

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

**The Mercuration of 5-Nitroguaiacol<sup>1,2</sup>**BY NATHAN L. DRAKE, HILLMAN C. HARRIS<sup>3</sup> AND CHARLES B. JAEGER, JR.<sup>4</sup>

The present work was undertaken to determine the structure of the compounds obtained by direct mercuration of 5-nitroguaiacol. In addition to the present work, other chemical, pharmacological and clinical studies are in progress and will be reported elsewhere.

For our purpose, it was of fundamental importance that the 5-nitroguaiacol used be authentic and pure. Undoubtedly all of the possible mononitroguaiacols have been prepared,<sup>5</sup> but no fully satisfactory characterization of them has appeared in the literature. One of us has developed a complete characterization of the mononitroguaiacols,<sup>6</sup> as well as a synthesis of pure 5-nitroguaiacol. Details of the synthesis appear in the Experimental Section of this paper.

2-Amino-5-nitroanisole is a well-known dye intermediate. It is converted readily in high yield to 4-nitroguaiacol by treatment under reflux with aqueous alkali. 4-Nitroguaiacol whose melting point is 102–103°, melts at 96–97° when mixed with 5-nitroguaiacol, whose melting point is 104–104.5°. Both of these nitroguaiacols are converted by dimethyl sulfate and alkali to the same nitroveratrole. Furthermore, they yield different amines, and these amines are converted through their diazonium salts to different hydroxyguaiacols.

Inasmuch as the structure of 4-nitroguaiacol, prepared as above, seems hardly debatable, it is reasonable to conclude that the nitroguaiacol whose melting point is 104–104.5° is 5-nitroguaiacol.

The product from the mercuration of 5-nitroguaiacol with mercuric acetate in aqueous acetic acid in the presence of sodium acetate is an orange colored, amorphous solid having no clearly defined melting point. It is soluble in none of the usual organic solvents except glacial acetic acid. The position of the mercury in the isomers which comprise this product has been demonstrated by the method of Dimroth.<sup>7</sup>

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(4) Associated with Lynch and Co., 2939 Frederick Avenue, Baltimore, Maryland.

(5) Cardwell and Robinson, *J. Chem. Soc.*, **107**, 250 (1915); Cousin, *Chem. Zentr.*, **70**, I, 877 (1899); Kauffmann and Franck, *Ber.*, **39**, 2725 (1906); Klemenc, *Monatsh.*, **33**, 704 (1912); Paul, *Ber.*, **39**, 2777 (1906); Pollecoff and Robinson, *J. Chem. Soc.*, **113**, 647 (1918); Reidel, *Chem. Zentr.*, **84**, II, 1181 (1913) (abstract of German Patent 264,012); Reverdin and Crepieux, *Ber.*, **36**, 2258 (1903); Reverdin and Crepieux, *ibid.*, **39**, 2725 (1906); Rupe, *ibid.*, **30**, 3446 (1897); Wegscheider and Klemenc, *Monatsh.*, **31**, 734 (1910).

(6) Jaeger, unpublished results.

(7) Dimroth, *Ber.*, **35**, 2032 (1902).

Analyses for mercury show that the product contains 49–54% mercury (depending upon the exact mercuration conditions), which indicates a mixture of mono- and dimercurated derivatives, containing up to 60% dimercurated compound.

Replacement of mercury by bromine<sup>7</sup> yields a mixture of bromonitroguaiacols from which two compounds were isolated by a prolonged and tedious fractional crystallization. The first, I, was a monobromonitroguaiacol, whose melting point was 151–152°; the second, II, was a dibromonitroguaiacol which melted at 119–120°.

Only two monobromoguaiacols are mentioned in the literature.<sup>8,9</sup> Raiford and Silker have very kindly furnished us with a sample of their compound, which they characterized as 4-bromo-5-nitroguaiacol (m. p. 118–119°). Mixed melting point tests showed this to be different from our monobromonitroguaiacol. We have been unable to repeat the synthesis of the compound reported by Robertson following his directions for the bromination of 5-nitroguaiacol. He cites no evidence of the source of his 5-nitroguaiacol; we have not been able to brominate 5-nitroguaiacol by any of the usual methods.

The identity of compound I was established by eliminating the nitro group by reduction, diazotization of the resulting amine, and reaction of the diazonium salt with hypophosphorous acid.<sup>10</sup> This series of reactions yielded a product which melted at 62–63° and which was found to be 6-bromoguaiacol; an authentic sample was obtained from 6-nitroguaiacol<sup>8</sup> by replacement of the nitro group with bromine by way of the amine according to the Sandmeyer method. Compound I is, therefore, 6-bromo-5-nitroguaiacol.

A similar series of reactions starting with II gave a dibromoguaiacol which melted at 64–65°. An identical product was synthesized from 4-nitroguaiacol by bromination followed by replacement of the nitro group with bromine in the same way as before. Compound II is, therefore, 4,6-dibromo-5-nitroguaiacol. This was confirmed by the replacement of the nitro group of II by bromine; the substance thus obtained was the same tribromoguaiacol formed by direct bromination of guaiacol,<sup>11</sup> namely, 4,5,6-tribromoguaiacol.

**Experimental**

**Guaicol Acetate.**—Redistilled guaiacol (b. p. 204–205°) was acetylated by mixing it (124 g., 1 mole) with acetic anhydride (204 g., 2 moles) and 1 ml. of concentrated sul-

(8) Robertson, *J. Chem. Soc.*, **93**, 788 (1911).

(9) Raiford and Silker, *J. Org. Chem.*, **2**, 346 (1937).

(10) Kornblum, "Organic Reactions, Roger Adams, Editor-in-Chief, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 262.

(11) Zaglorami, *Gazz. chim. ital.*, **62**, 570 (1932); *C. A.*, **27**, 72 (1933).

furic acid as catalyst and distilling the mixture until the acetic acid formed in the reaction was removed, as indicated by a still-head temperature equivalent to the boiling point of acetic anhydride. The reaction mixture was then cooled, washed with cold water, dried over calcium chloride, and fractionated under reduced pressure. The yield was 124 g. of guaiacol acetate which boiled at 123–124° (13 mm.).

**5-Nitroguaiacol.**—A solution of guaiacol acetate (135 g., 0.813 mole) in 120 ml. of glacial acetic acid was added all at once to a solution of 115 ml. of fuming nitric acid (sp. gr. 1.5) in 180 ml. of glacial acetic acid in a beaker of at least 3-liters capacity. The temperature rose slowly at first and then more rapidly, and an extremely vigorous nitration took place with much fuming and boiling and copious evolution of red-brown fumes. For safety this reaction was carried out under a closed hood. About ten minutes after the boiling had subsided, the mixture was poured over several liters of crushed ice and water. The oily precipitate first formed crystallized at once when it was stirred. The crystalline product was washed by decantation several times with cold water, separated by filtration, further washed with cold water until free from acid, and dried in a vacuum desiccator over concentrated sulfuric acid.

The crude 5-nitroguaiacol acetate so obtained was hydrolyzed by suspending it in 650 ml. of hot 10% sodium hydroxide and heating the mechanically stirred mixture to a temperature just below the boiling point until solution was complete. After addition of 65 g. of solid sodium chloride, the well-stirred mixture was cooled to 5°, and the thick precipitate of the sodium salt of 5-nitroguaiacol filtered off, pressed as dry as possible on the filter, and washed with a little cold, saturated sodium chloride solution. The product was dissolved in 1.5–2 liters of water and filtered. The solution was acidified with concentrated hydrochloric acid and the product separated by filtration, washed with water and dried in a vacuum desiccator over concentrated sulfuric acid. The material was purified by vacuum distillation (b. p. 110–112° (1 mm.)) and by recrystallization from benzene. The yield of material which melted at 104–104.5° was 57.7 g. (42%, based on guaiacol acetate). It is possible that the vacuum distillation may be unnecessary since the product from hydrolysis is fairly pure.

Nitration by the usual methods yields products containing appreciable amounts of 3-nitroguaiacol which is separated from 5-nitroguaiacol only with great difficulty. *Anal.* Calcd. for  $C_7H_7NO_4$ : C, 49.71; H, 4.15. Found: C, 49.91; H, 4.22.

**Mercuration of 5-Nitroguaiacol.**—5-Nitroguaiacol (100 g.) and 400 g. of mercuric acetate were dissolved in 3.5 liters of a 35% aqueous solution of acetic acid, containing 1% of sodium acetate. The solution was stirred mechanically and heated on a steam-bath for six hours, during which time an orange precipitate formed and gradually became thicker and deeper in color. After six hours, the mixture was cooled, the product separated by filtration, washed well with water, and dissolved in hot, dilute alkali; the solution was filtered through kieselguhr and the product precipitated with the desired acid. The yield was 290–325 g. (acetoxymercuri compound). *Anal.* Calcd. for  $C_7H_7O_6NHg$ : Hg, 46.90. Calcd. for  $C_{11}H_{11}O_8NHg_2$ : Hg, 58.45. Found: Hg, 48.90.<sup>13</sup>

Other runs were made in which the mercurated product contained up to 54% mercury. It appears that slight variations in procedure greatly affect the relative amounts of mono and di-mercurated products obtained.

**Bromomercuri Derivative.**—Fifty grams of acetoxymercuri compound was dissolved in hot 1 N potassium hydroxide and the solution filtered through kieselguhr. Hydrobromic acid (48%) was added dropwise, with stirring, to the cooled solution, until the yellow bromomercuri derivative had precipitated completely.

The product was separated by filtration, washed thoroughly with water, and pressed as dry as possible on the filter. It was dried in a vacuum desiccator over concentrated sulfuric acid. Yield was 51 g. *Anal.* Calcd. for  $C_7H_7O_4NBrHg_2$ : Hg, 44.71. Calcd. for  $C_7H_7O_4NBrHg_2$ : Hg, 56.18. Found: Hg, 46.50.

**Dimroth Reaction (Mercurated 5-Nitroguaiacol and Bromine).**—Fifty grams of bromomercuri derivative was dissolved in 500 ml. of glacial acetic acid on a steam-bath. Bromine was added slowly to the mechanically stirred solution while frequent tests for free bromine (starch-iodide paper) were made. When a positive test for free bromine persisted for thirty minutes, addition of bromine was halted and the solution was stirred for thirty minutes longer; about 18 g. of bromine was required. Excess bromine was destroyed by a little sodium bisulfite and the acetic acid was removed by distillation under reduced pressure. The residue was taken up in hot 1 N potassium hydroxide and the solution filtered through kieselguhr (or centrifuged) to remove inorganic mercury salts. Acidification by means of hydrochloric acid precipitated a yellow crystalline product which was contaminated with a small amount of gummy material. After it has been dried in an oven at 100°, the product was taken up in anhydrous ether, treated with 1–2 drops of bromine, and filtered. The ether solution was extracted with 1 N potassium hydroxide, and the bright red aqueous layer freed from ether by boiling and then acidified with hydrochloric acid. The crystalline product was separated by filtration, washed with water and dried *in vacuo* in an Abderhalden pistol over phosphorus pentoxide at the boiling point of ethyl alcohol. The yield was 23 g.; the product melted at 109–122°. *Anal.* Calcd. for  $C_7H_6BrNO_4$ : Br, 32.22. Calcd. for  $C_7H_6Br_2NO_4$ : Br, 48.89. Found: Br, 37.10.

Unsuccessful attempts were made to separate this mixture into pure components by fractional distillation and by fractional crystallization from a variety of solvent combinations. Separation was finally achieved by a prolonged and tedious fractional crystallization from aqueous acetic acid (50% by volume). The general procedure indicated by Morton<sup>13</sup> was used, and fractions of similar melting point were combined. For final purification, the end-products were washed thoroughly with cold water and recrystallized from methanol-water. From 20 g. of mixture were obtained 10.7 g. of a yellow crystalline compound, I, m. p. 151–152° and 2.2 g. of a second compound, II, m. p. 119–120° and 5.1 g. of intermediate fractions. *Anal.* I: Calcd. for  $C_7H_6BrNO_4$ : C, 33.87; H, 2.44; Br, 32.22. Found: C, 33.96; H, 2.53; Br, 32.33. II: Calcd. for  $C_7H_6Br_2NO_4$ : C, 25.71; H, 1.54; Br, 48.89. Found: C, 25.59; H, 1.70; Br, 48.51.

**6-Bromo-5-nitroguaiacol Acetate.**—One gram of product, I, above was acetylated with 0.5 ml. of acetic anhydride with a trace of concentrated sulfuric acid as catalyst. The solid product was recrystallized from a methanol-water mixture (ca. 4–1). The yield was 1 g. (85%); the substance melts at 126–127°. *Anal.* Calcd. for  $C_9H_8BrNO_6$ : C, 37.27; H, 2.78. Found: C, 37.40; H, 2.90.

**4,6-Dibromo-5-nitroguaiacol Acetate.**—Using the same procedure as in the previous experiment, 0.5 g. of product, II, was acetylated with 0.3 ml. of acetic anhydride. The yield was 0.52 g. (92%); the substance melts at 135–136°. *Anal.* Calcd. for  $C_9H_8Br_2NO_6$ : C, 29.30; H, 1.91. Found: C, 29.50; H, 2.13.

**6-Bromoguaiacol from I.**—Two grams of I was reduced with tin and hydrochloric acid. The solution was diluted with water, filtered, and freed from tin by treatment with hydrogen sulfide. After excess hydrogen sulfide had been removed by boiling, the residual solution was concentrated under reduced pressure to a volume of about 15 ml. Two ml. of concentrated hydrochloric acid was added and the solution was cooled to 5° and the amine diazotized by the slow addition of a cold solution of 0.6 g. of sodium nitrite in 5 ml. of water, using starch-iodide indicator. To the cold diazonium salt solution was added 16 g. of cold 50%

(12) Analyses for mercury by gravimetric and/or volumetric methods of Jamieson, *Ind. Eng. Chem.*, **4**, 206 (1919). Decompositions were effected by fuming nitric acid, cf. Hart and Herschfelder, *This Journal*, **42**, 2680 (1920).

(13) Morton, "Laboratory Technique in Organic Chemistry," The McGraw-Hill Book Co., Inc., New York, N. Y., 1935.

hypophosphorous acid. The temperature was maintained at 0–5° for one hour and then the solution was stored in a refrigerator at 5–10° for twenty hours. Steam distillation of this solution yielded a crystalline product which was recrystallized from an ethanol–water mixture (ca. 5:1). The yield was 0.46 g. (28%); the product melted at 62–63° and showed no depression of melting point when mixed with varied quantities of 6-bromoguaiacol. *Anal.* Calcd. for  $C_7H_7BrO_2$ : Br, 39.38. Found: Br, 39.76.

**4-Nitroguaiacol.**—2-Amino-5-nitroanisole (50 g.) (Eastman Kodak Co. product No. P 2329 recrystallized from ethanol, m. p. 140–141°) was hydrolyzed with a solution of 50 g. of sodium hydroxide in 450 ml. of water by heating at the boiling point for thirty hours under reflux. When the reaction mixture was cooled, the sodium salt of 4-nitroguaiacol crystallized in bright red needles. The cold solution was filtered and the red crystals dissolved in 1.5 liters of hot water; the solution was filtered, cooled, and acidified with hydrochloric acid. The 4-nitroguaiacol was separated by filtration and dissolved in benzene; the solution was dried by removing the benzene–water azeotrope by distillation. The product was then crystallized from the dry benzene. The yield was 43.2 g. (86%); the 4-nitroguaiacol melted at 102–103°. *Anal.* Calcd. for  $C_7H_7NO_4$ : C, 49.71; H, 4.17. Found: C, 49.61, 49.86; H, 4.15, 4.21.

**6-Bromo-4-nitroguaiacol from 2-Amino-3-bromo-5-nitroanisole.**—The anisole derivative (20 g.) was heated in a bomb at 130° under pressure for four and one-half hours with 4 g. of sodium hydroxide in 100 ml. of water. Six grams of starting material was recovered unchanged. The filtered alkaline solution was boiled to expel ammonia and acidified. The yellow product was recrystallized from an ethanol–water mixture (5:1). The yield was 13 g. (93%); this specimen of 6-bromo-4-nitroguaiacol melted at 150° (dec.), and was found to be identical with the substance described directly below.

**6-Bromo-4-nitroguaiacol from Bromination of 4-Nitroguaiacol.**—A solution of 11.7 g. of 4-nitroguaiacol in 100 ml. of glacial acetic acid was brominated by the slow addition of 12.5 g. of bromine in 40 ml. of glacial acetic acid. After 1–2 ml. of the bromine solution had been added, the mixture was warmed with a flame until the evolution of hydrobromic acid was evident, whereupon addition of the solution of bromine was continued during one hour; stirring was continued one hour longer and the reaction mixture was then poured into 300 ml. of cold water. The yellow precipitate was separated by filtration and recrystallized from an ethanol–water mixture (5:1). The yield was 12.1 g. (70.3%); the product melted at 150° (dec.)

**6-Bromo-4-nitroguaiacol Acetate.**—6-Bromo-4-nitroguaiacol (1 g.) was acetylated in the presence of a trace of sulfuric acid by means of 0.5 ml. of acetic anhydride. The product was recrystallized from a methanol–water mixture (3.5:1). The yield was 1.1 g. (91%) of a substance which melted at 102–103°. *Anal.* Calcd. for  $C_9H_9BrNO_4$ : C, 37.27; H, 2.78. Found: C, 37.13; H, 2.90.

**4,6-Dibromoguaiacol from 6-Bromo-4-nitroguaiacol.**—6-Bromo-4-nitroguaiacol (4 g.) was reduced with tin and hydrochloric acid. The solution was diluted, filtered and freed from tin by treatment with hydrogen sulfide. After the solution had been boiled to rid it of excess hydrogen sulfide, it was concentrated under diminished pressure to a volume of ca. 30 ml. Three ml. of concentrated hydrochloric acid was added, the solution was cooled to 0° by immersion in an ice and salt mixture, and the dissolved amine salt was diazotized by the addition of a cold solution of 1.2 g. of sodium nitrite in 20 ml. of water. Starch-iodide paper was used as indicator. A solution of cuprous bromide was prepared as follows: 5 g. of crystallized copper sulfate was dissolved in 16 ml. of boiling water and 2.4 g. of potassium bromide was dissolved in the hot solution. To this hot solution was added slowly a solution of 1.1 g. of sodium pyrosulfite ( $Na_2S_2O_5$ ), and 0.75 g. of sodium hydroxide in 8 ml. of water. The precipitated cuprous bromide was then washed twice with water by decantation and dissolved in 15 ml. of 40% hydrobromic acid. This solution was heated in an apparatus arranged for steam

distillation and the cold diazonium solution above was added dropwise while the mixture steam-distilled simultaneously. The white solid which crystallized in the distillate was separated by filtration and recrystallized from aqueous ethanol. The yield was 1.2 g. (25.5%); the product melted at 64–65°. *Anal.* Calcd. for  $C_7H_8Br_2O_2$ : C, 28.02; H, 2.14; Br, 56.70. Found: C, 28.13; H, 2.23; Br, 56.59.

**4,6-Dibromoguaiacol from II.**—One and one-half grams of II was reduced with tin and hydrochloric acid. As before, the solution was diluted with water, filtered, freed of tin by treatment with hydrogen sulfide, and concentrated under reduced pressure to 15 ml. whereupon 3 ml. of concentrated hydrochloric acid was added. The solution was then cooled to 0° and the dissolved amine salt diazotized by addition of a cold solution of 0.36 g. of sodium nitrite dissolved in 15 ml. of water again using starch-iodide paper as an indicator. To the cold diazonium salt solution was added 10 g. of a cold 50% solution of hypophosphorous acid. The solution was maintained at 0–5° for one hour and then kept in a refrigerator at 5–10° for twenty-four hours. When the resultant solution was steam distilled, a white solid crystallized in the distillate and was separated by filtration and recrystallized from an ethanol–water mixture. The yield was 0.4 g. (31%); the product melted at 63–64°.

This product proved to be identical with that previously obtained from 6-bromo-4-nitroguaiacol. Mixed melting point tests resulted in no depression in melting point.

**4,5,6-Tribromoguaiacol from II.**—One and one-half grams of II was reduced with tin and hydrochloric acid, freed from tin, concentrated and diazotized as in the previous experiments. A solution of cuprous bromide in hydrobromic acid was prepared and the cold diazonium solution added dropwise to it while steam was blown through the mixture. A white crystalline product was filtered from the distillate and recrystallized from an ethanol–water mixture. The yield was 0.31 g. (18.7%), m. p. 114–116°. This product shows no depression in melting point when mixed with varied quantities of authentic 4,5,6-tribromoguaiacol.

**4-Hydroxyguaiacol from 4-Aminoguaiacol.**—A solution of 4.2 g. of the amine obtained by reduction of 4-nitroguaiacol was dissolved in 33 ml. of water and 33 ml. of concentrated sulfuric acid. This solution was diluted with 300 ml. of water and treated at –8°, with a solution of 2.1 g. of sodium nitrite dissolved in a small amount of water. After the diazotization was complete, the solution was warmed quickly and heated on a water-bath for thirty minutes. Extraction with ether followed by evaporation of the ether yielded 1.3 g. of product which melted at 80–82°. Two recrystallizations from benzene raised the melting point to 90–91°. *Anal.* Calcd. for  $C_7H_8O_3$ : C, 59.99; H, 5.76. Found: C, 60.09; H, 5.80.

**5-Aminoguaiacol from 5-Nitroguaiacol.**—5-Nitroguaiacol was reduced in ether at 70–100° in the presence of Raney nickel at a pressure of 1600 p. s. i. of hydrogen. The yield of a product which melted at 131–133° was 79%. Substantially the same yield was obtained using Adams catalyst and alcohol as solvent. Recrystallization from benzene yielded a product which melted at 130–131°. *Anal.* Calcd. for  $C_7H_9O_2N$ : C, 60.43; H, 6.45. Found: C, 60.44, 60.55; H, 6.44, 6.44.

**5-Hydroxyguaiacol from 5-Aminoguaiacol.**—The method used was like that described above for the preparation of 4-hydroxyguaiacol; 2.8 g. of amine yielded 1.5 g. of product. The 5-hydroxyguaiacol melted at 71–72° after two recrystallizations from benzene and ligroin. *Anal.* Calcd. for  $C_7H_8O_3$ : C, 59.99; H, 5.76. Found: C, 59.95; H, 5.74.

**4-Nitroveratrole from 4- and 5-Nitroguaiacol.**—Methylation of 4-nitroguaiacol by means of dimethyl sulfate and alkali yielded a product which, after recrystallization from ligroin and then from alcohol, melted at 97–98°. *Anal.* Calcd. for  $C_9H_9NO_4$ : C, 52.46; H, 4.95. Found: C, 52.47; H, 5.03.

Methylation of 5-nitroguaiacol yielded a product which, after recrystallization from ligroin, melted at 96–97°. A

