dihydroxides from the ionic hydroxybromides, it is reasonable to assume that the former may also have an ionic structure $[R_3P{\cdot}OH]OH$. There is little doubt from Meisenheimer's work (discussed below) that in favourable circumstances this hydroxy-cation, $[R_3\overset{+}{P}{\cdot}OH]$, can exist in aqueous solution.

(b) *The resonance structure.* The properties of the tertiary phosphine (and arsine) dibromides show that they are true covalent compounds, and almost certainly are not salts of type $[R_3PBr]Br$. It is noteworthy, moreover, that in the analogous trimethylstibine dihalides, Me_3SbX_2 (where X represents Cl, Br, or I), Wells (*Z. Krist.*, **1938**, **99**, **367**) has shown by *X*-ray analysis that the antimony atom lies in the centre of an equilateral triangle, whose apices are occupied by the methyl groups (XIX) : the halogen atoms (for example, the bromine atoms) lie on an axis running through the antimony atom at right angles to the triangle. The important point is, however, that the two Sb—Br distances are identical and are intermediate between that required for a covalent and that for an electrovalent bond, *i.e.*, the bond is a resonance linkage. It is highly probable, therefore, that the analogous tertiary phosphine (and arsine) dihalides have a similar construction and configuration. Consequently it is possible that in certain cases the corresponding dihydroxides also have this constitution (XX), the hydroxy-groups being joined to the phosphorus or arsenic by identical resonance links. The adoption of this structure may therefore be the explanation of the high stability shown by certain phosphine and (in particular) arsine dihydroxides. An *X*-ray investigation of such compounds would be of the greatest interest. This structure gives the C—As—C angle a value of 120°, unless it is distorted by the three organic radicals being of widely different shape or mass. This value accords well with the fact that the two isomeric forms of 5 : 10-di-*p*-tolyl-5 : 10-dihydroarsanthren give the same tetrahydroxide, in which the three fused rings are undoubtedly coplanar (p. 67).



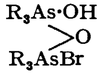
(XIX.)



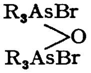
(XX.)

(c) *The hydrogen bond structure.* It has been suggested (Sidgwick, " The Organic Chemistry of Nitrogen," 2nd Edition, 1937, 168) that the feeble basic properties of the tertiary amine dihydroxides, $R_3N(OH)_2$, compared with those of quaternary ammonium hydroxides, indicate that the amine dihydroxides have the structure $R_3N{-}O{-}{-}HOH$, and therefore consist of the amine oxide linked through a hydrogen bond to a water molecule. The presence of the above resonance links in the amine dihydroxides would, however, account satisfactorily for the low basicity. It is unlikely, however, that a similar structure, $R_3P{-}O{-}{-}{-}HOH$, could apply to the tertiary phosphine dihydroxides, because this would imply that the above " sesqui " compounds $(R_3P{\cdot}OH)_2O$, had the structure $R_3P{-}O{-}{-}HOH{-}{-}O{-}PR_3$. But in the arsenic series, the two intermediate stages, the hydroxyoxybromide (XXI) and the oxydibromide (XXII), are encountered as definite crystalline compounds (Lyon and Mann, J., 1942, 666). These cannot be formulated as derivatives of the above hydrogen-bond compound,

(XXI.)



$$\begin{matrix} R_3As\cdot OH \\ \quad >O \\ R_3AsBr \end{matrix}$$



$$\begin{matrix} R_3AsBr \\ \quad >O \\ R_3AsBr \end{matrix}$$

(XXII.)

but can be readily formulated as derivatives of anhydrides obtained from either the above ionic or the resonance dihydroxides.

These considerations have a direct bearing on Meisenheimer's work (*Ber.*, 1911, **44**, 356; *Annalen*, 1926, **449**, 224) on the preparation and resolution of tertiary phosphine oxides, an investigation which, owing largely to retarded crystallisation, took about eleven years to complete. Meisenheimer prepared phenylmethylethylphosphine, and converted it into the oxide (XXIII) : the latter had the normal polar properties and combined with *d*-bromocamphorsulphonic acid to give the salt (XXIV), which, after repeated crystallisation from ethyl acetate, yielded the optically pure *d*-phenylmethylethylhydroxyphosphonium *d*-bromocamphorsulphonate. The latter in aqueous solution had $[M]_D + 313°$,* which fell to $[M]_D + 306°$ on the addition of one equivalent of sodium hydroxide : no indication of even partial racemisation is recorded for either solution. Meisenheimer argued that, since ammonium *d*-bromocamphorsulphonate at equivalent concentration in water has $[M]_D + 267°$, the phosphorus cation in (XXIV) has $[M]_D + 39°$. Meisenheimer then passed dry ammonia

$PhMeEtP\to O$	$[PhMeEtP\cdot OH]d\text{-}C_{10}H_{14}OBrSO_3$	$Ph(CH_2Ph)MeP\to O$
(XXIII.)	(XXIV.)	(XXV.)

through a benzene solution of the above bromocamphorsulphonate (XXIV), whereby the bromocamphorsulphonic acid was split off directly as the insoluble ammonium salt. The filtered solution on evaporation gave the *d*-phosphine oxide (XXIII), which had high optical stability and distilled under reduced pressure without detectable racemisation. This is what we should now expect, as there is no mechanism by which the phosphine oxide, if chemically stable, could racemise during this process. The crystalline deliquescent oxide so obtained had $[M]_D + 38°$ in aqueous solution, $[M]_D + 40°$ in water containing one equivalent of hydrochloric acid, and $[M]_D + 47°$ in benzene solution. Meisenheimer asserted that the second of these values represents the rotation of the salt $[PhMeEtP\cdot OH]Cl$, and compares this rotation with that predicted above for this cation. These results leave little doubt, I think, that the oxide in aqueous solution also forms this cation, and that an optically active ionic hydroxide, $[PhMeEtP\cdot OH]OH$, exists in the aqueous solution. Convincing evidence for this, however, would be afforded by the conversion of Meisenheimer's phosphine oxide (XXIII) by hydration into a definite crystalline dihydroxide without loss of optical activity.

Rather different factors apply, however, to phenylbenzylmethylphosphine oxide (XXV), which Meisenheimer combined with *d*-camphorsulphonic acid, and then by recrystallisation isolated both *l*-phenylbenzylmethylhydroxyphosphonium *d*-camphorsulphonate and its diastereoisomeride. The former salt, when treated even in hot aqueous solution with an excess of ammonia, deposited the crystalline *l*-phosphine oxide (XXV), which clearly therefore possessed such feebly polar properties that it does not form a dihydroxide. In this case, therefore, the action of alkalis on the hydroxy-salts is apparently the direct fission of the corresponding acid and immediate formation of the phosphine oxide.

It is noteworthy that the *l*-phosphine oxide (XXV), dissolved in water containing one equivalent of hydrochloric acid, had $[M]_D - 167°$: the *d*-oxide in aqueous solution had $[M]_D + 162°$, in the above hydrochloric acid solution had $[M]_D + 168°$, but in chloroform had $[M]_D - 17°$. No satisfactory explanation of this change of rotation in chloroform can be given, and there are clearly many points concerning the structure of tertiary phosphines and arsine dihydroxides that still await elucidation.

Until recently Meisenheimer's oxides were the only true organo-phosphorus derivatives to be obtained in optically active form. Recently, however, Davies and Mann (J., 1944, 276) have described an investigation the object of which was to isolate the optically active oxide, sulphide, and selenide of the same dissymmetric tertiary phosphine, $abcP\to O$, $abcP\to S$, $abcP\to Se$, so that the rotatory dispersions of the three compounds could be critically compared. Phosphine sulphides and selenides differ from the corresponding oxides in that the P—S and P—Se link is almost non-polar, and cannot be used for salt formation. Consequently compounds which carried an acidic or basic group for subsequent salt formation had to be prepared. Davies and Mann's results are concerned primarily with the synthetic methods developed for this purpose, and their application to the preparation of several apparently suitable racemic phosphine sulphides. Only one of the latter was resolved, however, and its synthesis is outlined below, because it illustrates the greater difficulty and complexity attending the preparation of such phosphorus compounds compared with those of similar arsenic compounds, such as (XV).

$$C_6H_5\cdot OMe \xrightarrow{PCl_3+AlCl_3} (p\text{-}C_6H_4\cdot OMe)Cl_2P \xrightarrow{HgPh_2} Ph(C_6H_4\cdot OMe)ClP \xrightarrow{n\text{-}BuMgBr}$$

$$Ph(C_6H_4\cdot OMe)BuP \xrightarrow{HI} Ph(C_6H_4\cdot OH)BuP \xrightarrow[+\,NaOH]{Ph\cdot COCl} Ph(C_6H_4\cdot O\cdot COPh)BuP \xrightarrow{S}$$

$$Ph(C_6H_4\cdot O\cdot COPh)BuP\to S \xrightarrow{Hydrolysis} Ph(C_6H_4\cdot OH)BuP\to S \xrightarrow[+\,NaOH]{CH_2Br\cdot CO_2Et} Ph(C_6H_4\cdot O\cdot CH_2\cdot CO_2H)BuP\to S$$

(XXVI.)

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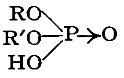
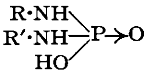
* These rotations are the amended values given in Meisenheimer's second paper.

The final product, phenyl-*p*-(carboxymethoxy)phenyl-*n*-butylphosphine sulphide (XXVI), was resolved by combination with α-phenylethylamine, and the free acid ultimately isolated in *d*- and *l*-forms, having $[M]_D$ + 9·6° and − 9·7° respectively in benzene solution. Neither this acid in benzene, nor its ammonium salt in water, showed any tendency to racemise.

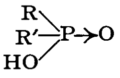
In earlier years, synthetic difficulties in the preparation of organo-phosphorus compounds had induced chemists to investigate the possibility of resolving esters (XXVII) and amides (XXVIII) of phosphoric acid (Caven, J., 1902, **81**, 1362; Luff and Kipping, J., 1909, **95**, 1993) and also phosphonic acids (XXIX) (Pope and Gibson, J., 1912, **101**, 740). It is now realised that such attempts must have been fore-doomed to failure, because ionisation of these acids in aqueous solution would have been immediately followed by resonance in the phosphorus anion, which thus would have become symmetric. It is noteworthy, however, that Hatt (J., 1933, 776) has separated ethyl triphenylmethylpyrophosphonate (XXX) into two forms, m. p. 222—223° and 228—231°; since the compound contained two similar asymmetric phosphorus atoms, one of these forms must have been the racemic, and the other the *meso*-form. In accordance with expectation, however, both forms on hydrolysis gave the same acid, in which resonance of the anion must necessarily make both phosphorus atoms symmetric.



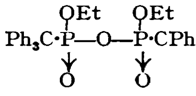
(XXVII.)



(XXVIII.)



(XXIX.)



(XXX.)

It must be emphasised that the optical resolution of the various 4-covalent phosphorus and arsenic compounds described above does not prove that these atoms have the tetrahedral configuration—it shows solely that the phosphorus or arsenic atom cannot be in the same plane as the other four groups to which it is attached. Although there is thus no direct chemical evidence that the 4-covalent arsenic and phosphorus atoms have the tetrahedral configuration, the study of other types of organic derivatives of these elements has provided unambiguous evidence on this point. Mann, Purdie, and Wells (J., 1936, 1503; 1937, 1828) have shown that, whereas tertiary phosphines and arsines combine with aurous salts to give simple non-ionic compounds of type $[R_3P\rightarrow AuCl]$, they combine with cuprous iodide and argentous iodide to form more complex non-ionic derivatives of type $[R_3As\rightarrow CuI]_4$ and $[R_3P\rightarrow AgI]_4$. The complete structure of one member, tetrakis(mono-iodotriethylarsine copper), $[Et_3As\rightarrow CuI]_4$, has been established, and the configuration of the 4-covalent arsenic, 4-covalent cuprous, and 3-covalent iodine atoms thus determined. The arsenic atoms in this compound lie each at the centre of a tetrahedron, having one cuprous and three carbon atoms at its apices: the isomorphism of the corresponding phosphine compounds shows that the 4-covalent phosphorus atom also has the tetrahedral configuration.

Further evidence has been obtained by the crystallographic examination of the " bridged " compound which trimethylarsine forms with palladous bromide, namely, dibromobis(trimethylarsine)-μ-dibromodipalladium, $[(Me_3As)BrPdBr_2PdBr(Me_3As)]$: the complete structure of this compound has been elucidated by *X*-ray analysis (Mann and Wells, J., 1938, 702; Wells, *Proc. Roy. Soc.*, 1938, *A*, **167**, 169), and here again the 4-covalent arsenic atoms have the tetrahedral configuration.