[Contribution from the Parke, Davis and Company Research Laboratories, and the Avery Laboratory of Chemistry of the University of Nebraska]

2-Hydroxy-4-aminophenylarsine Oxide and Related Oxides

By C. Kenneth Banks[1] and Cliff S. Hamilton

Because of the therapeutic value of "Mapharsen," 3-amino-4-hydroxyphenylarsine oxide, work was undertaken to investigate the isomeric oxide, 2-hydroxy-4-aminophenylarsine oxide, whose parent arsonic acid has the highest therapeutic index of the ten possible isomeric hydroxyaminophenylarsonic acids[2] against *T. brucei.*

The chief difficulties encountered were the ease of dearsonation and the resistance to reduction shown by 2-hydroxy-4-aminophenylarsonic acid. Bauer,[3] Hewitt and King,[4] and Beguin and Hamilton[5] all have reported on these factors. Phosphorus trichloride was used successfully by the last-named workers to reduce amino substituted derivatives of the acid and they prepared three such oxides, the 4-carbethoxy-, carbo-*n*-propoxy- and carbobenzoxy-2-hydroxyphenylarsine oxides.

Investigation of 2-hydroxy-4-aminophenylarsonic acid showed that hydrochloric acid and other hydrohalic acids, as well as hypophosphorous acid, hydrogen in the presence of Raney nickel, phosphorus trichloride, and sodium hydrosulfite caused dearsonation. This precluded the use of phosphorus halides as the reducing agent, as well as the use of hydrochloric acid as the solvent medium for sulfur dioxide reductions. Dilute sulfuric acid was found to be the best acid solvent medium. When reacting with sulfur dioxide alone, the reaction was very slow, and decomposition occurred before the reaction had progressed very far. Although iodides in the presence of acids tended to cause dearsonation and the formation of iodine complexes, this could not be avoided since other catalysts tried were not effective. By keeping the acid concentration between 2 and 6 *N* and using from 0.5 to 2 g. of potassium iodide per liter, sulfur dioxide gave the desired product in about eighteen hours. During the isolation it was found advisable to keep the temperature below 40–50°.

In the course of the investigation it was shown that the starting product, 2-hydroxy-4-carbethoxyaminophenylarsonic acid, as reported by Bauer,[3] probably contained an impurity. Beguin[6] had noted that the product isolated from the arsonation of *m*-carbethoxyaminophenol, when purified carefully, had a melting point of 221° (cor.) as compared with the value 214° recorded in the literature. By a different method of isolation, most of the product was found to have a melting point of 231–232° (cor.). Arsenic analyses were the same for all these products, indicating the presence of an impurity of the same or nearly the same arsenic content, probably an isomeric acid.

The compounds derived from 2-hydroxy-4-carbethoxyaminophenylarsonic acid changed but little in melting point from the values previously found[5] except for 2-hydroxy-4-carbethoxyaminophenylarsine oxide (from 159 to 241°) and 2-hydroxy-4-aminophenylarsonic acid (from 173 to 184°).

Several other oxides of the same general formula were investigated, each class requiring its own particular variation in conditions. It was found that stability in general, and in particular against hydrohalic acids, was increased by substitution in the hydroxyl or amine groups, or both.

Experimental

1. **2-Hydroxy-4-carbethoxyaminophenylarsonic Acid.**—*m*-Carbethoxyaminophenol (90 g.) and sirupy arsenic acid (100 g. of 87%) were placed in a liter flask, fitted with a stirrer and air-cooled reflux condenser, and heated on a steam-bath for twenty-four hours. The air condenser was removed and the heating and stirring continued until the contents of the flask became solid (from forty to sixty hours). The stirrer was then removed and the solid left on the steam-bath for an additional twenty-four hours. The material was heated with a saturated solution of sodium bicarbonate until all the product dissolved. The solution was charcoaled and filtered to remove the tar, and then cooled. Any unreacted *m*-carbethoxyaminophenol present crystallized out and was filtered off. On acidification of the filtrate to congo red paper, the arsonic acid precipitated and was purified by charcoaling and recrystallizing twice from hot water.

2. **2-Hydroxy-4-aminophenylarsonic Acid.**—2-Hydroxy-4-carbethoxyaminophenylarsonic acid (45 g.) was dissolved in 3 *N* sodium hydroxide (300 ml.) and refluxed for two hours. After charcoaling and cooling, the solution

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[1] Parke, Davis and Company Research Fellow during the initial part of the investigation.

[2] Fourneau, *et al.*, *Bull. soc. chim.*, **41**, 499 (1927).

[3] Bauer, *Ber.*, **48**, 1579 (1915).

[4] Hewitt and King, *J. Chem. Soc.*, 817 (1926).

[5] Beguin and Hamilton, This Journal, **61**, 355 (1939).

[6] Unpublished portion of doctor's thesis, University of Nebraska, 1938.

TABLE I

No.	Color	M. p., °C.	Yield, %	Formula	As analyses, %[a] Calcd.	As analyses, %[a] Found
1	White	231	62	$C_9H_{12}O_6NAs$	24.56	24.55
2	White	184	73	$C_6H_8O_4NAs$	32.16	32.18
3	White	<110	62	$C_{10}H_{14}O_6NAs \cdot 2H_2O$	21.11	21.15
4	White	241	78	$C_9H_{10}O_4NAs$	27.63	27.71
5	White	209	61	$C_{10}H_{12}O_4NAs$	26.28	26.19
6	White	224	54	$C_{14}H_{12}O_4NAs$	22.49	22.47
7	White	>300	52	$C_6H_6O_2NAs$	37.65	37.74
8	White	>225 decompn.	80	$C_6H_6O_2NAs \cdot H_2SO_4$	25.23	25.34
9	Lt. gray	>250	65	$C_6H_7O_3NAsNa$	31.3	31.5[b]
10	White	ca. 100	60	$C_8H_{10}O_3NAs \cdot H_2O$	28.7	28.95
11	White	ca. 90	45	$C_9H_{12}O_3NAs \cdot H_2O$	27.2	27.1[b]
12	White	222	79	$C_{11}H_{14}O_5NAs$	23.78	23.74
13	White	175	64	$C_{12}H_{16}O_5NAs$	22.77	22.74
14	White	>250	59	$C_{16}H_{16}O_5NAs$	19.84	19.92
15	White	147	47	$C_{10}H_{12}O_4NAs$	26.3	26.1[b]

[a] See Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] Microassays by C. S. Chamberlain, Research Laboratories, Parke, Davis & Company.

was made just neutral to congo red paper, precipitating the arsonic acid, which was recrystallized from hot water.

3. **2-Methoxy-4-carbethoxyaminophenylarsonic Acid.**—2-Hydroxy-4-carbethoxyaminophenylarsonic acid (10 g.) was dissolved in excess 2 *N* sodium hydroxide and an excess of dimethyl sulfate added with shaking. The solution was placed on a shaker for three hours. It was then made strongly acid, separating an oil that solidified slowly and was recrystallized from hot water. Under these conditions it contains two molecules of water of crystallization and has no definite melting point, dissolving completely in the water of crystallization at about 110°.

4. **2-Hydroxy-4-carbethoxyaminophenylarsine Oxide.**—Purified 2-hydroxy-4-carbethoxyaminophenylarsonic acid (10 g.) was suspended in anhydrous ether (400 ml.), the suspension cooled in an ice-bath and stirred vigorously while adding a slight excess of phosphorus trichloride. The ether solution, upon completion of the reaction (indicated by disappearance of the arsonic acid), was hydrolyzed by shaking with water (600 ml.) containing ammonium hydroxide (5 eq.). The ether was then evaporated by an air stream and the crude oxide filtered off in quantitative yields. The crude product was essentially pure but could be further purified by solution in *N* sodium hydroxide, stirring with activated charcoal for fifteen minutes, filtering, and reprecipitating with 2 *N* sulfuric acid.

5. **2-Hydroxy-4-carbo-*n*-propoxyphenylarsine Oxide.**—This compound was prepared in the same manner as no. 4 above from 2-hydroxy-4-carbo-*n*-propoxyphenylarsonic acid.[5]

6. **2-Hydroxy-4-carbobenzoxyphenylarsine oxide**' was prepared from 2-hydroxy-4-carbobenzoxyphenylarsonic acid[5] by the reaction of no. 4 above.

7. **2-Hydroxy-4-aminophenylarsine Oxide.**—Carefully purified clear white 2-hydroxy-4-aminophenylarsonic acid (10 g.) was dissolved in 2 *N* sulfuric acid (200 ml.) by warming. The solution was cooled with agitation, potassium iodide (0.2 g.) added, and then saturated with sulfur dioxide for six hours. It was placed in the refrigerator overnight, then boiled under reduced pressure, keeping the temperature below 40°, to remove the excess sulfur dioxide. After making alkaline with ammonia water, the solution was taken to dryness (below 40°). The residual solid was triturated with water and the suspended oxide filtered from the solution of inorganic salts. Further purification may be obtained by dissolving in sodium carbonate and reisolating at a *p*H of 6.

8. **Sulfate Salt of 2-Hydroxy-4-aminophenylarsine Oxide.**—2-Hydroxy-4-aminophenylarsine oxide (2 g.) was dissolved in 60% sulfuric acid (15 ml.) and the solution cooled in an ice–salt-bath. The sulfate salt precipitates in a crystalline form that decrepitates on drying.

9. **Sodium Salt of 2-Hydroxy-4-aminophenylarsine Oxide.**—2-Hydroxy-4-aminophenylarsine oxide (3 g.) was dissolved in *N* sodium hydroxide (15 ml.) and absolute ethyl alcohol (55 ml.) added. The sodium salt precipitates slowly. It was filtered off and dried.

10. **2-β-Hydroxyethoxy-4-aminophenylarsine Oxide.**—2-β-Hydroxyethoxy-4-aminophenylarsonic acid[5] (3 g.) was suspended in water (75 ml.) and sufficient 6 *N* sulfuric acid added to give a clear solution. The solution was saturated with sulfur dioxide for six hours after the addition of potassium iodide (0.1 g.). On neutralizing with ammonia and allowing to stand, the hydrate of the oxide crystallized.

11. **2-β-Hydroxypropoxy-4-aminophenylarsine oxide** was prepared in the same manner as no. 10 above from the corresponding arsonic acid.[5]

12. **2-β-Hyrdoxyethoxy-4-carbethoxyaminophenylarsine Oxide.**—2 - β - Hydroxyethoxy - 4 - carbethoxyaminophenylarsonic acid[5] (1 g.) was dissolved in alcohol (25 ml.), water (25 ml.), 60% sulfuric acid (5 ml.) and potassium iodide (0.15 g.). Sulfur dioxide was passed through the solution for two hours and the solution allowed to stand overnight. It was neutralized with ammonia and the alcohol removed *in vacuo*. On cooling, the oxide precipitated.

13. **2-β-Hydroxypropoxy-4-carbethoxyaminophenylarsine oxide** was prepared in a manner analogous to no. 12 above from the corresponding arsonic acid.[5]

14. **2-β-Hydroxyethoxy-4-carbobenzoxyaminophenylarsine oxide** was prepared in the manner of no. 12 above from the corresponding arsonic acid.[5]

15. **2-Methoxy-4-carbethoxyaminophenylarsine Oxide.**—2-Methoxy-4-carbethoxyaminophenylarsonic acid (1 g.) was suspended in dry ether (40 ml.) at room temperature and phosphorus trichloride (0.5 g.) added slowly with stirring. After one hour, the ether was evaporated, water added and the oxide filtered off.

Summary

1. 2-Hydroxy-4-aminophenylarsine oxide and eight derived oxides were prepared for the first time. Three derived oxides previously prepared were made again in purer form.

2. 2 - Hydroxy - 4 - carbethoxyaminophenylarsonic acid and 2-hydroxy-4-aminophenylarsonic acid were prepared in purer form.

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[CONTRIBUTION FROM THE BAILEY CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Chlorination of Phenyl Ether and Orientation in 4-Chlorophenyl Ether

BY RAY Q. BREWSTER AND GLENN STEVENSON

Orientation in the phenyl ether series of compounds has been studied by several investigators.[1] Work upon the iodo and methoxy derivatives has been done in this Laboratory[2] and the present report contains results obtained with 4-chlorophenyl ether. Mailhe and Murat[3] chlorinated phenyl ether and obtained a mixture of products from which they succeeded in separating 4-chlorophenyl ether and a liquid dichloro compound which they assumed to be the 4,4′ derivative. They make no mention of this latter solidifying upon cooling and very likely it was a mixture of 4,4′-dichlorophenyl ether and 3,4-dichlorophenyl ether. Our experiments have shown that chlorination of phenyl ether in acetic acid solution at room temperature gives chiefly monosubstitution at position 4 and that further reaction with chlorine introduces the second chlorine atom at either position 3 or position 4′. Likewise the bromination and nitration of 4-chlorophenyl ether yields a mixture of 3,4 and 4,4′-disubstitution products. In the case of iodination, however, by means of iodine chloride only the 4-chloro-4′-iodophenyl ether could be obtained.

Experimental Part

Chlorination of Phenyl Ether.—The chlorination of phenyl ether in the absence of a solvent produced hopeless mixtures, while poor results were obtained in the presence of carbon tetrachloride. The use of acetic acid solution, however, was found to give chiefly the 4-chlorophenyl ether.

Two moles (340 g.) of phenyl ether was dissolved in 1000 g. of glacial acetic acid and chlorine gas passed into the solution until the gain in weight (including that of the hydrogen chloride absorption apparatus) was 140–150 g. After standing overnight the chlorinated products were precipitated with water, washed well and dried. From three such lots (6 moles in all) which were combined and worked up together there were obtained by fractional distillation 50 g. of unchanged phenyl ether, 1105 g. of 4-chlorophenyl ether (I),[4] b. p. 146–150° (7 mm.), 15 g. of 4,4′-dichlorophenyl ether (II),[5] b. p. 168–172° (7 mm.), m. p. 30°, and 10 g. of 3,4,4′-trichlorophenyl ether (III), b. p. 180–190° (7 mm.), m. p. 46–47°. The position of all three chlorine atoms in compound III was proved by its preparation by the further chlorination of either 4,4′-dichlorophenyl ether (II) or 3,4-dichlorophenyl ether (V). The composition of all products was checked by analysis but analyses are here reported for only those substances which have not previously been recorded.

Anal. III. Calcd. for $C_{12}H_7OCl_3$: Cl, 38.94. Found: Cl, 38.65.

Any 2-chlorophenyl ether (IV) produced by this method of chlorination of phenyl ether must have been in small proportion as none was isolated. A sample prepared from 2-aminophenyl ether[6] was found to boil at 142–146° (12 mm.), and to melt at 47–48°.

Chlorination of 4-Chlorophenyl Ether.—Chlorine gas from a cylinder was passed through a solution of 102.5 g. (0.5 mole) of 4-chlorophenylether in 500 cc. of glacial acetic acid at room temperature until 35 g. of chlorine had been absorbed. The solution was allowed to stand overnight,

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[1] (a) Scarborough, *J. Chem. Soc.*, **132**, 2361 (1929); (b) Roberts and Turner, *ibid.*, **127**, 2004 (1925); (c) McCombie, Macmillan and Scarborough, *ibid.*, 529 (1931); (d) Groves, Turner and Sharp, *ibid.*, 512 (1929); (e) Fox and Turner, *ibid.*, 1853 (1930).

[2] (a) Brewster and Strain, THIS JOURNAL, **56**, 117 (1934); (b) Brewster and Choguill, *ibid.*, **61**, 2702 (1939).

[3] Mailhe and Murat, *Bull. soc. chim.*, [4] **11**, 329 (1912).

[4] Compound I was also obtained by the diazo reaction from 4-aminophenyl ether. Mailhe and Murat[3] prepared it along with other products by the chlorination of phenyl ether in carbon tetrachloride solution. Suter and Green[6] found that it could be made from potassium phenate and *p*-chloroiodobenzene.

[5] An identical specimen of II was made in 50% yield from 4-chloro-4′-aminophenyl ether by the Sandmeyer method. According to our observations a repeatedly crystallized sample of 4-chloro-4′-acetaminophenyl ether melted at 115°. *Anal.* Calcd. for $C_{14}H_{12}O_2NCl$: Cl, 13.58; N, 5.35. Found: Cl, 13.52; N, 5.37. Scarborough[1a] reports a melting point of 146°.

[6] Suter and Green, THIS JOURNAL, **59**, 2578 (1937), report 2-chlorophenyl ether as melting at 39°. By private correspondence Dr. Suter informed us that "further purification of the 2-chlorophenyl ether made from potassium phenoxide and *o*-chloro-iodobenzene raised the melting point to 46–47° and a mixed melting point with the material from 2-aminophenyl ether showed no depression."