

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

HYDROXY-NAPHTHOQUINONE STUDIES. V. DERIVATIVES OF 2-BROMO-5-HYDROXY-1,4-NAPHTHOQUINONE (MONOBROMO-JUGLONE)

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The halogenation of juglone was first studied by one of us with Scott² who found that the treatment of juglone with bromine in hot glacial acetic acid solution yielded a tribromo derivative with all bromine atoms in the nucleus, whereas in cold solution a dibromo addition product was obtained. The latter, on heating with absolute alcohol, lost 1 molecule of hydrobromic acid, the resulting product being monobromo-juglone. Our new studies show that this compound is very reactive and we have worked out only a few of the reactions which it will undergo. The bromine atom is readily replaced by chlorine by heating the compound with an alcoholic solution of hydrochloric acid. Both monohalogen products were converted into their benzoates. Furthermore, monobromo-juglone will take up by substitution another atom of bromine in hot glacial acetic acid solution. The acetate of the dibromo-juglone was prepared. It is a peculiar fact that only 1 bromine atom is taken up, whereas juglone will take up 3 atoms with avidity. The bromine already present seems to produce a repelling effect. Both bromine atoms in dibromo-juglone are replaced by chlorine under the influence of hydrochloric acid in alcoholic solution. Finally, 1 of the bromine atoms is replaced by the hydroxyl group when dibromo-juglone is heated with an alcoholic solution of sodium hydroxide. A red and a yellow product are obtained. The red substance contains 1 molecule of water of crystallization and the yellow seems to be the anhydrous form.

We were unable to prepare a potassium salt of monobromo-juglone and could isolate no product after treatment with sodium ethylate. Neither could any definite compound be identified when it was oxidized with nitric acid. It was hoped in this way more certainly to establish the position of the bromine atom.

The positions of the bromine atoms in juglone dibromide³ are undoubtedly 2 and 3, since hydrobromic acid is so readily split off. In the latter reaction we assume that the bromine atom left in the nucleus is in Position 2. When the second bromine atom is introduced into the ring, we believe it enters *ortho* to the bromine already present, since there is no place open which

¹ A portion of a thesis submitted in June, 1922, to the Faculty of the University of North Carolina by B. Naiman in candidacy for the degree of Master of Science.

² Wheeler and Scott, *THIS JOURNAL*, 41, 833 (1919).

³ Wheeler and Scott, *ibid.*, 41, 837 (1919).

is *para* to it. The chlorine atoms are naturally similarly placed. When one bromine atom in dibromo-juglone is replaced by hydroxyl, we assume that the second bromine atom (in Position 3) was displaced, on the ground that the last added is less strongly held in the ring.

Experimental Part

2-Bromo-5-hydroxy-1,4-naphthoquinone, (2-Bromojuglone), $C_{10}H_4O_2OHBr$.—This compound was first prepared by Wheeler and Scott, but we had difficulty with the method given and, therefore, worked out modifications so that the product was more certain to be obtained, the time was greatly shortened and the yield much increased. Five g. of juglone (care must be taken about its purity), suspended in 50 cc. of glacial acetic acid containing 1.5 cc. of bromine, was shaken mechanically for 15 minutes. The solution which soon took place was poured with stirring into much cold water. The dibromide separated as a reddish-yellow mass of crystals which melted at 102°. The dibromide is unstable in the light and in the air, but is stable in the presence of acetic acid. In filtering it off the acid was not completely washed out of it. It was then dissolved in 15 cc. of absolute alcohol and heated under a reflux condenser for 45 minutes when 6.1 g. of the monobromo-juglone crystallized in reddish-brown plates, the product at this stage being nearly pure with a melting point of 164°; the pure compound melts at 166°. The yield was more than doubled. The melting point of the acetate, 148°, agreed with that given by Wheeler and Scott. A potassium salt could not be obtained by treatment of an ether solution with an aqueous potassium carbonate solution. The solution became dark purple and only a black product was obtainable. The oxidation of monobromo-juglone was attempted with nitric acid of sp. gr. 1.15 in a sealed tube at 180°, but no compound could be identified in the product.

2-Bromo-5-benzyloxy-1,4-naphthoquinone, $C_{10}H_4O_2OCOC_6H_5Br$.—Half a gram of monobromo-juglone was heated with 5 cc. of benzoyl chloride under a reflux condenser for 3 hours. The red solution formed became brown and as it cooled a mass of lemon-yellow needles was deposited. These melted at 200–202° and weighed 0.44 g. After recrystallizing 4 times from benzene the melting point became constant at 222°. The product is slightly soluble in alcohol, easily in acetone, but is best recrystallized from benzene.

Analysis. Subs., 0.1590: AgBr, 0.0828. Calc. for $C_{17}H_9O_4Br$ (357): Br, 22.41. Found: 22.16.

2-Chloro-5-hydroxy-1,4-naphthoquinone, (2-Chlorojuglone), $C_{10}H_4O_2OHCl$.—To a solution of 0.5 g. of dry hydrogen chloride in 50 cc. of absolute alcohol was added 0.7 g. of monobromo-juglone. The mixture was warmed on the water-bath until solution was complete. When the solution became brown it was cooled with running water. A mass of light brown, flat needles separated. These melted at 162° and weighed 0.45 g. The melting point was raised to 164° on recrystallizing the substance from alcohol.

Analysis. Subs., 0.2179: AgCl, 0.1512. Calc. for $C_{10}H_6O_3Cl$ (208.5): Cl, 17.02. Found: 17.15.

This compound was prepared by another method by Wheeler and Scott⁴ who obtained it by heating the dichloride (addition product) of juglone with absolute alcohol.

2-Chloro-5-benzyloxy-1,4-naphthoquinone, $C_{10}H_4O_2OCOC_6H_5Cl$.—This compound was prepared in the same manner as was the benzoate of monobromo-juglone. The yield was 90% of the weight of the chlorojuglone used. The crude product melted at 212°, but on recrystallizing thrice from benzene the melting point was raised to 222°. It crystallizes in lemon-yellow needles.

⁴ Ref. 2, p. 836.

Analysis. Subs., 0.2455: AgCl, 0.1137. Calc. for $C_{17}H_9O_4Cl$ (312.5): Cl, 11.36. Found: 11.45.

2,3-Dibromo-5-hydroxy-1,4-naphthoquinone, (2,3-Dibromo-juglone), $C_{10}H_6O_4OH-Br_2$.—One-quarter g. of monobromo-juglone was dissolved in 10 cc. of glacial acetic acid and 0.1 cc. of bromine (2 mols.) was added. After heating on the water-bath for 3 hours, the solution was cooled. A mass of light red crystals separated. These melted at 167° and weighed 0.2 g. On recrystallizing from carbon tetrachloride the product was obtained in fine gold-bronze needles which melted at 169° . On slow crystallization, long needles were obtained, growing together in moss-like forms. The melting point is only 1° below that of tribromo-juglone.

Analysis. Subs., 0.1943: AgBr, 0.2204. Calc. for $C_{10}H_4O_3Br_2$ (332): Cl, 48.20. Found: 48.27.

2,3-Dibromo-5-acetoxy-1,4-naphthoquinone, $C_{10}H_6O_2OCOCH_3Br_2$.—Four-tenths g. dibromo-juglone was heated under a reflux condenser with 5 cc. of acetic anhydride for 6 hours. On cooling, light yellow needles, melting at 170° , were deposited. Recrystallization from alcohol or glacial acetic acid gave the pure compound melting at 172° ; yield, 0.5 g.

Analysis. Subs., 0.1812: AgBr, 0.1833. Calc. for $C_{12}H_8O_4Br_2$ (374): Br, 42.78. Found: 43.04.

2,3-Dichloro-5-hydroxy-1,4-naphthoquinone (2,3-Dichloro-juglone), $C_{10}H_6O_2OHCl_2$.—One-tenth g. of dibromo-juglone was dissolved in 8 cc. of absolute alcohol containing 0.1 g. of dry hydrogen chloride. The solution was heated on the water-bath until crystals began to appear; after cooling the solution they were filtered off. On recrystallizing from alcohol, golden-brown needles, melting at 153° , were obtained.

Analysis. Subs., 0.2614: AgCl, 0.3107. Calc. for $C_{10}H_4O_3Cl_2$ (243): Cl, 29.21. Found: 29.40.

This compound was made by Wheeler and Scott⁵ who chlorinated juglone in the glacial acetic acid solution. They gave 149° as the melting point.

Action of Sodium Hydroxide on Dibromo-juglone.—One part of dibromo-juglone was dissolved in 80 parts of alcohol and 40 parts of 10% sodium hydroxide solution. The solution immediately became deep violet and then blood-red after heating on the water-bath. After an hour the solution was poured into 100 parts of cold water and acidified with dil. sulfuric acid. A mass of yellow needles was precipitated. The washed, dried product melted at 190° . It was very soluble in ether and not so soluble in alcohol or chloroform. The alcoholic solution is deep red and when a few drops of water are added to it red needles crystallize. Upon heating, these red crystals turn brownish-yellow at about 80° and melt at 192° . When they are recrystallized from chloroform the same melting point is obtained. Analysis indicates that one bromine atom has been replaced by the hydroxyl group. The substance would be then a monobromo-dihydroxy-naphthoquinone. The red crystals contain one molecule of water of crystallization and the yellow form is undoubtedly the anhydrous compound.

Analyses. Subs. (red crystals), 0.0971, 0.1890: AgBr, 0.0638, 0.1230. Calc. for $C_{10}H_6O_2(OH)_2Br.H_2O$ (287): Br, 27.87. Found: 27.96, 27.70.

Further work on the yellow compound will be undertaken.

Summary

1. A new method of preparing monobromo-juglone is described which saves time, increases the yield and makes the reaction more certain to occur. The benzoate was prepared.

⁵ Ref. 2, p. 837.

2. Monobromo-juglone is converted into monochloro-juglone by the action of hydrochloric acid in alcoholic solution. Its benzoate was prepared.

3. Bromination of monobromo-juglone in hot glacial acetic acid solution gives a dibromo-juglone. It also gave a benzoate.

4. Dibromo-juglone becomes dichloro-juglone by the action of hydrochloric acid in alcoholic solution.

5. One bromine atom in dibromo-juglone is replaced by hydroxyl when treated with alcoholic sodium hydroxide.

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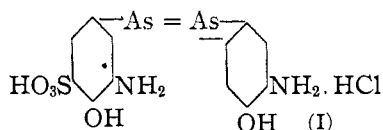
[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

THE SULFUR CONTENT OF ARSPHENAMINE AND ITS RELATION TO THE MODE OF SYNTHESIS AND TOXICITY. III¹

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In continuing the investigation of the formation of sulfur compounds during the reduction of 3-nitro-4-hydroxy-phenylarsonic acid to arspenamine base by sodium hydrosulfite, the action of pure hydrosulfite² has been examined to determine whether the presence of the sulfonic acid



in arspenamine is due to the action of the hydrosulfite or of the impurities present in commercial samples. When the reduction was carried out under the conditions favoring the formation of relatively toxic products with high sulfur content, the results were in fair agreement with those obtained using commercial hydrosulfite (Table I).

A known⁴ characteristic of this type of arspenamine is the deposition of a solid, mainly the sulfonic acid (I), when a methyl alcohol solution

¹ This is the ninth of a series of studies on the properties contributing to the toxicity of arspenamine being made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work is under the general direction of Dr. Reid Hunt, who is also responsible for the biological tests reported in this paper.

² Christiansen and Norton, *J. Ind. Eng. Chem.* (To be published soon.)

³ King, *J. Chem. Soc.*, 120, 1107, 1414 (1921), found this substance in English commercial samples of arspenamine; it was shown later that it forms only when the nitro acid is reduced under certain conditions; *THIS JOURNAL*, 44, 847 (1922).

⁴ Fargher and Pyman, *J. Chem. Soc.*, 117, 370 (1920). King, Ref. 3. Christiansen *THIS JOURNAL*, 44, 854 (1922).