[CONTRIBUTION FROM THE PARKE, DAVIS & CO. RESEARCH LABORATORIES AND THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenated Phenoxybutanols

BY WALTER F. HOLCOMB AND CLIFF S. HAMILTON

4-β-Hydroxyethoxyphenylarsonic acid,[1] 4-γ-hydroxypropoxyphenylarsonic acid,[1] and 4-β-hydroxypropoxyphenylarsonic acid[2] have been prepared by condensing 4-hydroxyphenylarsonic acid with the appropriate chlorohydrin. Since the arsenical containing the secondary hydroxy group was found to be more effective against *T. equiperdum*[3] than that with the primary hydroxyl it was thought that an analog containing a tertiary hydroxyl group would be interesting. In the present investigation 4-β-methyl-β-hydroxypropoxyphenylarsonic acid and a number of its derivatives were prepared.

Condensation of isobutylene chlorohydrin[4] with 4-hydroxyphenylarsonic acid in alkaline solution gave only traces of the arsenated phenoxyalkanol. However, when isobutylene oxide[5] was used and the reaction carried out in a pressure bottle in 4 *N* sodium hydroxide, excellent yields were obtained.

4-β-Methyl-β-hydroxypropoxyphenylarsonic acid was nitrated in a manner similar to that of the analogous ethyl and propyl compounds but the reaction was effected so much more readily that one hour at 0° was sufficient to obtain the mono nitro derivative. 3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid was isolated directly from the diluted acid solution. Sweet and Hamilton[6] found that on nitration of the primary phenoxyalkanols the nitro derivatives were obtained from the nitration mixture only as the nitrate esters which were subsequently hydrolyzed in 3 *N* hydrochloric acid. It appears, therefore, that the isobutylene oxide has split in the normal manner to give the tertiary alcohol, whose inorganic ester would of course be easily hydrolyzed.

Reduction of 3-nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid by means of alkaline ferrous hydroxide gave the corresponding amine but better yields were obtained by catalytic reduction in alkaline solution using Raney nickel catalyst. The arsine oxide was obtained in crystalline form by reduction of the arsonic acid with sulfurous acid in the presence of hydriodic acid.

(1) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).
(2) Stevinson and Hamilton, *ibid.*, **57**, 1600 (1935).
(3) Kuhs and Tatum, *J. Pharmacol.*, **61**, 451 (1937).
(4) Michael and Leighton, *Ber.*, **39**, 2157 (1906).
(5) Obtained from Shell Chem. Co., San Francisco, California.
(6) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).

Experimental

4-β-Methyl-β-hydroxypropoxyphenylarsonic Acid and its Sodium Salt.—To a cooled solution of 65 g. of 4-hydroxyphenylarsonic acid in 225 cc. of 4 *N* sodium hydroxide was added 65 g. of isobutylene oxide. The mixture was placed in two small pressure bottles and heated to 80° for twelve hours with occasional shaking. It was diluted to 3 volumes, charcoaled, filtered, cooled, and the arsonic acid precipitated by making the solution just acid to congo red paper with concentrated hydrochloric acid.

The acid was dissolved in sufficient 2 *N* sodium hydroxide to yield a solution neutral to litmus paper. This solution was filtered into cold absolute ethanol, whereupon the monosodium salt separated.

3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic Acid.—4-β-Methyl-β-hydroxypropoxyphenylarsonic acid (10.5 g.) was added gradually to a solution of 20 cc. of nitric acid (sp. gr. 1.50) and 4 cc. of concd. sulfuric acid at 0°. After all the arsonic acid was added (about fifteen minutes) it was stirred at 0° for one hour. The product was precipitated by pouring into one liter of ice water.

3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsonic Acid. 1. Ferrous Hydroxide Method.—To a suspension of 27 g. of ferrous chloride ($FeCl_2 \cdot 4H_2O$) in 40 cc. of water and 33 cc. of 10 *N* sodium hydroxide at 20° was added a solution of 6.5 g. of 3-nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid in 20 cc. of 1 *N* sodium hydroxide. The mixture was stirred for one-half hour, filtered, the residue extracted with 20 cc. of 2% sodium hydroxide, and the combined filtrates made just neutral to congo red paper. The solution was warmed with a little activated charcoal and filtered. The colorless filtrate was concentrated *in vacuo* to a saturated salt solution whereupon the amine crystallized out.

2. Catalytic Method.—3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid (20 g.) was dissolved in 240 cc. of 0.5 *N* sodium hydroxide and the solution placed in the reduction container with about 5 g. of Raney catalyst. After the air was expelled from the apparatus the hydrogen pressure was set at 60 lb. (4 atm.) and the mixture was agitated for two hours. The solution of the reduced product was charcoaled and filtered free of catalyst. It was made just neutral to congo red paper with hydrochloric acid and the neutral solution concd. *in vacuo* to 100 cc. The crystalline amine was filtered off and an additional yield obtained by concentrating the filtrate to 50 cc.

3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsine Oxide.—A solution of 6 g. of 3-amino-4-β-methyl-β-hydroxypropoxyphenylarsonic acid in 30 cc. of water and 15 cc. of concd. hydrochloric acid was cooled to 10° and 0.8 g. of potassium iodide added. Into this solution was passed 2 g. of sulfur dioxide gas. After cooling to 10°

TABLE I

Micro assays by C. S. Chamberlain, Research Laboratories, Parke, Davis & Co. Macro assays by the method of Cislak and Hamilton, THIS JOURNAL, **52**, 632 (1930).

	Name	Crystal form	M. p., °C.	Formula	As analyses, % Calcd.	Found
1	4-β-Methyl-β-hydroxypropoxyphenylarsonic acid	Blunt needles[a]	189–192	$C_{10}H_{15}O_5As$	25.83	25.65
2	Sodium salt of 1		>325	$C_{10}H_{14}O_5AsNa$	24.05	23.90
3	3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid	Hexagonal plates[a]	210–215	$C_{10}H_{14}O_7NAs$	22.38	22.30
4	3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsonic acid	Rectangular prisms[b]	150–155	$C_{10}H_{16}O_5NAs$	24.55	24.40[c]
5	3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsine oxide	Irregular bars[a]	123–124	$C_{10}H_{14}O_3NAs \cdot H_2O$	25.9	25.7[d]
6	4,4′-Di-β-methyl-β-hydroxypropoxyarsenobenzene	Yellow amorphous powder	135–140	$C_{20}H_{26}O_4As_2$	31.30	31.50
7	3,3′-Diamino-4,4′di-β-methyl-β-hydroxypropoxyarsenobenzene	Yellow amorphous powder	125–130	$C_{20}H_{28}O_4N_2As_2$	29.4	29.15

[a] By recrystallization from water. [b] With one molecule of water of crystallization, m. p. 65–70°. [c] Micro Dumas for N % calcd. 4.58, found 4.45. [d] Micro arsenic.

again 75 cc. of 6% ammonium hydroxide solution was added. The neutral solution was cooled to 0°, made slightly alkaline for fifteen minutes, then made neutral to litmus paper with acetic acid. It was then charcoaled, filtered, and cooled for three days before crystallization was complete.

4,4′-Di-β-methyl-β-hydroxypropoxyarsenobenzene and 3,3′-Diamino-4,4′-di-β-methyl-β-hydroxypropoxyarsenobenzene.—To 100 cc. of hot water was added 4 g. of 4-β-methyl-β-hydroxypropoxyphenylarsonic acid and 25 cc. of 50% hypophosphorous acid. The solution was boiled for one-half hour and the pale yellow amorphous solid which separated was filtered off, washed well with water, and finally with a little ethanol. The corresponding 3,3′-diamino-arseno derivative was obtained in a similar manner except that the reaction mixture was neutralized with sodium hydroxide before the arseno separated.

Summary

4-Hydroxyphenylarsonic acid was condensed with isobutylene oxide to form 4-β-methyl-β-hydroxypropoxyphenylarsonic acid and this was reduced to the corresponding arseno derivative with hypophosphorous acid.

3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid was obtained directly from the nitration of 4-β-methyl-β-hydroxypropoxyphenylarsonic acid.

3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsonic acid was obtained by reduction of the corresponding nitro derivative with ferrous hydroxide and catalytically with Raney nickel catalyst. The corresponding arsine oxide and arseno derivatives of this amino arsenical were also prepared.

DETROIT, MICH. RECEIVED FEBRUARY 3, 1939

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Structure of Vitamin B_6. I

BY ERIC T. STILLER, JOHN C. KERESZTESY AND JOSEPH R. STEVENS

Since the reports by Keresztesy and Stevens[1,2] from this Laboratory on the isolation and characterization of crystalline vitamin B_6, further research work has been carried out with the object of determining the chemical constitution of this vitamin. This objective was reached and we now wish to record the evidence which led us to the structure of vitamin B_6. Recently, Kuhn and his coworkers[3–5] have announced the results of researches which led to the same structure for the vitamin.

Other workers[6–9] have confirmed the original findings of Keresztesy and Stevens.[1,2]

(1) Keresztesy and Stevens, *Proc. Expll. Biol. Med.*, **38**, 64 (1938).

(2) Keresztesy and Stevens, THIS JOURNAL, **60**, 1267 (1938).

(3) Kuhn and Wendt, *Ber.*, **72**, 305, 311 (1939).

(4) Kuhn, Andersag, Westphal and Wendt, *ibid.*, **72**, 309 (1939).

(5) Kuhn, Wendt and Westphal, *ibid.*, **72**, 310 (1939).

(6) Lepkovsky, *Science*, **87**, 169 (1938); *J. Biol. Chem.*, **124**, 125 (1938).

(7) Kuhn and Wendt, *Ber.*, **71**, 780, 1118 (1938).

(8) Ichiba and Michi, *Sci. Papers Inst. Phys. Chem. Research*, **34**, 623, 1014 (1938).

(9) György, THIS JOURNAL, **60**, 983 (1938).