Hydroxyethylhydrocupreine is very interesting in this connection since it proved to be far less toxic to mice than optochin, and was highly efficient in protecting them against pneumococcic infection.

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

The Reactivity of Nuclear Chlorine in Certain 5-Substituted Derivatives of 2-Chlorophenylarsonic Acid

BY W. E. CRAIG[1] AND CLIFF S. HAMILTON

The Ullmann reaction, as applied in the field of organic arsenicals to date, has revealed that the halogen atoms in 2-chlorophenylarsonic acid,[2] 3-nitro-4-halogenophenylarsonic acids[3] and 2-chloro-5-nitrophenylarsonic acid[4] are quite reactive.

It was of interest to study the reactivity of the halogen in 2-chloro-5-carboxyphenylarsonic acid. This acid was readily condensed in an anhydrous alkaline medium in the presence of cuprous iodide, with ethanolamine, glycine and phenol. A comparison of reaction times and yields revealed that the reactivity of the chlorine atom in 2-chloro-5-carboxyphenylarsonic acid was the same as that of 2-chlorophenylarsonic acid. Incidental to the preparation of 2-chloro-5-carboxyphenylarsonic acid, 2-chloro-5-cyanophenylarsonic acid was isolated and identified. Condensations with this acid are more difficult to carry out due to tarry formations; however, it was condensed with phenol to form 2-arsono-4-cyanophenyl ether.

The effect of an ortho–para directing group substituted in the para position to the halogen in 2-chlorophenylarsonic acid was also studied, employing the 2-chloro-5-aminophenylarsonic acid and its acetyl derivative, as well as 2-chloro-5-hydroxyphenylarsonic acid and its carbethoxy derivative. Attempts to condense *p*-chlorophenol and various primary amines with these arsonic acids were unsuccessful.

This investigation has resulted in the preparation of several new organo arsenicals, one of which, 3-arsono-4-chlorobenzenediazonium chloride, in its general type is new to the field as an isolated and identified compound.

Experimental

2-Chloro-5-acetylaminophenylarsonic Acid.—To 5 g. of 2-chloro-5-aminophenylarsonic acid[5] dissolved in 20 cc. of *N* sodium hydroxide was added 10 cc. of acetic anhydride. When stirred with a glass rod, an instantaneous reaction occurred with the generation of much heat, and a white pasty mass resulted. To this solid was added 15 cc. of water and 6 *N* hydrochloric acid until the liquid was acid to Congo red paper, whereupon 2-chloro-5-acetylaminophenylarsonic acid separated as a mass of crystals; m. p. 225–227°. The needles rapidly absorbed one molecule of water of hydration, which they lost with effervescence at 160°.

2,2′-Dichloro-5,5′-diaminoarsenobenzene.—A mixture of 1.5 g. of 2-chloro-5-aminophenylarsonic acid, 5 cc. of 12 *N* hydrochloric acid and 30 cc. of water was heated until solution resulted and then 8 cc. of 50% hypophosphorous acid was added. The solution was heated at 60° for two hours. Upon the addition of sodium hydroxide until an alkaline reaction with Congo red paper was obtained, a light yellow, granular solid separated.

3-Arsono-4-chlorobenzenediazonium Chloride.—A mixture of 3 g. of 2-chloro-5-aminophenylarsonic acid and 3.5 cc. of 4 *N* hydrochloric acid was stirred into a white paste and placed in an ice–salt mixture. Nitrogen trioxide was passed into the paste until a clear dark green colored solution resulted. When this liquid was poured into a chilled mixture of 50 cc. of ethanol and 50 cc. of ether with stirring, the diazonium chloride separated as slender needles and was dried in a desiccator over sodium hydroxide sticks. The salt intumesced at 140°. It gradually assumed a red color upon standing in air, and heating increased this decomposition. It rapidly took up two molecules of water of hydration upon exposure to the atmosphere. When the diazonium chloride was refluxed with methyl alcohol, *o*-chlorophenylarsonic acid was obtained in a 70% yield.

2-Chloro-5-hydroxyphenylarsonic Acid.—A solution of 5 g. of 2-chloro-5-aminophenylarsonic acid in 50 cc. of water and 4 cc. of concentrated hydrochloric acid was diazotized with normal sodium nitrite solution until starch–iodide paper indicated an excess of nitrous acid. The resulting light red solution was heated on a water-bath at 70° until the evolution of nitrogen had ceased, water being added from time to time in order to maintain the original volume. The liquid was then divided into two parts and each evaporated to dryness on a water-bath in a 400-cc. beaker. The solid was dried completely in the oven at 110°, and the phenol extracted with anhydrous methyl alcohol. The methyl alcohol was evaporated on a water-bath and the red phenol extracted with *n*-butyl alcohol to remove any remaining inorganic salts. Upon the addition of

(1) Parke, Davis and Company Fellow.
(2) Etzelmiller, THIS JOURNAL, **53**, 3085 (1931).
(3) Maclay, *ibid.*, **54**, 3310 (1932).
(4) Hall, *ibid.*, **56**, 1779 (1934).
(5) Boehringer and Soehne, German Patent 286,547.

TABLE I

	Name	Crystal form	Yield, %	Formula	As analyses, %[a] Calcd.	Found
1	2-Chloro-5-acetylaminophenylarsonic acid	Needles[b]	80	$C_8H_9O_4NClAs \cdot H_2O$	24.06	24.10
2	2,2′-Dichloro-5,5′-diaminoarsenobenzene	Light yellow granules[c]	100	$C_{12}H_{10}N_2Cl_2As_2$	37.20	37.02
3	3-Arsono-4-chlorobenzenediazonium chloride	Needles	93	$C_6H_5O_3N_2Cl_2As$	25.07	25.01
4	2-Chloro-5-hydroxyphenylarsonic acid	Red granules	70	$C_6H_6O_4ClAs$	29.68	29.67
5	2-Chloro-5-carbethoxyhydroxyphenylarsonic acid	Tan flakes	40	$C_9H_{10}O_6ClAs$	23.09	23.02
6	2,2′-Dichloro-5,5′-dihydroxyarsenobenzene	Brown granules	70	$C_{12}H_8O_2Cl_2As_2$	37.02	36.79
7	2-Chloro-5-cyanophenylarsonic acid	Tan rods[b]	60	$C_7H_5O_3NClAs$	28.66	28.64
8	2-Chloro-5-carboxyphenylarsonic acid	Needles[b]	72	$C_7H_6O_5ClAs$	26.72	26.33

[a] Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] By recrystallization from water. [c] By reprecipitation from acid solution.

TABLE II

	Name	Reactants
1	2-Arsono-4-cyanophenyl ether	2-Chloro-5-cyanophenylarsonic acid + phenol
2	2-Arsono-4-carboxyphenyl ether	2-Chloro-5-carboxyphenylarsonic acid + phenol
3	2-β-Hydroxyethylamino-5-carboxyphenylarsonic acid	2-Chloro-5-carboxyphenylarsonic acid + ethanolamine
4	2-Arsono-4-carboxyphenylglycine	2-Chloro-5-carboxyphenylarsonic acid + glycine
5	2-Arsono-4-nitrophenylglycine	2-Chloro-5-nitrophenylarsonic acid + glycine
6	2-Arsono-4-aminophenylglycine	.....

	Crystal form	M. p., °C.	Time of heating, hrs.	Yield, %		As analyses, % Calcd.	Found
1	Pink granules[c]		15	25	$C_{13}H_{10}O_4NAs$	23.49	23.52
2	Granules[c]		15	25	$C_{13}H_{11}O_6As$	22.17	22.12
3	Light yellow needles[a]	240–243 (dec.)	3	40	$C_9H_{12}O_6NAs \cdot H_2O$	23.19	23.10
4	Needles[a]		15	26	$C_9H_{10}O_7NAs$	23.49	23.36
5	Yellow needles[a]	208–210	15	26	$C_8H_9O_7N_2As$	23.41	23.35
6	Square plates[b]	210 (dec.)	..	90	$C_8H_{11}O_5N_2As$	25.84	26.01

[a] By recrystallization from water. [b] By reprecipitation from acid soln. [c] By reprecipitation from alkaline soln.

ether to the alcoholic solution a red gum separated and the liquid part was decanted. The red gum was again treated with ether. It was solidified by stirring with a glass rod or by adding acetone and stirring. The compound has also been prepared free from inorganic salts and as a light red, rather crystalline solid in 85% yield by merely heating a water solution of 3-arsono-4-chlorobenzenediazonium chloride, and after the evolution of nitrogen had ceased evaporating to dryness on a water-bath. Upon standing in air the red solid absorbed approximately one molecule of water.

2-Chloro-5-carbethoxyhydroxyphenylarsonic Acid.—A mixture of 2 g. of 2-chloro-5-hydroxyphenylarsonic acid, 25 cc. of ethyl chlorocarbonate, and two drops of pyridine was placed in a round-bottomed flask and refluxed for one and one-half hours. Gradually the solid went into solution, leaving a small amount of a black tar in the bottom. The solution was poured into 200 cc. of water and a light tan flocculent precipitate resulted. This was treated with 200 cc. of boiling water, dissolved in 3 *N* sodium hydroxide, reprecipitated with hydrochloric acid and washed with several portions of water.

2,2′ - Dichloro - 5,5′ - dihydroxyarsenobenzene.—Two grams of 2-chloro-5-hydroxyphenylarsonic acid was dissolved in 25 cc. of methyl alcohol and 5 cc. of hypophosphorous acid added. Upon heating at 50° for one hour, a brown solid separated and was thoroughly washed with hot water. The solid upon standing took up approximately one molecule of water.

2-Chloro-5-cyanophenylarsonic Acid.—A mixture of 15 g. of 2-chloro-5-aminophenylarsonic acid, 12 cc. of 12 *N* hydrochloric acid, and 300 cc. of water was heated until solution resulted, allowed to cool to room temperature and then diazotized with sodium nitrite solution. In the meantime 15 g. of copper sulfate was dissolved in 60 cc. of water and placed in a 2-liter beaker. To this was added slowly with stirring 16.9 g. of potassium cyanide dissolved in 30 cc. of water. Then the diazotized solution was added slowly and the whole stirred for two hours. The precipitated cuprous cyanide was filtered off and the red filtrate made just acid to Congo red paper with hydrochloric acid and evaporated on a water-bath to a small volume. After cooling, the precipitated brown solid was filtered off. The purified product decomposed at 200°.

2-Chloro-5-carboxyphenylarsonic Acid.—In the above preparation the red filtrate, after filtering off the precipitated cuprous cyanide, was treated with 33.3 g. of potassium hydroxide, and the liquid was heated in an evaporating dish with a direct flame until potassium sulfate crystals started coming out of solution. The red filtrate was carefully acidified with hydrochloric acid until a definite blue was obtained with Congo red paper, and the crude product isolated.

Condensations.—The general procedure was to introduce a mixture of 5 g. of the 2-chloro-5-substituted-phenylarsonic acid, 10 g. of a phenol or 5 cc. of an amine (10 cc. of ethanolamine) or 2 g. of glycine, 5 g. of anhydrous potassium carbonate, 30 cc. of amyl alcohol and a trace of freshly prepared cuprous iodide into a 200-cc. Erlenmeyer flask fitted with ground glass connections. The reaction mixture was agitated by means of a mechanical stirrer which extended down through the condenser, and

was heated in an oil-bath at 130–135° for a varying time. The mixture was then steam distilled, charcoaled and acidified to Congo red paper with concentrated hydrochloric acid. From this the condensation product was isolated and purified.

2-Arsono-4-nitrophenylglycine formed by such a condensation was reduced by means of molecular hydrogen in the presence of nickel[6] to the corresponding amine.

Summary

1. 2-Chloro-5-carboxyphenylarsonic acid was condensed with ethanolamine, phenol and glycine.

2. Under the conditions of an Ullmann reaction, 2-chloro-5-cyanophenylarsonic acid reacted with phenol.

3. 2-Chloro-5-nitrophenylarsonic acid was successfully condensed with glycine, and the corresponding amino derivative of the condensation product synthesized.

4. Under the ordinary conditions found successful for condensing halogenophenylarsonic acids 2-chloro-5-aminophenylarsonic acid did not condense with itself, isoamylamine, ethanolamine or *p*-chlorophenol, and its acetyl derivative did not react with aniline or *p*-chlorophenol.

5. All attempted condensations between 2-chloro-5-hydroxyphenylarsonic acid and itself, ethanolamine or *p*-chlorophenol, and between its carbethoxy derivative and aniline or *n*-butyl amine were unsuccessful.

6. Apparently, the presence of an amino or a hydroxyl grouping, in the para position to an activated chlorine, strengthens the attachment of the halogen to carbon, and makes it less labile.

7. Several organic arsenicals, incidental to the problem, have been prepared and identified for the first time.

(6) Stevinson, Doctor's Thesis, University of Nebraska, 1934.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 117]

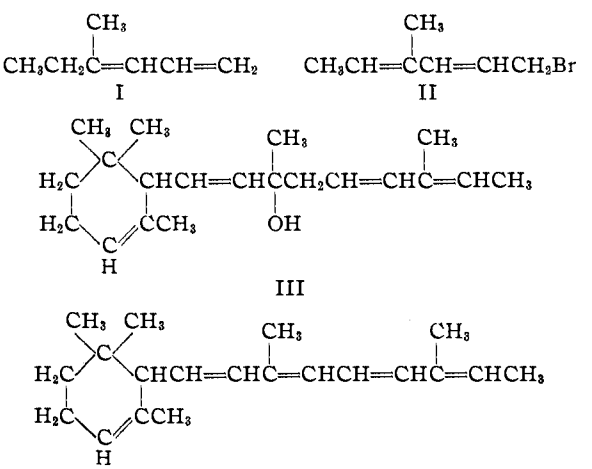
Synthetic Studies with the Ionones. I. Synthesis of an Alcohol Related to Vitamin A

BY NICHOLAS A. MILAS AND AMBROSE MCALEVY[1]

A considerable amount of research has been done during the past few years in the field of vitamin A and related naturally occurring products. This work culminated in the important studies of Karrer and his students[2] in the determination of the structure of this vitamin. The vitamin itself has not yet been synthesized, nor have any of its derivatives or other substances closely related to it.

A little over two years ago, we began working in this field with the object of procuring some necessary information prior to making attempts to synthesize the vitamin itself or some one of its derivatives. Since much work is being done at present in this field by other investigators, it seems advisable to publish some of our preliminary results although the work has not yet been completed.

When 1-bromo-4-methyl-2,4-hexadiene (II) is condensed by means of the Grignard reaction with α-ionone,[3] 1,2 addition takes place yielding, after hydrolysis, the tertiary alcohol (III). That the Grignard reaction results in 1,2 addition in the case of α-ionone has also been shown by Karrer and his students[4] using allylmagnesium bromide.



I II

III

IV

(1) Abstracted from Part II of the Ph.D. Dissertation of Ambrose McAlevy, M. I. T., June, 1934.

(2) Karrer, Morf and Schopp, *Helv. Chim. Acta*, **14**, 1431 (1931); **16**, 557 (1933).

(3) The condensation with β-ionone is being investigated.

(4) Karrer, Salomon, Morf and Walker, *Helv. Chim. Acta*, **15**, 878 (1932).