compound forms fine white needles from alcohol, melting at 161°. It is very soluble in chloroform, moderately soluble in benzene and fairly soluble in ether.

Anal. Calcd. for $C_{19}H_{17}O_6N$: C, 67.3; H, 5.0. Found: C, 67.3; H, 5.1.

Summary

The synthesis of berberine described by Pictet and Gams is in all probability erroneous, the error arising from overlooking the 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-3,4-dihydroprotopapaverine formed by air oxidation of their cyclized product. The "veratryl-nor-hydrohydrastinine" described by them is 6,7-methylenedioxy-3′,4′-dimethoxy-9-keto-protopapaverine, which cannot react with methylal. Any product which was obtained by the action of methylal must have been pseudoberberine and have been obtained by operating with crude reaction mixtures.

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[Contribution from the Pearson Memorial Laboratory of Tufts College]

STUDIES IN THE DIPHENYL SERIES. SOME ARSENIC DERIVATIVES OF DIPHENYL

By David E. Worrall

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Diphenyl, a substance now available in quantity at a low cost, is the starting point for the preparation of arsenic-containing compounds of possible therapeutic value. Yet despite the vast amount of attention received by arsenicals during the past two decades, apparently only one paper has appeared in the literature on diphenyl derivatives of arsenic. Adams and Bauer[1] developed a method of entering this series, using the method of Bart with benzidine. Consequently a study has been made of tri-biphenylarsine and related compounds.

The actual starting material used in this investigation was *p*-bromoaniline, which was converted into 4-bromodiphenyl through the diazo reaction.[2] A pure product was obtained, but the process is time consuming, especially if the bromo-aniline has to be prepared, and the final yield is not particularly inspiring. Since then 4-chlorodiphenyl has appeared in the market and at a price much lower than bromo-aniline. While only one experiment was conducted, chlorodiphenyl appeared to be just as effective as the bromo derivative for a synthetic reagent. Several general methods have long been known for the preparation of arylated arsenic from aryl halides. One of these was ruled out because of inability to obtain biphenylmercuric acetate, while poor results attended the use

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[1] Adams and Bauer, This Journal, **46**, 1925 (1924).

[2] Gomberg, "Organic Syntheses," John Wiley and Sons, Inc., New York, **1928**, Vol. VIII, p. 42.

of magnesium. Excellent results, however, were obtained with sodium, over 80% in some instances.

$$AsCl_3 + 3C_6H_5C_6H_4Br + 6Na = As(C_6H_4C_6H_5)_3 + 3NaCl + 3NaBr$$

It was found that benzene could be substituted for ether in the synthesis. An unexpected result was the discovery of diphenyl in working up the mother liquors from the purification of tri-biphenylarsine. It does not seem likely that diphenyl formation could have resulted from the action of moisture on tri-biphenylarsine, for the latter was found to be insensitive to water at 80° in the presence of alkali. Neither does it appear at all probable that nascent hydrogen resulting from the interaction of water and sodium could replace bromine with hydrogen. It is possible to interpret the appearance of diphenyl as evidence of the formation of free biphenyl which subsequently picked up hydrogen.

The following diagram indicates how the various classes of organic derivatives were prepared from tri-biphenylarsine.

$$\begin{tikzcd}
 & (C_6H_5C_6H_4)_3CH_3AsI \\
(C_6H_5C_6H_4)_3As \arrow[ur, "CH_3I"] \arrow[r, "AsCl_3"] \arrow[dr, "Cl_2"] & C_6H_5C_6H_4AsCl_2 \\
 & (C_6H_5C_6H_4)_3AsCl_2 \arrow[dl, "Heat"] \\
(C_6H_5C_6H_4)_2AsCl &
\end{tikzcd}$$

The chlorine and bromine addition products are not sensitive to moisture when free from solvent, but when hydrolysis does take place both halogen atoms are involved. Thus if tri-biphenylarsine dibromide is mixed with a small volume of alcohol, it quickly dissolves and in a few minutes a crystalline precipitate forms. It contains bromine but the amount is approximately one-half of the theoretical, assuming that tri-biphenylarsine hydroxy bromide was formed. The halogen content varies in different preparations, but some bromine persists after recrystallization. The product may be regarded as a mixture of the hydroxide and hydroxy bromide, although the latter was not isolated.

Experimental

Tri-biphenyl.—To 4.2 g. of granulated sodium suspended in 150 cc. of dry benzene were added 21 g. of 4-bromo-diphenyl and 5.5 g. of arsenic chloride. As the initial reaction was somewhat sluggish, it was speeded up by heating the mixture under a reflux condenser. The source of heat was removed as soon as boiling started. A vigorous reaction ensued and continued spontaneously for over half an hour. Heat was again applied for some time, after which the mixture while still warm was filtered by suction. The residue was washed with 100 cc. of hot benzene, the combined filtrate concentrated to approximately 35 cc. and 25 cc. of ordinary alcohol added. The resulting bulky crystalline precipitate was filtered, washed thoroughly with cold ethyl alcohol and dried; yield, 12 g. of fairly pure material.

Anal. Calcd. for $C_{36}H_{27}As$: As, 14.0. Found: As, 13.8.

This last filtrate was evaporated to dryness and the residue steam distilled. About one-half a gram of residual tri-biphenylarsine was found. The distillate contained 2.6 g.

of a substance identified by its odor and properties as diphenyl. It evidently contained traces of 4-bromodiphenyl as it responded to the Beilstein test for halogen and the melting point was low (68–69°) even after recrystallization from alcohol. However, the melting point was not changed after mixing with diphenyl, while on nitration a substance was obtained identical in all respects with a known sample of 4-nitrodiphenyl.

Tri-biphenylarsine was also obtained in good yield by substituting 4-chlorodiphenyl for the bromo compound in the above preparation. Less desirable results attended the use of the reagent of Grignard. Thus in one experiment to 10 g. of 4-iododiphenyl in ether solution was added 1 g. of magnesium turnings. Precautions were taken to have the reagents dry and the apparatus was swept out with dry air. Activated magnesium was added, but the resulting action was slow and incomplete. Barely enough heat was evolved to warm the mixture, to which arsenic chloride was added after standing overnight. This caused some heat evolution, and the formation of a bulky precipitate. Previous to decomposition with water the mixture was heated under a reflux condenser for an hour, then it was steam distilled. Diphenyl, 1.2 g. in amount, came over first followed by approximately 5 g. of iododiphenyl. The two substances were easily distinguished as the latter, melting as it does above the boiling point of water at atmospheric pressure, formed a sublimate. The difference in vapor pressure of the two substances at this temperature made a separation practicable. The residue (2 g.) was found to contain tri-biphenylarsine. Similar results were obtained with bromodiphenyl.

Tri-biphenylarsine dissolves readily in hot glacial acetic acid, methyl iodide, benzene and chloroform. It is less soluble in ether and practically insoluble in cold ethyl alcohol. It dissolves in about two volumes of hot benzene, separating in aggregates of tiny needle-like crystals melting at 182–183° with preliminary softening. At the boiling point decomposition takes place with the formation of free arsenic.

Action of Water.—The interpretation of some of the results obtained necessitated a knowledge of whether or not hydrolysis of tri-biphenylarsine took place. It was found that hydrolysis did not take place on heating the substance for many hours under a reflux condenser with alcoholic potash. At higher temperatures and pressure, on the contrary, positive results were obtained with dilute hydrochloric acid. A gram of tri-biphenylarsine was heated in a sealed tube with water containing hydrochloric acid to 250° for twelve hours. On opening the tube and steam distilling the contents a sufficient amount of volatile material was collected to be identified by the odor and a mixed melting point as diphenyl.

Tri-biphenylarsine-dibromide.—To 5 g. of tri-biphenylarsine dissolved in 40 cc. of pure dry chloroform was added 1.5 g. of dry bromine. Instant absorption took place with considerable heat evolution. The resulting cream-colored precipitate of flattened needles was filtered and dried; yield, 5.5 g.

Anal.[3] Calcd. for $C_{36}H_{27}AsBr_2 \cdot CHCl_3$: Br, 19.7. Found: Br, 19.8.

The dibromide has no definite melting point, gradually softening above 200°. It was not obtained free from chloroform of crystallization. An excess of bromine inhibits completely crystal formation in the preparation of the dibromide, while the presence of moisture brings about tar formation. Once formed and freed from the solvent the solid substance is surprisingly insensitive toward moisture, perhaps because it is so insoluble in water. At any rate, it is unaffected by cold water or long standing exposed to the atmosphere. It is decomposed by hot water and by ordinary alcohol at room temperature.

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[3] A weighed amount of the substance after short heating with alcoholic ammonia was evaporated to dryness, extracted with water containing a few drops of nitric acid and the filtered solution used in the regular way.

Tri-biphenylarsine-dichloride.—On bubbling chlorine through a chloroform solution of 5 g. of tri-biphenylarsine until no further absorption took place, a white crystalline precipitate quickly formed; yield, 6 g.

Anal. (for labile chlorine). Calcd. for $C_{36}H_{27}AsCl_2{\cdot}CHCl_3$: Cl, 9.8. Found: Cl, 9.8.

The chlorine addition product melts at 272–273° with preliminary softening. It is only sparingly soluble in cold chloroform; accordingly an excellent yield is obtainable.

Action of Water.—The dichloride or dibromide was changed to a gum, which subsequently became crystalline on boiling with water. Chloroform was set free as well as halogen acid. Similar changes took place in cold alcohol, except that the new substance separated out directly in the solid phase. It was identified as tri-biphenylarsine dihydroxide, although an impure form as halogen was present even after recrystallization from alcohol. No evidence was found of the existence of the hydroxy bromide of tri-biphenylarsine.

Tri-biphenylarsine Dihydroxide.—Several grams of dichloride was heated on a steam-bath for a few minutes with a small volume of alcohol containing a few drops of ammonium hydroxide solution. The substance promptly dissolved, but a crystalline precipitate quickly appeared. It was purified by dissolving in the minimum amount of hot alcohol and adding water drop by drop until a slight turbidity resulted.

Anal. Calcd. for $C_{36}H_{29}O_2As$: As, 13.2. Found: As, 13.1.

It is sparingly soluble in alcohol, separating in microscopic prismatic needles melting at 262–263° with preliminary softening. It is easily dissolved by chloroform. Tri-biphenylarsine dihydroxide is also formed by the action of potassium permanganate on tri-biphenylarsine.

Tri-biphenylarsine Sulfide.—This was prepared by running hydrogen sulfide into an alcohol solution of the dihydroxide. The resulting precipitate of small rod-shaped crystals was filtered, washed and dried.

Anal. Calcd. for $C_{36}H_{27}AsS$: S, 5.7. Found: S, 5.5.

The sulfide is insoluble in most of the common solvents with the exception of chloroform, from which it is precipitated by alcohol as a crystalline powder melting at 239–240°. Both the sulfide and dihydroxide are reduced by tin and hydrochloric acid in glacial acetic acid to tri-biphenylarsine.

Tri-biphenylmethylarsonium Iodide.—Obtained by heating for several hours under a reflux condenser 1 g. of tri-biphenylarsine dissolved in benzene with an excess (3 molar equivalents) of methyl iodide. Crystal formation started in a few minutes if the mixture was seeded, otherwise an oil separated out at first; yield, 0.8 g.

Anal. Calcd. for $C_{37}H_{30}AsI$: I, 18.8. Found: I, 18.9.

The arsonium compound is sparingly soluble in hot alcohol, separating in glittering gold-yellow plates melting at 151–152° with foaming. It decomposes at the melting point into methyl iodide and tri-biphenylarsine.

Tri-biphenylmethylarsonium iodochloride was obtained by bubbling chlorine through a warm solution of the arsonium iodide.

Anal. Calcd. for 0.1 g. of $C_{37}H_{30}AsICl_2$: AgI + AgCl, 0.0696 g. Found: AgI + AgCl, 0.0708.

It crystallizes from alcohol as a yellow powder melting at 86–88°.

Tri-biphenylarsonium Hydroxide.—Two grams of the arsonium iodide derivative was shaken in alcohol with moist silver oxide. The mixture was filtered after the disappearance of the yellow color and evaporated *in vacuo* over sulfuric acid to a brittle colorless glass-like solid. This material probably contained some carbonate and sulfate picked up during the manipulation.

Anal. Calcd. for $C_{37}H_{31}OAs$: As, 13.3. Found: As, 12.8.

No definite melting point was observed. It gradually softens on heating and foams at 120°, at which point it decomposes into methyl alcohol and tri-biphenylarsine. It is alkaline, absorbing carbon dioxide from the air on standing and turning red litmus paper blue.

Di-biphenylarsenious Chloride.—Ten grams of tri-biphenylarsine dichloride was heated to melting in a beaker; then the temperature was carefully raised until gentle boiling took place. Chloroform and chlorodiphenyl vapors were evolved. After several minutes of heating at this temperature the mixture was cooled and the resulting tar repeatedly extracted with absolute alcohol. A yellowish gummy material was deposited as the alcoholic extract cooled. The resulting solution was colorless and on concentration a white precipitate of small needle-like crystals usually was obtained. Altogether less than a gram of substance was obtained. Approximately a gram of diphenyl was isolated by the steam distillation of the residues.

Anal. Calcd. for $C_{24}H_{18}AsCl$: Cl, 8.5. Found: Cl, 7.8.

The chloride obviously was not obtained in a pure form. The substance as isolated softened above 110°, melting at 123°. It decomposes at the boiling point *in vacuo* and is easily dissolved by benzene or chloroform. It is sparingly soluble in alcohol. It is rapidly attacked by hot water, more slowly by ordinary alcohol, changing into the oxide and liberating hydrochloric acid. The hot vapors of the substance are irritating to the throat, but have no apparent effect on the skin.

Di-biphenylarsenious Oxide.—Prepared by heating the chloride with alcoholic ammonia, recrystallizing from alcohol.

Anal. Calcd. for $C_{48}H_{36}As_2O$: As, 19.3. Found: As, 19.4.

It is soluble in hot alcohol, separating as an oil in which crystalline aggregates form on standing. It gradually softens above 90° without any definite melting point.

Di-biphenylarsenious Sulfide.—Obtained as an amorphous powder by the action of hydrogen sulfide on an alcohol solution of the oxide. No definite melting point was observed, the substance gradually softening above 110°.

Anal. Calcd. for $C_{48}H_{36}As_2S$: S, 4.0. Found: S, 4.5.

Di-biphenylarsinic acid was produced by passing moist chlorine through the chloride dissolved in chloroform. The oil resulting from evaporation of the solvent was dissolved in dilute sodium hydroxide solution, filtered and precipitated as an amorphous powder by dilute sulfuric acid. It was heated to melting and on cooling became crystalline.

Anal. Calcd. for $C_{24}H_{19}O_2As$: As, 9.1. Found: As, 9.1.

It softens above 95°, partially melting at 110°. This acid is soluble in alcohol and in water containing alkali-forming water-soluble salts.

Mono-biphenylarsenious Oxide.—A solution of 10 g. of tri-biphenylarsine in 50 g. of arsenic chloride was heated in a sealed tube to 300° for thirty-six hours. The mixture was then distilled up to 300° to remove arsenic chloride. Some diphenyl was also removed by this treatment. The residue (12 g.) was first washed with water containing hydrochloric acid to remove arsenious oxide; then it was extracted with alcohol. By this process any unchanged tri-biphenylarsine was left behind. The alcohol extract was concentrated and steam distilled to remove traces of diphenyl. A cream colored residue of 6 g. was obtained. It was finally purified by concentration of an alcohol solution.

Anal. Calcd. for $C_{12}H_9AsO$: As, 30.7. Found: As, 30.4.

It separates from alcohol, in which it is readily soluble, as an amorphous white powder melting at 163–165° with preliminary softening.

Mono-biphenylarsenious sulfide was prepared by the action of hydrogen sulfide on a dilute alcohol solution of the oxide. Ball-like aggregates of microscopic needles separated out. No definite melting point was observed, the substance softening above 108°.

Anal. Calcd. for $C_{12}H_9AsS$: S, 12.3. Found: S, 12.0.

Mono-biphenylarsenic Acid.—To a gram of the arsenious oxide derivative suspended in water containing a little ethyl alcohol was conducted a slow stream of chlorine for an hour. Then an excess of dilute sodium hydroxide solution was added and the mixture saturated with carbon dioxide. It was filtered and hydrochloric acid added. The resulting bulky precipitate was filtered with difficulty by suction and precipitated from alcohol by water.

Anal. Calcd. for $C_{12}H_{11}O_3As$: As, 27.0. Found: As, 27.2.

The new acid separates from alcohol as an amorphous powder partially melting at 180–181° with preliminary softening.

It is planned to continue work with these substances, also to investigate the diphenyl derivatives of antimony and bismuth.

Summary

It has been found that tri-biphenylarsine is obtainable in good yield from the interaction of arsenic chloride, 4-bromodiphenyl and sodium.

Using tri-biphenylarsine as a starting point, some representative tri- and pentavalent arsenic derivatives have been prepared containing one, two and three biphenyl groups.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

CATALYTIC REDUCTION OF O-ALKYL SUBSTITUTED OXIMES[1]

BY LAUDER W. JONES AND RANDOLPH T. MAJOR

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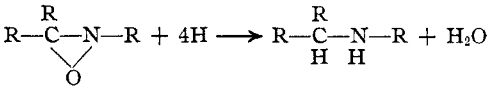
The reduction of N-alkyl substituted oximes was studied about thirty years ago by Dunstan and Goulding,[2] who found that sodium amalgam in absolute alcohol converted them into dialkylamines, according to the equation



$$R{-}\underbrace{\overset{R}{C}{-}N}_{O}{-}R + 4H \longrightarrow R{-}\overset{R}{\underset{H}{C}}{-}\underset{H}{N}{-}R + H_2O$$

The corresponding reduction of the O-alkyl substituted oximes apparently has not been investigated.

It has long been known, however, that oximes could be reduced to primary amines by the use of a number of different reducing agents.[3] Re-

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[1] Presented at the Columbus meeting of the American Chemical Society, May, 1929.

[2] Dunstan and Goulding, *J. Chem. Soc.*, **79**, 639, 640 (1901).

[3] Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Verlag von Veit and Company, Leipzig, **1907**, Vol. I, Part 1, p. 349.