# Liversidge Research Lecture

No. 3
1940

## ORGANIC ARSENICALS IN PEACE AND WAR

G. J. BURROWS

The Royal Society of New South Wales

**George Joseph Burrows**

This photograph is reproduced by permission of the Australian Academy of Science from an article by D.P. Mellor in *Records of the Australian Academy of Science*, 1975, **3**, 29-40.

[The Burrows Memorial Lecture was established by the Metal-Organic Division of the Royal Australian Chemical Institute in 1975]

Liversidge Research Lecturer No. 3, 1940

## GEORGE JOSEPH BURROWS 1888-1950

**George Joseph Burrows** studied science at the University of Sydney, and graduated B.Sc. in 1910 with a double University Medal in Chemistry and in Geology and Mineralogy. Later that year he was appointed Lecturer in the Department of Chemistry, University of Sydney. His first researches were in the corrosion of steel in water, and on the decomposition of carbamide carried out in collaboration with Professor C.E. Fawsitt. His first individual research, published in 1914, was on the inversion of sucrose. For the period August 1915 to April 1919 Burrows was a temporary lecturer in Chemistry at the Royal Military College at Duntroon, then he returned to his position at the University of Sydney. A significant turning point in Burrow's career came later in 1919 with the appointment of Eustace Ebenezer Turner (1893-1966) as Lecturer in Chemistry at the University of Sydney. Turner's great enthusiasm about the revolutionary work of Alfred Werner (Nobel laureate) on coordination compounds rubbed off on Burrows and the two young men became collaborators. After a study of the constitution of nitroprussides they turned to research on compounds of arsenic. This included some work on tertiary arsines, and the demonstration of optical activity in a quaternary arsonium salt. Turner returned to England in 1921, but Burrows maintained and expanded his interest in coordination chemistry, and he attracted a succession of collaborators. One of these was another member of staff, namely, Dr Ian (later Sir Ian) Wark who was appointed Lecturer in Chemistry at the University of Sydney in 1925. Wark only remained there about a year, but in that time Burrows and Wark worked together on the constitution of some aluminium complexes. Burrows continued work on some alumino-oxalates until about 1932, but then he revived his interest in the chemistry of arsenic: with a succession of research students he prepared tertiary arsine complexes of silver, platinum, mercury, copper, cadmium and zinc. One of his last students was R.S. Nyholm (later Sir Ronald) who spent his Honours year (1937) working with Burrows on the reaction of tertiary arsines with ferric chloride. Burrows' research activity waned at the end of the 1930s, and early in 1940 his health deteriorated. His Liversidge Lecture, reproduced below, was his swan-song, and he retired in 1941 from his position of Senior Lecturer.

No official obituary of George Burrows was published at the time of his death, an unfortunate omission remarked upon by Mellor.[1] The University of Sydney Archives do not include documents relevant to his original appointment, nor, for example, the date of his promotion to Senior Lecturer. Details of his early life and education have not been found.

In 1974 the Coordination and Metal-Organic Chemistry Division of the Royal Australian Chemical Institute established the biennial Burrows Memorial Lecture in recognition of the major influence that Burrows had on the development of coordination chemistry in Australia. The first Burrows lecture was presented by Dr. (later Professor) A.M. Sargeson at the University of Adelaide in 1975.

## Honours and Awards

1940 Liversidge Research Lecture, Royal Society of New South Wales

1975 The Burrows Memorial Lecture established by the Coordination and Metal-Organic Division, Royal Australian Chemical Institute.

## Biographical Sources


(1) Mellor, D.P., 'The Development of Coordination Chemistry in Australia', *Records of the Australian Academy of Science*, 1975, **3**(2), 29-40.

(2) Professor A.T. Baker, personal communication.

(3) Baker, A.T., 'The Foundation of the Sydney School of Cooordination Chemistry', *J. Proc. Roy. Soc. N.S.W.*, 2000, **133**, 45-60.

(4) Branagan, D. and Holland, G., 'Ever Reaping Something New: a Science Centenary', University of Sydney Science Centenary Committee, 1985.

(5) University of Sydney Archives, Fisher Library, University of Sydney.


## Scientific Publications of G.J. Burrows

The 40 scientific publications of G.J. Burrows are listed by Professor A.T. Baker in reference (3) given above under Biographical Sources.

Liversidge Research Lecture No. 3, 1940

# ORGANIC ARSENICALS IN PEACE AND WAR*

G. J. BURROWS
*Department of Chemistry, University of Sydney, N.S.W.*

Mr. President, Ladies and Gentlemen,

I fully appreciate the high honour that the Society has conferred upon me. I feel, however, that there are some among you who are more worthy of that honour. At the same time, I cannot but feel pleased that it is my privilege to give this lecture tonight, since, as many of you know, it was under the guidance of the late Professor Liversidge that I commenced my studies in chemistry - I was a first year student during his last year at the University. Professor Liversidge was well known to the senior members of the Society on account of the large number of papers he presented for publication in the Society's Proceedings. I can remember him only as the Professor of Chemistry whose lectures I had to attend - lectures full of detail and illustrated with an extraordinary number of experiments. Judging by the extent of his publications, one would conclude that Professor Liversidge must have lived for research. If we, his pupils, have failed to devote as much time to the search for knowledge as we should have done, it is not for want of an example.

I have taken as the title of my address Organic Arsenicals in Peace and War. I do not, however, intend to dissect the subject in the manner that the title might suggest. I propose, in the short time at my disposal, to treat the subject rather from an academic viewpoint and to review briefly some of the methods available for the preparation of organic derivatives of arsenic. At the same time I will use for illustrations compounds which have been of service to man, either as agents of destruction or the reverse.

Today there are many thousands of organic arsenicals known, a fact to be attributed to the ease with which carbon-arsenic linkages are formed and also to the stability of such linkages. Once an organic arsenical is prepared, it can be subjected to many diverse types of reaction to yield fresh derivatives without severing the C-As bond. Yet in spite of this ease of formation and stability, the vast number of organic arsenicals are almost exclusively products of the laboratory.

The first organic derivative of arsenic was prepared by Cadet de Gassicourt, who, in 1760, distilled a mixture of arsenious oxide and potassium acetate and obtained a mixture of two oils, the heavier one (cacodyl) being inflammable and possessing a most objectionable odour - so much so that it was not further investigated until 1804. It is interesting to note that during the next fifty years Cadet's fuming oil attracted the attention of such men as Berzelius, Laurent, Dumas, Gerhardt, Bunsen, Frankland and Kolbe. But it was not till 1854 that Cahours and Riche[1] definitely established the constitution of cacodyl and obtained the chloride. Five years later Cahours,[2] by heating methyl iodide with zinc or cadmium

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* Liversidge Research Lecture delivered on October 29th at Science House, Sydney, arranged by the Royal Society under the terms of the Liversidge bequest. Reproduced by permission of the Royal Society of New South Wales from *J. Proc. Roy. Soc. N.S.W.*, 1940, **74**, M1-M16.

arsenite, succeeded in preparing tetramethyl arsonium iodide, and by distilling this with potassium hydroxide he obtained trimethyl arsine. He also prepared tetramethyl arsonium triiodide, and from this, by distillation, he obtained dimethyl iodo arsine (cacodyl iodide). And by heating dimethyl iodo arsine with iodine, he finally obtained methyl diiodo arsine, thus completing the series $MeAsI_2$ $Me_2AsI$, $Me_3As$ and $Me_4AsI$. Cahours thus laid the foundation of aliphatic arsenical chemistry.

Another example of the high quality of the work of the last century is to be found in the publications of Michaelis. Beginning in 1876 with the preparation of phenyl dichloro arsine by the action of arsenious chloride on mercury diphenyl,[3] he continued his work until 1915, during which period he prepared nearly every type of aromatic arsenical known today, including (in 1881) arsenobenzene,[4] the parent substance of compounds prepared years later by Ehrlich in his quest for successful specifics for the treatment of syphilis, trypanosomiosis and other diseases. The method employed by Michaelis for the formation of an arsenobenzene was essentially the method used today in the preparation of this type of compound, i.e. the reduction of an arsonic acid or an oxyarsine. This type of reaction was subsequently fully exploited by Ehrlich and his co-workers in the preparation of compounds such as salvarsan and neosalvarsan, the synthesis of which I will refer to later.

I would like to pass on to consider a few of the methods now in use for the preparation of compounds containing carbon-arsenic linkages, and of some of the reactions whereby derivatives of these compounds may be obtained.

## Aliphatic Compounds

(1) Tertiary arsines of the type $R_3As$ are readily prepared by the interaction of Grignard reagents and arsenic halides.[5] Arsenious iodide has been found to be a most useful reagent for this purpose. These tertiary arsines on treatment with iodine will yield progressively, compounds of the type $R_2AsI$ and $RAsI_2$.[6]

(2) *Alkylation.* The alkylation of sodium arsenite was first described by Meyer in 1883, and the method has since been modified by Klinger and Kreutz (1889) and others.[7] When sodium arsenite is treated with methyl iodide in aqueous alcohol, sodium methyl arsonate is formed together with sodium iodide. Alkylation is due to the tendency of the arsenic atom to pass from the tervalent to 4-covalent state by virtue of the lone pair of electrons present in tervalent arsenic. On treatment with acid, sodium methyl arsonate yields methyl arsonic acid which is readily reduced in acid solution by hydriodic acid (sulphur dioxide and iodine) to methyl diiodo arsine,[8] from which by treatment with a weak alkali methyl arsenious oxide may be obtained. This may be dissolved in sodium hydroxide and the sodium methyl arsenite again methylated to yield the sodium salt of dimethyl arsinic acid (cacodylic acid), and from this in turn one can prepare the iodide (or chloride) and oxide.[9] (See Fig. 1.)

Ethylation proceeds quite satisfactorily, but as would be expected is a slower reaction. The reaction makes possible the preparation of mixed arsines, e.g. sodium arsenite may be methylated and the sodium methyl arsenite obtained after reduction and addition of alkali may then be ethylated giving methyl ethyl arsinic acid from which methyl ethyl iodo arsine[10] may ultimately be obtained. By coupling these mixed halogeno arsines with suitable Grignard reagents prepared from either alkyl or aryl halides one can readily obtain asymmetrical tertiary arsines in good yield.[11] Iodo arsines react with potassium cyanide[12] yielding

cyano arsines and the cyanogen group may be hydrolysed in the ordinary way to carboxyl yielding carboxy arsines.(13)

Arsonic acids may be reduced by means of amalgamated zinc in acid solution to primary arsines, e.g. $MeAsO(OH)_2 \rightarrow MeAsH_2$.(14) Reduction of dimethyl arsenious oxide by platinised zinc in acid solution yields the secondary arsine, $Me_2AsH$.(15) (Unlike the nitrogen analogues, these arsines do not possess basic properties.) Ethyl dichlorarsine (b.pt. 156°) was used by the Germans in March, 1918. It is a lung-injuriant agent and also a fairly powerful sternutator and vesicant. A concentration of 0.010 mg. per litre is not tolerable for more than a minute on account of irritation of nose and throat. There is no record of casualties, but on account of its quick action and low persistency it should be suitable for use prior to an infantry offensive. The German method of manufacture was to ethylate sodium

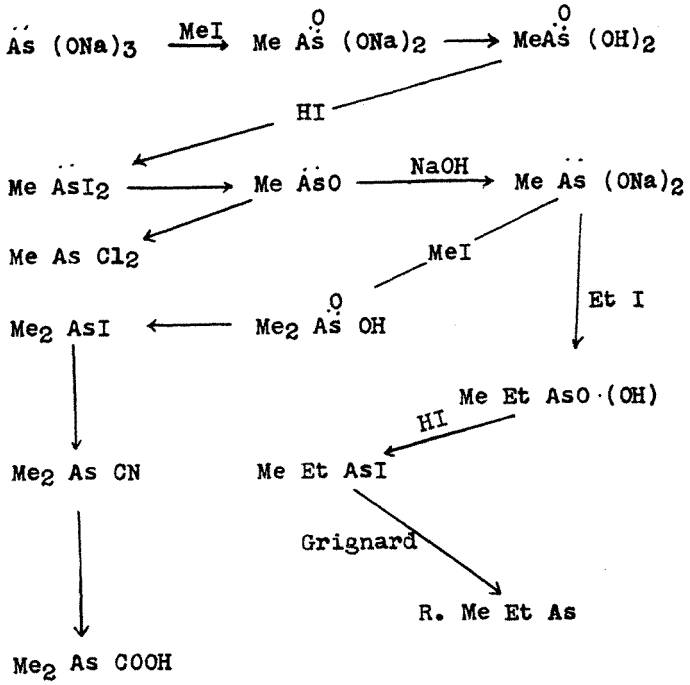



Figure 1

arsenite with ethyl chloride under pressure, followed by reduction by sulphur dioxide in the usual way.

Before leaving the aliphatic compounds I would like to refer to one other special reaction. When acetylene is passed into anhydrous arsenious chloride in the presence of aluminium chloride, a series of compounds is obtained. In 1919 Dafert[16] described a compound, obtained in this way, to which he assigned the formula $AsCl_3.2C_2H_2$. The properties of the substance are similar to those of ββ'-dichloro divinyl chloroarsine. Actually the reaction produces a mixture of three compounds:

β-chloro vinyl dichloroarsine $ClCH{=}CHAsCl_2$
ββ'-dichloro divinyl chloroarsine $(ClCH{=}CH)_2AsCl$
ββ'β"-trichloro trivinyl arsine $(ClCH{=}CH)_3As$.

These compounds were described by Price and Green in 1921[17] but actually they were being manufactured in quantity in America in 1917-18. The most important is the first, the

dichloroarsine, and in its manufacture the product is fractionated to avoid as far as possible the inclusion of the other two. The product "Lewisite" (b. pt. 190°) has properties very similar to those of mustard gas. It is a strong vesicant and it will pass through ordinary clothing. It is hydrolysed with water yielding hydrochloric acid and chloro vinyl arsine oxide, which also is described as a vesicant. Like mustard gas, it is quickly destroyed by caustic soda, and is easily oxidized. Though much has been claimed for "Lewisite" as a vesicant, it has yet to be tried out under war conditions, as the first shipment from America in 1918 never reached Europe. On account of the armistice, it was dumped at sea.

## Aromatic Compounds

(1) As in the case of aliphatic compounds, tertiary arsines are easily prepared by the action of Grignard reagents on arsenious halides[18]. The tertiary arsines may then be degraded by reaction with arsenious chloride to give diaryl mono chloro arsines[19].

(2) Tertiary arsines may also be prepared by the action of sodium on a mixture of arsenious chloride and aryl halides[20].

(3) The Bart reaction[21] (1912) probably affords the most important method of preparation of aromatic arsonic and arsinic acids. In this reaction, a diazonium salt is added to a solution of sodium arsenite in the presence of a suitable catalyst (usually copper sulphate). Nitrogen is evolved on heating, sodium chloride split out and the sodium salt of an arsonic acid obtained. The free arsonic acid is obtained by acidifying the solution of the sodium salt. Many modifications of the original Bart reaction have been described,(22) but experience has shown that if the solution of the diazonium salt is added to the sodium arsenite solution maintained at a temperature of 45°-50° C then the original method generally gives good yields. The arsonic acid may be reduced in hydrochloric acid solution by sulphur dioxide (after the addition of a small quantity of iodine or potassium iodide) yielding a dichloroarsine. On treatment with a weak alkali the dichloroarsine may be converted to the oxy-arsine which will dissolve in sodium hydroxide to give sodium aryl arsenite. This may be coupled with another molecule of a diazonium salt to give a diaryl arsinic acid(23) ($R_2AsO.OH$), which can be reduced as before by sulphur dioxide to give a diaryl mono chloroarsine such as $Ph_2AsCl$. This sodium aryl arsenite may also be alkylated to give mixed alkyl aryl halogeno arsines(24) of the type RR'AsX. (See Fig. 2.). Halogeno arsines will all react with Grignard reagents, and these

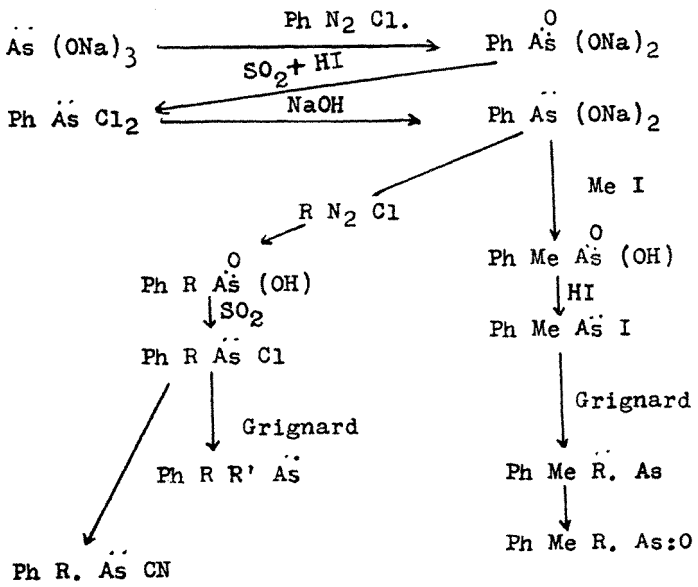



FIGURE 2

reactions obviously afford a method of preparation of tertiary arsines[25] in which the arsenic atom may be combined with three different groups. In 1929 Blicke and Smith[26] showed that mixed arsine oxides could be prepared by the action of Grignard reagents on aryl arsine oxides dissolved in benzene. Thus from *p*-tolyl magnesium bromide and phenyl arsine oxide they obtained p-tolyl phenyl arsenious oxide ($p$-$C_7H_7$.PhAs)$_2$O. This also affords a ready method of preparing asymmetric tertiary arsines. If diphenyl chloroarsine be treated with a solution of potassium cyanide, the chlorine atom is replaced by the cyanogen group giving diphenyl cyano arsine. Both of these compounds were used as sternutators by the Germans during the world war. They are both solids, the chloro compound melting at 45° when pure (generally below 40° C.), and the cyano compound at 31° C. They were dispersed in the form of fine dust by heavy explosive charges, the clouds lasting only a short time. Fortunately for the Allies the German technique in this case was at fault, as the dispersal of the arsine was on the whole a failure. Diphenyl chloroarsine is hydrolysed slowly in moist air. It is stated to be effective at concentrations as low as 1 part in 25,000,000. It is immediately effective and readily penetrated the existing masks of the Allies. Diphenyl cyanoarsine was used by the Germans in May, 1918. It is more stable towards water than the chloro compound, and also more irritant, being effective at concentrations as low as 1 part in 50,000,000. Phenyl dichloroarsine (b.pt. 252° C.) was used by the Germans in 1917-18 and also by the Allies. It is a lung irritant and also a vesicant and sternutator. A concentration of 0.26 mg. per litre is fatal in 10 minutes. It is hydrolysed in water and is easily oxidised. Actually it was not used to any great extent in the last war, being used mainly as a solvent for diphenyl chloroarsine. The corresponding bromo compound, $PhAsBr_2$ was the last lung irritant introduced during the World War, and there is very little record of its effects. It is claimed that 0.020 mg. per litre will prove fatal in 10 minutes. Its toxicity exceeds that of any other lung irritant used.

Tertiary arsines are readily oxidised by oxidising agents (e.g. hydrogen peroxide), to arsine oxides of the type $R_3AsO$. It was found, however, that on exposure to moist air, phenyl dimethyl arsine and *p*-tolyl dimethyl arsine were both slowly oxidised to arsinic acids, with the loss of a methyl group (presumably as methyl alcohol).[27]

$$PhAsMe_2 + H_2O + O_2 = PhMeAs.O.OH + MeOH.$$

This reaction could be accelerated by bubbling oxygen through the arsine in the presence of water.

It was later found that *p*-tolyl methyl dihydroxy arsonium chloride and *p*-tolyl methyl arsinic acid could be demethylated by lead tetrachloride, yielding *p*-tolyl arsonic acid.[28]

$$PhMeAsO.OH \longrightarrow PhAsO(OH)_2$$

Arsine oxides and arsinic acids possess basic properties to the extent that they will combine with acids to give hydroxy salts, e.g.

$$PhMeAsO.OH \longrightarrow PhMeAsO.OH.HCl$$

$$PhMe_2AsO \longrightarrow PhMe_2As.O.HCl.$$

Both types are soluble in water, acetone, and alcohol, and give acid reactions. The aqueous solutions may be titrated (quantitatively) with barium hydroxide solution. The

formulae assigned to them, viz. ($PhMe_2AsOH$)Cl and ($PhMeAs(OH)_2$)Cl,[29] are consistent with their reactions in solution. Thus the hydroxy nitrate and hydroxy sulphate may be prepared by treating the hydroxy chloride with the calculated amount of silver nitrate or sulphate. The acid reaction in aqueous solution must be attributed to secondary dissociation of the complex ion. It is rather remarkable that some of these hydroxy salts are also soluble in chloroform and can be obtained in the pure form by recrystallisation from this solvent. Presumably they break down into their original components in hot chloroform, and, on cooling, recombine and separate in the crystalline form.

It is interesting to note that diphenyl methyl arsine dichloride is soluble in water, giving an acid reaction due no doubt to hydrolysis to the hydroxy chloride and hydrochloric acid. It is also soluble, however, in benzene, and the molecular weight, determined by the cryoscopic method, in this solvent (317) agrees very closely with that calculated from the formula $Ph_2MeAsCl_2$ (315).[30] This result indicates definitely that in benzene solution the compound is not split up into simpler molecules. This raises the question of the valency of the arsenic atom, and the mode of attachment of the chlorine in this type of compound. It is obvious that further experimental work should be carried out with arsine dihalides, dihydroxides, and hydroxy salts.

Hydroxy salts formed from asymmetric tertiary arsines (e.g. phenyl α-naphthyl methyl arsine) and *d*-bromo camphor sulphonic acid have been obtained, and attempts made to separate the two optically active forms by fractional crystallisation, but without success.

(4) *Friedel and Kraft Reaction*

Prior to 1921, it had been considered that the Friedel and Kraft reaction was not generally applicable to chloroarsines. In that year, however, it was shown that not only was triphenyl arsine formed from diphenyl chloroarsine and benzene in the presence of aluminium chloride, but also that in carbon disulphide solution, aluminium chloride converted γ-phenyl-propyl ethyl chloroarsine into the cyclic compound As-methyl tetrahydro arsinoline.[31] Two years later Wieland[32] found that the Friedel and Kraft reaction could be used for the production of primary, secondary and tertiary arsines. As a result of this we now have a simple method of preparing triphenylarsine, by the action of arsenious chloride on benzene in the presence of aluminium chloride. As triphenyl arsine can be easily degraded to diphenyl chloroarsine by treatment with arsenious chloride, it would appear that this will be the most satisfactory method of producing diphenyl chloroarsine in quantity in the event of this compound being required for war purposes.

Heating secondary aromatic amines with arsenious chloride gives rise to the phenarsazines.[33] For example, when diphenylamine is heated under reflux with arsenious chloride, the product is 10-chloro-5,10-dihydro phenarsazine (Fig. 3A). Actually this compound was prepared in Britain and America for use in the last war and is referred to in the literature as diphenyl amine chloro arsine. It is a powerful sternutator. It is a yellow to green solid with a m.pt. of 195°C., insoluble in water and only very slowly hydrolysed in moist air. Its effective concentration is given as 1 in 30,000,000. It is far more easily and cheaply manufactured than diphenyl chloroarsine and is stated to be at least just as effective. Apparently, production came too late for use in the last war. Quite a number of phenarsazines have been prepared by using other secondary amines and their substitution products. By heating diphenyl amine with β-chlorovinyl dichloroarsine β-chlorovinyl phenarsazine is obtained[34] (Fig. 3D).

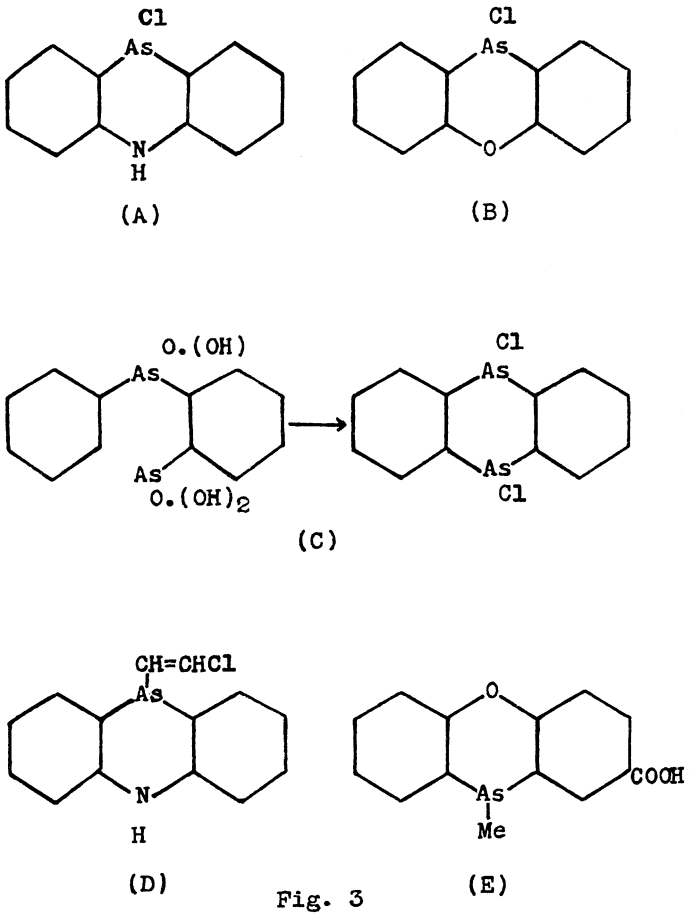



Fig. 3

The chlorine atom in these compounds is reactive. The chloroarsine may be oxidised to the corresponding arsonic acid, or it may be coupled with a Grignard reagent to give an arsine.[35]

In a similar manner, aryl ethers react with arsenious chloride on heating and in this case aluminium chloride is used as catalyst.[36] Thus diphenyl ether and arsenious chloride yield 5-chloro phenoxarsine (Fig. 3B). A phenoxarsine of particular interest is 3-carboxy-5-methyl phenoxarsine, obtained in optically active form by Turner and Lesslie[37] (Fig.3E). Arsanthrene chloride (Fig. 3C) is prepared by passing a current of sulphur dioxide into a hydrochloric acid solution of diphenyl arsinic *o*-arsonic acid to which a little potassium iodide has been added, and then distilling.[38]

Phenols and primary amines may be directly arsonated by heating with arsenic acid, yielding *p*-hydroxy[39] or (amino)[40] phenylarsonic acid.

Fig. 4 illustrates a few of the methods now available for the preparation of 3-amino 4-hydroxy phenyl arsonic acid,[41] a compound which may easily be converted into several arsenicals of great therapeutic importance. A few of the methods of preparation are as follows:

(1) Aniline $\xrightarrow{\text{Bart}}$ phenylarsonic acid $\longrightarrow$ p-nitrophenylarsonic acid.

p-aminophenylarsonic acid $\longrightarrow$ 4-amino-3-nitrophenylarsonic acid

$\longrightarrow$ 4-hydroxy-3-aminophenylarsonic acid.

(2) Aniline $\xrightarrow{H_3AsO_4}$ p-aminophenylarsonic acid $\longrightarrow$ p-hydroxyphenylarsonic acid

$\longrightarrow$ 4-hydroxy-3-aminophenylarsonic acid.

(3) p-chloroaniline $\longrightarrow$ p-chlorophenylarsonic acid $\longrightarrow$ 3-nitro-4-chlorophenylarsonic acid

$\longrightarrow$ 3-nitro-4-hydroxyphenylarsonic acid $\longrightarrow$ 3-amino-4-hydroxyphenylarsonic acid.

(4) p-nitraniline $\longrightarrow$ p-nitrophenylarsonic acid $\longrightarrow$ p-aminophenylarsonic acid

$\longrightarrow$ 3-nitro-4-aminophenylarsonic acid $\longrightarrow$ 3-nitro-4-hydroxyphenylarsonic acid

$\longrightarrow$ 3-amino-4-hydroxyphenylarsonic acid.

(5) phenol $\xrightarrow{H_3AsO_4}$ p-hydroxyphenylarsonic acid $\longrightarrow$ 3-nitro-4-hydroxyphenylarsonic acid

$\longrightarrow$ 3-amino-4-hydroxyphenylarsonic acid.

(6) Aniline $\xrightarrow{H_3AsO_4}$ p-aminophenylarsonic acid $\longrightarrow$ diazonium compound $\xrightarrow{\text{HCl and Cu}}$

$\longrightarrow$ p-chlorophenylarsonic acid $\longrightarrow$ 3-nitro-4-chlorophenylarsonic acid $\xrightarrow{\text{KOH}}$

$\longrightarrow$ 3-nitro-4-hydroxyphenylarsonic acid $\longrightarrow$ 3-amino-4-hydroxyphenylarsonic acid.

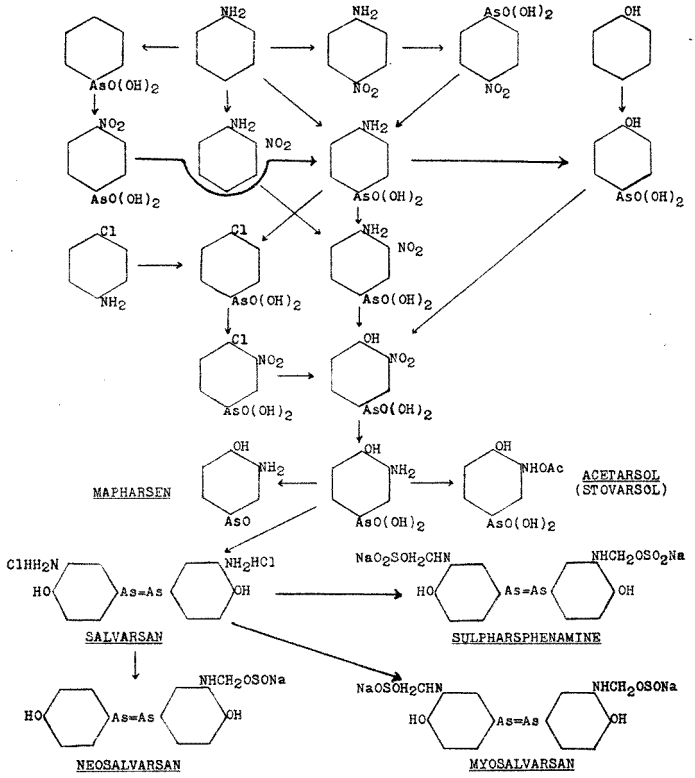



FIGURE 4

3-Amino-4-hydroxyphenyl arsonic acid is converted into the following drugs:

(a) *Mapharsen* by reducing the arsonic acid to oxide with sulphur dioxide in the usual way.

(b) *Acetarsol* (*stovarsol* ) by acetylation.[42]

(c) *Salvarsan* (*arsphenamine* ) by reducing the arsonic acid with hypophosphorus acid (in presence of hydriodic acid). [43]

(d) *Neosalvarsan* (*neoarsphenamine* ) by the action of sodium formaldehyde sulphoxylate on salvarsan. [44]

(e) *Sulpharsphenamine* by the action of formaldehyde and sodium bisulphite on salvarsan.[45]

The preparation of 3-amino-4-hydroxyphenyl arsonic acid is represented diagrammatically in Fig. 4.

In conclusion, I would like to refer to the stability of 4-covalent derivatives of arsenic.

An outstanding property of the arsenic atom is the readiness with which it passes from the tervalent to the 4-covalent state. This is shown by the ease with which sodium arsenite or sodium phenyl arsenite may be alkylated or arylated as in the Meyer and Bart reactions. It is also shown by the readiness with which a tertiary arsine combines with methyl iodide to give a quaternary arsonium iodide. These reactions are of course associated with the lone pair of electrons present in tervalent arsenic.

For the same reason tertiary arsines are found to coordinate with metallic salts, and during the past few years compounds of this type have been described with salts of silver,[46] platinum[47] mercury,[48] copper,[49] cadmium[50] and zinc,[51] the number of molecules of the arsine to one of the salt being either one or two. In many cases these compounds were found to be quite stable. In others it was impossible to recrystallise the compound without losing arsine. In exceptional cases the compounds could not even be washed with cold ether or benzene without loss of arsine. This result would indicate that the coordinate link in some of these compounds is weak, a fact which is well illustrated by the behaviour of certain compounds of tertiary arsines with compounds such as methyl diiodo arsine described some years ago.[52] Although these compounds crystallised well from alcohol or acetone and gave sharp characteristic melting points, yet in benzene solution their molecular weights indicated that they were completely broken down again into the original components. This result was confirmed by adding methyl iodide to such a solution in benzene. The arsine was recovered quantitatively as methiodide.

Compounds formed with salts of silver, platinum and copper were found generally to be quite stable. One compound prepared from cupric chloride and diphenyl methyl arsine is of particular interest. It is quite stable, its composition agreeing with the empirical formula $Cu_2Cl_3(Ph_2AsMe)_3$. The compound is readily prepared in two isomeric forms, one of which is brown and the other blue. They have the same molecular weight and melt at the same temperature. The blue form slowly changes to the brown in the solid state or more rapidly on heating in nitrobenzene. Under the right conditions the two forms separate simultaneously from solution. In both forms one of the copper atoms is in the cuprous condition, the other being cupric. Certain alternative formulae which would account for the isomerism were suggested when the compounds were first described. Since then it has been shown that the following formulae are more consistent with the accepted views of the stereochemistry of cuprous and cupric complexes.[53]

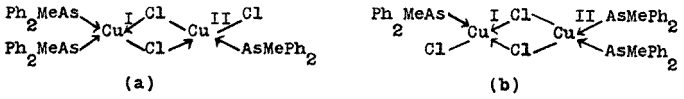



FIGURE 5

Both $Cu^{I}$ and $Cu^{II}$ are 4-covalent, the former having a tetrahedral and the latter a planar configuration.

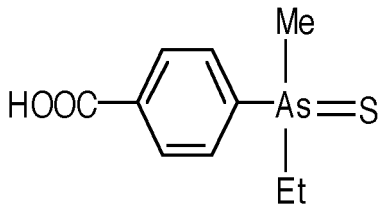
Coordination compounds have been prepared by the action of asymmetric tertiary arsines (such as phenyl α-naphthyl methyl arsine and *p*-tolyl methyl ethyl arsine) and the copper and silver salts of d-bromocamphor sulphonic acid. In each of these compounds the arsenic atom should function as a centre of asymmetry, and if the coordinate link is a true covalent bond it was thought, that by fractional crystallisation, evidence of the existence of different optically active forms would be obtained. So far, however, these attempts have not met with any success.

The behaviour of arsonium iodides also is frequently abnormal. Thus if phenyl methyl ethyl arsine is treated with methyl iodide the product obtained under all conditions is found to be phenyl dimethyl ethyl arsonium iodide melting at 142° C. But if phenyl dimethyl arsine is treated with ethyl iodide, instead of always obtaining the same arsonium iodide as before, mixtures are obtained varying in composition and melting point according to the conditions.[54]

This result would indicate that the quaternary arsonium iodide when formed, has a tendency to split up again into tertiary arsine and alkyl iodide - in other words, there is a state of equilibrium between tervalent arsine and 4-covalent arsonium iodide:

$$R_4AsI \rightleftharpoons R_3As + RI.$$

In this respect, these arsonium ions differ from their ammonium and phosphonium analogues. This, no doubt explains why, so far, no asymmetric arsine oxide has been resolved into optically active forms although Meisenheimer apparently had little difficulty in resolving phosphine and amine oxides. It also explains the difficulty of resolving simple quaternary arsonium ions. The only optically active salt of this type so far described is *d*-phenyl-α-naphthyl benzyl methyl arsonium iodide,(55) and even this could be prepared with only a small rotation and was found to racemise quickly. On the other hand Mills and Raper(56) had no difficulty in resolving *p*-carboxyphenyl methyl ethyl arsine sulphide $MeEtAsC_6H_4COOH$,




and found the active forms to be optically stable. In this compound there is no possibility of a change of valency of the arsenic atom.

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