5. *Hydrolyses and Derivatives of Some Vesicant Arsenicals.*

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The hydrolyses of pure 2-chlorovinyldichloroarsine (Lewisite-I) and of phenyldichloroarsine have been studied by using the partitions of their solutions between benzene and water. Several dialkyloxy-derivatives of Lewisite-I, and some analogous dithiols, have been made, and it has been found that dithiocarbamates are particularly useful for characterising the arsenical vesicants. Lewisite-I gives a characteristic solid with dioxan, and arsenic trichloride with thioxan.

Hydrolysis of β-Chlorovinyldichloroarsine.—The hydrolysis of Lewisite-I by water involves the following equilibria:

$$\mathrm{ClCH{:}CH{\cdot}AsCl_2} + 2\mathrm{H_2O} \overset{\text{(fast)}}{\rightleftharpoons} \mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2} + 2\mathrm{HCl}$$

$$\underset{\text{(I.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2}} \underset{\text{(slow)}}{\rightleftharpoons} \mathrm{H_2O} + \underset{\text{(II.)}}{\mathrm{Cl{\cdot}CH{:}CH{\cdot}AsO}} \underset{\text{(slow)}}{\rightleftharpoons} \underset{\text{(III.)}}{\mathrm{(Cl{\cdot}CH{:}CH{\cdot}AsO)_n}}$$

The only substance which can be isolated is polymerised 2-chlorovinylarsinoxide (III), a white insoluble powder of indefinite m. p. Measurements of the equilibria, however, indicate that both the hydroxide (I) and the unpolymerised oxide (II) must be capable of existence in solution in water and benzene respectively.

On treatment with water, Lewisite-I immediately gives a strongly acid solution and a sticky gum, consisting of unchanged Lewisite and (III). If however Lewisite-I is mixed with benzene and then treated with water two clear liquid layers are obtained which, when shaken, rapidly attain an equilibrium which is independent of the initial concentration of the Lewisite-I in the benzene layer. Both the layers can be analysed for (i) chlorine content, (ii) acidity, and (iii) tervalent arsenic by titration with silver nitrate, alkali, and iodine, respectively, and in this way the equilibria attained in the hydrolysis can be found. Figs. 1 and 2 show the results obtained.

The equilibrium attained on shaking a benzene solution of Lewisite-I with aqueous hydrochloric acid corresponds exactly to that reached on shaking a corresponding amount of Lewisite-I with a proportionately smaller volume of water; that is, the percentage of Lewisite-I which remains as such in the benzene layer depends only on the acidity, the bulk of the aqueous layer being immaterial.

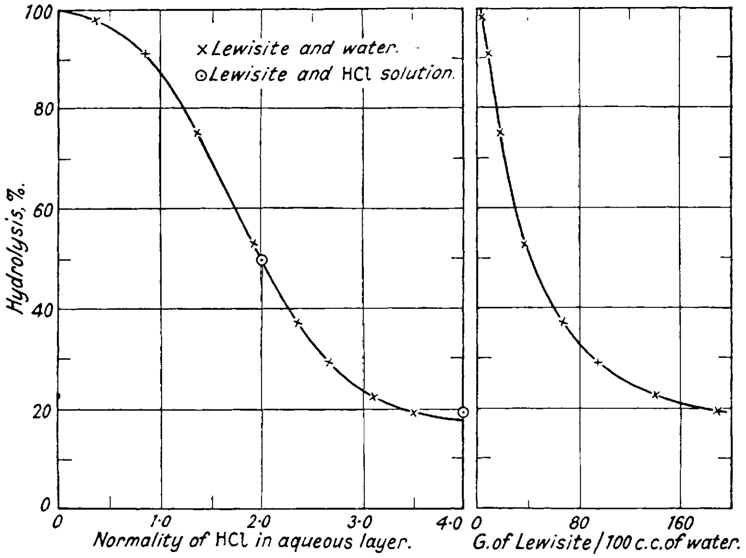

FIG. 1. FIG. 2.

Hydrolysis of Lewisite-I in benzene at 17° *in* ½ *hour.*

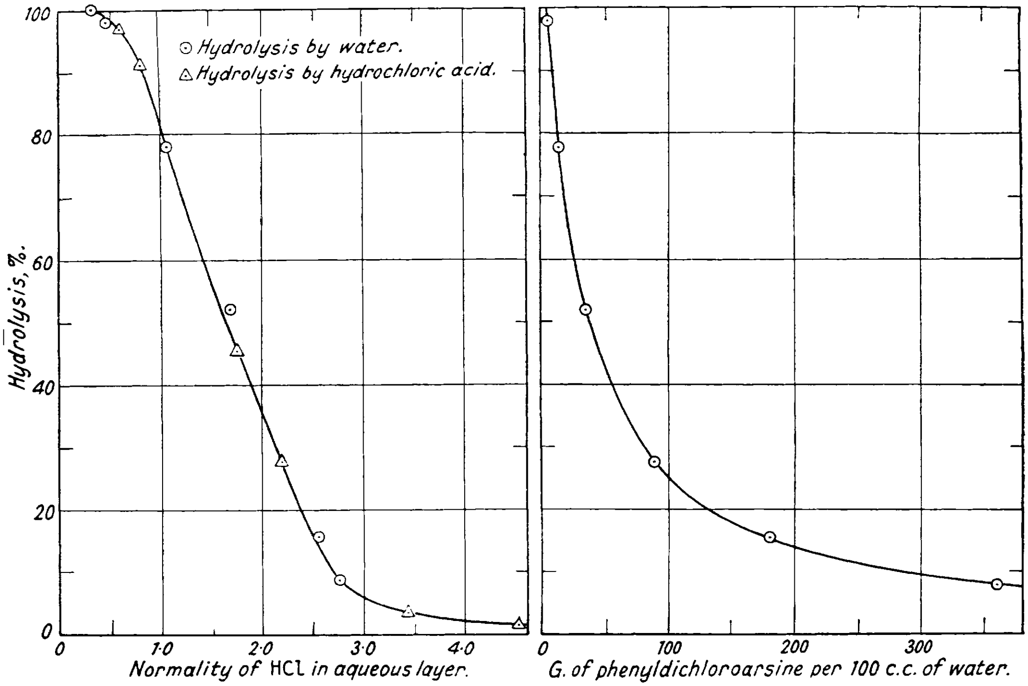

FIG. 3. FIG. 4.

Hydrolysis of phenyldichloroarsine in benzene at 15°.

The hydrolysis of phenyldichloroarsine has been studied in a similar way, giving results which are shown in Figs. 3 and 4.

The evidence for the separate existence of the dihydroxide (I) is as follows. A 4% solution of Lewisite-I oxide (possibly II) in benzene can be obtained by boiling the dry polymerised oxide (III) for a long time with this solvent. The solution is vesicant, and on storage deposits colourless crystals which soon change to the amorphous white polymer. When this benzene solution is shaken with water the arsenic content of the benzene drops *slowly* during some hours. Only a 1% solution of lewisite oxide in water can be obtained by leaving the constituents in contact. When this solution is shaken with benzene the arsenic content of the benzene slowly rises during some hours. The aqueous solution has a pH of 6·8, but by allowing Lewisite-I to remain in contact with water containing chalk a 2·8% solution can be obtained; and a solution of still higher normality can be obtained in aqueous sodium hydrogen carbonate of pH about 8. Thus the dihydroxide of Lewisite-I is, like that of phenyldichloroarsine, a very weak acid giving soluble salts.

Lewisite-I however is decomposed by *cold* caustic alkali as follows :

$$\mathrm{Cl{\cdot}CH{:}CH{\cdot}As(OH)_2 + (OH)^- \longrightarrow Cl^- + C_2H_2 + As(OH)_3}$$

In the cold (16°), only alkaline solutions of pH 10·5 or more will bring about this decomposition, but at 50° solutions of pH 9 or more are effective. Prolonged boiling with water alone brings about some decomposition of Lewisite-I oxide.

It is significant that the curves shown in Figs. 1—4 show no irregularities indicative of the existence of hydroxy-chlorides R·AsCl·OH.

Alkyl-oxy- and -thio-derivatives of Lewisite-I and its Analogues.—The vesicant character of arsenicals such as Lewisite-I and phenyldichloroarsine is not a property of the $AsCl_2$ group, since carefully prepared solutions of the corresponding oxides or dihydroxides are equally vesicant. In order to enhance the lipoid solubility of 2-chlorovinyldihydroxyarsine and its analogues, a number of derivatives of the general type $R{\cdot}As(OR')_2$ has been made by the action of sodium alkoxides on the arsenical vesicants. The products are all volatile, vesicant, liquids which are hydrolysed *irreversibly* on contact with water.

A number of analogous thioethers $R{\cdot}As(SR')_2$ has also been made. These are very slightly soluble in water and in general are hydrolysed *reversibly*, giving toxic, and sometimes vesicant, solutions, though the equilibrium $R{\cdot}As(SR')_2 + 2H_2O \rightleftharpoons R{\cdot}As(OH)_2 + 2R'SH$ generally favours thioether formation (cf. Cohen, King, and Strangeways, *J.*, **1931**, 3043; Barber, *J.*, 1932, 1365).

Aqueous and alcoholic solutions of sodium diethyldithiocarbamate, and its analogues, react readily with Lewisite-I to give crystalline solids of sharp melting-point which are very useful for the characterisation of the arsenical war gases. These dithiocarbamates are much more stable than are the simple thioethers of the alkyldichloroarsines, but only in cyclic structures, such as that given by " B.A.L." (Peters, Stocken, and Thompson, *Nature*, 1945, **136**, 616) does the degree of hydrolysis become negligible. Alkali hydrolyses all these compounds rapidly, acetylene being evolved from the Lewisite-I derivatives. Hydrogen peroxide also breaks up the ethers and thioethers in neutral or acid solution, giving free arsonic acids which are much less toxic than the corresponding tervalent substituted arsines.

Compound Formation with Dioxan.—When pure Lewisite-I is mixed with an equimolecular proportion of dioxan, heat is evolved and the whole mass solidifies on cooling to an addition product, m. p. 58—59°. This however dissociates into its constituents both when vaporised and when dissolved in anhydrous solvents such as benzene or chloroform. Di-2-chlorovinylchloroarsine (Lewisite-II) and tri-2-chlorovinylarsine (Lewisite-III) do not give similar products, and hence Lewisite-I may be separated in this way from these associated compounds. Arsenic trichloride also forms crystalline addition compounds with both dioxan and thioxan, but few of the other arsenical war gases, such as ethyldichloroarsine and phenyldichloroarsine, seem to react. The arsenic trichloride–dioxan adduct has been previously described by Doak (*J. Amer. Pharm. Soc.*, 1934, **23**, 541).

EXPERIMENTAL.

Quantitative Hydrolysis of Lewisite-I and Phenyldichloroarsine.—The results shown in Figs. 1—4 were obtained by dissolving a weighed amount of carefully fractionated Lewisite-I or phenyldichloroarsine in 50 ml. of benzene and shaking the solution with a known volume of water for ½ hour at 17°. Figs. 1 and 3 show the relation between the amount of the vesicant, $R{\cdot}AsCl_2$, which remains as such in the benzene layer and the acidity attained by the aqueous layer.

The points indicated as " hydrolysis by hydrochloric acid " show that the degree of hydrolysis depends on the acidity of the aqueous phase and not on its total volume. Figs. 2 and 4, which refer to hydrolysis by water alone, show the extent to which the vesicants are hydrolysed on admixture with limited quantities of water. Again the degree of hydrolysis is independent of the initial concentration in the benzene layer.

Arsine, AsR_3.	B. p.	Formula.	Found. C, %.	Found. H, %.	Found. As, %.	Found. Cl, %.	Found. Equiv.	Required. C, %.	Required. H, %.	Required. As, %.	Required. Cl, %.	Required. Equiv.
Dimethoxy-2-chlorovinyl-	59°/6 mm.	$C_4H_8O_2ClAs$	—	—	—	17·8	98·6	—	—	—	17·9	99·2
Diethoxy-2-chlorovinyl-	71°/3 mm.	$C_6H_{12}O_2ClAs$	—	—	—	15·5	113	—	—	—	15·7	113
Diisopropoxy-2-chlorovinyl-	80°/3 mm., 88°/6 mm.	$C_8H_{16}O_2ClAs$	—	—	—	13·8	127	—	—	—	13·9	127
Diamyl-2-chlorovinyl-	130—138°/3 mm.	$C_{12}H_{24}O_2ClAs$	—	—	—	—	155	—	—	—	—	155
Diisooctyl-2-chlorovinyl-	184—186°/2 mm.	$C_{18}H_{36}O_2ClAs$	—	—	—	—	198	—	—	—	—	197
Diallyl-2-chlorovinyl-	99°/4 mm.	$C_8H_{12}O_2ClAs$	—	—	—	13·9	125	—	—	—	14·2	125
Di-(2-ethoxyethoxy)-2-chlorovinyl-	150°/3 mm.	$C_{10}H_{16}O_4ClAs$	—	—	—	11·4	155	—	—	—	11·3	157
Dimethoxyethyl-	129°/760 mm.	—	—	—	44·1	—	—	—	—	44·4	—	—
Methoxydiphenyl-	138°/2 mm., 150°/7 mm.	$C_{13}H_{13}OAs$	—	—	—	—	130	—	—	—	—	130
Methyldimethoxy-	111°/760 mm.	$C_3H_9O_2As$	—	—	—	—	76	—	—	—	—	76
Methyldiethoxy-	137°/760 mm.	$C_5H_{13}O_2As$	—	—	—	—	89	—	—	—	—	90
Methyldimethylthio-	75—77°/2 mm.	$C_3H_9S_2As$	—	—	40·4	—	—	—	—	40·7	—	—
Methyldiphenylthio-	195—198°/1 mm.	$C_{13}H_{13}S_2As$	—	—	24·5	—	—	—	—	24·5	—	—
Methyldi-p-*tolylthio-*	230°/0·5 mm.	$C_{15}H_{17}S_2As$			(S, 18·4)					(S, 19·0)		
Diphenylthio-2-chlorovinyl-	180—190°/2 mm. (decomp.)	—										
Di-(NN-*diethylthiocarbamylthio*)*-2-chlorovinyl-* [1]	m. p. 87°	$C_{12}H_{22}ClS_4N_2As$	32·6	5·1	17·4	—	—	33·3	5·1	17·3	—	—
Di(*morpholine-4-thiocarboxythio*)*methyl-* * [2]	m. p. 178°	$C_{11}H_{19}O_2S_4N_2As$	32·0	4·65	18·0	—	—	31·9	4·6	18·1	—	—
Di(*morpholine-4-thiocarboxythio*)*ethyl-* * [3]	m. p. 154°	$C_{12}H_{21}O_2S_4N_2As$	33·5	5·0	17·3	—	—	33·6	4·9	17·5	—	—
Di(*morpholine-4-thiocarboxythio*)*-2-chlorovinyl-* * [4]	m. p. 161°	$C_{12}H_{18}O_2ClS_4N_2As$	31·3	4·0	16·2	—	—	31·3	3·9	16·3	—	—
Di(*morpholine-4-thiocarboxythio*)*phenyl-* * [5]	m. p. 218—219°	$C_{16}H_{21}O_2S_4N_2As$	40·5	4·45	15·9	—	—	40·3	4·4	15·8	—	—

* $[O<([CH_2]_2)_2>N\cdot CS\cdot S]AsR$. [1] $(NEt_2\cdot CS\cdot S)_2As\cdot CH{:}CHCl$, crystd. from EtOH (Found: S, 29·4. Reqd.: S, 29·6%). [2] Needles from aqueous acetone. [3] Prisms from aqueous acetone. [4] Highly refracting rectangular plates. [5] Small needles or spherical aggregates.

Partition Coefficient of Lewisite-I Oxide.—The solution of the oxide in water was shaken with benzene, and samples of each layer, removed at intervals, were analysed for arsenic by addition of excess of iodine and back-titration with standard arsenite solution in the presence of sodium hydrogen carbonate. The following figures show that the equilibrium between the benzene-soluble oxide and the water-soluble dihydroxide is attained only slowly.

	Partition coefficient, $C_{H_2O}/C_{C_6H_6}$.			
Time of shaking (mins.)	10	60	120	1020
Initial aqueous solution + Benzene	8·13	4·74	2·63	1·67
Initial benzene solution + Water	0·07	0·23	0·26	0·69

The influence of the hydrogen carbonate buffer on the partition coefficient is shown by the following figures :

Lewisite + benzene + excess of aqueous $NaHCO_3$:	$C_{H_2O}/C_{C_6H_6}$ 13·5
Lewisite oxide (II or III) in benzene + aqueous $NaHCO_3$:	$C_{H_2O}/C_{C_6H_6}$ 13·4

Fission of Lewisite-I by the Hydroxyl Ion.—Lewisite-I hydroxide solution was prepared by adding 1 g. of Lewisite-I to 400 ml. of very dilute sodium hydrogen carbonate solution, shaking the mixture until reaction was complete, and acidifying cautiously with dilute hydrochloric acid until pH 7 was reached (B.D.H. Universal Indicator). 10-Ml. samples of this solution were added to 20 ml. of a buffer and maintained at 17°. Fission was detected by adding to each solution 1 ml. of ammoniacal cuprous chloride solution. A reddish-brown precipitate of cuprous acetylide indicated that fission had occurred. Results were :

Buffer used.	Reaction time (hours) before test.			
	2	6	17	24
4% Na_2HPO_4, pH 8·5	—	—	—	—
4% Borax, pH 9·5	—	—	Trace	Slight
4% K_2CO_3, pH 10·5	+	+	+	+

From similar experiments at 50° it was found that at this temperature fission was appreciable at pH 9·5 after 1 hour: 1% (or stronger) solutions of sodium carbonate gave evidence of fission at 50° after only 15 minutes.

A 4% solution can be obtained by boiling Lewisite-I oxide (III) with water for some time; if, however, the evolved vapours are led into ammoniacal cuprous chloride solution a positive acetylene reaction is obtained though a solution of Lewisite-I oxide prepared in the cold gives no positive reaction with this reagent.

Lewisite-I itself, when similarly boiled with water, gives no positive reaction for acetylene.

When administered (*a*) as droplets of Lewisite to the skin, (*b*) by injection, or (*c*) as dihydroxide by mouth, to experimental animals, Lewisite-I is slowly excreted in the form of its water-soluble dihydroxide and can be detected throughout the digestive system and particularly in the urine, by the cuprous chloride reaction which is sensitive to 0·001 mg. and can be used for approximate quantitative assay.

Derivatives of Lewisite-I and its Analogues.—The new compounds shown in the table were prepared in the course of this investigation. Values recorded as As,% were determined iodometrically after destruction of organic matter. The values recorded as equiv. were obtained by titrating the compound directly with iodine, to covert ter- into quinque-valent arsenic.

Adducts with Dioxan and Thioxan.—When equimolar amounts of Lewisite-I and dry dioxan were mixed, considerable heat was generated and, on cooling, the mixture solidified to a mass of white crystals. Recrystallised from light petroleum (b. p. 40—60°) the *compound* formed long colourless needles, m. p. 58—59° [Found : C, 24·3; H, 3·5%; equiv. (As), 146, 148; equiv. (Cl), 148·5. $C_6H_{10}O_2Cl_3As$ requires C, 24·37; H, 3·86%; equiv. (Cl or As), 147·5]. The " equiv. (As) " was determined as recorded above. The " equiv. (Cl) " was determined by titration in acid solution with silver nitrate, which reacts only with the chlorine bound to arsenic. The complex is almost completely dissociated in solution, as shown by molecular-weight determinations : Found : (cryoscopic in benzene) 145; (ebullioscopic in benzene) 195, 198; (ebullioscopic in chloroform) 124. Required : 124.

The arsenic trichloride dioxan complex, prepared in the same way, formed colourless crystals, m. p. 68—70°, from light petroleum, and had the composition assigned to it by Doak (*loc. cit.*) [Found: C, 23·0; H, 3·8%; equiv. (As), 158; equiv. (Cl), 105·0. Calc. for $3(C_4H_8O_2),2AsCl_3$: C, 22·9; H, 3·8%; equiv. (As), 156·6; equiv. (Cl), 104·4]. The molecular weight (cryoscopic in benzene) was 119; the required value is 627, so that the substance is strongly dissociated in solution, as stated by Doak.

The *arsenic trichloride–thioxan* complex, similarly prepared, formed colourless needles, m. p. 70—72° [Found : C, 16·8; H, 2·78%; equiv. (As), 143·5; equiv. (Cl), 96·0. $C_4H_8OSCl_3As$ requires C, 16·8; H, 2·8%; equiv. (As), 142·6; equiv. (Cl), 95·1]. Molecular-weight determination (cryoscopic in benzene) gave a value of 147 (Required : 285), again indicating almost complete dissociation.

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