[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenicals Derived from *m*-Aminophenol

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The primary purpose of this investigation was to study the preparation of the arsenious oxides of 4-amino-2-hydroxyphenylarsonic[2] acid and of its amino and phenolic derivatives. Second, two series of arsenated phenylglycol ethers were synthesized and their structures proved by replacing the arsono group with a hydrogen atom and comparing the resulting products with some synthesized by methods which could produce only certain compounds.

Several amino substituted arsenious oxides of 4-amino-2-hydroxyphenylarsonic acid were prepared by suspending the corresponding arsonic acids in anhydrous ether, adding phosphorus trichloride, and treating the resulting solution with cold water. The arsenious oxide of the parent arsonic acid itself, however, could not be prepared by any of several methods tried.

4-Carbethoxyamino-2-hydroxyphenylarsonic acid was synthesized by direct arsonation of 3-carbethoxyaminophenol, while the corresponding carbo-*n*-propoxy- and carbobenzoxy-arsonic acids were prepared by treating an alkaline solution of 4-amino-2-hydroxyphenylarsonic acid with *n*-propyl chlorocarbonate and benzyl chlorocarbonate. The arsenated phenylglycol ethers were formed by treating the above amino derivatives with ethylene oxide or propylene oxide in dry, alcoholic potassium hydroxide solution.

Three non-arsenated phenylglycol ethers incidental to the main problem were prepared by condensing *m*-nitrophenol with certain halohydrins, reducing the resulting nitro ethers to the amines and treating the latter with acid chlorides.

Experimental

4-Carbethoxyamino-2-hydroxyphenylarsenious Oxide, I.—An ice-cooled suspension of 2 g. of 4-carbethoxyamino-2-hydroxyphenylarsonic acid in 40 cc. of anhydrous ether was stirred rapidly while 0.91 g. of phosphorus trichloride was added slowly. The arsonic acid dissolved and the solution was allowed to warm to approximately 15°, after which it was shaken vigorously with 100 cc. of cold water. The arsenious oxide which immediately precipitated as a white solid was dissolved in cold 1 *N* aqueous sodium hydroxide. The solution was filtered, cooled in ice, and neutralized with 2 *N* hydrochloric acid. The reprecipitated oxide was dried in a vacuum desiccator over sulfuric acid.

Monosodium Salt of 4-Carbethoxyamino-2-hydroxyphenylarsonic Acid, II.—The above arsonic acid (4 g.) was dissolved in a small amount of warm water containing an exactly equivalent amount of sodium carbonate. When the solution was poured slowly with stirring into 400 cc. of isopropyl alcohol, the arsonic acid salt precipitated.

β-3-Carbethoxyamino-6-arsonophenoxyethanol, III.—In a heavy-walled four-ounce bottle was placed 10 g. of dry I, 50 cc. of absolute ethyl alcohol, and 2.34 g. of potassium hydroxide. When the acid had dissolved the solution was cooled, 3.2 cc. of ethylene oxide added, the bottle clamped in a cage to hold the tight-fitting rubber stopper, and the solution warmed again for four hours, when a third portion of ethylene oxide was added and the heating continued for two hours. The alcohol was distilled, the residue dissolved in water and the solution made neutral, when it was decolorized with charcoal. The solution was made acid to congo red paper and soon a slightly pink precipitate appeared which was recrystallized from hot water. Some of the precipitate was dissolved in 1 *N* sodium carbonate solution and a drop of ferric chloride solution added. If a reddish-brown color appeared, indicating an open phenolic group, the ethylene oxide treatment was repeated for a few hours.

6,6′-Arseno-3,3′-dicarbethoxyamino-di-β-phenoxyethanol, IV.—Compound III (1.5 g.) was dissolved in a hot mixture of 45 cc. of ethyl alcohol and 70 cc. of water. The solution was cooled and 10 cc. of 50% hypophosphorous acid and a few small crystals of potassium iodide added. After standing for a week the precipitate of very small yellow needles formed was purified by treating a few minutes with a boiling alcohol–water (3:1) mixture and filtering while hot.

4-Acetylamino-2-hydroxyphenylarsonic Acid, V.—To a mixture of 5 cc. of glacial acetic acid and 5 cc. of acetic anhydride was added 3 g. of 4-amino-2-hydroxyphenylarsonic acid. The suspension was heated and stirred long enough to start the reaction, after which the mixture boiled spontaneously. When the solution had cooled, 50 cc. of water was added and a white precipitate appeared which was purified by dissolving in sodium carbonate solution and reprecipitating with dilute acid.

4-Carbo-*n*-propoxyamino-2-hydroxyphenylarsonic Acid, VI.—4-Amino-2-hydroxyphenylarsonic acid (2 g.) was dissolved in enough 2 *N* aqueous sodium hydroxide to give a definitely alkaline solution to which was added in small portions 0.95 cc. of *n*-propyl chlorocarbonate. The mixture was shaken vigorously and kept alkaline by adding aqueous sodium hydroxide in small portions. After standing for an hour, the solution was made strongly acid to congo red paper, when a heavy white precipitate formed which was recrystallized from hot isopropyl alcohol–water mixture (1:3).

4-Carbo-*n*-propoxyamino-2-hydroxyphenylarsenious Oxide, VII.—This oxide was prepared by the same

(1) Parke, Davis and Company Fellow.

(2) Bauer, *Ber.*, **48**, 1579 (1915).

TABLE I

Compound no.	Crystal form and system	Yield, %	M. p., °C.	Formula	As analyses, %[a] Calcd.	Found
I	Amorphous	100	159	$C_9H_{10}O_4AsN$	27.63	27.92
II	Amorphous	100	...	$C_9H_{11}O_5AsNNa$	22.90	22.86
III	Tetragonal needles	65	233	$C_{11}H_{16}O_7AsN$	21.45	21.52
IV	System indef. needles	90	222	$C_{22}H_{28}O_8As_2N_2$	25.04	25.14
V	Monoclinic prisms	88	Dec. 266	$C_8H_{10}O_5AsN$	27.23	27.07
VI	Orthorhombic leaflets	79	Dec. 220	$C_{10}H_{14}O_6AsN$	23.47	23.40
VII	Amorphous	73	198	$C_{10}H_{12}O_4AsN$	26.28	26.58
VIII	Hexagonal needles	82	Dec. 223	$C_{14}H_{14}O_6AsN$	20.40	20.40
IX	Amorphous	92	217	$C_{14}H_{12}O_4AsN$	22.49	22.47
X	Tetragonal needles	79	235	$C_{16}H_{18}O_7AsN$	18.22	18.19
XI	Tetragonal prisms	68	164	$C_8H_{12}O_5AsN$	27.03	27.09
XII	Tetragonal needles	41	176	$C_{17}H_{20}O_7AsN$	17.62	17.78
XIII	Glassy solid	75	Soften 159	$C_9H_{14}O_5AsN$	25.73	25.52
XIV	Tetragonal needles	70	185	$C_{12}H_{18}O_7AsN$	20.63	20.53
					Nitrogen, %	
XV	Triclinic needles	86	106	$C_{10}H_{13}O_3N$	7.17	6.91
XVI	Orthorhombic plates	80	56	$C_{11}H_{15}O_4N$	6.22	6.38
XVII	Colorless oil		B. p. 225 (11 mm.)	$C_{12}H_{17}O_4N$	5.85	5.61

[a] See Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

general procedure used in preparation of I. Compound VI (2 g.) in 40 cc. of anhydrous ether was reduced by 0.48 cc. of phosphorus trichloride. The ether solution was allowed to warm to room temperature and when it had been shaken with water the ether layer was allowed to evaporate. The oxide was purified by washing on the filter with several small portions of *N* sodium carbonate solution followed by considerable cold water.

4-Carbobenzoxyamino-2-hydroxyphenylarsonic Acid, VIII.—The general method outlined in the synthesis of VI was used in preparing this acid. 4-Amino-2-hydroxyphenylarsonic acid (12 g.) was treated with 9.5 g. of benzyl chlorocarbonate[3] added in 1-cc. portions. When all the benzyl chlorocarbonate had been added the mixture was warmed slightly and allowed to stand for two hours.

4 - Carbobenzoxyamino - 2 - hydroxyphenylarsenious Oxide, IX.—The procedure used in preparing I was followed in general. Pure VIII (2 g.) in 40 cc. of dry ether was reduced with 0.6 cc. of phosphorus trichloride. The precipitated oxide was washed with *N* sodium carbonate solution and water to purify it.

β-3-Carbobenzoxyamino-6-arsonophenoxyethanol, X.—The procedure outlined in the preparation of III was used. Compound IX (6 g.) was heated with 60 cc. of absolute alcohol, 1.15 g. of potassium hydroxide and ethylene oxide for forty hours. The ethylene oxide was added in 1.5-cc. portions at ten-hour intervals.

β-3-Amino-6-arsonophenoxyethanol, XI.—Compound X (3.87 g.) was dissolved in 75 cc. of 0.5 *N* aqueous sodium hydroxide and the solution refluxed for fifteen minutes. Next it was neutralized with concd. hydrochloric acid, charcoaled, and made slightly acid to congo red paper. The solution was then evaporated to a small volume under a cold air stream. The amine precipitated and was recrystallized from hot water.

α - Methyl - β - 3 - carbobenzoxyamino - 6 - arsonophenoxyethanol, XII.—The procedure outlined in the preparation of III was employed in treating 7.3 g. of VIII suspended in 77 cc. of dry alcohol with 1.5 g. of potassium hydroxide and propylene oxide added in 2-cc. portions at twenty-hour intervals. The mixture was heated for approximately seventy hours.

α - Methyl - β - 3 - amino - 6 - arsonophenoxyethanol, XIII.—This compound was prepared by the method employed in preparing XI. Compound XII (2.1 g.) was dissolved in 45 cc. of 0.5 *N* aqueous sodium hydroxide and the solution refluxed for twenty minutes. The latter was neutralized, charcoaled, made acid to congo red paper, evaporated to dryness and extracted with three 10-cc. portions of absolute alcohol. When the alcohol was distilled a red oil remained which was purified by dissolving in a few cc. of alcohol and pouring the solution drop by drop with stirring into 50 cc. of dry ether and then decanting the ether from the oil. When the oil was dried at 100° under reduced pressure it formed a dry foam which could be ground into a very hygroscopic powder which had to be dried in a 120° oven.

α - Methyl - β - 3 - carbethoxyamino - 6 - arsonophenoxyethanol, XIV.—Using the method employed in the preparation of VI, 2.5 g. of XIII was treated with successive small portions of ethyl chlorocarbonate. The solution was heated nearly to boiling after all the ethyl chlorocarbonate had been added. The product was recrystallized from hot water.

β - 3 - Acetylaminophenoxyethanol, XV.—β - 3 - Nitrophenoxyethanol (45.8 g.) was reduced to the amine with molecular hydrogen at 40 pounds (2.67 atm.) pressure in the presence of Raney[4] catalyst. As soon as the reduction was complete, 25 cc. of acetic anhydride was added, the mixture heated to boiling, the catalyst filtered off, and the solvent distilled. The oily residue was taken up in hot water, from which the product crystallized as a white solid.

β - 3 - Carbethoxyaminophenoxyethanol, XVI.—β - 3-Nitrophenoxyethanol (27.7 g.) was reduced as in preparing

(3) Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

(4) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

XV and the amine isolated by distilling the solvent. The amine was dissolved in 123 cc. of hot dry ethyl acetate and 9.9 cc. of ethyl chlorocarbonate added. Some hydrochloride of the amine separated as an oil and the ethyl acetate solution of the carbethoxyamino derivative was decanted from the oil. The ethyl acetate was distilled and the oily residue dissolved in hot toluene, from which it crystallized. All of the procedure involving the amine had to be performed in a carbon dioxide atmosphere to avoid air oxidation.

α - Methyl - β - 3 - carbethoxyaminophenoxyethanol, XVII.—α-Methyl-β-3-nitrophenoxyethanol (8.39 g.) was reduced and the amine isolated and treated with 2.6 cc. of ethyl chlorocarbonate following the procedure outlined in the synthesis of XVI. Removal of the solvent left the product as an uncrystallizable oil which was purified by fractional distillation under reduced pressure.

Structure Proof.—The structures of β-3-carbethoxyamino-6-arsonophenoxyethanol and of α-methyl-β-3-carbethoxyamino-6-arsonophenoxyethanol were proved by suspending these arsonic acids in acetone and treating them with molecular hydrogen at 40 lb. (2.67 atm.) pressure in the presence of Raney nickel catalyst. This treatment replaced the arsono group with an atom of hydrogen. The residues were isolated and proved to be identical with β-3-carbethoxyaminophenol and α-methyl-β-3-carbethoxyaminophenol prepared as described above.

Summary

The 4-acetyl-, 4-carbo-*n*-propoxy-, and 4-carbobenzoxyamino-2-hydroxyphenyl-arsonic acids were prepared from 4-amino-2-hydroxyphenylarsonic acid. The arsenated phenylglycol ethers β-3-carbethoxy- and α-methyl-β-3-carbobenzoxyamino-6-arsonophenoxyethanol were prepared from the corresponding hydroxy compounds while β-3-amino-6-arsonophenoxyethanol and the α-methyl derivative were derived by hydrolysis of the last two ethers in the preceding group. α-Methyl-β-3-carbethoxyamino-6-arsonophenoxyethanol was prepared from the corresponding amino compound. 4-Carbethoxy-, 4-carbo-*n*-propoxy- and 4-carbobenzoxyamino-2-hydroxyphenylarsenious oxides and 6,6′-arseno-3,3′-dicarbethoxyamino-di-β-phenoxyethanol were obtained by reduction of the arsonic acids. The non-arsenated ethers, β-3-acetyl-, β-3-carbethoxy- and α-methyl-β-3-carbethoxyaminophenoxyethanol were newly prepared during this investigation.

LINCOLN, NEBRASKA RECEIVED OCTOBER 31, 1938

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenic Derivatives of Phenylmethylcarbinol

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Although numerous aromatic arsonic acids with aliphatic side chains containing alcohol groups connected to the nucleus through oxygen or nitrogen have been prepared, little work has been done on arsenic derivatives of the phenylalkylcarbinols. Fourneau and Lestrange[2] prepared the only compounds of this type listed in the literature. Their work dealt with the three arsonobenzyl alcohols and the ortho and para arsono-2-phenylethanols, all of which were found to have some therapeutic value. It was felt that the arsenic derivatives of phenylmethylcarbinol, containing an optically active secondary alcohol group, might have even greater value.

The only practical method available for the synthesis of such compounds was the reduction of arsonoacetophenones to the corresponding secondary alcohols. A number of arsonoacetophenones are known[3-5] but none of these compounds seemed to have the properties desired. Therefore the arsenic derivatives of *p*-hydroxyacetophenone were investigated because they have no ortho substituents which might form hetero rings on reduction.

3-Arsono-4-hydroxyacetophenone was prepared by the Bart reaction[6] from the corresponding amine hydrochloride previously prepared by Edkins and Linnell[7] and was found to be sensitive to acids, cleaving arsenic trioxide. This property was not entirely unexpected as previous work had indicated that an arsono group substituted ortho to an hydroxyl group was very unstable[4,8,9] in the presence of acids. In order to obtain a more stable arsenic compound, 3-arsono-4-methoxyacetophenone was prepared.

None of the usual methods for reducing the keto group were applicable. However, following a

(1) Parke, Davis and Company Fellow.

(2) E. Fourneau and Mme. Y. de Lestrange, *Bull. soc. chim.*, **53**, 330 (1933).

(3) Gibson and Levine, *J. Chem. Soc.*, 2388 (1931).

(4) R. E. Omer and C. S. Hamilton, THIS JOURNAL, **59**, 642 (1937).

(5) C. K. Banks and C. S. Hamilton, *ibid.*, **60**, 1370 (1938).

(6) H. Bart, *Ann.*, **429**, 55 (1922).

(7) R. P. Edkins and W. H. Linnell, *Quart. J. Pharm. Pharmac.*, **9**, 75 (1936).

(8) S. B. Binkley and C. S. Hamilton, THIS JOURNAL, **59**, 1716 (1937).

(9) A. E. Beguin and C. S. Hamilton, *ibid.*, **61**, 355 (1939).