NITRATION OF ACYL DERIVATIVES OF 4,5-DIBROMO- AND 4,5,6-TRIBROMOGUAIACOL

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Armstrong and Harrow¹ found that when 2,4,6-tribromophenol is gradually added to concentrated nitric acid (relative amounts of material and temperature not specified) 2,4-dinitro-6-bromophenol is obtained. If the tribromophenol is dissolved in acetic acid, one molecular proportion of nitric acid is added, and the mixture is heated on a steam bath, the para bromine atom only is replaced and 2,6-dibromo-4-nitrophenol is obtained. In a similar way Claus and Hirsch² converted sym-tribromo-m-cresol into 2,6-dibromo-4-nitro-m-cresol.

In later work Zincke and students³ showed that nitrous acid reacts with bromine substitution products of phenols to replace hydrogen or halogen from an ortho or para position with respect to hydroxyl to give a mononitro compound. Raiford⁴ and others found that in most cases this method of nitration gives isomeric mononitro derivatives and that the method is selective⁵ to the extent that chlorine is not replaced. More recently Raiford and Scott⁶ studied the behavior of the tribromo derivative of resorcinol monomethyl ether. When this product was subjected to the action of nitrous acid under the conditions indicated by Zincke and modified by Raiford and Grosz⁷ it gave a high yield of 2,4-dibromo-3methoxy-6-nitrophenol in which a halogen atom ortho to hydroxyl had been replaced by the nitro radical.

In view of the last-named observations it was of particular interest to study the behavior of related compounds in which the substituents had somewhat different positions. For this purpose 4,5-dibromo- and 4,5,6-tribromoguaiacol (OH = 1) were selected. When these compounds were subjected to the action of nitrous acid, in accordance with the general

¹ ARMSTRONG AND HARROW, J. Chem. Soc., 29, 477 (1876).

² CLAUS AND HIRSCH, J. prakt. Chem., [2], 39, 61 (1889).

³ ZINCKE, *ibid.*, [2], **61**, 561 (1900); ZINCKE AND JANNEY, Ann., **398**, 361 (1913) These papers contain important references to the authors' other work in this field.

⁴ RAIFORD AND WOOLFOLK, J. Am. Chem. Soc., 46, 2253 (1924).

⁵ RAIFORD AND MILLER, *ibid.*, **55**, 2131 (1933).

⁶ Raiford and Scott, J. Org. Chem., 2, 213 (1937).

⁷ RAIFORD AND GROSZ, *ibid.*, **53**, 3422 (1931).

method of Zincke, no reaction product could be isolated. With cold fuming nitric acid a vigorous reaction went on but no product was obtained. Possibly complete oxidation took place. Failure to obtain a nitro compound by these methods suggested study of the acyl derivatives.

It has been shown in several cases that acylation of a phenol suppresses the directive influence of the substituent involved, and that if the compound under consideration contains some other o, p-directing radical the latter may determine in large measure the position to be occupied by the entering group. Thus, nitration of guaiacol with red fuming nitric acid has been reported to give a mixture of 4-nitro-, 6-nitro- and 4,6-dinitroguaiacol⁸, but when acetylguaiacol is used the 5-nitro derivative is obtained⁹. Nitration of vanillin (CHO = 1) gives 5-nitrovanillin in about 95 per cent. yield¹⁰, while the acetyl derivative gives a 75 per cent. yield of the 2-nitro compound¹¹. Similarly, when p-cresol (OH = 1) is nitrated a 51 per cent. yield of the 2-nitro derivative, along with some dinitro compound¹², is produced, while nitration of p-cresyl carbonate gives a very good yield of the 3-nitro compound¹³. Introduction of halogen follows the same course. Bromination of vanillin gives an 85 per cent. yield of the 5-bromo compound¹⁴, while acetylvanillin gives the 6-bromo derivative in 87 per cent, yield and nothing else can be isolated from the reaction mixture¹⁵. o-Cresol reacts with bromine to give a 66 per cent. yield of the 4-bromo derivative¹⁶, but when 2-methoxyphenyl carbonate (guaiacol carbonate) is used, an almost quantitative yield¹⁷ of the 5-bromo compound is obtained. Apparently in the second example in each of the above cases the position taken by the entering group is determined by alkyl or alkoxyl.

In the present work the acetyl and benzoyl derivatives of the above bromoguaiacols have been examined.

The dibromoguaiacol that melts at 94-95°, which was prepared by

⁸ KLEMENC, Monatsh., 33, 701 (1912).

⁹ CARDWELL AND ROBINSON, J. Chem. Soc., 107, 256 (1915).

¹⁰ VOGL, Monatsh., 20, 384 (1899).

¹¹ PSCHORR AND SUMULEANU, Ber., **32**, 3408 (1899). This was confirmed by RAI-FORD AND STOESSER [J. Am. Chem., Soc., **50**, 2558 (1928).] who found that about 5% of the 6-nitro isomeride is also formed in this experiment. RAIFORD AND MILBERY [*ibid.*, **56**, 2727 (1934)] obtained similar results with benzoylvanillin.

¹² STAEDEL, Ann., 217, 53 (1883).

¹³ German Pat., 206638; Frd., 9, 151 (1908).

¹⁴ DAKIN, Am. Chem. J., 42, 493 (1909).

¹⁵ RAIFORD AND STOESSER, J. Am. Chem. Soc., 49, 1079 (1927).

¹⁶ The method followed was outlined by CLAUS AND JACKSON [J. prakt. Chem., [2], **38**, 324 (1888)] who recorded no yield. This was determined by MILLER [Thesis, Iowa (1930) p. 40] who had occasion to repeat the work.

¹⁷ HINDMARSH, KNIGHT, AND ROBINSON, J. Chem. Soc., 111, 942 (1917).

Cousin¹⁸, and in which the halogen atoms have been oriented in positions 4 and 5¹⁷, failed to give a definite product when attempts were made to nitrate it. Accordingly, its acyl derivatives were studied. Treatment of the acetyl compound (II) with fuming nitric acid as described below gave two nitro compounds, (IIIa or IIIb, and VI). The formation of IIIa or IIIb involved the replacement of a bromine atom by the nitro radical and the product must have one of the structures shown. Since it has been proved in other cases that -OCH₃⁸ has a more pronounced directing influence than -OCOCH₃, at least when hydrogen is replaced, it seems probable that the product in hand had structure IIIa. Hydrolysis of this compound gave the corresponding bromonitroguaiacol (IVa or IVb), that melted at 118-119°. This product may be identical with that described by Meldola and Streatfield¹⁹, which melted at 120°, but it seems improbable that it can have the structure they assigned, viz., 2-methoxy-4-bromo-6-nitrophenol. Their structure is based in part on the observation that the compound formed a deep red sodium salt which suggested an ortho nitrophenol. They also argued that hydroxyl and the nitro radical have in this compound the same structural relations as in the nitrobenzoylguaiacol, m.p., 88-89°, which was isolated by them and in which they claim that the nitro group and the benzoyloxy radical are adjacent to each other, though they established no direct experimental relations between these compounds. Doubt concerning the structure of this benzovl derivative has been raised by Oxford²⁰ who found 88-89° for the melting point of the benzoate of that nitroguaiacol obtained by treatment of acetylguaiacol with acetyl nitrate, which latter was shown by Pictet and Khotinsky²¹ to give high yields of ortho nitro derivatives, especially when the alkoxyl group is present. This indicates that the compound in question is 2-methoxy-3-nitrophenyl benzoate, and its formation agrees with the observations of Cardwell and Robinson²² who noted that methoxyl has a far greater orienting effect than acyloxyl. In the present work nitration of II was effected with nitric acid, which may be expected to give the para isomeride (IIIa) as the chief product. Hydrolysis of this must lead to IVa which is the most likely structure for our product, and also for that of Meldola and Streatfield.

This view is supported by other facts. In the nitrobromoguaiacol isolated by us it seems almost certain that the bromine atom and the nitro

¹⁸ COUSIN, Ann. chim. phys., [7], 29, 63 (1903).

²⁰ OXFORD, J. Chem. Soc., 1926, 2007.

²² CARDWELL AND ROBINSON, J. Chem. Soc., 107, 255 (1915).

¹⁹ MELDOLA AND STREATFIELD, Proc. Chem. Soc., **12**, 125 (1896), and J. Chem. Soc., **73**, 689 (1898).

²¹ Pictet and Khotinsky, Ber., 40, 1165 (1907).

group are in positions 4 and 5, the nitro group most probably in the latter, because the compound was obtained directly from 4,5-dibromoguaiacol, and was finally converted by methylation into 4-bromo-5-nitroveratrol (V) that melted at 122°. The structure of the latter has been established by nitration of 4-bromoveratrol²³, and also by nitration of the bromo compound obtained when the bromoamine prepared from 3-acetylamino-4-bromoveratrol was diazotized and the diazo complex was replaced by hydrogen.²⁴



Examination of product (VI) showed that it was a nitrodibromo derivative of acetylguaiacol which on hydrolysis gave the corresponding guaiacol (IX). When the latter was methylated in the usual way it gave a nitrodibromoveratrol (X) that melted at $150-151^{\circ}$ and which is probably identical with that obtained by Cousin²⁵ by bromination of 3-nitroveratrol

²³ GASPARI [Gazz. chim. ital., **26**, II, 231 (1896)] found 124.5-125°; JONES AND ROBINSON [J. Chem. Soc., **111**, 916 (1917)] recorded 125° for this product.

²⁴ SIMONSEN AND RAU [J. Chem. Soc., 113, 786 (1918)] found 123°.

²⁵ COUSIN, Ann. chim. phys., [7], 13, 505 (1898).

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and also by nitration of that dibromoveratrol melting at $92-93^{\circ}$,²⁶ the latter of which has been proved by Jones and Robinson²⁷ to be the 4,5-derivative.

Treatment of the benzoyl derivative of 4,5-dibromoguaiacol (VII) with fuming nitric acid gave a nitro compound (VIII) without loss of bromine, and hydrolysis of the latter gave the nitrodibromoguaiacol (IX) mentioned above. These relations are shown in Fig. 1.



4,5,6-Tribromoguaiacol, (XI) prepared as described below was converted into the acetyl and benzoyl derivatives, respectively. Treatment of the acetyl derivative (XII) with fuming nitric acid at room temperature gave a nitro compound (XIII) without loss of halogen, which indicated that the entering group had taken position 3, and that the chief directive influence was probably exercised by alkoxyl. Nitration of the

 ²⁶ COUSIN [Ann. chim. phys., [7], 13, 490 (1898)] found 91°.
²⁷ JONES AND ROBINSON, J. Chem. Soc. 111, 913 (1917).

benzoyl derivative (XIV) in the same way gave a mononitro compound (XV) and a dinitro derivative (XVI) in which the nitro radicals occupy position 3 in each of the phenyl nuclei. This is in general agreement with the observations of Raiford and Wickert²⁸ who studied the nitration of the benzoyl derivative of sym-tribromoaniline. Hydrolysis of products XIII, XV, and XVI gave compound XVII, 2-methoxy-3-nitro-4,5,6-tribromophenol, which was further characterized by the preparation of several of its derivatives. These relations are shown in Fig. 2.

EXPERIMENTAL

4,5-Dibromoguaiacol.—One gram-molecular proportion of guaiacol mixed with about half its weight of chloroform was placed in a suitable vessel provided with a mechanical stirrer and cooled to about 5°. A solution of two molecular proportions of bromine in about twice its weight of chloroform was added from a dropping funnel at such a rate that only a small amount of free halogen was present at any time, while the mixture was stirred continuously and held between 5° and 10°. About half the bromine was added in thirty minutes, while the remainder required ninety. Next the mixture was transferred to a suitable flask and the chloroform was distilled on a steam bath. To avoid the formation of an oily mixture in crystallization it was necessary to remove the chloroform used as solvent as completely as possible and the last portion was distilled under reduced pressure. Crystallization from a mixture of 2 volumes of alcohol and 3 volumes of water gave nearly colorless needles that melted at 94–95°. By working up the mother liquor a total yield 88 per cent was obtained. Its properties agree with those on record.

2-Methoxy-4,5-dibromophenyl acetate was obtained in almost theoretical yield by heating the above guaiacol with excess of acetic anhydride on a steam bath for one and one-half hours. Crystallization of the product from ligroïn, $(65-70^{\circ})$ gave colorless granules that melted at 101-102°.

Anal. Calc'd for C₉H₈Br₂O₃: Br., 49.38. Found: Br, 49.43.

Nitration of the acetyl derivative.—A portion of the dry powdered material was gradually added with stirring during one to one and one-half hours to twice its weight of fuming nitric acid at 25–28°; the mixture was stirred for two hours longer and then poured slowly into twice its volume of ice water. The average yield from several runs was 82 per cent. When a hot saturated methyl alcohol solution of this material was allowed to cool to room temperature it deposited fine nearly colorless needles that melted at 160–161°. Recrystallization did not change this. Analysis for halogen agrees with that required by 2-methoxy-4-bromo-5-nitrophenyl acetate.

Anal. Cale'd for C₉H₈BrNO₅: Br, 27.58. Found: Br, 27.63.

The alcohol from the filtrate left when the above compound had crystallized out was distilled off, and the residue was crystallized from ligroin (65-70°) from which it separated in colorless square prisms that melted at 91.5-92.5°. The yield of purified product was 51 per cent. Analysis for halogen corresponds to 2-methoxy-3-nitro-4, 5-dibromophenyl acetate.

Anal. Calc'd for C₉H₇Br₂NO₅: Br, 43.36. Found: Br, 43.37.

2-Methoxy-4-bromo-5-nitrophenol.—About 3 grams of the above nitrobromoacetyl derivative melting at 160-161° was hydrolyzed by warming with alcoholic solution of sodium hydroxide. The alcohol was evaporated, the residue was dissolved in water,

²⁸ RAIFORD AND WICKERT, J. Am. Chem. Soc., 53, 3146 (1931).

and the liquid was acidified with hydrochloric acid. From dilute methyl alcohol the substance was deposited in canary-yellow masses that were not well crystallized, and that melted at 118–119°.

Anal. Calc'd for C₇H₆BrNO₄: Br, 32.25. Found: Br, 32.29.

The above phenol was further characterized by alkylation with dimethyl sulfate in the usual way. The product was crystallized from dilute alcohol from which it separated in pale yellow needles that melted at 122°, and is probably identical with the 4-bromo-5-nitroveratrol isolated by Simonsen and Rau,²⁴ and which melted at 123°.

2-Methoxy-3-nitro-4,5-dibromophenol.—A portion of the nitrodibromoacetyl derivative indicated above, mixed with aqueous-alcoholic sodium hydroxide, was heated on a steam bath under a return condenser until a red solution was obtained. Treatment of the latter with acid precipitated an almost quantitative yield of the phenol. By crystallization from methyl alcohol it was obtained in yellow microscopic needles that melted at $164-165^{\circ}$.

Anal. Calc'd for C₇H₅Br₂NO₄: Br, 48.93. Found: Br, 48.97.

3-Nitro-4, 5-dibromoveratrol.—Three grams of the above guaiacol was dissolved in sodium hydroxide solution, and warmed to about 45°; the required amount of dimethyl sulfate was added, and the mixture was shaken frequently during an hour. The solid product separated in a yield of 93 per cent. Crystallization from alcohol gave colorless square prisms that melted at 150–151°. Cousin²⁹ found 149–150° for a compound of this composition which he prepared by bromination of 3-nitroveratrol and also by nitration of 4,5-dibromoveratrol, and for which he obtained satisfactory analytical data. The products are probably identical.

2-Methoxy-4,5-dibromophenyl benzoate.—Ten grams of the required guaiacol was dissolved in pyridine, cooled to 0° and shaken with slight excess of benzoyl chloride.³⁰ After standing for two hours the mixture was acidified, diluted with two volumes of water and allowed to stand overnight. The product was collected and extracted with dilute alkali. The yield was 98%. By crystallization from alcohol it was obtained in very small nearly colorless needles that melted at 110.5-111.5°.

Anal. Calc'd for C14H10Br2O3: Br, 41.45. Found: Br, 41.44.

2-Methoxy-3-nitro-4,5-dibromophenyl benzoate.—Twenty grams of the required benzoate, in finely powdered form, was slowly added with stirring, in about one hour, to 75 g.* of fuming nitric acid, the mixture was stirred for two hours longer and then poured into ice water. A yield of 80% was obtained. Crystallization from methyl alcohol gave colorless plates that melted at 116-117°.

Anal. Calc'd for C14H9Br2NO5: Br, 37.12. Found: Br, 37.16.

Five grams of the nitrobenzoate was warmed with an aqueous-alcoholic solution of sodium hydroxide until hydrolysis was complete, most of the alcohol was distilled off, the residue was cooled to $40-50^{\circ}$ and a 25% excess of dimethyl sulfate was added dropwise with stirring which was continued for half an hour longer. The yield of product was 81%. Crystallization from alcohol gave colorless prisms that melted at 151°. The melting point of a mixture with an authentic sample of 3-nitro-4,5dibromoveratrol (X) showed no depression.

²⁹ COUSIN, Ann. chim. phys., [7], 13, 505 (1898).

³⁰ EINHORN AND HOLLANDT, Ann., **301**, 101 (1898). The Schotten-Baumann method gave unsatisfactory results here.

^{*} When smaller portions of acid were used the product separated as a sticky oil that could not be crystallized.

4, 5, 6-Tribromoguaiacol, the structure of which was established by Zangirolami,³¹ was prepared as follows: One molecular proportion of guaiacol, dissolved in about half its weight of acetic acid was placed in a three-necked flask provided with a mechanical stirrer and an outlet tube connected with an absorption trap for hydrogen bromide. A solution of three molecular proportions of bromine in about an equal weight of acetic acid was dropped in at such a rate that only a small amount of free bromine was present at any time, while the mixture was stirred continuously. The first half of the bromine was added in an hour while the temperature was kept about 25°. Addition of the remainder required about two hours, and the temperature was maintained between 30° and 35° in order to keep the product in solution. The mixture was allowed to cool, the crystalline solid was filtered off and the filtrate concentrated under reduced pressure. Crystallization of the combined residues from 50% alcohol gave nearly colorless needles that melted at 115–116°.³² The yield of purified material was 67%.

2-Methoxy-4,5,6-tribromophenyl acetate. Fifty grams of the required tribromo compound and an excess of acetic anhydride were heated on a steam bath for one and one-half hours. The yield was nearly quantitative. Crystallization from alcohol gave colorless blocks that melted at 119-120°.

Anal. Calc'd for C₉H₇Br₃O₃: Br, 59.55. Found: Br, 59.76.

2-Methoxy-3-nitro-4,5,6-tribromophenyl acetate.—A portion of the above dry powdered acetyl derivative was gradually added with stirring during a period of one to one and one-half hours to twice its weight of fuming nitric acid at 25-28°, the mixture was stirred for two hours longer, and then slowly poured into twice its volume of ice cold water. The average yield from several runs was 56%. Crystallization from ligroïn (65-70°) gave yellow needles that melted at 98-99°.

Anal. Calc'd for C₉H₆Br₃NO₅: Br, 53.57. Found: Br, 53.86.

3-Nitro-4,5,6-tribromoguaiacol.—Sixty grams of the required acetyl derivative was shaken at room temperature with slightly more than two molecular proportions of sodium hydroxide dissolved in 50% alcohol, and the resulting red liquid was acidified. The yellow oil that separated at this stage solidified when the mixture was poured into cold water and stirred. A yield of 60% was obtained. Crystallization from ligroïn (90-100°) gave nearly colorless needles that melted at 101-102°. When allowed to stand in the light this product becomes more deeply colored.

Anal. Cale'd for C₇H₄Br₃NO₄: Br, 59.11. Found: Br, 59.28.

2-Methoxy-3-nitro-4,5,6-tribromophenyl methyl carbonate.—Five grams of the above-described compound was dissolved in sodium hydroxide solution, shaken with 1.1 molecular proportions of methyl chlorocarbonate, and the resulting solid was collected, washed with dilute alkali, and then with water. Though the product was repeatedly crystallized from ligroïn $(65-70^{\circ})$ from which it was deposited in colorless flakes, it showed a melting rage of $105-108^{\circ}$. The yield of purified material was 56%.

Anal. Calc'd for $C_{9}H_{6}Br_{3}NO_{6}$: Br, 51.72. Found: Br, 51.79.

The corresponding ethyl carbonate was prepared by the method given above. It was crystallized from petroleum ether from which it was obtained in irregular masses that melted at $93-94^{\circ}$. The yield of purified product was 29%.

Anal. Calc'd for $C_{10}H_8Br_3NO_6$: Br, 50.21. Found: Br, 50.28.

A third portion of the phenol was converted into the methyl ether in nearly quan-

³¹ ZANGIROLAMI, Gazz. chim. ital., 62, 570 (1932).

³² TIEMANN AND KOPPE [Ber., 14, 2017 (1881)], who first obtained this compound, recorded 102° as the melting point; but HILL AND JENNINGS [Am. Chem. J., 15, 164 (1893)], who obtained it in a different way, found 115-116°.

titative yield by treatment with dimethyl sulfate in the usual maner. Crystallization from ligroïn (65-70°) gave fine colorless needles that melted at 122-123°.³³ Determination of halogen indicated that our product was nearly pure.

Anal. Calc'd for C₈H₆Br₃NO₄: Br, 57.14. Found: Br, 57.37.

2-Methoxy-4,5,6-tribromophenyl benzoate.—Thirty grams of the required tribromoguaiacol was dissolved in 50 cc. of pyridine, cooled to 0°, and shaken with excess of benzoyl chloride as previously indicated. After standing for two hours the mixture was acidified, diluted with two volumes of water, and allowed to stand overnight. The precipitate was washed with dilute alkali and then with dilute acid. A yield of 97% was obtained. Crystallization from alcohol gave hexagonal plates that melted at 148-149°.

Anal. Cale'd for C14H9Br3O3: Br, 51.61. Found: Br, 51.77.

Nitration of the benzoate.—Thirty-three grams of the required tribromo compound, in finely powdered form, was nitrated in the manner described above for the acetate, though the reaction went more slowly in this case. Preliminary examination of the product indicated that it was a mixture. Repeated extractions of it with small portions of boiling acetone made it possible to remove the more soluble compound which was obtained in a yield of 85%. This material separated in irregularly shaped crystals that melted at 140–141°. Analysis for halogen suggested a mononitro derivative. To fix its structure a portion of the 3-nitro-4,5,6-tribromoguaiacol described above, melting at $101-102^\circ$, was benzoylated. This product, after crystal-.ization from acetone, melted at 140–141°, and a mixture melting point determination showed no depression. The product in question must be 2-methoxy-3-nitro-4,5,6tribromophenyl benzoate.

Anal. Calc'd for C14H8Br8NO5: Br, 47.06. Found: Br, 47.22.

The residue left from the above extraction with acetone, which was obtained in yields of 3 to 4%, was crystallized from a larger portion of this solvent. It separated in the form of nearly colorless square prisms that melted 202-203°. Its structure was determined by preparing it from 3-nitro-4,5,6-tribromoguaiacol and m-nitrobenzoyl chloride. A mixture of the products melted without depression.

Anal. Calc'd for C14H7Br3N2O7: Br, 43.24. Found: Br, 43.35.

The product in question was further identified by hydrolysis which gave 3-nitro-4,5,6-tribromoguaiacol that melts at $101-102^\circ$, as given above.

SUMMARY

1. When the 4,5-dibromo and 4,5,6-tribromo substitution products of guaiacol were treated with nitrous acid as directed by Zincke no nitro compound could be isolated. When nitric acid was used a reaction seemed to take place but again no product was obtained. Possibly complete degradation occurred.

2. Treatment of the acyl derivatives with fuming nitric acid gave nitro compounds in all instances. When the dibromo acetate was tested a mixture was obtained. In one portion the bromine atom in position 5

³³ COUSIN [Compt. rend., **135**, 968 (1902)] reported 116-117° for a product which he states was obtained by nitration of 4,5,6-tribromoveratrol and also by bromination of 3-nitro-4,5-dibromoveratrol, and for which he later obtained satisfactory analytical data [Ann. chim. phys., [7], **29**, 76 (1903)]. was replaced by the nitro radical, and in the other hydrogen in position 3 was substituted. In the benzoate a 3-nitro compound only was obtained. When the tribromo compounds were tested no bromine was replaced. The acetate gave the corresponding 3-nitro derivative, while the benzoate gave, in addition to the 3-nitro compound, a dinitro product in which the nitro radicals are in position 3 in each of the phenyl nuclei.

3. Additional data have been secured to support the view that acylation of hydroxyl in a benzene derivative suppresses its directive influence.

4. Further work is in progress.