

neutral. The benzene solution was dried and concentrated. The crystalline residue was recrystallized from benzene-ether and washed on the filter with ether, yield 1.28 g., m. p. 177–180°. An additional 0.17 g. was obtained from the mother liquor (total 83%). Recrystallization from the same solvent raised the m. p. to 189–190.5°, $[\alpha]_D^{27} - 46.5 \pm 3^\circ$ (dioxane).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found⁵: C, 76.01; H, 9.06.

allo-Pregnan-3,6,20-trione.—A solution of 200 mg. of pregnan-3,6,20-trione in 5 ml. of acetic acid and 0.5 ml. of concentrated hydrochloric acid was heated one hour on the steam-bath, diluted with water and the precipitate filtered. A light yellow solid (130 mg.) was obtained, m. p. 213–223°. Recrystallization from acetone-ether raised the m. p. to 223–227°. In another experiment 140 mg. of the triketone gave 50 mg. of the *allo* compound, m. p. 227–230.5°, $[\alpha]_D^{25} + 52.9 \pm 3^\circ$ (dioxane).

4-Bromo-pregnan-3,6,20-trione.—To a solution of 660 mg. of pregnan-3,6,20-trione in 10 ml. of acetic acid, 0.23 ml. of 0.499 *N* bromine in acetic acid was added at room temperature. After shaking for two minutes the bromine color disappeared. The solution was cooled to 15° and the remainder of the bromine solution (total 8.0 ml.) was added dropwise with swirling during fifteen minutes. The solution was kept cold for an additional five minutes and then diluted with water. The suspension was chilled, filtered, washed with water, and dried in a vacuum desiccator. The substance was rubbed with warm dry ether,

filtered and dried; yield 570 mg. (69.5%), m. p. 132–132.5° (dec.), $[\alpha]_D^{25} + 25.9 \pm 3^\circ$ (dioxane).

Anal. Calcd. for $C_{21}H_{29}O_3Br$: Br, 19.52. Found¹⁹: Br, 20.25.

6-Ketoprogesterone.—A solution of 440 mg. of the bromo compound in 2 ml. of dry pyridine was refluxed for two hours, cooled and taken into ether. The ether solution was washed with dilute hydrochloric acid and then with water. The ether was distilled leaving a crystalline residue which was recrystallized from acetone-ether giving 13 mg. of material, m. p. 185–187°.⁴

Summary

1. Hyodesoxycholic acid has been degraded by two methods to pregnan-3(α),6(β)-diol-20-one.

2. Several previously unreported intermediates were isolated, and the physical constants of some other compounds were found to be at variance with those previously reported.

3. Pregnan-3,6,20-trione (a) was converted to 6-ketoprogesterone by bromination and dehydrobromination; and (b) was rearranged by acid or alkali to *allo*-pregnan-3,6,20-trione.

(19) Analysis by Charlotte Hart in this Laboratory.

KANSAS CITY, MISSOURI

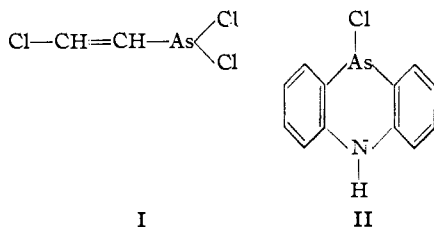
RECEIVED MAY 23, 1946

[CONTRIBUTION FROM THE C. W. S. TECHNICAL COMMAND, EDGEWOOD ARSENAL]

Some Organic Arsenicals Containing the Arsenic-Sulfur Linkage¹

BY WALTER H. C. RUEGGEBERG,² ABRAM GINSBURG³ AND WALTER A. COOK⁴

In the production of certain chemical warfare agents such as lewisite (β -chlorovinyl-dichloroarsine, I) and adamsite (10-chloro-5,10-dihydrophenarsazine, II), arsenic trichloride is used as one of the basic raw materials.



The end of the war left considerable stores of all three of these materials and it appeared of interest to convert them to relatively non-toxic substances which might find peace-time applications. To this end the substances shown below were prepared, among others, and their toxicities investigated. Since these all contain the As-S linkage, they may be considered to be derivatives of thioarsenic acid.⁵

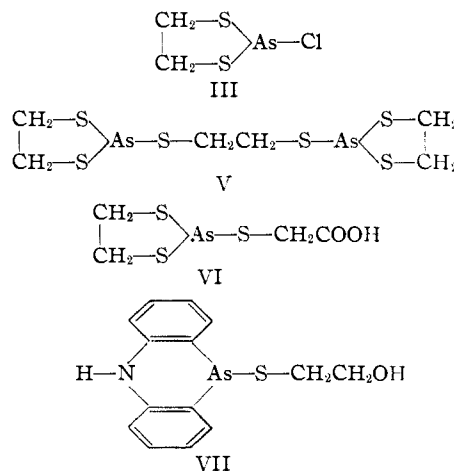
(1) Published with the permission of the Chief, Chemical Warfare Service.

(2) Captain, C. W. S., Army of the United States.

(3) Technician, 3rd grade, Army of the United States.

(4) Present address: University of Akron, Akron 4, Ohio.

(5) The reaction between mercaptans and lewisite constitutes the basis of the chemistry of BAL (see Waters and Stock, *Science*, **102**, 601 (1945)). Since BAL was studied by other investigators prior



Experimental

2-Chloro-4,5-dihydro-1,3,2-dithiarsenole (III).—This substance was obtained by allowing ethanedithiol to react with arsenic trichloride in carbon tetrachloride at room temperature. To a solution of 200 g. (1.1 mole) of arsenic trichloride in 250 cc. of carbon tetrachloride was added dropwise 94 g. (1 mole) of ethanedithiol. The liberation of hydrogen chloride was almost instantaneous accompanied by self-cooling of the reaction mixture. After standing an hour, the mixture was chilled in a Dry Ice chest and the crystalline product thus obtained was filtered off with suction and air-dried: yield, 90% or higher.

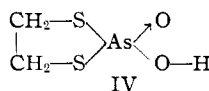
to the work here described, the reactions of lewisite with mercaptans will not be discussed in this publication.

TABLE I
 CHEMICAL AND TOXICOLOGICAL DATA ON ARSENICALS

R = 4,5-Dihydro-1,3,2-dithiarsenole	Formula	M. p., °C.	Percentage composition				Toxicity of arsenicals— Effect on—			
			As		S		Rats ^a min. lethal dose mg./kg.	Mex. bean beetle ^b Killed, %	Inca- pac- itated, %	Feeding on plant
III 2-Chloro-R	C ₂ H ₄ AsClS ₂	37.5-38	36.99	36.85	31.66	31.54 ^c	250	0	0	Moderate
V 1,2-Bis-(R-2-ylmercapto)-ethane	C ₈ H ₁₂ As ₂ S ₄	82-83	35.14	35.07	45.11	44.54 ^d	500	60	20	Very slight
VI 2-Carboxymethylmercapto-R	C ₄ H ₇ AsO ₂ S ₃	77-80	29.91	29.83	37.25	36.54	100	0	100	Slight
VII 5,10-Dihydro-10-(2-hydroxyethylmercapto)-phenarsazine	C ₁₄ H ₁₄ AsNOS	164-166	23.47	22.81	10.04	9.83, 9.68 ^e	50	30	70	Very slight

^a The experimental animals used were, in all cases, adult albino and hooded laboratory rates. The approximate minimum lethal dose, after administering progressively decreasing doses, was considered that required to kill 2 out of 2 rats. ^b Each compound was made up as a 2% dust in an inert diluent and was used at a concentration of approximately 15 to 18 lb. of dust per acre of beans. Each plant carried about 250 mg. of dust and was then infested with healthy Mexican bean beetle larvae under climatic conditions favorable for the maximum activity of the insect. Observations were made at the end of ninety-six hours. ^c Calcd.: Cl, 17.51. Found: Cl, 17.64. ^d Calcd.: C, 16.90; H, 2.84. Found: C, 17.0, 16.7; H, 2.78, 2.72. ^e Calcd.: N, 4.39. Found: N, 4.34, 4.17.

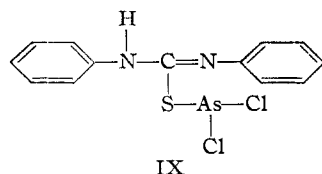
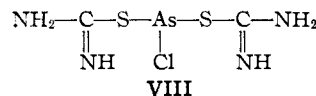
1,2-Bis-(4,5-dihydro-1,3,2-dithiarsenol-2-ylmercapto)-ethane (V).—An attempt was made to synthesize 4,5-dihydro-2-hydroxy-1,3,2-dithiarsenole oxide (IV)



from the corresponding chloride (III).

Procedure.—A solution of 50.6 g. (III) in 400 cc. of a 1:1 ethanol-water mixture was heated for two hours at 80°, allowing a stream of air to bubble through the reaction mixture during the heating period. The mixture turned strongly acid and the presence of chloride ion was evident from the silver chloride test. The solid residue was filtered off on a Büchner funnel yielding 24.5 g. of product after recrystallization from benzene. This the authors believe to be 1,2-bis-(4,5-dihydro-1,3,2-dithiarsenol-2-ylmercapto)-ethane (V), rather than the expected acid (IV).

It is assumed that in all probability the chloroarsenole (III) is first hydrolyzed at the As-Cl bond followed by splitting of the As-S linkage by water, thus giving rise to a free sulfhydryl group which in turn reacts with (III) with the elimination of hydrochloric acid. This type of breakdown at the As-S linkage has been reported previously for chloro-bis-(guanlylmercapto)-arsine (VIII) and dichloro-(N,N-diphenylguanlylmercapto)-arsine (IX).^{6,7}



2-(Carboxymethylmercapto)-4,5-dihydro-1,3,2-dithiarsenole (VI).—A solution of 48.1 g. of thioglycolic acid, 101.3 g. of (III) and 50 cc. of benzene was refluxed at 75-80° for three hours, after which time the evolution of hydrogen chloride had subsided. Most of the benzene was subsequently distilled from the reaction product at atmospheric pressure. After standing overnight, 24 g. of crystals was filtered off with suction and about an equal quantity was recovered from the mother liquor. The two were combined and recrystallized from benzene.

(6) Walter, *Ber.*, **64B**, 1087 (1931).

(7) Malinovskii, *Trudy Gor'kov. Gosudarst. Pedagog. Inst.*, 1940, No. 5, 35; *C. A.*, **37**, 3070 (1943).

5,10-Dihydro-10-(2-hydroxyethylmercapto)-phenarsazine (VII).—Nine and four-tenths grams of ethanol mercaptan was added slowly to a solution of 6.7 g. of potassium hydroxide in 100 cc. of absolute ethanol contained in a 500-cc. round-bottom flask, equipped with reflux condenser, mercury seal stirrer and dropping funnel. From the dropping funnel 27.8 g. of adamsite (II), dissolved in 250 cc. of C. P. acetone was added to the other reagents with stirring. The temperature rose rather rapidly to 33° and was allowed to remain at this point for one hour. The reaction mixture was then stirred for one additional hour at 40°. After standing about two days at room temperature, the product was filtered off on a Büchner funnel and was recrystallized from acetone, yielding about 9-10 g. of VII. An approximately equal quantity of product was recovered from the mother liquor.

The chemical and toxicological data on these compounds are collected in the Table.

Relative Solubilities (visual).—III is soluble in absolute ethanol, benzene and carbon tetrachloride; slightly soluble in ether and hexane, and decomposes in hot water. V is slightly soluble in ether, absolute ethanol, benzene, carbon tetrachloride and hexane and is insoluble in water. VI is soluble in ether, absolute ethanol and benzene, sparingly soluble in water and insoluble in carbon tetrachloride and in hexane. VII is slightly soluble in benzene and acetone, tending to oxidize to a green color; is insoluble in water, hexane and carbon tetrachloride.

Discussion

It was hoped that compound VI might possess sufficient water solubility at room temperature so that water might be employed as a dispersal medium for insecticidal evaluation of compound VI. The property of water solubility was uncommon to all compounds prepared and in the case of one compound at least, (III), water apparently decomposed the dithiarsenole ring at 80°.

It becomes of interest, of course, particularly when faced with the problem of finding a potential outlet for this type of compound, to know how toxic these substances are. All of them have been tested against rats as well as the Mexican Bean Beetle. It will be seen from Table I that three of the four compounds tested possess rather remarkable effects when used as stomach poisons against the bean beetle. Against rats as well as the bean beetle there exists a considerable gradation of toxicity as the structure of the compound varies. Of particular interest is the fact that the order of toxicity of the four candidate compounds is nearly

identical in both the entomological and the toxicological work with compound VII being somewhat superior to compound VI in both series of tests.

The authors are indebted to Dr. Frank B. Maughan of the Rohm and Haas Co., Philadelphia, Pa., and Dr. Ray Treichler, of the Fish and Wildlife Service, U. S. Department of Interior, for having rendered their skillful services in performing the entomological and toxicological work, respectively.

Summary

The preparation of four new compounds containing the arsenic-sulfur linkage has been described. These compounds were prepared by the action of mercaptans containing one or more sulfhydryl groups on chloroarsines.

EDGEWOOD ARSENAL, MARYLAND

RECEIVED⁸ JUNE 26, 1946

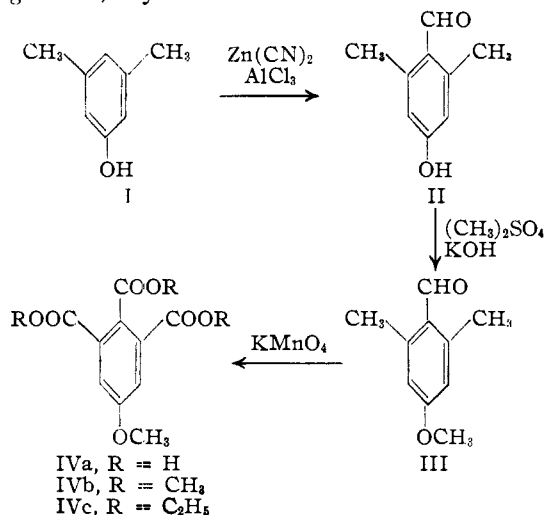
(8) Original manuscript received January 18, 1946.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation of 5-Methoxybenzene-1,2,3-tricarboxylic Acid¹

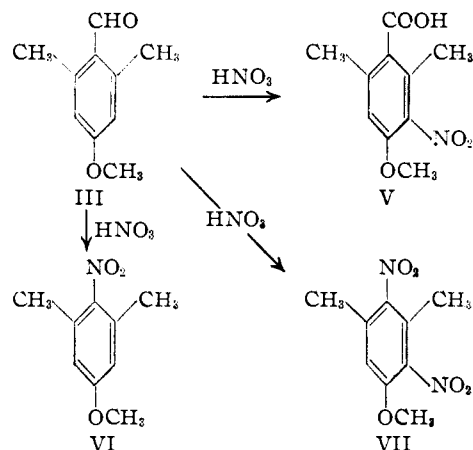
BY A. L. WILDS AND CARL DJERASSI^{2,3}

A sample of 5-methoxybenzene-1,2,3-tricarboxylic acid (IVa) was wanted in connection with another problem.⁴ We have synthesized this new acid according to the following scheme, starting with 3,5-xylenol



The acid was obtained in 52% yield as the trimethyl ester by alkaline permanganate oxidation of the methyl ether III, followed by methylation with diazomethane. The free acid and crystalline triethyl ester also were prepared.

Oxidation of the methyl ether III with nitric acid also was investigated. While this reagent did not prove suitable for preparing IVa, the results were of interest. When III was heated with concentrated nitric acid for fifteen minutes at reflux, 25% of the nitro acid V was isolated. In addition about 8% of the product VI in which the aldehyde group was replaced by a nitro group, and about 9% of the dinitro compound VII were



obtained. When the period of heating was increased to two hours, the yield of the nitro acid V was lowered to 15% and that of the dinitrodimethylanisole VII was raised to 30%. A similar susceptibility of the carboxyl group to cleavage in nitric acid solution has been observed by Jackson and Earle⁵ in the nitration of anisic acid and by Reverdin⁶ with *p*-dimethylaminobenzoic acid.

Experimental⁷

2,6-Dimethyl-4-hydroxybenzaldehyde (II) and 2,4-Dimethyl-6-hydroxybenzaldehyde.—The general procedure of Adams and Montgomery,⁸ for the modified Gattermann reaction was followed, using 12.3 g. of 3,5-xylenol, 50 cc. of dry, thiophene-free benzene, 23.5 g. of zinc cyanide and 20 g. of aluminum chloride. After hydrolysis and steam distillation, 3.1 g. (20%) of 2,4-dimethyl-6-hydroxybenzaldehyde was isolated from the distillate, m. p. 47–48° (reported 48–49°),⁹ and 9.45 g. (63%) of the other isomer, m. p. 186–190° with previous sintering, from the residue. Recrystallization from alcohol yielded 6.15 g. of long prisms of 2,6-dimethyl-4-hydroxybenzaldehyde (II), m. p. 195–196.5°, and 1.19 g. of m. p. 188–192° (reported,^{9a,10} m. p. 190°).

(5) Jackson and Earle, *Am. Chem. J.*, **29**, 104 (1903).

(6) Reverdin, *Ber.*, **40**, 2442 (1907).

(7) All melting points are corrected.

(8) Adams and Montgomery, *THIS JOURNAL*, **46**, 1518 (1924).

(1) From part of the Ph. D. Thesis of Carl Djerassi.
 (2) Wisconsin Alumni Research Foundation Research Assistant, 1943–1945.

(3) Present address, Ciba Pharmaceutical Products, Inc., Summit N. J.

(4) Wilds and Djerassi, *THIS JOURNAL*, **68**, 1712 (1946).

(9) (a) v. Auwers and Borsche, *Ber.*, **48**, 1713 (1915); (b) v. Auwers and Saurwein, *ibid.*, **55**, 2379 (1922).

(10) Gattermann, *Ann.*, **357**, 328 (1907).