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

ARSONO-ARYLAMINO ALCOHOLS

BY C. W. RODEWALD WITH ROGER ADAMS[1]

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During the past few years many new organic arsenic compounds have been made in this Laboratory which have various types of substituted, nitrogen-containing groups in aryl arsonic acids.[2] These have been prepared in order to determine whether the presence of the new groups might not cause a decrease in the toxicity of the products as compared with the corresponding arsanilic acids which may be looked upon as the basic substances of all these derivatives. This communication is a report on a part of this work involving the preparation of certain aryl arsonic acids containing β-hydroxyethylamino and γ-hydroxypropylamino groups. Arsenic compounds containing these groups are of special interest because these groups are found so frequently in naturally occurring and synthetic compounds of marked physiological action.

The procedure for their preparation is similar to that described for other β-arylamino-ethanols and γ-arylamino-propanols described recently by Adams and Segur,[3] and Pierce and Adams.[4] The amino-arylarsonic acids are dissolved in aqueous alkali and treated with β-chloro-ethyl chloroformate, yielding β-chloro-ethyl-(arsono-aryl) carbamates. These latter compounds when refluxed with 2 molecular equivalents of aqueous or alcoholic alkali yield arsono-aryl oxazolidones or when refluxed with excess of aqueous alkali yield the hydrolytic products of the arsono-aryl oxazolidones, namely, β-arsono-aryl amino-ethanols: $H_2O_3AsC_6H_4NH_2 \longrightarrow H_2O_3AsC_6H_4NHCOOCH_2CH_2Cl \longrightarrow H_2O_3AsC_6H_4\underline{NCOOCH_2CH_2} \longrightarrow H_2O_3AsC_6H_4NHCH_2CH_2OH$.

In a similar manner γ-chloropropyl chloroformate and amino-aryl arsonic acids were condensed to γ-chloropropyl-(arsono-aryl) carbamates. These upon treatment with 2 molecular equivalents of aqueous alkali yielded 3-(arsono-aryl)-tetrahydro-1,3,2-oxazones or with excess of aqueous alkali yielded hydrolytic products of the oxazones, namely, γ-arsono-arylamino-propanols: $H_2O_3AsC_6H_4NH_2 \longrightarrow H_2O_3AsC_6H_4NHCOOCH_2CH_2CH_2Cl \longrightarrow H_2O_3AsC_6H_4\underline{NCOOCH_2CH_2CH_2} \longrightarrow H_2O_3AsC_6H_4NHCH_2CH_2CH_2OH$.

[1] This communication is an abstract of a portion of a thesis submitted by C. W. Rodewald in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Johnson and Adams, THIS JOURNAL, **45**, 1307 (1923). Quick and Adams, *ibid.*, **44**, 805 (1922). Completed but as yet unpublished work at the University of Illinois comprises the formation of three new types of organic arsenic compounds.

[3] Adams and Segur, *ibid.*, **45**, 785 (1923).

[4] Pierce and Adams, *ibid.*, **45**, 790 (1923).

Various carbamates, oxazolidones or oxazones and β-amino-ethanols or γ-aminopropanols from different *o*- and *p*-amino-aryl-arsonic acids were prepared. All of the substances proved to be white crystalline compounds readily made and purified. Every one of these derivatives was less toxic than the corresponding arsanilic acid, but the amino alcohols were the least toxic of the different types of compounds. Moreover, the amino-alcohols were much less toxic than the arsanilic acids from which they were derived, the β-amino-ethanols being slightly less toxic than the corresponding γ-aminopropanols. The toxicities of these compounds were kindly tested by Dr. G. W. Raiziss of the Dermatological Laboratories of Philadelphia.

Experimental Part

All of the compounds made in this investigation did not have distinct melting points owing to the decomposition which took place at the same time. The figures given, therefore, are those obtained as an average of a number of determinations. By varying the speed of heating the points are varied, sometimes as much as 10°.

β-Chloro-ethyl-(arsono-aryl) Carbamates.—To a solution of 1 molecular equivalent of amino-aryl-arsonic acid in about 8 times its weight of water and one equivalent of sodium hydroxide in 5 *N* solution was added in small portions with vigorous shaking or mechanical stirring, one molecular equivalent of β-chloro-ethyl chloroformate. Heat was developed during the reaction that took place and the temperature was kept below 35° by immersion of the flask from time to time in an ice-bath. The product separated as a granular precipitate during the course of the reaction. Shaking or stirring was continued for 10 minutes after the addition of the chloroformate in order to make certain of the completion of the reaction. Concd. hydrochloric acid was added in sufficient quantity to dissolve any small amount of unchanged amino-aryl-arsonic acid and the product was then filtered off and washed with water. The substances thus produced were very readily purified by crystallization from 30% acetic acid, forming in every case white needles. The carbamates were soluble in aqueous sodium carbonate or sodium bicarbonate.

TABLE I

CARBAMATES

Substance		Yield %	M. p. °C.	Wt. G.	Analyses Obt. or req. Cc. of 0.0963 *N* I_2	Calc. %	Found %
β-chloro-ethyl-(*p*-arsonophenyl)-	$C_9H_{11}O_5NClAs$	93	> 250	0.3630	22.83	23.18	22.83
β-chloro-ethyl-(*o*-arsonophenyl)-	$C_9H_{11}O_5NClAs$	81	156–157	.3630	23.02	23.18	23.02
β-chloro-ethyl-(2-methyl-5-arsonophenyl)-	$C_{10}H_{13}O_5NClAs$	68	193–195	....	...	...	...
γ-chloropropyl-(*p*-arsonophenyl)-	$C_{10}H_{13}O_5NClAs$	92	245–246	.2047	12.65	22.26	22.43
γ-chloropropyl-(*o*-arsonophenyl)-	$C_{10}H_{13}O_5NClAs$	67	130–132	.2286	14.28	22.26	22.67
γ-chloropropyl-(2-methyl-5-arsonophenyl)-	$C_{11}H_{15}O_5NClAs$	72	160–162	....	...	...	...

3-*p*-Arsonophenyl-2-oxazolidone, $(p)H_2O_3AsC_6H_4NCOOCH_2CH_2$.—A mixture of 24 g. of β-chloro-ethyl-(*p*-arsonophenyl) carbamate with 150 cc. of water and 5.9 g. (2 molecular equivalents) of sodium hydroxide was refluxed for 5 hours. At the end of that time the solution was cooled and concd. hydrochloric acid added until the mixture

was strongly acid to congo red; this caused the solution of any amino-alcohol which might have formed as a by-product during the reaction, and at the same time caused the precipitation of the oxazolidone. The product was filtered, washed with water and purified by crystallization from 30% acetic acid. There was thus obtained 20 g. (95%) of colorless plates melting above 280°.

Analysis. Subs., 0 3178: 22.36 cc. of 0.0963 N I_2. Calc. for $C_9H_{10}O_5NAs$: As, 26.13. Found: 25.54.

3-*o*-Arsonophenyl-2-oxazolidone, $(o)H_2O_3AsC_6H_4\underline{NCOOCH_2CH_2}$.—A mixture of 2.1 g. of β-chloro-ethyl-(*o*-arsonophenyl) carbamate with 2.6 cc. (2 molecular equivalents) of 5 N sodium hydroxide and 20 cc. of water was refluxed for 3 hours. The solution was cooled and acidified with concd. hydrochloric acid until strongly acid. The product separated as a white powder which was purified by crystallization from 20% acetic acid. There was thus obtained 1.3 g. (69%) of colorless plates melting at 212–213° with decomposition.

Analysis. Subs., 0.3630: 25.63 cc. of 0.0963 N I_2. Calc. for $C_9H_{10}O_5NAs$: As, 26.13. Found: 25.63.

3-*p*-Arsonophenyl-1,3,2-oxazone, $(p)H_2O_3AsC_6H_4\underline{NCOOCH_2CH_2CH_2}$.—A mixture of 4.2 g. of γ-chloropropyl-(*p*-arsonophenyl) carbamate with 20 cc. of boiling absolute alcohol and 14 cc. (2 molecular equivalents) of a 10% solution of potassium hydroxide in absolute alcohol was refluxed for 2.5 hours. A granular precipitate of potassium chloride started to form at the very beginning and increased in amount until the end of the time mentioned. The mixture was cooled, the granular precipitate filtered off, and hydrogen chloride passed into the alcoholic filtrate until it reacted strongly acid. The solvent was then evaporated and the sol d residue combined with the original precipitate. By treatment of the total solid with dil. sodium hydroxide solution in the cold, the potassium chloride and sodium chloride dissolved, and the product was readily precipitated with an excess of hydrochloric acid. It was purified by crystallization from dil. acetic acid, yielding 2.8 g. (72%) of white plates which melted at 245–247° with decomposition.

Analysis. Subs., 0.2007: 13.52 cc. of 0.0963 N I_2. Calc. for $C_{10}H_{12}O_5NAs$: As, 24.58. Found: 24.43.

Arsono-arylamino-ethanols and -propanols.—A β-chloro-ethyl- or γ-chloro-propyl-(arsono-aryl) carbamate was dissolved in 10% aqueous sodium hydroxide containing 5 molecular equivalents of alkali. The solution was refluxed for 4 hours, cooled, and concd. hydrochloric acid added until the mixture was neutral to congo red. The amino-alcohols separated usually as white solids but occasionally as oils which solidified on

TABLE II

ETHANOLS AND PROPANOLS

Substance	Formula	Yield %	M. p. °C.	Analysis Wt. G.	Obt. or req. Cc. of 0.0963 N I_2	Calc. %	Found %
β-(*p*-arsonophenyl)-amino-ethanol	$C_8H_{12}O_4NAs$'	85	173–174	0.3039	23.53	28.78	28.11
β-(*o*-arsonophenyl)-amino-ethanol	$C_8H_{12}O_4NAs$	50	144–146	.3630	28.26	28.74	28.26
β-(2-methyl-5-arsonophenyl)-amino-ethanol	$C_9H_{14}O_4NAs$	....	144–146	.2314	17.88[a]	27.09	26.89
γ-(*p*-arsonophenyl)-amino-propanol	$C_9H_{14}O_4NAs$	87	167–168	.2025	15.17	27.09	27.21
γ-(*o*-arsonophenyl)-amino-propanol	$C_9H_{14}O_4NAs$	66	84–85	.2108	15.62	27.09	26.81
γ-(2-methyl-5-arsonophenyl)-amino-propanol	$C_{10}H_{16}O_4NAs$	....	142–143	.2053	15.21[a]	25.95	25.78

[a] 0.0928 N I_2 used.

standing. The products were filtered, washed with cold water and recrystallized from water. The amino-alcohols thus produced are readily soluble in dil. hydrochloric acid.

They may be formed also by hydrolysis of the corresponding oxazolidone or oxazone but the isolation of these intermediate products is quite unnecessary.

***p*-Arsonophenyl-β-hydroxyethyl Nitrosamine,** $(p)H_2O_3AsC_6H_4N(NO)CH_2CH_2OH$.—To a solution of 3.5 g. of β-*p*-arsonophenyl-amino-ethanol in 6 g. of concd. hydrochloric acid and 6 cc. of water was added a solution of 2 g. of sodium nitrite in 10 cc. of water, with stirring and the mixture then heated to boiling. While still hot it was made alkaline to litmus by addition of 10% sodium hydroxide solution, then cooled and concd. hydrochloric acid was added until the solution was just acid to congo red. A crystalline precipitate separated which was purified by crystallization from water. It formed bright yellow needles which started to darken at 170–175° and melted at 236° with decomposition.

***p*-Arsonophenyl-γ-hydroxy-propyl Nitrosamine,** $(p)H_2O_3AsC_6H_4N(NO)CH_2CH_2CH_2OH$.—This substance was prepared in a manner exactly analogous to that used for the nitrosamine described above, and formed yellow crystals which were purified from water and melted at 142–143°.

These nitroso compounds gave the expected nitroso-amine reactions.

Summary

1. Various amino-aryl-arsonic acids were condensed with β-chloro-ethyl- and γ-chloropropyl chloroformates to form the corresponding ω-chloro-alkyl-(arsono-aryl) carbamates.

2. By treatment with 2 molecular equivalents of aqueous alkali, the β-chloro-ethyl-(arsono-aryl) carbamates were converted into arsono-aryl oxazolidones and the γ-chloropropyl-(arsono-aryl) carbamates into 3-arsono-aryl-1,3,2-oxazones.

3. By treatment with excess of aqueous alkali the arsono-aryl-oxazolidones or β-chloro-alkyl-(arsono-aryl) carbamates were converted into arsono-aryl-amino-ethanols and the β-arsono-aryl-1,3,2-oxazones or γ-chloropropyl-(arsono-aryl) carbamates into γ-arsono-aryl-amino-propanols. The arsono-aryl-amino alcohols were much less toxic than the corresponding arsanilic acids.

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