ARSINIC ACIDS

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INTRODUCTION

Although aromatic arsinic acids have been investigated extensively[1], the dialkylarsinic acids have received relatively little attention.

Bunsen[2] prepared dimethylarsinic acid by heating potassium acetate with arsenic trioxide. The cacodyl oxide, $(CH_3)_2AsOAs(CH_3)_2$, formed from this reaction oxidizes in air to cacodylic acid. Baeyer[3] converted cacodyl oxide to cacodylic trichloride, $(CH_3)_2AsCl_3$, and obtained dimethylarsinic acid by hydrolysis of this compound. Alkylarsonic acids, obtained by means of the Meyer reaction[4], can be reduced to the arsenosoalkanes. Dimethyl-, diethyl-, methylethyl-, and methyl-*n*-propylarsinic acids were prepared[5,6] by the reaction of arsenosoalkanes with alkyl halides. The conversion of alkylarsonic acids to alkyldichloroarsines by SO_2 and HCl, and their reaction with alkyl halides yielded[7] diethyl-, di-*n*-propyl-, *n*-propyl-*n*-butyl-, di-*n*-butyl-, diisopentyl-[8], *n*-butyl-*n*-pentyl-[9], *n*-butyl-*n*-hexyl-[10], and *n*-butyl-*n*-heptylarsinic acids[9]. Diethyl-[11,13], methylethyl-[12], ethyl-*n*-propyl-[12], and methyl-*n*-propylarsinic acids[12] have also been prepared by the oxidation of dialkylhaloarsines. Small amounts of arsinic acids have also been shown to form from the oxidation of trialkylarsines by atmospheric oxygen or hydrogen peroxide. Diethyl-[14,15], di-*n*-propyl-[15], di-*n*-butyl-[15], dicyclohexyl-[15], and ethyl-*n*-butylarsinic[14] acids were isolated from such reaction mixtures.

The reaction of isoamyl chloride with $AsCl_3$ in the presence of sodium metal followed by treatment of the resulting diisopentylchloroarsine with bromine yielded diisopentylarsinic acid[16]. Oxidation of Et_2AsOR and $MeBuAsOR$ with SeO_2 yielded diethyl- and methyl-*n*-butylarsinic acids[17]. Finally, the reaction of arsenic trioxide with iso-Bu_3Al and oxidation of the resulting oxybis(diisobutylarsine) has yielded diisobutylarsinic acid[18].

We have had need for water insoluble long chain dialkylarsinic acids in our metal ion extraction program, but none of the above mentioned methods was found suitable for the synthesis of these compounds. It has been shown[19] that the Meyer reaction[4] gives low yields and requires extremely long reaction times when higher alkyl halides are employed.

This paper describes the use of (diethylamino)dichloroarsine[20], Cl_2AsNEt_2, as an intermediate in the preparation of the C_5-C_{20} arsinic acids in yields from 50–80 %. This reagent, which contains only two chlorine atoms, reacts with the Grignard reagent with very small amounts of impurities being formed. The product of the Grignard reaction is hydrolyzed with HCl. The hydrolysis product, which enters the ether layer, following oxidation yields the dialkylarsinic acid.

EXPERIMENTAL

Reagents

The C_5-C_8, C_{10}-C_{12} and C_{15}-C_{17} *n*-alkyl bromides were Eastman Organic Chemicals; the bromides C_{11} and C_{14} and the chloride C_{18}, Matheson, Coleman and Bell Chemicals; C_{13} was supplied by Columbia Organic Chemicals. 1-Bromoeicosane and 1-nonadecyl alcohol were purchased from K&K Laboratories. 1-Nonadecyl bromide was prepared from 1-nonadecanol[21]. Technical grade arsenic trichloride was purchased from Baker Chemical Co., and was distilled prior to use. Diethylamine was purchased from Matheson, dried over sodium hydroxide and redistilled. Diethyl ether anhydrous, a "Baker Analyzed Reagent", was refluxed over sodium wire after addition of benzophenone until a dark blue color indicated complete dryness[22]. Prior to use, the dry ether was distilled into the reaction vessel under an atmosphere of nitrogen. Di-*n*-butyl ether, an Eastman Organic Chemical, practical grade, was refluxed over metallic sodium and redistilled twice. All other solvents were used without purification.

(Diethylamino)dichloroarsine

(Diethylamino)dichloroarsine was prepared according to Kamai and Khistova[20]. The final distillation of the product was carried out at reduced pressure. The observed b.p. was 64° at 2 mm. The compound was collected in a calibrated, pressure equalizing dropping funnel. Thus, the yield (85–90 %) could be easily determined, and the amounts needed in the various reactions could be dispensed in the absence of any air. This compound is extremely sensitive to air and moisture.

Di-n-octylarsinic acid

n-Octylmagnesium bromide was prepared by the addition of 386 g (2 moles) of *n*-octyl bromide dissolved in 1 liter of diethyl ether to 48.6 g Mg turnings under nitrogen. The Grignard solution was stored in a brown bottle and its concentration determined by acid titration[23].

Into a nitrogen-flushed 1-liter three-necked round-bottom flask, equipped with a reflux condenser, mechanical stirrer, and calibrated dropping funnel was placed 250 ml of dry diethyl ether. By means of a calibrated funnel, 120 ml of the solution containing the *n*-octylmagnesium bromide (0.15 moles; 10 % excess) were measured into the flask. While maintaining a positive nitrogen pressure inside the flask this funnel was exchanged for one containing the (diethylamino)dichloroarsine. While stirring, and cooling with ice and water, 10 ml of the arsine (0.0675 moles) were dropped slowly into the Grignard solution. After all the arsine was added the cooling bath was removed and the reaction mixture was brought to room temperature.

The mixture was then refluxed for an additional 2 h. Hydrolysis was carried out at ice-water temperature by the addition of 10 ml of concentrated hydrochloric acid diluted with 300 ml water. After refluxing for an additional hour, the layers were separated, and 40 ml of 30 % hydrogen peroxide were dropped into the ether solution at ice-bath temperature. The oxidation reaction was quite exothermic and precipitation of dioctylarsinic acid as a white crystalline solid was noted. After completion of the hydrogen peroxide addition the mixture was refluxed for several hours. The solution was cooled and the acid which separated was removed by filtration through a glass fritted funnel. The acid was washed with acetone, and dried. After two re-

crystallizations from an ethanol/water solution the acid was obtained in flakes which, after drying at 60°, melted at 129°. The yield of recrystallized product was 18.2 g (80 % of theory).

Di-n-eicosylarsinic acid

Magnesium turnings (1.35 g, 0.055 mole) were placed into a nitrogen-flushed 500-ml three-necked flask equipped with stirrer, reflux condenser, and calibrated pressure equalizing dropping funnel. A 20-g quantity of bromoeicosane was dissolved in 100 ml of sodium-dried, freshly distilled diethyl ether and this was added at once to the turnings. A small crystal of iodine was put into the flask, the ether was refluxed, and the iodine color disappeared. Heating was continued until most of the magnesium was consumed. This required an entire day. The eicosylmagnesium bromide solution was transferred through the pressure equalizing arm back into the dropping funnel by rotation of the reaction vessel. The total volume of the solution was determined and 5 ml were withdrawn in order to determine its concentration[23]. The remaining solution, 110 ml (0.042 moles), was allowed to flow back into the flask. Then 2.8 ml of (diethyl-amino)dichloroarsine (0.019 moles) were added dropwise. Hydrolysis was accomplished by the addition of 5 ml concentrated hydrochloric acid diluted with 150 ml water. Oxidation was carried out with 30 ml 30 % hydrogen peroxide. The arsinic acid separated as a very fine crystalline solid. After the addition of 200 ml of n-butanol, which functions as the recrystallizing solvent, the mixture was refluxed for 12 h and cooled. The precipitate was filtered, washed with acetone, recrystallized from n-butanol and dried at 60°. The acid had a melting point of 119–20°. The yield of recrystallized product was 7.5 g (60 % of theory).

Other arsinic acids

The C_{15}, C_{16}, C_{17}, C_{18}, and C_{19} acids were prepared according to the method described for the C_{20} compound. The procedure described for the preparation of dioctylarsinic acid was the one used for the preparation of the C_5 to C_{14} acids. In the case of the C_5, C_6, and C_7 compounds, cooling of the reaction mixture prior to isolation of the acids is advisable. The solvents used for recrystallization are shown in Table 1.

Preparation of di-n-octylarsinic acid from arsenic trichloride

n-Octylmagnesium bromide was added to arsenic trichloride in a mole ratio of 2:1 and the ether solution was oxidized with hydrogen peroxide. The solution was treated in the conventional manner, and a yield of 9 % of theory of di-n-octylarsinic acid was obtained. This product was identical in every respect with that prepared from Cl_2AsNEt_2.

Neutralization equivalent

A Corning pH meter model 12 was used to obtain titration curves. The C_5, C_6, C_7, and C_8 acids were dissolved in 95 % ethanol; the C_9–C_{15} acids were dissolved in 95 % ethanol containing sufficient chloroform to effect dissolution. The C_{16}–C_{20} acids were titrated at 70° in isopropanol containing a small amount of chloroform.

RESULTS AND DISCUSSION

The sixteen dialkylarsinic acids prepared are listed in Table 1 along with pertinent data. The series of di-n-alkylarsinic acids is now complete from C_1 through
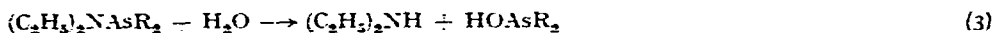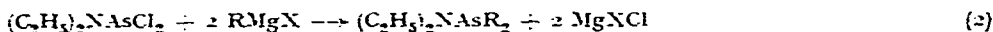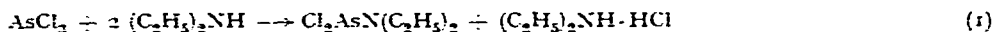
TABLE 1

DIALKYLARSINIC ACIDS, R₂As(O)OH

n-R	Analyses calcd. (found)			Recryst. solvent(s)	M.p.[b]	Neutral. equiv. calcd. (found)	Yield[d] (%)
	C	H	As				
C_3H_{11}	48.00 (48.22)	9.26 (9.29)	29.94 (29.76)	acetone, water, n-C₇H₁₆, EtOH	132°	250.2 (250.2)	50
C_6H_{13}	51.83 (52.01)	9.77 (9.84)	26.90 (27.06)	acetone, benzene, n-C₇H₁₆, n-Bu₂O[c]	131–2°	278.5 (279.4)	50
C_7H_{15}	54.89 (55.01)	10.20 (10.38)	24.46 (24.73)	acetone/EtOH, n-C₇H₁₆, n-Bu₂O	126–7°	306.3 (305.2)	69
C_8H_{17}	57.47 (57.36)	10.55 (10.39)	22.40 (22.48)	EtOH, n-Bu₂O, benzene	129°	334.4 (336.0)	81
C_9H_{19}	59.65 (59.41)	10.84 (10.94)	20.67 (20.91)	EtOH, n-Bu₂O, n-C₇H₁₆	126°	362.4 (362.8)	60
$C_{10}H_{21}$	61.52 (61.65)	11.10 (11.04)	19.18 (19.44)	EtOH, n-Bu₂O	127°	390.5 (390.4)	65
$C_{11}H_{23}$	63.13 (63.17)	11.32 (11.21)	17.90 (17.60)	EtOH, n-Bu₂O, n-C₇H₁₆	123–4°	418.5 (416.0)	70
$C_{12}H_{25}$	64.55 (64.58)	11.51 (11.57)	16.77 (16.91)	EtOH, n-Bu₂O, benzene	125°	446.6 (442.1)	70
$C_{13}H_{27}$	65.79 (65.09)	11.68 (11.50)	15.78 (15.63)	EtOH, n-Bu₂O, n-C₇H₁₆	123–4°	474.6 (478.0)	60
$C_{14}H_{29}$	66.90 (66.62)	11.83 (11.70)	14.90 (14.78)	EtOH, n-Bu₂O, n-heptane	124°	502.7 (507.0)	70
$C_{15}H_{31}$	67.89 (67.78)	11.96 (11.87)	14.11 (14.20)	EtOH, n-Bu₂O, n-C₇H₁₆	123–4°	530.7 (530.3)	60
$C_{16}H_{33}$	68.78 (68.90)	12.08 (11.89)	13.41 (13.15)	n-C₇H₁₆, n-Bu₂O, iso-PrOH	122–3°	558.8 (550.0)	60
$C_{17}H_{35}$	69.58 (69.64)	12.19 (12.29)	12.79 (12.82)	n-C₇H₁₆, n-BuOH	120–1°	580.9 (590.0)	69
$C_{18}H_{37}$	70.32 (70.04)	12.29 (12.39)	12.18 (12.37)	EtOH, n-C₇H₁₆, n-BuOH	121–2°	614.9 (620.4)	72
$C_{19}H_{39}$	70.98 (70.88)	12.38 (12.38)	11.65 (11.69)	n-C₇H₁₆, n-BuOH	120°	643.0 (646.0)	61
$C_{20}H_{41}$	71.60 (71.41)	12.47 (12.48)	11.16 (10.96)	n-C₇H₁₆, n-BuOH, EtOH iso-PrOH	119–20°	671.0 (664.0)	60

[a] Elemental analyses have been performed by Galbraith Laboratories, Knoxville, Tennessee. [b] Melting points are uncorrected. [c] 100 ml water was added to the n-Bu₂O to keep the temperature at ~ 100°. [d] Yield based upon final, recrystallized product.

C_{20}. The first four acids (C_1–C_4) can be synthesized according to Quick and Adams[7], while the others are easily obtained by the method described in this paper in yields of at least 50%.

The reaction sequence is represented as follows:

$$AsCl_3 + 2 (C_2H_5)_2NH \longrightarrow Cl_2AsN(C_2H_5)_2 + (C_2H_5)_2NH \cdot HCl \tag{1}$$

$$(C_2H_5)_2NAsCl_2 + 2 RMgX \longrightarrow (C_2H_5)_2NAsR_2 + 2 MgXCl \tag{2}$$

$$(C_2H_5)_2NAsR_2 + H_2O \longrightarrow (C_2H_5)_2NH + HOAsR_2 \tag{3}$$

$$R_2AsOH + H_2O_2 \longrightarrow R_2As(O)OH + H_2O \tag{4}$$

The (diethylamino)dichloroarsine is conveniently distilled and collected in a calibrated dropping funnel for future use. While stored therein it must be sealed from the at-

mosphere. During three months' storage no major decomposition was noted, but the colorless liquid became yellow or light brown. Reactions (2), (3), and (4) are conveniently carried out in the same flask. The water layer, after hydrolysis, is withdrawn under reduced pressure.

All of the di-n-alkylarsinic acids are white crystalline solids*. At room temperature all are soluble in chloroform.

Refluxing of the reaction mixture for several hours after oxidation improves the crystallinity and purity of the products and facilitates their filtration. Dialkylarsinic acids with alkyl groups $C_{15}H_{31}$ and higher are precipitated as very fine crystalline solids and sometimes form emulsions. The latter can be broken up by the addition of di-n-butyl ether or n-butanol and additional refluxing. The lower acids (C_5–C_7) are somewhat soluble in diethyl ether and their yields are improved by cooling the reaction mixtures prior to filtration. The intermediates, (diethylamino)dialkylarsines and their hydrolysis products were not isolated.

Tzschach and Lange[25] showed that in the presence of excess Grignard reagent, the arsenic–nitrogen bond is cleaved according to the equation:

$$(C_2H_5)_2N-As(C_2H_5)_2 + C_2H_5MgBr \rightarrow (C_2H_5)_3As + BrMgN(C_2H_5)_2.$$

Because of this, the Grignard solution should be added slowly to the arsine with vigorous stirring. It is very difficult to prepare ether sufficiently dry to avoid some hydrolysis of the aminoarsinedichloride. For convenience, (dialkylamino)dichloroarsine was dropped into the Grignard solution. Thus, there was always present an excess of Grignard reagent until two thirds of the calculated amount of the arsine was added. If the reaction had proceeded in the manner described by Tzschach and Lange, the main product of the Grignard reaction should have been trialkylarsine. The latter would then have been converted to the arsine oxide upon oxidation with hydrogen peroxide.

If the splitting of the arsenic–nitrogen bond would have taken place in the syntheses reported herein, it would have been impossible to obtain these acids in yields of 70 %. Since the oxidation of trialkylarsines has been shown to yield the arsinic acids in yields of only 2–5 %[15], it is unlikely that the trialkylarsines were formed and then oxidized to the arsinic acids by cleavage of one of the alkyl groups. The relatively low yields in the case of the C_5 and C_6 arsinic acids (see Table 1) and the failure of the present method to give the C_2 and C_4 acids suggests that the arsenic–nitrogen bond in (diethylamino)dichloroarsine is cleaved by an excess of Grignard reagent. This cleavage takes place almost completely when the alkylmagnesium halide is C_4 or lower; to a limited extent with C_5 and C_6 alkylmagnesium halides and not at all with larger alkyl groups. The reason for this behavior might be due to steric factors, viz., that the long chain alkyl groups prevent excess Grignard reagent from approaching the arsenic–nitrogen linkage. Further experiments are being carried out and more data will be accumulated in order to better understand the behavior of the arsenic–nitrogen bond towards Grignard reagents.

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* The preparation of Grignard solutions of C_{15} and higher halides[24] must be done with extremely dry ether and great care must be taken to avoid formation of hydrocarbons which makes purification of the higher dialkylarsinic acids difficult.

In Fig. 1 the melting points of the di-*n*-alkylarsinic acids, $R_2As(O)OH$, are plotted against the number of the carbon atoms in the acids. With the exception of the dimethyl derivative, the melting points of these acids exhibit alternation, *i.e.*
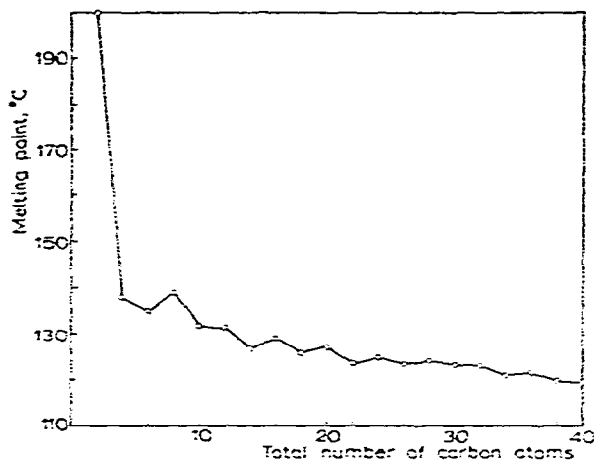

Fig. 1. Melting points of dialkylarsinic acids as a function of the total number of carbon atoms in the molecule. Obtained from ref. 5 $[(CH_3)_2AsOOH]$, refs. 7 and 15 $[(C_2H_5)_2AsOOH, (C_3H_7)_2AsOOH$ and $(C_4H_9)_2AsOOH]$; all others were observed during the course of this study.

the odd members of the series melt at a lower temperature than the two neighboring even members. The alternation decreases rapidly with increasing length of the alkyl groups. The compounds C_6–C_{20} all melt in the rather narrow temperature range of 119–130°. It appears that the series of di-*n*-alkylarsinic acids tends to reach the same convergence temperature of 112–115° as has been calculated for the carboxylic acids by King and Garner[26]. This alternation in the melting points may be attributable to the same reasons that have been suggested for the carboxylic acids[27].

The marked drop in melting point from 200° to 138° in going from dimethyl-arsinic acid to diethylarsinic is quite striking. The high melting temperature of the $Me_2As(O)OH$ is probably due to the existence of unusually strong hydrogen bonds in this molecule which are not hindered by the small methyl group. In the case of the diethyl and higher acids, the alkyl groups may be too bulky to allow for the formation of a hydrogen-bonded system of equal strength.

In Fig. 2 is shown the differential thermal analysis curve obtained for the C_{20} arsinic acid. The small endothermic peak observed at a point just preceding the large peak at the melting point was noted also for the C_5 and C_7 acids, the only ones thus far studied using this tool. This peak might be due to a crystalline phase transition, which occurs prior to melting. Similar transitions have been found to be a general property of long chain compounds[28]. The endothermic peak may result also from a thermal dehydration process.

Either cause will bring about a change in the basic hydrogen bonded structure. A complete study of the differential thermal analysis and thermogravimetric behavior of these compounds along with infrared and NMR investigations has been initiated in this laboratory to aid in understanding this behavior.
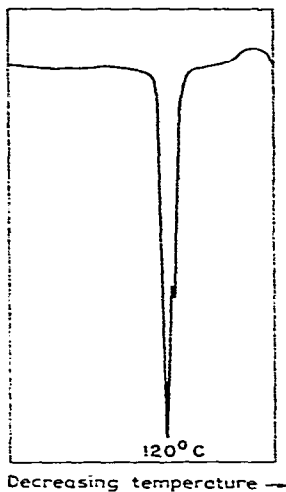
120° C

Decreasing temperature →

Fig. 2. Differential thermal analysis curve of $(C_{20})_2$ arsinic acid.

SUMMARY

The use of (diethylamino)dichloroarsine as a very useful intermediate in the preparation of C_5–C_{20} arsinic acids is described in this paper. This reagent, which contains only two chlorine atoms, reacts with the Grignard reagent with very small amounts of impurities being formed. The melting points of the arsinic acids exhibit alternation of the type observed in the fatty acids and the melting point appears to reach a convergence temperature. The differential thermal analysis curve exhibits an endothermic peak just prior to melting which is probably due to a crystalline phase transition.

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