[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY]

3-Amino-4-hydroxybenzenearsonous Acid. I. Salts and Structural Considerations

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While 3-amino-4-hydroxybenzenearsonous acid[1] ("arsenoxide" or 3-amino-4-hydroxyphenyl arsenoxide) has become increasingly important in the therapy of treponemal diseases, the chemistry of this compound is for the most part unpublished. Ehrlich and Bertheim[2] isolated a gummy product which they assumed to be 3-amino-4-hydroxyphenyl arsenoxide (IA). The product was very impure, containing 25.54% As (the arsonous anhydride, $C_6H_6AsNO_2$, requires 37.64% As and the arsonous acid, $C_6H_8AsNO_3$, 34.51%), and was also unstable. From this oxide they prepared two unstable salts which they designated as the arsenoxide hydrochloride hemialcoholate (IIA) and the arsenoxide hydrochloride hydrate (IIIA) on the basis of the analytical determinations. In addition to being soluble in water, all three products were very soluble in ethanol and methanol. 2-Amino-4-dichloroarsinophenol hydrochloride XI has been described by Binz and Bauer[3] and in several patent specifications.[4,5] The corresponding 2-amino-4-dibromoarsinophenol hydrobromide[5] and 2-amino-4-diiodoarsinophenol hydriodide[6] also have been reported. 2-Amino-4-dichloroarsinophenol is claimed in the patent literature,[7] but its formation by the method described is questionable. More recently Scott, Hummel, Tullar and Wainwright[8] have described the production of a crystalline form of 3-amino-4-hydroxybenzenearsonous acid (IB) of a purity of 99% or better.

Since previous investigators have ascribed markedly different properties to the same compounds, it was considered advisable to prepare analytically pure 3-amino-4-hydroxybenzenearsonous acid and then reinvestigate the derivatives prepared from this material. The crystalline form (IB) was prepared by the method of Scott, *et al.*[8] It was much more stable than the crude oxide obtained by the method of Ehrlich and Bertheim and was found to be 98–99% pure. Ordinary recrystallization methods did not improve the purity of the product and manipulation of solutions of the compound generally resulted in destruction by oxidation and hydrolysis. It was found that a solution of the nearly pure oxide in oxygen-free water which had been treated with sodium sulfite and an equivalent of hydrochloric acid could be decolorized with iron-free, oxygen-free activated carbon. The *p*H was then adjusted to 6.5 and, on cooling, the product crystallized in large colorless crystals which proved to be analytically pure 3-amino-4-hydroxybenzenearsonous acid (IC).

Analytically pure 3-amino-4-hydroxybenzenearsonous acid (IC) was quite different in properties from both the amorphous product IA and the crystalline form IB. These properties are tabulated in Table I. While the data is not absolutely conclusive, it would appear that IB and IC are different crystalline forms. In this connection, the Ehrlich and Bertheim product was prepared in a nearly pure form by dissolving IC in acid to give a concentrated solution and then neutralizing and salting out the amorphous product (ID). When obtained in this manner it still retained the solubility properties of the Ehrlich and Bertheim product.

It was also of interest to determine if the anhydrous or arsenoso form of the compound could be prepared. Dehydration with heat and vacuum resulted in decomposition before any loss of water occurred. Scott and Sultzaberger have described a procedure for converting the Ehrlich and Bertheim product to an anhydro form[9] (IVA). In attempting to duplicate this procedure, it was found that the amorphous hydrate crystallized before the dehydration was completed and attempts to duplicate this preparation were unsuccessful. Apparently the equipment and air were sufficiently saturated with nuclei of the crystalline forms to cause conversion of the amorphous solid. IC was then dissolved in absolute alcohol by prolonged refluxing. This solution was distilled azeotropically with benzene, gradually displacing the water. Following this, benzene was added slowly to gradually replace the alcohol. When no more alcohol appeared in the distillate, the solid in the flask was removed and dried *in vacuo* (IVB). It was bright yellow and at first considered impure since it was thought that all compounds derived from this nucleus should be white. Examination showed that it assayed correctly for the arsenoso compound. In water it was first converted to a white product and then it dissolved. On exposure to a limited amount of moisture, it turned colorless and the analysis for arsenic and water then indicated that the substance was the arsenoso hemihydrate (VA) which could be again dehydrated to the arsenoso form or rehydrated to the arsonous acid.

In attempting the preparation of 2-amino-4-arsenosophenol hydrochloride hemialcoholate

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[1] 2-Amino-4-arsenosophenol has been given the official Pharmacopoeia name, oxophenarsine. Two derivatives have been admitted to the U. S. Pharmacopoeia and a third is now marketed in Great Britain. They are (1) "Mapharsen" (oxophenarsine hydrochloride), (2) "Dichloro-Mapharsen" and "Chlorarsen" (dichlorophenarsine hydrochloride) and (3) oxophenarsine tartrate (G. B.).

[2] Ehrlich and Bertheim, *Ber.*, **45**, 756 (1912).

[3] Binz and Bauer, *Z. angew. Chem.*, **34**, 261 (1921).

[4] German Patents 272,289 and 281,101.

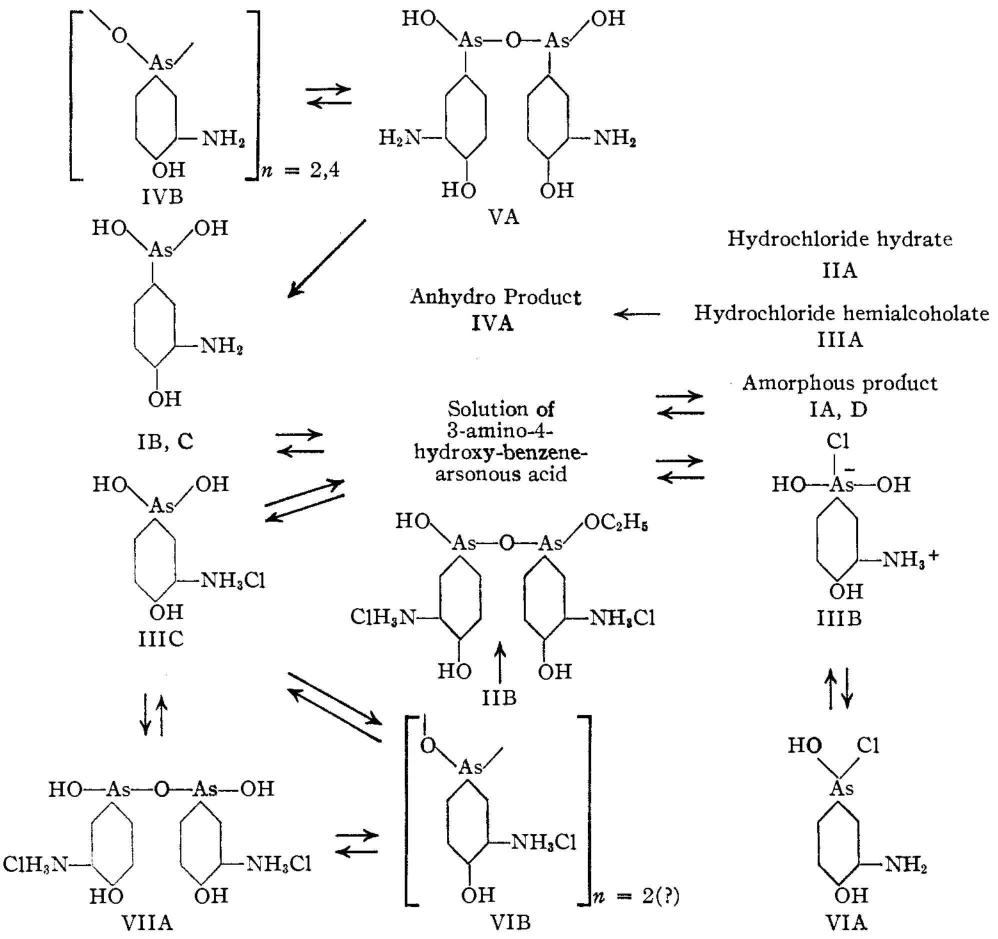
[5] U. S. Patent 2,222,384 (1940).

[6] Newberry and Phillips, *J. Chem. Soc.*, **130**, 2375 (1928).

[7] British Patent 260,382 (1925).

[8] U. S. Patent 2,221,817 (1940).

[9] U. S. Patent 2,280,132 (1942).



(IIA) by the procedure of Ehrlich and Bertheim,[2] in which the salt is precipitated from an alcoholic solution with ether, while it was noted that material, the composition of which corresponded closely to this formula was frequently obtained, differential assay demonstrated the presence of ethyl ether, ethyl alcohol and water. It was also found that such a composition appeared to be fortuitous since different drying conditions eliminated varying amounts of each volatile constituent. Similarly, while the exchange of organic solvents by water proceeded as described (IIIA), the product never became entirely free of alcohol and ether. Newberry and Phillips[6] reported the separation of 3-amino-4-hydroxybenzenearsonous acid hydrochloride (IIIB) from an aqueous solution of 2-amino-4-dichloroarsinophenol hydrochloride but gave no details and the product was apparently presumed to be identical with IIIA. Experiments showed that IC, when dissolved in slightly more than one equivalent of any strong acid and this solution cooled until ice separated and then allowed to warm to just above the melting point, would deposit an insoluble product when the side of the container was rubbed. Analyses of the products obtained in this manner indicated that they possessed the general formula $C_6H_6AsNO_2 \cdot HX \cdot H_2O$. After they had been dried in a vacuum desiccator over phosphorus pentoxide they were found to have been converted into compounds of the formula $C_6H_6AsNO_2 \cdot HX$. Both hydrated and anhydrous products were white and did not redissolve readily in water. In the instance of the products formed with hydrochloric acid, the hydrated form (IIIB) would dissolve in absolute ethanol on standing but the anhydrous form (IVA) did not dissolve. The hydrated form dissolved in water in a few hours but the anhydrous material gave a milky suspension which required twenty-four hours to change to a clear solution. This was not a question of particle size since almost colloidal dispersions could be prepared. Both forms redissolved instantly in water containing one equivalent of acid.

On the other hand, when 3-amino-4-hydroxybenzenearsonous acid was dissolved in concentrated solution with exactly one equivalent of an acid and this solution shell-frozen at −36° and then dried under high vacuum in a manner similar to that used to prepare plasma powder, the products also analyzed for the formula $C_6H_6AsNO_2 \cdot HX \cdot H_2O$. By careful dehydration, products of the general formula $[C_6H_6AsNO_2 \cdot HX]_2 \cdot H_2O$ were obtained and further dehydration yielded compounds of the formula $C_6H_6AsNO_2 \cdot HX$. The hydrates and hemihydrates were colorless but the anhydro forms ranged in color from light yellow to yellowish-green. The three hydrochloride derivatives produced by this technique (hydrate, IIIC; hemihydrate, VIIA; anhydro, VIB) were all instantly soluble in water. IIIC was also easily soluble in absolute alcohol, VIIA less easily soluble and VIB was insoluble in cold alcohol. By prolonged refluxing, VIB gradually dissolved in absolute ethanol and when the volume of the solution was reduced, the hydrochloride hemialcoholate (IIB) crystallized. This product appeared to differ from that of Ehrlich and Bertheim (IIA) only in that it was free of ether and water. The hydrochloride products are compared in Table II.

The sulfate and iodide salts separated in both forms from aqueous solutions. Concentrated solutions on chilling gave products identical with those obtained by shell-freezing while more dilute solutions gave the analogs of the difficultly soluble hydrochloride, IIIB.

In order to differentiate between the two series, both of which appear to be salts, the products obtained from frozen solutions are referred to as the "soluble" series while those separating from solution at 0° are called the "insoluble" series. A number of salts changed to the "insoluble" series so rapidly as to make the isolation of the "soluble" form impractical. The "insoluble" ascorbate was not obtained in spite of numerous attempts. The various salts are summarized in Table III.

Experimental[10]

The starting product, 3-amino-4-hydroxybenzenearsonic acid hydrochloride, was available as a commercial intermediate. Its synthesis is described by Jacobs, *et al.*[11] In all of the preparations care was taken to prevent undue oxidation by excluding air whenever possible. When indicated, anaerobic conditions were used. Representative preparations of the various salts are given. The other salts were prepared by using the appropriate acid.

3-Amino-4-hydroxybenzenearsonous Acid (IC).—3-Amino-4-hydroxybenzenearsonic acid hydrochloride (270 g.) was dissolved in water (1500 ml.) and hydrochloric acid (500 ml.). Potassium iodide (1 g.) was added and the solution cooled to 0°. Sulfur dioxide (75 g.) was introduced as rapidly as possible, maintaining the temperature below 5° by the use of Dry Ice. The mixture was stirred for two hours and then concentrated ammonia added until the solution was neutral to congo red paper maintaining the temperature below 5°. The solution was treated with iron-free Darco, diluted to 12 liters and then adjusted to *p*H 6.5 with ammonium carbonate. On scratching the vessel or seeding, the crude white product crystallized (IB). The yield was about 195 g. (90%). This material assayed as 98–99% pure. The crude product was dissolved under as nearly anaerobic conditions as possible in oxygen- and iron-free water (4.5 l.) and concentrated hydrochloric acid (90 ml., reagent grade). After cooling to 0° with solid carbon dioxide, sodium sulfite (4 g., reagent grade, iron-free) was added and then iron-free Darco (20 g.) which had been heated at 200° under nitrogen for three hours. After stirring for twenty minutes the solution was filtered in an atmosphere of carbon dioxide and maintained at 0°. Ammonium carbonate solution, prepared from reagent grade ammonia and carbon dioxide, was added slowly until the *p*H was 6.5 and crystallization initiated by adding a seed crystal. The crystallized product was filtered off and washed with two portions of oxygen- and iron-free water. After drying *in vacuo* over phosphorus pentoxide, the product was further dried at 35° in a vacuum oven. The yield was 185 g. or 95% for the recrystallization. The over-all yield was 85%. The product was a colorless, crystalline solid, soluble about 0.1% in water on shaking for an hour, but soluble 0.35% after standing in contact with water for twenty-four hours. It was insoluble in absolute ethanol and absolute methanol but dissolved slowly in 95% ethanol. It was readily soluble in hydrochloric, sulfuric, phosphoric and other acids and remained unchanged in tightly stoppered brown bottles over a period of six months.

Anal. Calcd. for $C_6H_8AsNO_3$: As, 34.51; N, 6.45. Found: As (total), 34.50; As (organic trivalent), 34.51; N (Kjeldahl), 6.46.

2-Amino-4-arsenosophenol (IVB).—3-Amino-4-hydroxybenzenearsonous acid (IC) (40 g.) was dissolved in absolute alcohol (750 ml.) by refluxing for six hours. Benzene was added and the water–alcohol–benzene azeotrope distilled until no more water was apparent. Anhydrous benzene was then added slowly and the distillation continued until no ethanol was found in the distillate. The product remaining in the flask was filtered off and dried *in vacuo* at 70°. The yield was 34 g. of a bright yellow powder which did not appear to be crystalline. In water it first turned white and then dissolved to give a 0.7% solution. It was immediately soluble in both absolute and 95% ethanol.

Anal. Calcd. for ($C_6H_6AsNO_2$): As, 37.64. Found: As (organic trivalent), 37.63.

bis-[(3-Amino-4-hydroxyphenyl)-hydroxyarsine] Oxide (VA).—Four grams of IVB was placed in a desiccator in a nitrogen atmosphere with slightly more than one-half equivalent of water. After twenty-four hours the powder was white and had gained in weight to correspond to a hemihydrate. The powder was soluble in alcohol and slightly soluble in water. The product did not dehydrate over anhydrous calcium chloride.

Anal. Calcd. for $C_{12}H_{14}As_2N_2O_5$: As, 36.01. Found: As (organic trivalent), 36.04%.

"Soluble" **3-Amino-4-hydroxybenzenearsonous Acid Hydrochloride (IIIC).**—3-Amino-4-hydroxybenzenearsonous acid (0.05 mole) was dissolved in water (30 ml.) and hydrochloric acid (0.05 mole) and the solution decolorized (1 g. of Darco) and filtered. The filtrate was placed in a 250-ml. Pyrex bottle and frozen into a shell around the side of the bottle by rotating rapidly in an acetone–Dry Ice-bath, the bottle was placed on a vacuum system containing a Dry Ice trap and evacuated to 0.5 mm. pressure. After forty-eight hours, the product was nearly dry and was removed from the bottle and dried for several hours over calcium chloride. The yield was practically the theoretical. The product was white and was readily soluble in water, absolute and 95% ethanol.

Anal. Calcd. for $C_6H_9AsClNO_3$: As, 29.54. Found: As (total), 29.60; As (organic trivalent), 29.55.

"Soluble" **bis-[(3-Amino-4-hydroxyphenyl)-hydroxyarsine] Oxide Dihydrochloride (VIIA).**—Ten grams of the "soluble" arsonous acid hydrochloride (IIIC) was dehydrated at room temperature over phosphorus pentoxide for twenty-four hours. The product was white and dissolved readily in water, absolute and 95% ethanol.

Anal. Calcd. for $C_{12}H_{16}As_2Cl_2N_2O_5$: As, 30.78; H_2O, 3.68. Found: As (organic trivalent), 30.71; H_2O, 3.70.

"Soluble" **2-Amino-4-Arsenosophenol Hydrochloride (VIB).**—Twenty-five grams of the "soluble" arsonous acid hydrochloride (IIIC) was dehydrated by first drying *in vacuo* over phosphorus pentoxide for forty-eight hours and then for sixteen hours *in vacuo* at 70°. The resulting

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(10) Total arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930); organic trivalent arsenic by the method of Banks and Sultzaberger, *ibid.*, **69**, 1 (1947).

(11) Jacobs, Heidelberger and Rolf, *ibid.*, **40**, 1580 (1918).

TABLE I

PROPERTIES OF 3-AMINO-4-HYDROXYBENZENEARSONOUS ACID

	IC	IB	IA and ID
Color	Colorless	Colorless	(A) Pink, violet or brown (D) Colorless, darkened rapidly in air
Stability	Unchanged for six months in absence of air	Turns gray in three months in absence of air	(A) Decomposed in a few days in the absence of air (D) Decomposed in a month in the absence of air
Soly. in water	Extremely insoluble (0.10%) but slowly converts to a more soluble form	Soluble 0.35%	Moderately soluble, solubility depends on purity
Soly. in abs. ethanol and methanol	Insoluble cold, soluble upon prolonged refluxing	Very slowly soluble cold, readily hot	Instantly soluble cold
Soly. in 95% ethanol	Very slowly soluble cold	Soluble cold	Instantly soluble cold

TABLE II

PROPERTIES OF THE VARIOUS ISOMERS OF 2-AMINO-4-ARSENOSOPHENOL HYDROCHLORIDE[a]

			Ehrlich and Bertheim product (IIIA)[b]	
	"Soluble" form	"Insoluble" form	Original[c]	Prepared from pure starting material[d]
Color	Greenish-yellow	White	[e]	White
Solubility in water	Over 30%—Instantly	Over 30%—Requires 24 hrs.	Over 30%	Over 30%
Solubility in 95% ethanol	Instantly soluble	Slowly soluble	Instantly soluble	Instantly soluble
Solubility in abs. ethanol	Insoluble cold; soluble upon refluxing	Insoluble	Instantly soluble	Instantly soluble
Stability at 20°	Over 3 years	Over 10 years	Less than 6 months	About 2 years
Stability at 70°	Over 96 hours	Over 192 hours	Less than 4 hours	About 16–24 hours
Stability at 100°	24 hours	Over 24 hours	Decomposes rapidly	Decomposes rapidly
Crystalline	Yes	Yes	No	No

[a] The properties of the hydrochlorides are representative of all the salts. [b] Prepared from an alcoholic solution by precipitation with ether. [c] Since the original literature did not supply all of the properties, the procedure was duplicated as accurately as possible. All of the volatile solvent could not be removed. Average assay for As, 29.8 (theory, 31.81). [d] Average assay for As, 30.5. Non-volatile occluded solvent was principally ether. [e] Product was occasionally white on precipitation but turned pink, red, purple or black during isolation.

TABLE III

ISOMERIC FORMS OF THE SALTS OF 2-AMINO-4-ARSENOSOPHENOL

			"Soluble" series 3-Amino-4-hydroxybenzenearsonous anhydride salts			"Insoluble" series[a] 2-Amino-4-(hydroxy)(X)arsinophenol		
Salt	Empirical formula	% As Calcd.	% Yield	Color	% As found[b]	% Yield	Color	% As found[b]
Hydrobromide	$C_6H_7AsBrNO_2$	26.75	91	Greenish-yellow	26.75	74	White	26.73
Hydriodide	$C_6H_7AsINO_2$	22.92	98	Orange-yellow	22.88	96	Orange-yellow	22.94
Sulfate	$C_{12}H_{14}As_2N_2O_8S$	30.20	97	Yellow-green	30.20	79	White	30.28
Phosphate	$C_6H_9AsNO_6P$	24.40	[c]			68	White	24.42
Nitrate	$C_6H_7AsN_2O_5$	28.59	90	Yellow	28.66	62	White	28.74
Tartrate	$C_{10}H_{12}AsNO_8$	21.46	90	Light yellow	21.41	71	White	21.47
Lactate	$C_9H_{12}AsNO_5$	25.91	92	Light yellow	25.86	86	White	25.84
Oxalate	$C_8H_8AsNO_6$	25.90	[c]			87	White	25.85
Maleate	$C_{10}H_{10}AsNO_6$	23.77	[d]			65	White	23.55
Sulfamate	$C_6H_9AsN_2O_6S$	25.30	90	Light yellow	25.20	55	White	25.16
Malate	$C_{10}H_{12}AsNO_7$	22.50	[d]			62	White	22.53
Ascorbate	$C_{12}H_{16}AsNO_9$	19.05	89	Light yellow	19.08	[d]		
Citrate	$C_{12}H_{14}AsNO_9$	19.15	89	Light yellow	19.18	72	White	19.14

[a] The hydrates of several of these compounds were first isolated by Mr. B. F. Tullar, formerly of these laboratories. They were reprepared and dehydrated for the purposes of this study. [b] Organic trivalent, all compounds also checked by determination of total arsenic content. [c] Converted to "insoluble" form too rapidly for isolation. [d] Not obtained.

product was a greenish-yellow, crystalline solid which dissolved readily in water and alcohol.

Anal. Calcd. for ($C_6H_7AsClNO_2$): As, 31.81; N, 5.95; Cl, 15.09. Found: As (total), 31.84; As (organic trivalent), 31.84; N (Kjeldahl), 5.90; Cl (ionic), 15.05.

The anhydrous material obtained above was placed in a closed vessel in a nitrogen atmosphere over hydrated calcium chloride. After a week the product was examined and found to be identical with the "soluble" hemihydrate (VIIA) in color, properties and analysis.

"Insoluble" 3-Amino-4-hydroxybenzenearsonous Acid Hydrochloride [(3-Ammonium-4-hydroxyphenyl)-chloroarsonite] (IIIB).—A solution of 3-amino-4-hydroxybenzenearsonous acid in water and hydrochloric acid was prepared as in the directions for IIIC. The solution was cooled to 0° and a 10% excess of hydrochloric acid added. The solution was placed in an ice–salt mixture until it was partially frozen and then the sides of the vessel scratched while cooling in an ice-bath. The product separated slowly as the ice melted. It was filtered off and dried over calcium chloride. Because of its great instability, it had to be handled rapidly. The product was white and dissolved very slowly in water and ethanol.

Anal. Calcd. for $C_6H_9AsClNO_3$: As, 29.54. Found: As (organic trivalent), 29.48.

"Insoluble" 2-Amino-4-chlorohydroxyarsinophenol (VIA).—The product was prepared exactly as was type IIIB except that the final product was dried *in vacuo* for forty-eight hours over phosphorus pentoxide. The product was a fine, white, crystalline powder which dissolved very slowly in water and 95% ethanol and was insoluble in absolute ethanol; yield 82%.

Anal. Calcd. for $C_6H_7AsClNO_2$: As, 31.81; N, 5.95; Cl, 15.09. Found: As (total), 31.79; As (organic trivalent), 31.82; N (Kjeldahl), 5.92; Cl (ionic), 15.11.

Hemialcoholate (IIB).—VIB (10 g.) was dissolved in absolute ethanol (100 ml.) by gentle refluxing. After filtering to remove a small amount of suspended solid, the solution was concentrated to about 12 ml. by the use of high vacuum at room temperature. Six grams of a white solid separated and was filtered off and dried over calcium chloride.

Anal. Calcd. for $C_{14}H_{20}As_2Cl_2N_2O_5$: As, 28.98. Found: As (organic trivalent), 29.04.

Amorphous 3-Amino-4-hydroxybenzenearsonous Acid (ID).—IC (25 g.) was dissolved in 150 ml. of water with a minimum of hydrochloric acid, the solution treated with Darco G-60 and filtered. The filtrate was neutralized with concentrated ammonia to *p*H 6.5 and saturated with salt. The resulting solution was cooled by the introduction of Dry Ice. A gum separated and was filtered off in a nitrogen atmosphere. After grinding under anhydrous ether, it solidified to an amorphous mass which was dried over phosphorus pentoxide *in vacuo*. When protected from oxygen, it was colorless. The yield was 16 g. or 64%.

Anal. Calcd. for $C_6H_8AsNO_3$: As, 34.51. Found: As (total), 34.36; As (organic trivalent), 34.02.

Discussion

The structures of many organic arsenicals have been based on certain empirical relations for many years. Thus, arseno compounds have been written as R—As=As—R by analogy with the azo compounds. Similarly, arsenoso compounds have been assigned the structure R—AsO analogous to the nitroso compounds. With the advent of the modern concepts of valence, little has been done to clarify the obvious anomalies presented by these structures. If the postulation that electrons outside the L shell cannot participate in the formation of a dicovalent bond is correct, then the structures assigned to both the arseno and arsenoso compounds are incorrect. Waser and Schomaker[12] have reviewed the evidence for the structure of arsenomethane and carried out vapor density and X-ray diffraction measurements from which they concluded that a puckered five-membered ring of arsenic atoms was most compatible with the data. Prior to this, Blicke and Smith[13] had investigated the behavior of solutions of a number of arsenicals of the general formula R—As=Q. In those instances in which Q consisted of two univalent radicals, the compounds were monomolecular in nonpolar solvents. When Q was =O, =S or =NH, the compounds appeared to be molecular aggregates, $(R—As{=}Q)_n$. In most instances $n \approx 4$ but occasionally was ≈ 2 or 3. One compound gave different values in different solvents.

The compounds prepared in this study were not sufficiently soluble in organic solvents to determine molecular weights in solution. Since the means of studying the crystals by X-ray diffraction were not available, no direct measurements indicative of molecular form were possible. However, the chemical properties of the compounds are such that certain deductions concerning structure are possible. Also, the existence of two series of salts of the same empirical formula indicates that two different structures are required.

On the basis of chemical behavior and properties, there seems to be no reason to question the arsonous acid structure of crystalline 3-amino-4-hydroxybenzenearsonous acid (IB and IC). The instability of the amorphous form (IA and ID) indicates some difference from IC as does the formation of a white anhydro form IVA in contrast to the yellow anhydro IVB obtained from IC. It is conceivable that different molecular alignments would result in different stabilities. The dehydration of IC apparently proceeds through VA. On the basis of the work of Blicke and Smith,[13] IVB might be a di-, tri- or tetramer. However, the reformation of VA from IVB suggests that $n = 2$ or 4.

By analogy, the structure of IIIC, the "soluble" hydrochloride, appears to be in agreement with all the chemical and physical properties. The dehydration to VIIA and then to VIB seems logical. The formation of VIIA in the conversion of IIIC to VIB and its reformation upon hydrating VIB again suggests that the arsenoso compound VIB has a ring structure where $n = 2$ or 4. The alcoholysis of VIB to IIB suggests that $n = 2$ since it is hardly likely that an eight-membered ring would break exactly into two equal fragments. One significant feature is the color produced with all of the "soluble" salts when they are dried to the VIB type. An examination of the literature indicates that in no other instance does the trivalent arsenoso form have color where the pentavalent form is colorless. Even the arsenosomono- and dinitrobenzenes show very little color. The color produced here is unique and suggests that n for both IVB and VIB is 2 and that a somewhat highly strained four-membered ring is formed.

The "insoluble" series of salts presents another problem. While isomeric with the "soluble"

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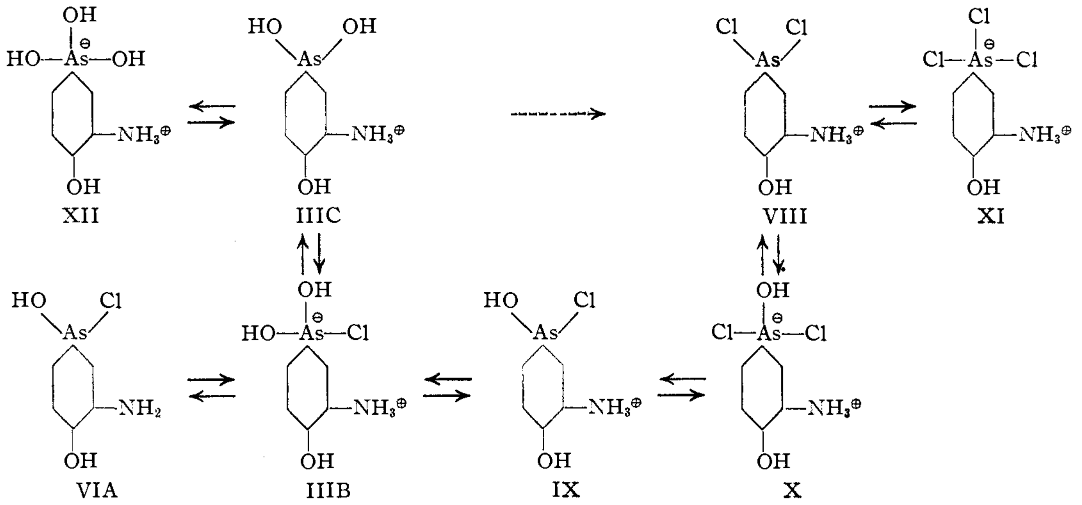
[12] Waser and Schomaker, THIS JOURNAL, **67**, 2014 (1945).

[13] Blicke and Smith, *ibid.*, **52**, 2946 (1930).



series, their properties suggest a totally different structure. Whereas the members of the "soluble" series behave as amine salts, the "insoluble" series have none of the properties of amine salts and actually appear to be free amines. This suggests that the acid radical is attached to the arsenic as indicated in VIA. Since VIA proceeds through a form having an additional mole of water, the structure of this form is of extreme interest.

The conversion of the hydrochloride IIIC to the dichloroarsino hydrochloride XI by hydrochloric acid is well-known. This type of reaction is general for all arsenoso compounds but no mechanism for the exchange of halogen for hydroxyl has been presented other than the tacit assumption that since both hydroxyl and chloride ions exist in the solution, the exchange was probably ionic in nature. The isolation of IIIB suggests that the replacement of hydroxyl by halogen proceeds through a coördination compound of the arsenic. While arsenic has a coördination number of 4 or 6, coördination compounds of organic arsenicals are practically unknown, or at least unrecognized. Arsenic, with two electrons in the 4s orbital and three electrons in the 4p orbitals adds electrons to fill out the 4p orbitals. In IIIC such a condition exists. For arsenic in such a valence state to form a coördinate compound requires that either an entity lacking two electrons conjugates with the unshared 4s electrons of arsenic (in which case we generally consider it a pentavalent arsenical) or that the fourth group around the arsenic furnishes two electrons which enter the 5s orbital of arsenic. The 4s electrons then become an "inert pair." This situation is quite analogous to some of the coördination complexes of cobalt.[14] Such complexes tend to be unstable and the conversion to VIA is not surprising. The structure of VIA accounts for all the properties of the "insoluble" series. The instability of such complexes also suggests the stepwise conversion of IIIB to IX, X and then to VIII.

As a logical extension of the theory it would appear that 2-amino-4-dichloroarsinophenol hydrochloride should be written as 3-ammonium-4-hydroxybenzenetrichloroarsonite (structure XI). The manner in which 3-amino-4-hydroxybenzenearsonous acid separates from aqueous solution, and the highly hydrated nature of the products separated when solutions are concentrated, suggests that the form in solution may be 3-ammonium-4-hydroxybenzenearsonite (structure XII). At least one other arsenical probably has this type of structure. The compound 2-[4'-arsenosoanilino]-4,6-diamino-*s*-triazine dihydrate reported in a previous paper[15] has all the properties that might be expected of 4-[2',4'-diamino-6'-triazinylammonium]-benzenearsonite. While these postulates lack the support of X-ray studies of the crystalline forms, the chemistry of the compounds appears to be most logically explained on this basis. It seems worthwhile to point out that the accepted structures of organic derivatives of arsenic, antimony and bismuth are in need of revision so as to make them harmonious with modern structural concepts.

Summary

1. Analytically pure 3-amino-4-hydroxybenzenearsonous acid and 3-amino-4-hydroxybenzenearsonous acid hydrochloride have been prepared and characterized.

2. 2-Amino-4-arsenosophenol, bis-[(3-amino-4-hydroxyphenyl)-hydroxyarsine] oxide and their hydrochlorides have been described for the first time. Nine other salts of 2-amino-4-arsenosophenol are reported.

3. 2-Amino-4-chlorohydroxyarsinophenol and its hydrated form were prepared. Similar derivatives of twelve other acids have been described.

4. The relationship between the "insoluble" 2-amino-4-hydroxychloroarsinophenol and the

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(14) Pauling, "Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1945.

(15) Banks, Gruhzit, Tillitson and Controulis, This Journal, **66**, 1771 (1944).

"soluble" 2-amino-4-arsenosophenol hydrochloride has been demonstrated and a mechanism for the conversion of arsonous acids to dichloroarsines suggested.

5. Structures for the various isomeric derivatives of 3-amino-4-hydroxybenzenearsonous acid have been postulated.

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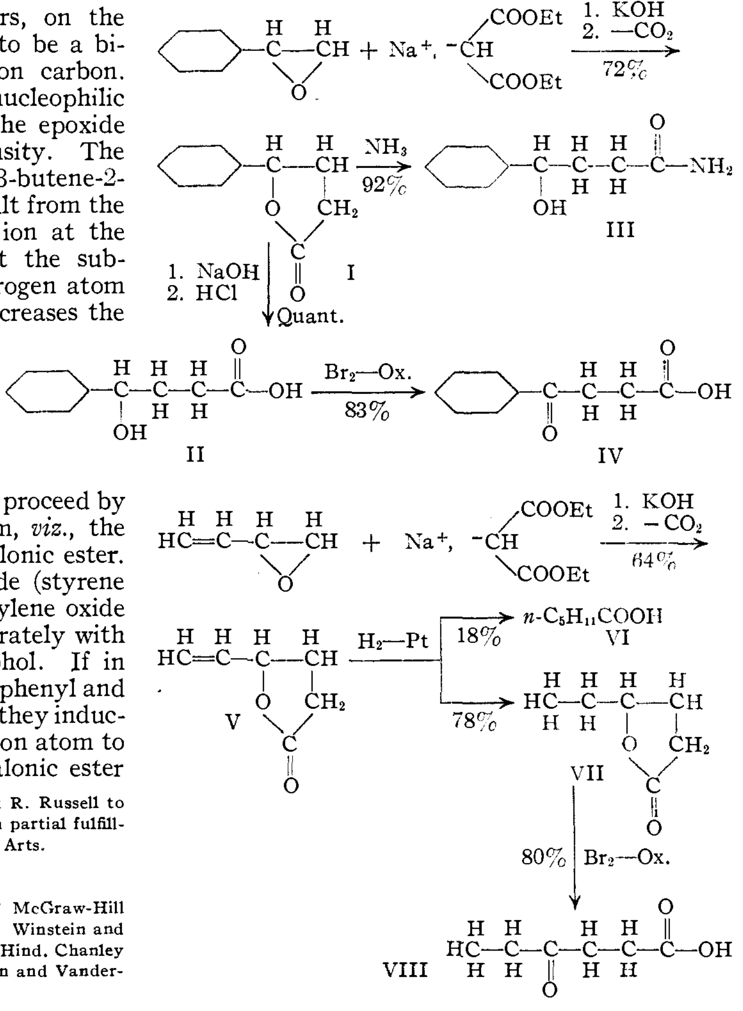
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Malonic Ester Synthesis with Styrene Oxide and with Butadiene Oxide[1]

BY ROBERT R. RUSSELL AND CALVIN A. VANDERWERF

Although both the phenyl and vinyl groups are ordinarily considered by advocates of the electronic theory to be more electronegative than hydrogen,[2] nevertheless there is some indication that the vinyl group, when substituted for a hydrogen atom in ethylene oxide, serves to increase the electron density at the carbon to which it is attached. Kadesch[3] has shown that the addition of methanol to butadiene oxide (3,4-epoxy-1-butene) in the presence of sodium produces predominantly 1-methoxy-3-butene-2-ol. The mechanism of this, and similar reactions of nucleophilic reagents with epoxides, appears, on the basis of the occurrence of inversion,[4] to be a bimolecular nucleophilic displacement on carbon. Further, it is to be expected that the nucleophilic reagent would attack the carbon of the epoxide ring that has the lower electron density. The predominant formation of 1-methoxy-3-butene-2-ol in the reaction cited above must result from the preferential attack of the methoxide ion at the unsubstituted carbon, indicating that the substitution of the vinyl group for a hydrogen atom on a carbon atom in ethylene oxide increases the electron density at that carbon.

In the present investigation a study was made of the effect of the phenyl and vinyl groups in determining the direction of epoxide ring opening in a reaction which has been shown,[4c,d] almost beyond any doubt, to proceed by a nucleophilic displacement mechanism, *viz.*, the condensation reaction with sodium malonic ester. The phenyl derivative of ethylene oxide (styrene oxide) and the vinyl derivative of ethylene oxide (butadiene oxide) were condensed separately with sodium malonic ester in absolute alcohol. If in these derivatives of ethylene oxide, the phenyl and vinyl groups exhibit a $-I_s$ effect, *i.e.*, if they inductively withdraw electrons from the carbon atom to which they are attached, then the malonic ester anion would be expected to attack at that carbon. Successive protolysis, hydrolysis and decarboxylation starting with the products thus formed would be expected to yield β-phenyl-γ-butyrolactone and β-vinyl-γ-butyrolactone, respectively. If, on the other hand, the effect of the phenyl and vinyl groups is $+I_s$, the malonic ester anion would be expected to attack at the terminal carbon atom and the predicted final products are, respectively, γ-phenyl-γ-butyrolactone, I, and γ-vinyl-γ-butyrolactone, V.



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[1] Abstracted from a thesis presented by Robert R. Russell to the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the Degree of Master of Arts.

[2] See Ingold, *Chem. Revs.*, **15**, 225 (1934).

[3] Kadesch, THIS JOURNAL, **68**, 41 (1946).

[4] a) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 301–303; (b) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (c) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2606 (1942); (d) Newman and VanderWerf, *ibid.*, **67**, 233 (1945).