THE ARSENAMIDES.   COMPOUNDS CONTAINING THE As-N LINKAGE.[*,1]

BY G. O. DOAK.

The reaction between arsenous halides and amines has been investigated by several workers with rather conflicting results.   Thus Leeds (1), Landau (2), Schiff (3), Leonard (4), and Schmidt (5) all obtained compounds of the type $3RNH_2 \cdot AsX_3$.   The latter three assigned structural formulas to these compounds, regarding them as substituted ammonium halides, $As\equiv(NH_2RX)_3$.   On the other hand Anschutz and Weyer (6) obtained compounds of the type $X_2As\text{-}NHR$ and $XAs=(NHR)_2$, by using aniline and arsenous chloride and bromide.   They could not obtain the compounds obtained by Landau and Schiff and believed these workers had been dealing with impure mixtures.   Similarly Michaelis and Luxembourg (7) obtained $Cl_2AsN(C_4H_9)_2$ from diisobutylamine and arsenous chloride. Substituted arsenous halides and amines have also been investigated and yield similar products.   Michaelis obtained $Cl(C_6H_5)As\text{—}NHC_4H_9$ and $Cl(C_6H_9)AsN\text{-}(C_4H_9)_2$ from phenyl dichlorarsine and butylamine and dibutylamine (8).   With triethylamine Michaelis obtained a product to which he assigned the formula $Cl_2(C_6H_5)As=N(C_2H_5)_3$.   With ammonia he obtained the imide $C_6H_5As=NH$. Hugot had previously obtained an amide $As(NH_2)_3$ from arsenous chloride and ammonia which gave the imide $As_2(NH)_3$ on heating (9).   Ipatiew, Rasuwajew and Stromski (10) obtained $(C_6H_5)_2AsNH_2$ from diphenyl chlorarsine and ammonia.

From the work described in the present paper the reaction appears to be more complex than the previous work showed, and the conflicting results are due to the failure of the previous workers to isolate all the products of the reaction.   Thus in nearly all the reactions studied, two or more products have been obtained or indicated.   The reaction between an arsenous halide and an amine takes place according to the following equations:

1. $AsX_3 + RNH_2 \longrightarrow X_2As \cdot NHR \cdot HX.$
2. $X_2AsNHR \cdot HX + RNH_2 \longrightarrow X_2AsNHR + RNH_2 \cdot HX.$
3. $AsX_3 + 2RNH_2 \longrightarrow XAs(NHR \cdot HX)_2.$
4. $XAs(NHR \cdot HX)_2 + 2RNH_2 \longrightarrow XAs(NHR)_2 + 2RNH_2 \cdot HX.$
5. $AsX_3 + 3RNH_2 \longrightarrow As(NHR \cdot HX)_3.$

The course of the reaction is influenced by several different factors, namely: the order of mixing, strength of the base and the arsenous halide used.   Certain steric effects also seem to influence the course of the reaction.   When a n-heptane solution of aniline was added to a n-heptane solution of arsenous chloride, an 84.75 per cent yield of $As(NHC_6H_5 \cdot HCl)_3$ was obtained, identical with the product obtained by Schmidt.   When the order of mixing was reversed, a 33.56 per cent yield was obtained, and $Cl_2AsNHC_6H_5$ was isolated in considerable amounts from the heptane filtrate.   Monomethylaniline gave only a 14.32 per cent yield of $As[N(CH_3)C_6H_5 \cdot HCl]_3$ as compared to the 33.56 per cent yield with aniline, while under similar conditions dimethylaniline did not react with arsenous chloride.

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In addition to these arsenic compounds there is always a large amount of the ammonium halide formed in the course of the reaction and it is difficult, sometimes impossible, to separate the arsenic compounds.

Several types of compounds have definitely been isolated in the various reactions studied. Compounds of the type $XAs(NHR.HX)_2$ and $As(NHR.HX)_3$ are high melting solids, soluble in water, usually with decomposition, and insoluble in organic solvents. They resemble the corresponding ammonium halides in properties, and are best regarded as arsenic substituted ammonium halides. Thus the piperidine compound, $As(NC_5H_{10}.HCl)_3$, which is only slightly decomposed by cold water, precipitates silver chloride and lead chloride with silver nitrate and lead acetate solutions, forming $As(NC_5H_{10}.HCOOCH_3)_3$ and $As(NC_5H_{10}.HNO_3)_3$.

Compounds of the type X_2AsNHR are high-boiling liquids or low melting solids, obtained by distillation of the solvent after removal of the precipitated ammonium halide and the insoluble arsenic compounds. They fume in the air and are decomposed violently by water. Leonard (4) obtained only a 66 per cent yield of $As(NC_5H_{10}.HCl)_3$ using arsenous chloride and piperidine in n-heptane solution. This low yield was explained by the solubility of this compound in heptane, which is incompatible with the hydrochloride formula he proposed for the compound. He found, however, that ether precipitated the compound from heptane solution. In repeating Leonard's work, the author determined the solubility of $As(NC_5H_{10}.HCl)_3$ in heptane and found it to be 4×10^{-6} Gm. per cc. at $25°$. The low yield obtained by Leonard is due to the formation of other heptane-soluble compounds of the type X_2AsNHR. Unless the ether is anhydrous these compounds are decomposed by the water present into arsenous oxide and piperidine hydrochloride.

NOMENCLATURE OF THE ARSENIC COMPOUNDS.

The name "arsenamide" is suggested for compounds containing the As-N linkage. Thus the following compounds, prepared by the author, are named: $C_2H_5(I)As-NHC_6H_5$, aniline-ethyliodoarsenamide; $Cl_2AsN(C_2H_5)_2$, diethylamine-dichlorarsenamide; $As(NC_5H_{10}.HCl)_3$, piperidine-arsentriamide trihydrochloride; and $ClAs(NH.CH_2.CH_2NH_2.HCl)_2$, ethylenediamine-chlorarsendiamide dihydrochloride.

EXPERIMENTAL.

The arsenous halides and amines were commercial products, purified by distillation. The substituted arsenous halides were prepared by the author. In the majority of the reactions studied anhydrous n-heptane was used as the solvent. This was prepared from Diggers Pine oil by the method of Kremers (11). Where other solvents were used, they were rendered completely anhydrous. The heptane solution of the amine or arsenous halide was placed in a tall form beaker and surrounded with an ice-bath. The tall form beaker was found most convenient for removal of the precipitate formed in the course of the reaction. The beaker was equipped with a cork, mechanical stirrer and dropping funnel. In some cases nitrogen gas was passed into the vessel during the course of the reaction, but this was usually found to be unnecessary. The n-heptane solution of the arsenous halide or amine was then added dropwise and the mixture stirred during the addition and for one hour longer to ensure the completion of the reaction. A heavy white precipitate formed immediately on addition of the solution. At the completion of the reaction the mixture was filtered, using suction. Nitrogen gas was used to protect the product from oxidation. The filter was further protected from moisture by placing P_2O_5 tubes in the

suction and nitrogen lines. The precipitate was washed several times with the pure solvent, transferred to a vacuum desiccator, and the air removed by flushing several times with nitrogen gas, and finally dried for several days at 20-mm. pressure. This precipitate consisted of the hydrohalide of the amine used, mixed with any insoluble arsenic compounds. Since these compounds are insoluble in organic solvents, and in most cases are decomposed by water or alcohol, their separation from the amine hydrohalide is extremely difficult. In the case of the piperidine compound it can be purified by fractional crystallization from alcohol. In several other cases separation can be effected by vacuum sublimation, as described by Schmidt for purifying the aniline compound. In most cases, however, no means of separation was found. In these cases the arsenic content was determined by analysis and computed to percentage of arsenous halide converted into arsenamide hydrohalides.

The filtrate from the original reaction contains the compounds of the type X_2AsNHR. The solvent was removed by distilling in an atmosphere of nitrogen at reduced pressure, and the arsenic compounds fractionated at 1–2-mm. pressure. These were collected in special receiving bottles, filled with nitrogen gas, and analyzed in thin-walled glass bulbs which could be crushed beneath the liquid used for analysis. In spite of these precautions it was difficult to obtain accurate analyses of these extremely unstable liquids.

<div align="center">REACTIONS STUDIED.</div>

(1) Arsenous chloride and aniline. A n-heptane solution of aniline added to a n-heptane solution of arsenous chloride gave an 84.74 per cent yield of aniline-arsentriamide trihydrochloride, $As(NH.C_6H_5.HCl)_3$. It is a yellow solid, decomposed by water, insoluble in organic solvents.

Calculated for $As(NH.C_6H_5.HCl)_3$: arsenic 16.28 per cent. Found: arsenic 16.36 per cent. This compound is identical with that prepared by Schmidt (5). When the order of mixing was reversed the precipitate consisted largely of aniline hydrochloride. Arsenic analysis on the precipitate showed that there were present 33.56 per cent of the original arsenous halide used, but no means could be found of separating any arsenic compounds from the aniline hydrochloride. The filtrate, after removal of the heptane, yielded aniline-dichlorarsenamide, $Cl_2As-NHC_6H_5$, a yellow crystalline solid, m. p. 89°, decomposed violently by water.

Calculated for $Cl_2AsNHC_6H_5$: arsenic 31.50, chlorine 29.83. Found: arsenic 31.88, chlorine 29.92.

(2) Arsenous chloride and piperidine. A n-heptane solution of arsenous chloride added to a n-heptane solution of piperidine gave a 20.95 per cent yield of piperidine-arsentriamide trihydrochloride, $As(NC_5H_{10}.HCl)_3$. The compound was purified by fractional crystallization from absolute alcohol. It crystallized in long needles, m. p. 240–242°, and was decomposed by hot water and boiling alcohol. Calculated for $As(NC_5H_{10}.HCl)_3$: chlorine 24.39. Found: chlorine, 23.44. This compound is identical with that prepared by Leonard (4). The filtrate gave a yellow oil, b. p. 98°/1 mm. It fumed in the air and accurate analyses could not be made. It is probably piperidine-dichlorarsenamide, $Cl_2AsNC_5H_{10}$. The piperidine-arsentriamide trihydrochloride gave piperidine-arsentriamide trinitrate with silver nitrate in theoretical amounts, m. p. 144°.

Calculated for $As(NC_5H_{10}.HNO_3)_3$: arsenic 14.52. Found: 14.89. With lead acetate, piperidine-arsentriamide triacetate, $As(NC_5H_{10}.CH_3COOH)_3$, was obtained, m. p. 304°.

(3) Arsenous chloride and diethylamine. A n-heptane solution of arsenous chloride added to a n-heptane solution of diethylamine gave a precipitate consisting largely of diethylamine hydrochloride. Arsenic analysis on the precipitate showed that there was present 24.30 per cent of the original arsenous halide used. No arsenic compounds could be separated from the diethylamine hydrochloride. The filtrate gave diethylamine-dichlorarsenamide, $Cl_2-AsN(C_2H_5)_2$, a yellow liquid, b. p. 107°/38 mm., fuming in the air, decomposed violently by water.

Calculated for $Cl_2AsN(C_2H_5)_2$: chlorine 32.58. Found: 32.35, 32.16.

(4) Arsenous chloride and ethylenediamine. A n-heptane solution of arsenous chloride added to a n-heptane solution of ethylenediamine gave a white precipitate. Ethylenediamine-chlorarsendiamide dihydrochloride, $ClAs(NH.CH_2CH_2NH_2.HCl)_2$ was obtained by extracting with boiling anhydrous acetone. It was a white solid, charring above 225° without melting.

Calculated for $ClAs(NHCH_2CH_2NH_2HCl)_2$: arsenic 24.86, chlorine 34.99. Found: arsenic 24.20, chlorine 34.09. The heptane filtrate was not examined.

(5) Arsenous chloride and methylaniline. A n-heptane solution of arsenous chloride added to a n-heptane solution of methylaniline gave a precipitate consisting largely of methylaniline hydrochloride. Arsenic analysis on the precipitate showed that there was present 14.32 per cent of the original arsenous chloride used. No arsenic compounds could be separated from the methylaniline hydrochloride. The filtrate gave methylaniline-dichlorarsenamide, $Cl_2AsN(CH_3)C_6H_5$, b. p. 116°/3 mm., fuming in the air and decomposed by water.

Calculated for $Cl_2AsN(CH_3)C_6H_5$: chlorine 28.18. Found: chlorine 28.29.

(6) Arsenous chloride and benzylamine. A n-heptane solution of arsenous chloride added to a n-heptane solution of benzylamine gave a white precipitate from which benzylamine-arsentriamide trihydrochloride was separated by sublimation at 170–200° and 2-mm. pressure. It was a white solid, m. p. 246° (decomposition), decomposed by water and alcohol.

Calculated for $As(NH.CH_2C_6H_5.HCl)_3$: arsenic 14.91, chlorine 21.19, nitrogen, 8.36. Found: arsenic 14.84, 14.87; chlorine 21.05, 21.44; nitrogen 8.38, 8.18. The benzylamine compounds were among the first studied and the heptane filtrates were not examined for possible arsenic compounds.

(7) Arsenous chloride and dibenzylamine. Dibenzylamine-arsentriamide trihydrochloride, $As[N(CH_2C_6H_5)_2.HCl]_3$, was prepared in a similar manner from dibenzylamine and arsenous chloride, and purified by vacuum sublimation. It is a white solid, m. p. 252–254° (decomposition) and decomposed by water and alcohol.

Calculated for $As[N(CH_2C_6H_5)_2.HCl]_3$: arsenic 9.69, chlorine 13.78, nitrogen 5.43. Found: arsenic 8.23, chlorine 13.56, nitrogen 5.30.

(8) Arsenous chloride and tribenzylamine. Just as alkyl halides may be added to tertiary amines to form quaternary ammonium salts, so arsenous chloride adds to tertiary amines to form arsenamide chlorides. Tribenzylamine-arsentriamide trichloride, $As[N(CH_2C_6H_5)_3Cl]_3$, was prepared in a similar manner to the other two benzylamine compounds and was purified by sublimation at 130–140° and 1-mm. pressure. It is a white solid, m. p. 209–211° with decomposition.

Calculated for $As[N(CH_2C_6H_5)_3Cl]_3$: arsenic 7.19, chlorine 10.22, nitrogen 4.03. Found: arsenic 7.47, chlorine 9.49, nitrogen 3.67.

(9) Ethyldichlorarsine and piperidine. A n-heptane solution of ethyldichlorarsine added to a n-heptane solution of piperidine gave a white precipitate consisting partially of piperidine hydrochloride. By vacuum sublimation at 95–105° and 1-mm. pressure, piperidine-ethylarsendiamide dihydrochloride was separated from the piperidine hydrochloride. It is a white solid, m. p. 196°, decomposed by water.

Calculated for $C_2H_5As(NC_5H_{10}.HCl)_2$: arsenic 21.7, chlorine 21.0. Found: arsenic 21.22, chlorine 20.5. The heptane filtrate gave piperidine-ethyldichlorarsenamide, $C_2H_5As(Cl)$-NC_5H_{10}. It is a yellow liquid, b. p. 108°/8 mm. It reacts violently with water to give ethylarsenoxide and piperidine hydrochloride.

Calculated for $C_2H_5As(Cl)NC_5H_{10}$: arsenic 33.52, chlorine 15.87. Found: arsenic 33.30, chlorine 15.88.

(10) Ethyldiiodoarsine and aniline. A n-heptane solution of ethyldiiodoarsine added to a n-heptane solution of aniline gave a white precipitate consisting largely of aniline hydroiodide. Arsenic analysis on the precipitate showed that there were present 12.92 per cent of the original ethyldiiodoarsine used. No arsenic compounds could be separated from the aniline hydroiodide. The filtrate gave aniline-ethyliodoarsenamide, $C_2H_5(I)AsNHC_6H_5$, as a light yellow oil, b. p. 110°/10 mm. which crystallized to a yellow solid on standing. It fumed in the air and reacted violently with water. Calculated for $C_2H_5(I)AsNH.C_6H_5$: arsenic 23.93, iodine 39.30. Found: arsenic 23.84, 23.69; iodine 39.62.

(11) Dimethylchlorarsine and piperidine. A n-heptane solution of dimethylchlorarsine added to a n-heptane solution of piperidine gave a white precipitate consisting almost entirely of piperidine hydrochloride. The heptane filtrate gave piperidine-dimethylarsenamide, $(CH_3)_2As$-NC_5H_{10}. It is a colorless liquid, b. p. 75°/8 mms. This compound is considerably more stable toward moisture than the corresponding halogen arsenamides.

Calculated for $(CH_3)_2AsNC_5H_{10}$: arsenic 39.64. Found: arsenic 39.44, 39.50.

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THE PREPARATION AND PROPERTIES OF 3,3'BIS(AZOMETA-PHENYLENEDIAMINE)-4,4'-DIHYDROXYARSENOBENZENE AND 3,3'-BIS-(AZO-2,6-DIAMINOPYRIDINE)-4,4'-DIHYDROXYARSENOBENZENE.*

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It is well known that certain azo dyes penetrate tissue very readily, thereby being disseminated widely throughout the body. Further, some azo dyes, such as trypan blue and trypan red, are absorbed by trypanosomes and have a definite trypanocidal action. Consequently it was decided to prepare some azo dyes from arsphenamine base by diazotizing the latter and coupling with diamines. A number of arsono and arseno azo compounds have been described by Andreyev (1), Karrer (2), Barrowcliff, Pyman and Remfry (3), Benda (4), Jacobs and Heidelberger (5), and Ehrlich and Bertheim (6). Also some patents have been issued covering such compounds. However, none of them are of the type which we prepared by diazotizing arsphenamine and coupling with metaphenylenediamine and with 2,6-diaminopyridine.

The two substances prepared in this investigation were 3,3'-bis(azometaphenylenediamine)-4,4'-dihydroxyarsenobenzene (I) and 3,3'-bis(azo-2,6-diaminopyridine)4,4'-dihydroxyarsenobenzene (II).

(I)   (II)
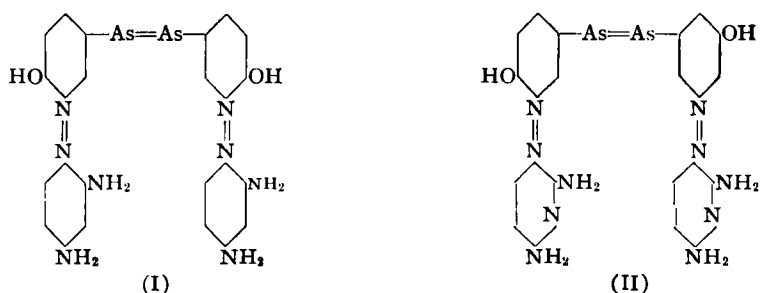
When aqueous sodium hydroxide solutions of these compounds were injected intravenously into albino rats, the anticipated tissue staining characteristics resulted. Thus, within a short time after injection the conjunctiva, ears and abdominal cavities of the animals were stained. However, both of these compounds