[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Aliphatic Chloroarsines[1]

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In order to attempt the synthesis of new alkyl- and substituted alkyldichloroarsines and also prepare large quantities of some of the known compounds of this type for toxicity studies it was necessary to investigate the various procedures for preparing such compounds. An excellent summary of these methods has been made by Goddard.[3] The reaction of alkyl halides with sodium arsenite or sodium alkylarsonites to yield alkylarsonic and dialkylarsinic acids[4] and the subsequent reduction of these products with sulfur dioxide in the presence of hydrochloric acid to yield the corresponding alkyldichloro- and dialkylchloroarsines is probably the most efficient and generally applicable, but least investigated, of the available methods. Although the sulfur dioxide reduction method has been used extensively in the synthesis of aryldichloroarsines, its general applicability to aliphatic types has not been investigated.

In general, it was found that arsenation of primary aliphatic halides proceeded smoothly to yield alkylarsonic acids but secondary halides reacted only slightly and tertiary halides not at all. Alkenyl halides varied in reactivity, depending on the relative positions of the halogen, the double bond and of any additional substituents. While allyl chloride reacted only partially, the bromide gave almost theoretical yields. On the other hand, 2-methylallyl chloride was as reactive as allyl bromide but Δ-4-pentenyl chloride failed to react to any significant degree and it was necessary to utilize the bromide to obtain the product. Vinyl halides did not react. The effect of substituents varied considerably. Alkoxyalkyl halides reacted readily, as did the thio analogs, but aryloxy compounds were much less reactive. Symmetrically substituted dihalo compounds gave diarsonic acids. A few compounds gave evidence of reaction as measured by the utilization of arsenic trioxide but the reaction products and their common derivatives were not isolated because of instability or other factors. Among these were tetrahydrofurfuryl bromide, vinyloxyethyl bromide, 3-chloroallyl chloride, 3-chloro-2-methylallyl chloride and 4-chloropentyl iodide. Dialkylarsinic acids were prepared readily when unsubstituted but the introduction of substituent groups in the alkyl radicals caused difficulties similar to those encountered in the preparation of alkylarsonic acids. Arsenosobenzene proved to be an excellent test agent to determine the reactivity of alkyl halides.

Although only four examples of the use of sulfur dioxide as a reducing agent for alkylarsonic acids are recorded in the literature, a large number of the arsonic acids prepared by the Meyer reaction reduced to give almost the theoretical yields of the crude arsines. These crude compounds were easily purified to products of greater than 99% purity but analytically pure samples were difficult to obtain. It was frequently necessary to prepare the dichloroarsine, oxidize to the arsonic acid and reduce a second time to completely eliminate all traces of bromides. Hydrobromic acid, substituted for hydrochloric acid, led to the production of bromoarsines. Allylarsonic acid reduced to a mixture of products which were difficult to separate. A large portion of the mixture proved to be arsenic trichloride. The residue proved to contain two products, allyldichloroarsine and another arsenical, thought to be β-chloropropyldichloroarsine. The latter product decomposed slowly during distillation to arsenic trichloride and propene and separation was finally achieved by refluxing the mixture under a partial pressure at a temperature which sufficed to decompose the chloropropyl compound yet was below the critical decomposition temperature of the allyl compound. 2-Methylallylarsonic acid reduced to a very unstable product which could not be separated without decomposition. In contrast to the β-unsaturated compounds, δ-unsaturation did not appear to affect stability as evidenced by the ease with which Δ-4-pentenyldichloroarsine was produced.

While the alkoxyalkylarsonic acids reduced readily to the desired products, phenoxyethylarsonic acid gave a product which appeared to be a mixture of the desired product and 4-chloro-2,3-dihydro-1,4-benzoxarsane. The thio analogs gave unstable oils. Because of the variation in the reported data on β-chloroethyldichloroarsine, the compound was investigated and it was found that an extremely stable product could be isolated by careful purification, in contradistinction to the literature. The only ω-haloalkoxyalkyldichloroarsine obtained was γ-chloromethoxypropyldichloroarsine, the reaction product of γ-hydroxypropyldichloroarsine, formaldehyde and hydrogen chloride.

An unusual product was obtained during the reduction of the diarsonic acids. When crude bis-(β-arsonoethyl)-ether was reduced, the product

(1) The work herein described was done under contracts NDCrc-16 and OEMsr-85, recommended by the National Defense Research Committee between the Office of Scientific Research and Development and the Board of Regents of the University of Nebraska.

(2) Official investigator.

(3) "Textbook of Inorganic Chemistry," Vol. XI, Part II, by A. E. Goddard, edited by J. N. Friend, Charles Griffin and Co., London, 1930.

(4) Meyer, *Ann.*, **240**, 310 (1884).

TABLE I[a]

ALKYLARSONIC ACIDS

R—AsO_3H_2, R =	Alkyl intermediate	Yield, %	M. p., °C.	% Arsenic Calcd.	Found
Methyl[b]	Sulfate	85	159.8	53.52	53.53
Ethyl[4,6]	Bromide	87	99.6	48.65	48.67
n-Propyl[4,6]	Bromide	64	134.6–135.2	44.59	44.54
n-Butyl[4,6]	Bromide	96	159.5–160	41.15	41.20
n-Pentyl[c]	Bromide	53	162–163	38.21	38.11
3-Methylbutyl[d]	Bromide	53	192–194	38.21	38.18
2-Methylbutyl	Bromide	38	171–172	38.21	38.15
n-Hexyl[e]	Bromide	35	165–166	35.65	35.49
n-Heptyl	Bromide	35	156–157	33.42	33.20
Allyl[6]	Bromide	85	128–129	45.12	45.30
2-Methylallyl	Chloride	98	S. 81	37.83[f]	37.71
δ-4-Pentenyl	Bromide	40	144–146	38.60	38.65
β-Phenoxyethyl[g]	Bromide	10	167.5–168	30.44	30.44
β-Methoxyethyl	Bromide	60	Sirup	...	...
β-Ethoxyethyl	Bromide	65	Sirup	...	...
β-Ethylmercaptoethyl	Bromide	25	109–110	34.99	35.30
H_2O_3As—M—AsO_3H_2, M =					
$—CH_2CH_2OCH_2CH_2—$	Bromide	10	173–174	46.53	46.36
$—CH_2CH_2SO_2CH_2CH_2—$	Chloride	54	215	40.49	40.40
$[C_6H_5As(O_2H)—CH_2CH_2]_2S$	Bromide	64	189	32.70	32.66
$[C_6H_5As(O_2H)—CH_2CH_2]_2SO_2$	Chloride	87	197	30.56	30.44

[a] All compounds colorless. [b] Adapted from initial reaction in preparation of methyldichloroarsine by Uhlinger and Cook, *Ind. Eng. Chem.*, 11, 105 (1919). [c] Prepared by indirect method, Backer and Bolt, *Rec. Trav. Chim.*, **54**, 186 (1935). [d] From iodide, Dehn and McGrath, THIS JOURNAL, **28**, 353 (1906). [e] Indirect preparation, Gibson and Johnson, *J. Chem. Soc.*, 2518 (1931). [f] Isolated as hydrate. [g] Quick and Adams[6] reported no reaction.

proved to be bis-(β-dichloroarsinoethoxy)-ethyl ether rather than the expected bis-(β-dichloroarsino)-ethyl ether. It was found that the crude arsonic acid was not more than 20% pure. Pure bis-(β-arsonoethyl) ether reduced to an extremely high-boiling oil which could not be distilled below 230° (the decomposition temperature) at 0.1 mm. The identified product was produced from one of the impurities, of which there were at least three. 1,3-Diarsonopropane decomposed on reduction to γ-chloropropyldichloroarsine and arsenic.

Cyano- and thiocyanoarsines were also prepared. Most of the compounds of this type reported in the literature were prepared by pyrolysis of di- or trialkylarsine cyanobromides. It was found that they were more simply prepared by metathetic reactions of the chloroarsines with an appropriate salt. A new molecular aggregate of β-chlorovinylarsonous acid anhydride was isolated during experiments with β-chlorovinyldichloroarsine. The new form had a m. p. of 217° as contrasted with the previously reported value of 143°.

A number of methods were investigated for the preparation of compounds such as di-(β-chloroethyl)-chloroarsine, β-chloroethyldimethylarsine and di-(β-chloroethyl)-methylarsine, but in every instance the β-chloroethyl group was eliminated by the loss of ethylene whenever another alkyl group was present. Thus, the products resulting from the attempted preparation of the above examples were β-chloroethyldichloroarsine, dimethylchloroarsine and methyldichloroarsine.

Experimental[5]

(1) **Alkylarsonic Acids by the Meyer Reaction.**—A solution of arsenic trioxide (4 moles) in sodium hydroxide (24 moles) and water (2 liters) was placed in a 5-liter three-necked flask equipped with an efficient stirrer, dropping funnel and condenser. The alkyl halide (8 moles) in 95% ethanol (200 ml.) was added slowly with stirring at room temperature and the mixture then refluxed until titration aliquots as determined by the method of Quick and Adams[6] indicated that the progress of the reaction had been halted. An oil-bath was found to be advisable for heating because of the strain placed on the glass by the highly alkaline solution. The time of reaction varied from seventy to two hundred hours. When reaction had ceased all volatile organic residues were distilled off and the residual solution made acid to phenolphthalein paper, cooled and the unreacted arsenic trioxide filtered off. The filtrate was acidified to congo red paper, cooled and any arsonic acid that separated was removed. The filtrate was concentrated, the separated salt filtered off hot and the solution cooled to yield a further quantity of the arsonic acid. The process was repeated until the entire yield was obtained. On occasion, the arsonic acid was extremely soluble and was obtained in a crude form by total evaporation of the solution. The arsonic acids could be purified by dissolving in alcohol, filtering off any salt present and evaporating the filtrate to dryness, followed by recrystallization from water. In a few instances the arsonic acids were isolated as thick sirups that did not crystallize.

(2) **Dialkylarsinic Acids.**—The alkyldichloroarsine (1 mole) was added slowly with stirring to a solution of sodium hydroxide (4 moles) in water (250 ml.), refluxed one hour, cooled to room temperature, the alkyl halide (1 mole) added slowly with vigorous stirring and then refluxed for six hours. After cooling, the solution was treated as in the preparation of arsonic acids. The products were isolated as oils consisting of solutions of

(5) Arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

(6) Quick and Adams, *ibid.*, **44**, 811 (1922).

water in the arsinic acid and were used without further purification.

(3) Reduction of Alkylarsonic and Dialkylarsinic Acids to Chloro- and Bromoarsines.—The acid, or crude sirup concentrate thereof, was dissolved in concentrated hydrochloric or hydrobromic acid and any salt residues filtered off. The solution was saturated with sulfur dioxide in the presence of a trace of potassium iodide. After six hours, the oil layer was removed, dried over calcium chloride or sodium sulfate and distilled from a Vigreux-Claisen flask. When further purification was desired, the product was fractionated from a still having an 18 in.

TABLE II

ALKYLDICHLOROARSINES AND DIALKYLCHLOROARSINES[a]

R—$AsCl_2$, R =	Boiling point, °C.	Mm.	Yield,[b] %	Molecular formula	Analyses, % Arsenic Calcd.	Arsenic Found	Chlorine Calcd.	Chlorine Found
Methyl	129.5–130	740	50	CH_3AsCl_2			44.08	43.55
Ethyl[c]	152–155	740	27	$C_2H_5AsCl_2$	42.84	42.88	40.55	40.48
n-Propyl[c]	98.3–99.5	70	47	$C_3H_7AsCl_2$			37.54	37.09
n-Butyl[c]	120	60	45	$C_4H_9AsCl_2$			34.95	34.85
n-Pentyl[d]	115	25	40	$C_5H_{11}AsCl_2$	34.53	34.50	32.68	32.59
3-Methylbutyl[d]	72.5–74	4	38	$C_5H_{11}AsCl_2$	34.53	34.57		
2-Methylbutyl[e]	101–105	21	12	$C_5H_{11}AsCl_2$			32.68	32.29
n-Hexyl[d]	125–127	28	10	$C_6H_{13}AsCl_2$			30.70	30.59
n-Heptyl[f]	131–131.5	14	6	$C_7H_{15}AsCl_2$	30.57	30.39	28.93	28.41
Allyl	42	4.5	52	$C_3H_5AsCl_2$	40.08	39.48	37.95	38.00
δ-4-Pentenyl	102.5–105.5	3.5	32	$C_5H_9AsCl_2$	34.85	34.81		
β-Methoxyethyl	94–95	6	40	$C_3H_7AsCl_2O$			34.61	34.61
β-Ethoxyethyl	95–97	10	20	$C_4H_9AsCl_2O$	34.22	34.17	32.39	32.37
β-Chloroethyl	99.8–100.0	18	60	$C_2H_4AsCl_3$	35.70	35.60		
γ-Chloromethoxypropyl	136–137	5	36	$C_4H_8AsCl_3O$	29.56	29.93		
bis-(β-Ethoxy)-ethyl ether	185–190	0.1	5	$C_8H_{16}AsCl_4O_3$	33.16	33.16	31.39	31.36
bis-(β-Ethyl)-sulfone	79.5–80.5	G.	55	$C_4H_8As_2Cl_4O_2S$	36.38	36.22	34.44	34.01
β-Chloroethyl[h]	99.8–100.0	18	40	$C_2H_4AsCl_3$	35.78	35.70		
RR'AsCl								
Chlorodiethylarsine	156	736	60	$C_4H_{10}AsCl$			21.04	20.61
Chloroethyl-N-propylarsine	176	729	21	$C_5H_{12}AsCl$			19.43	19.58
n-Butylchloroethylarsine	89–92	19	35	$C_6H_{14}AsCl$			18.04	18.09

[a] All compounds colorless. [b] Over-all yield from alkyl intermediate. [c] Prepared by similar reactions but not bromide free. Ref. 6. [d] Previously prepared by indirect methods. [e] d^{25}_{25} 1.4302. [f] d^{25}_{25} 1.296. [g] M. p. of solid recrystallized from chloroform. [h] Previously reported b. p.: 92–93° (32 mm.), ref. 7; 90–93° (30 mm.); Renshaw and Ware, THIS JOURNAL, **47**, 2989 (1925); 89–90° (12 mm.), Nekrassov and Nekrassov, *Ber.*, **61**, 1816 (1928); 90.8° (12.5 mm.), 87° (10 mm.), 80.6 (8 mm.), Scherlin and Epstein, *ibid.*, **61**, 1821 (1928); 90° (12 mm.), Edee, THIS JOURNAL, **50**, 1936 (1928). Nekrassov and Nekrassov also reported a supposed secondary arsine, b. p. 96–99° (15 mm.) which was probably the primary product freed of arsenic trichloride. Product stable for two years in sealed ampoules protected from light.

TABLE III

MISCELLANEOUS ARSINES

Compound	Color	Yield, %	Boiling point °C.	Mm.	Molecular formula	As analyses, % Calcd.	As analyses, % Found
Ethyldibromoarsine[a]	Colorless	44	87–88	16	$C_2H_5AsBr_2$	28.40	28.24
Dibromo-*n*-amylarsine	Lt. yellow	35	125.5–127	18	$C_5H_{11}AsBr_2$	24.05	24.01
n-Propyldicyanoarsine	Colorless	72	82–86[b]		$C_5H_7AsN_2$	44.06	44.56
n-Butyldicyanoarsine	Colorless	68	61–63[b]		$C_6H_9AsN_2$	40.70	40.16
n-Amyldicyanoarsine	Colorless	40	69–69.5[b]		$C_7H_{11}AsN_2$	37.81	37.52
n-Hexyldicyanoarsine	Colorless	57	67.8–69.8[b]		$C_8H_{13}AsN_2$	35.32	35.47
Ethyldi-(*n*-propoxy)-arsine	Colorless	71	86–90	18	$C_8H_{19}AsO_2$	33.74	33.71
n-Propyldiacetoxyarsine	Colorless	51	120–123	13	$C_7H_{13}AsO_4$	31.73	31.52
n-Amylarsine	Colorless	30	125–127	730	$C_5H_{13}As$	50.65	50.06
As,N-Diethylarsenimide	Lt. yellow	37	165–175	3.5	$C_4H_{10}AsN$	50.95	50.61
Dimethylcyanoarsine[c]	Colorless	80	159–160	730	C_3H_5AsN	57.19	57.28
Diethylcyanoarsine[d]	Colorless	81	80–81	13	$C_5H_{10}AsN$	47.10	46.81
Ethyl-*n*-propylcyanoarsine[e]	Colorless	72	110–113	27	$C_6H_{12}AsN$	43.28	43.14
n-Butylethylcyanoarsine	Colorless	65	112–112.5	65	$C_7H_{14}AsN$	40.04	40.00
Ethyl-*n*-propylthiocyanoarsine	Colorless	52	102–110	0.65	$C_6H_{12}AsNS$	36.52	36.62

[a] Previously obtained from ethylarsine and bromine, Dehn and Williams, *Am. Chem. J.*, **40**, 103 (1908). [b] Melting point. [c] Bunsen, *Ann.*, **37**, 31 (1841), obtained this product from cacodyl oxide and hydrogen cyanide. [d] Obtained as one product of pyrolysis of triethylarsine cyanobromide, Steinkopf and Muller, *Ber.*, **54**, 841 (1921). [e] Thought to be a component of the mixture obtained by pyrolysis of ethyldipropylarsine cyanobromide, Steinkopf and Mieg, *Ber.*, **53**, 1015 (1920).

column, 0.75 in. diam., packed with 0.25 in. Raschig rings. The reflux ratio was 15 to 1.

(4) **Cyanoarsines.**—Dry benzene (750 ml.) and silver cyanide (2 moles) reacted with the alkyldichloroarsine (1 mole) or dialkylchloroarsine (2 moles) by refluxing with stirring for forty-eight hours in equipment protected from moisture. The insoluble silver chloride was filtered off, the filtrate treated with charcoal, concentrated and the product precipitated with petroleum ether. Mixtures of benzene and petroleum ether were used for recrystallization.

(5) **Ethyldipropoxyarsine.**—Sodium (25 g.) was dissolved in dry propanol (500 ml.), ethyldichloroarsine (95 g.) was added over a period of two hours and the reaction stirred an additional two hours. After removing the salt formed, the excess propanol was distilled and the product purified by fractionation.

(6) ***n*-Propyldiacetoxyarsine.**—Silver acetate (0.75 mole), benzene (400 ml.) and propyldichloroarsine (0.3 mole) were stirred under reflux for six hours. The silver chloride formed was removed and the filtrate distilled to obtain the product.

(7) **As,N-Diethylarsenimide.**—The ethylamine (2.2 moles) was cooled to −15° and added with stirring to chloroform at −5°. Ethyldichloroarsine (0.7 mole) was added over a two-hour period with cooling and the mixture stirred overnight. After filtering, the chloroform was distilled off *in vacuo* and the viscous residue fractionated.

(8) **Dimethylcyanoarsine.**—Sodium cyanide (10.5 g.) in water (21 ml.) was stirred under nitrogen and dimethylchloroarsine (25 g.) added dropwise. After an hour, the solution was extracted with benzene and the benzene extracts washed with water, dried over calcium chloride and distilled.

(9) **γ-Chloromethoxypropyldichloroarsine.**—Di-(γ-dichloroarsinopropoxy)(γ-hydroxypropyl)-arsine, $(Cl_2AsCH_2CH_2CH_2O)_2AsCH_2CH_2CH_2OH$, (210 g.)[7] was added to 40% formaldehyde solution (174 g.) and saturated with hydrogen chloride. The insoluble oil formed was extracted with chloroform and the extract dried over calcium chloride and distilled.

(10) ***n*-Pentylarsine.**—Zinc amalgam prepared from zinc dust (275 g.) and mercuric chloride (55 g.) and *n*-pentylarsonic acid (120 g.) were placed in a 3-liter flask protected from oxygen, water (10 ml.) and ether (500 ml.) added. Concentrated hydrochloric acid (1 liter) was added over seven hours and the mixture allowed to stand twenty-four hours. The ether layer was removed, dried over calcium chloride and distilled in a stream of carbon dioxide. *n*-Pentylarsine was very sensitive to oxygen.

(7) Gough and King, *J. Chem. Soc.*, 2426 (1928).

(11) **Ethyl-*n*-propylthiocyanoarsine.**—A solution of ethyl-*n*-propylchloroarsine (50 g.) in acetone (100 ml.) was added dropwise to potassium thiocyanate (50 g.) in acetone (100 ml.) with stirring. After stirring overnight at room temperature, the mixture was filtered, the filtrate concentrated *in vacuo* and the residue treated with benzene. The precipitated salt was removed, the filtrate concentrated, treated with more benzene and the process repeated until all solids were removed. The product was then distilled.

Summary

1. Alkyldichloroarsines and dialkylchloroarsines have been prepared by reducing the corresponding pentavalent compounds in concentrated hydrochloric acid with sulfur dioxide in the presence of potassium iodide as a catalyst. Sixteen alkyldichloroarsines and three dialkylchloroarsines were prepared in this manner.

2. Two alkyldibromoarsines were synthesized by an analogous reaction.

3. Δ-4-Pentenyl-, β-methoxyethyl-, β-ethoxyethyl-, 2-methylallyl-, β-phenoxyethylarsonic acids, bis-(β-arsono)-ethyl ether, bis-(β-arsono)-ethyl sulfone, bis-(β-phenylarsinico)-ethyl sulfide and bis-(β-phenylarsinico)-ethyl sulfone are reported for the first time.

4. Allyl-, Δ-4-pentenyl-, *n*-heptyl-, β-methoxyethyl-, β-ethoxyethyl- and γ-chloromethoxypropyldichloroarsine, bis-β-(β-dichloroarsinoethoxy)-ethyl ether and bis-(β-dichloroarsino)-ethyl sulfone have been prepared for the first time.

5. Cyano, thiocyano, propoxy and imide derivatives of alkyl- and dialkylarsines are described.

6. The Meyer reaction has been found to be generally applicable to the synthesis of primary alkylarsonic acids. Unsaturation β to the reactive halogen aids the reaction.

7. It has been shown that the stability of substituted alkyldichloroarsines is not affected by β-alkoxy groups or unsaturation more than three carbon atoms from arsenic; β-unsaturation and β-halogen caused instability.

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Nitroaryldichloroarsines and Related Compounds[1]

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Isacescu[3] has reported that 3-nitrophenyldichloroarsine has sternutatory properties. In order to investigate the toxicity of this and other nitroaryldichloroarsines, a series of nitrobenzenearsonic acids were reduced in concentrated hydrochloric acid with sulfur dioxide, using potassium iodide as a catalyst. A few of the resulting products have been reported previously but, for the most part, they were prepared by more cumbersome methods.

Most of the arsonic acids were available from previous studies but several new acids were prepared by standard procedures. bis-(3-Nitrophenyl)-arsinic acid was also converted to the chloroarsine and this compound in turn to the cyano and thiocyano derivatives. In the course of some experiments with the related 2-aminophenyldichloroarsine, the diazonium complex analogous to that reported for the corresponding

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(2) Official investigator.

(3) Isacescu, *Bull. Soc. Chem. Roumania*, **18A**, 131 (1936).