2. Iodination proceeds very rapidly under these conditions, in fact practically as fast as in the presence of water.

3. The explanation of Coffman which requires that the active iodinating agent is not free iodine but hypoiodous acid may or may not be correct for the reaction in aqueous solutions, but it does not account for iodination under anhydrous conditions.

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Behavior of Mixed Halogenated Phenols in the Zincke Method of Nitration[1]

BY L. CHAS. RAIFORD AND GLEN R. MILLER

Zincke and others[2] proved that when a brominated phenol or cresol is treated with nitrous acid, bromine or a hydrogen atom in a favorable position as respects hydroxyl may be replaced by the nitro group. Raiford and collaborators[3] have shown that when both ortho and the para positions are occupied by bromine isomeric *o*- and *p*-mononitrohalogenated derivatives may be obtained in this way in a single experiment. Chlorine compounds are much less reactive[4] and on this account compounds containing bromine and chlorine in the same molecule have been studied. The relative positions of these substituents have been varied in order to learn if replacement can occur in positions other than ortho and para, and whether chlorine can be replaced at all by the Zincke method.

Nitration of 2-bromo-4-chlorophenol (2) replaced the ortho hydrogen atom to give the 6-nitro compound (1). When the isomer, 2-chloro-4-bromophenol (10), was used, the ortho hydrogen was again displaced from one portion and the para bromine atom from another, giving a mixture of products (9) and (11). The isomeric monobromodichlorophenols, (3) and (6), lost bromine from the ortho and para positions, respectively, and gave the corresponding 2- and 4-nitrodichloro compounds, (4) and (7). Of the monochlorodibromo compounds (5) and (12), the first lost an ortho bromine atom to give the 6-nitro product (1), while the second gave a mixture of the 4-nitro (8) and the 6-nitro (11) derivatives.

With the cresols similar results were obtained. From *o*-cresol (CH_3 = 2) there were prepared the isomeric compounds (13) and (15) in which chlorine occupies the ortho and para positions, respectively, with bromine

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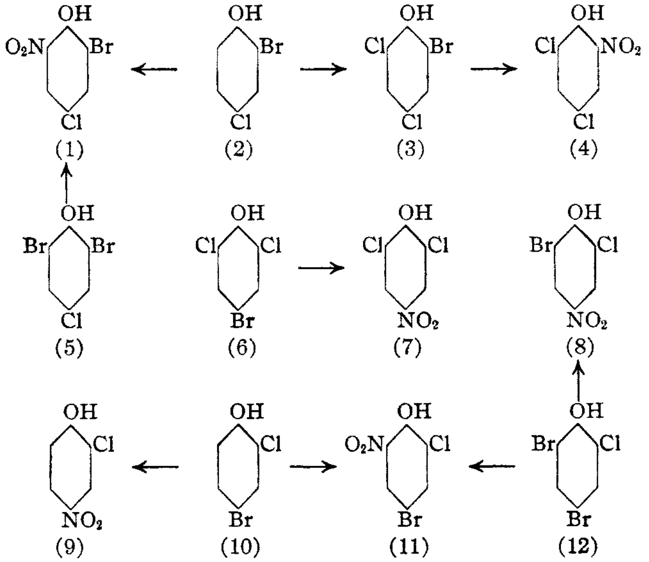
[1] From the thesis submitted in partial fulfilment of the requirements for the Ph.D. degree in the University of Iowa.

[2] Zincke, *J. prakt. Chem.* [2], **61**, 56 (1900); Dahmer, *Ann.*, **333**, 353 (1904).

[3] Raiford, THIS JOURNAL, **44**, 158 (1922).

[4] Raiford and Heyl [*Am. Chem. J.*, **43**, 397 (1910)] and Raiford [*ibid.*, **46**, 425 (1911)] failed to replace chlorine in *sym*-trichlorophenol and *m*-cresol by this method.

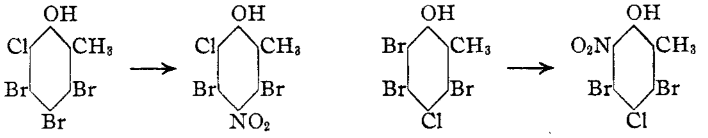


(1) (2) (3) (4)

(5) (6) (7) (8)

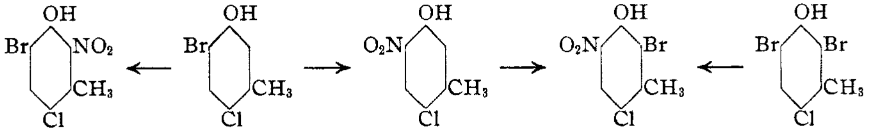
(9) (10) (11) (12)

in all other available places. Nitration of these products replaced bromine to give compounds (14) and (16). When both ortho and para positions in a given compound were occupied by chlorine and the others by bromine, no nitration occurred although two molecular proportions of sodium nitrite[5] were used.



(13) (14) (15) (16)

In the meta series (CH_3 = 3) nitration of the 4-chloro-6-bromo compound, (18), gave a mixture of products: (17), in which an ortho hydrogen atom was replaced, and (19), in which bromine was substituted by the nitro radical. Under similar treatment the 2,6-dibromo compound, (21), lost bromine from position 6 to give product (20). The latter was also obtained by bromination of compound (19).



(17) (18) (19) (20) (21)

With the *p*-cresol derivatives nitration of the 2-bromo-6-chloro compound, (22), replaced bromine to give product (25). The di- and tribromo compounds, (23) and (26), each lost the ortho bromine atom to

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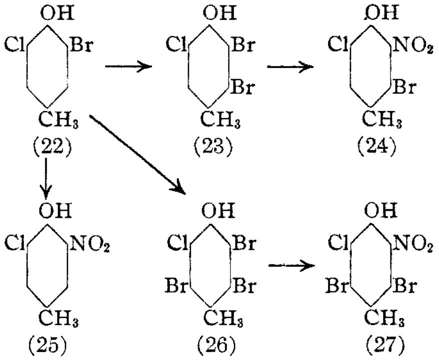
[5] Raiford and Grosz, THIS JOURNAL, **53**, 3422 (1931).

give products (24) and (27), respectively. Both the 2,6-dichloro- and the 2,6-dichloro-3,5-dibromo compounds were prepared, but neither could be nitrated by the Zincke method.



Experimental Part

2-Chloro-4-bromophenol.—Eastman's purest *o*-chlorophenol was fractionated and the portion boiling at 173.5–174° was reserved. One hundred and fifty grams was dissolved in four volumes of carbon tetrachloride, slightly more than one molecular proportion of bromine was slowly added with stirring, the mixture allowed to stand overnight, the solvent distilled off, and the residue fractionated. Nearly all boiled at 233–234°, and solidified on standing; yield, 87%. Recrystallization from ligroin gave colorless needles, m. p. 48–49°.[6]

Anal. Calcd. for C_6H_4OClBr: X, 55.66. Found: X, 55.47.

2-Bromo-4-chlorophenol.—To a solution of one molecular proportion of *p*-chlorophenol dissolved in 800 cc. of carbon tetrachloride, 165 g. of bromine was slowly added with stirring at room temperature, and the mixture allowed to stand overnight. The solvent was distilled off, the residue extracted with sodium hydroxide solution, and the extract acidified. Distillation at 10 mm. gave a 62% yield of material that boiled at 121–123°, and solidified on cooling; m. p. 33–34°. Recrystallization from ligroin did not change this.

Anal. Calcd. for C_6H_4OClBr: X, 55.66. Found: X, 55.71.

The compound was characterized by preparation of the benzoyl derivative; yield, 91%; colorless needles from alcohol, m. p. 99–100°.

Anal. Calcd. for $C_{13}H_8O_2ClBr$: X, 37.07. Found: X, 37.05.

4-Chloro-3,5,6-tribromo-*o*-cresol was obtained as colorless needles in nearly quantitative yield[7] by slowly adding to 4-chloro-*o*-cresol excess of bromine in which had been dissolved about 1% of aluminum,[8] while the mixture was kept cold. Much solid separated and the whole was allowed to stand for eight hours at room temperature, after which unused bromine was evaporated and the residue extracted with hot chloroform. Concentration and cooling the extract gave colorless needles; m. p. 194–195°. Oxidation with fuming nitric acid at 0° gave 3,5,6-tribromotoluquinone;[9] m. p. 238–240°.

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(6) While this work was in progress Fox and Turner [*J. Chem. Soc.*, 1858 (1930)] published data on a product, m. p. 50–51°, made by chlorination of *p*-bromophenol, that probably has the composition of this one. They recorded no yield and their halogen value was nearly 1% too high.

(7) Kohn and Rabinowitsch [*Monatsh.*, **48**, 372 (1927)] obtained in a slightly different way pale brown crystals, but recorded no yield.

(8) Bodroux, *Compt. rend.*, **126**, 1283 (1898).

(9) Kohn and Rabinowitsch (Ref. 7) recorded 232°.

2-Bromo-6-chloro-*p*-cresol (OH = 1).—Ten per cent. more than one molecular proportion of chlorine was bubbled slowly with stirring at 15–20° into a carbon tetrachloride solution of 250 g. of 2-bromo-*p*-cresol,[10] the liquid allowed to stand for several hours, shaken several times with water, and dried over calcium chloride for a day. The solvent was distilled off, the residue fractionated at 127–128° and 5 mm.; yield, 69% of colorless oil that solidified on standing; crystallization from ligroin (40–60°) gave colorless needles; m. p. 30°.

Anal. Calcd. for C_7H_6OClBr: X, 52.14. Found: X, 51.89.

2,3-Dibromo-6-chloro-*p*-cresol.—To a solution of 83 g. of the above described product in 400 g. of chloroform about 0.25 g. of iodine and 2 g. of iron powder were added, then an excess of bromine was dropped in with stirring. After four days the mixture was poured into an evaporating dish and the solvent and excess of bromine allowed to evaporate at room temperature. The residue was extracted with caustic alkali solution and the phenol liberated by acid. Repeated crystallization from ligroin (70–80°) gave pale brown needles; m. p. 80–81°.[11]

Anal. Calcd. for $C_7H_5OClBr_2$: X, 65.05. Found: X, 65.26.

2,3,5-Tribromo-6-chloro-*p*-cresol.—An excess of bromine in which about 1% of aluminum had been dissolved was added to 150 g. of 2-bromo-6-chloro-*p*-cresol, the mixture allowed to stand for ten hours and the excess of bromine evaporated; yield, 78%. Crystallization from chloroform gave colorless needles; m. p. 197–198°.

Anal. Calcd. for $C_7H_4OClBr_3$: X, 72.58. Found: X, 72.71.

Nitration.—With the exceptions noted below the halogenated phenols were nitrated as described by Foster[12] and modified by Raiford and collaborators.[5] Analytical data and properties are given in Table I.

The nitrophenols were reduced to the amino compounds as previously described,[13] and the ortho isomerides were identified by showing that only one acetyl-benzoyl derivative could be prepared from a given amine regardless of the order in which the acyl radicals were introduced, and that in this product benzoyl was attached to nitrogen. Previous work[14] had shown that this behavior is characteristic of *o*-aminophenols, and that to bring about this result migration of acyl from nitrogen to oxygen must occur when one acyl is introduced. When the *p*-aminophenols were subjected to this treatment isomeric acetyl-benzoyl derivatives were obtained and no rearrangement was observed.

4-Chloro-6-amino-*o*-cresol[15] was obtained in 93% yield by reduction of the required nitro compound, and the free base was prepared by treatment of the hydrochloride with ammonium carbonate.[13] Crystallization from benzene gave grayish needles; m. p. 107°.[16]

Anal. Calcd. for C_7H_8ONCl: Cl, 22.54. Found: Cl, 22.65.

Data for derivatives are given in Table II.

2-Amino-4-chloro-6-bromo-*m*-cresol.—Nearly a quantitative yield of the hydrochloride was obtained by reduction of the required nitro compound and the free base

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[10] Zincke and Wiederhold, *Ann.*, **320**, 203 (1902).

[11] Zincke and Buff [*Ann.*, **341**, 347 (1905)] found 65° for a product they did not analyze but which is recorded in Richter's "Lexikon" as 2,5-dibromo-6-chloro-*p*-cresol. If that structure is accepted our product is probably isomeric. The second bromine atom has not been oriented in either case.

[12] Foster, Dissertation, Marburg, 1898, p. 20.

[13] Raiford, *Am. Chem. J.*, **46**, 419 (1911).

[14] Raiford and Clark, THIS JOURNAL, **48**, 483 (1926).

[15] Derivatives of this base were prepared by C. E. Kaslow in this Laboratory.

[16] Zincke [*Ann.*, **417**, 223 (1918)] obtained this product from a different starting material but recorded no analysis.

TABLE I

COMPOSITION OF NITROHALOGENATED PHENOLS

Substituents	Yield	Solvent	Crystal form	Formula	M. p., °C.	Analyses, halogen % Calcd.	Found
2-Chloro-4-bromo-6-nitro-	34	Alcohol	Yellow prisms	$C_6H_3O_3NClBr$	112[a]	45.71	45.57
2-Methyl-3,5-dibromo-4-chloro-6-nitro-	87	Chloroform	Yellow needles	$C_7H_4O_3NClBr_2$	149–150[b]	56.56	57.01
2-Methyl-3,5-dibromo-4-nitro-6-chloro-	91[c]	Chloroform	Pale yellow plates	$C_7H_4O_3NClBr_2$	182–183	56.56	56.91
3-Methyl-4-chloro-6-nitro-	25[d]	Alcohol	Yellow plates	$C_7H_6O_3NCl$	133–134	18.91	19.19
2-Nitro-3-methyl-4-chloro-6-bromo-	..	Ligroin (40–60°)	Yellow needles	$C_7H_5O_3NClBr$	103–104	43.32	43.10
2-Bromo-3-methyl-4-chloro-6-nitro-	Nearly quant.	Alcohol	Yellow prisms	$C_7H_5O_3NClBr$	87[e]	43.32	43.45
2-Nitro-3-bromo-4-methyl-6-chloro-	97	Alcohol	Yellow needles	$C_7H_5O_3NClBr$	109–110	43.32	43.36
2-Nitro-3,5-dibromo-4-methyl-6-chloro-	96	Chloroform	Pale yellow needles	$C_7H_4O_3NClBr_2$[f]	157–158	56.56	56.67

[a] Ling [*J. Chem. Soc.*, **51**, 794 (1887)] recorded 117° for this product made differently from ours, and later [*ibid.*, **55**, 585 (1889)] 114°, while Gossner [*Z. Krist.*, **40**, 78 (1905)] found 112°.

[b] Obtained by nitration of 3,5,6-tribromo-4-chloro-*o*-cresol with 2.5 molecular proportions of sodium nitrite at 35°. The product contained some starting material and was purified as sodium salt. The benzoyl derivative was obtained in colorless needles from alcohol; m. p. 131–132°. *Anal.* Calcd. for $C_{14}H_8O_4NClBr_2$: X, 43.47. Found: X, 43.50.

[c] Prepared from 3,4,5-tribromo-6-chloro-*o*-cresol, m. p. 214–216°. Kohn and Rabinowitsch [*Monatsh.*, **48**, 371 (1927)] reported 209–211° for the product prepared differently. Ours was identified by oxidation to 2-methyl-3,5-dibromo-6-chloroquinone, m. p. 235°. Kohn and Rabinowitsch found 231°.

[d] Represents purified material of one product obtained when nitration was carried out at 14–18° with 50% excess of sodium nitrite.

[e] Obtained, also, by bromination of 4-chloro-6-nitro-*m*-cresol.

[f] Nitration at 35° with three times the theoretical amount of sodium nitrite. Purified as sodium salt. *Anal.* Calcd. for $C_7H_3O_3NClBr_2Na$: X, 53.19. Found: X, 53.32.

TABLE II

DERIVATIVES OF 4-CHLORO-6-AMINO-*o*-CRESOL

Position of acyl group	Solvent	Crystal form	M. p., °C.	Formula	Analyses, halogen, % Calcd.	Found
N-Acetyl-O-acetyl	Dilute HAc	Pinkish needles	195–196	$C_{11}H_{12}O_3NCl$	...[a]	...
Acetylaminophenol	20% Alcohol	Brownish hair-like needles	110	$C_9H_{10}O_2NCl$	17.77	17.77
N-Benzoyl-O-acetyl	80% HAc	Colorless fibrous masses	159	$C_{16}H_{14}O_3NCl$	11.69	11.81
Benzoylaminophenol	Alcohol	Brownish needles	203	$C_{14}H_{12}O_2NCl$	13.57	13.56

[a] This derivative was analyzed by Zincke.

TABLE III

DERIVATIVES OF *o*-AMINOPHENOLS FROM *m*-CRESOL

(a) 2-Amino-4-chloro-6-bromo-; (b) 2-bromo-4-chloro-6-amino-

Position of acyl group	Solvent	Crystal form	M. p., °C.	Formula	Analyses, halogen, % Calcd.	Found
(a)						
N-Acetyl-O-acetyl	Alcohol	Colorless needles	215	$C_{11}H_{11}O_3NClBr$	36.03	36.01
Acetylaminophenol	Alcohol	Brownish prisms	184–185	$C_9H_9O_2NClBr$	41.47	41.66
N-Benzoyl-O-acetyl	Alcohol	Nearly colorless needles	166–167	$C_{16}H_{13}O_3NClBr$	30.19	30.30
Benzoylaminophenol	Alcohol	Short colorless needles	247	$C_{14}H_{11}O_2NClBr$	33.92	34.00
(b)						
N-Acetyl-O-acetyl	Alcohol	Colorless needles	220	$C_{11}H_{11}O_3NClBr$	36.03	36.24
N-Acetylaminophenol	Water	Pale brown granules	180 dec.	$C_9H_9O_2NClBr$	41.47	41.54
N-Benzoyl-O-acetyl	Alcohol	Pink needles	189	$C_{16}H_{13}O_3NClBr$	30.19	30.46
Benzoylaminophenol	Alcohol	Brownish needles	192–193[a]	$C_{14}H_{11}O_2NClBr$	33.92	34.05
N-Benzoyl-O-benzoyl	Alcohol	Nearly colorless needles	191[a]	$C_{21}H_{15}O_3NClBr$	25.98	26.36

[a] A mixture of these products melts with a depression of about 30°.

TABLE IV

DERIVATIVES OF 2-AMINO-3-BROMO-6-CHLORO-*p*-CRESOL

Position of substituents	Solvent	Crystal form	M. p., °C.	Formula	Analyses, halogen, % Calcd.	Found
N-Acetyl-O-acetyl	Abs. alc.	Colorless needles	194–195	$C_{11}H_{11}O_3NClBr$	36.03	36.19
Acetylaminophenol	Abs. alc.	Brown crusts	149–149.5	$C_9H_9O_2NClBr$	41.47	41.39
N-Benzoyl-O-acetyl	Alc.	Colorless needles	220–221	$C_{16}H_{13}O_3NClBr$	30.19	30.33
Benzoylaminophenol	Alc.	Pale brown needles	178	$C_{14}H_{11}O_2NClBr$	33.92	33.56

was prepared as explained above. Crystallization from dilute alcohol gave brownish needles; m. p. 131–132°.

Anal. Calcd. $C_7H_7ONClBr$: X, 48.83. Found: X, 49.04.

The isomer, 2-bromo-4-chloro-6-amino-*m*-cresol, was obtained in pale brown needles; m. p. 111–112°.

Anal. Calcd. for $C_7H_7ONClBr$: X, 48.83. Found: X, 48.78.

Data for derivatives are given in Table III.

2-Amino-3-bromo-6-chloro-*p*-cresol was prepared from the corresponding nitro compound as described above. Treatment of a hot alcoholic solution with an equal volume of water gave brownish plates; m. p. 146–147°.

Anal. Calcd. for $C_7H_7ONClBr$: X, 48.83. Found: X, 48.84.

Summary

1. Several new mixed halogenated phenols and cresols have been prepared and nitrated as directed in the Zincke method. The following observations were made. (a) When bromine occupies both ortho and the para positions in a phenol or cresol, isomeric mononitro compounds may be formed. (b) For the first time it has been shown that a phenol having hydrogen in one ortho position and bromine in the other may undergo nitration at both positions in the same experiment. Thus, 2-chloro-4-bromophenol gave a mixture of 2-chloro-4-nitrophenol and 2-chloro-4-bromo-6-nitrophenol. 4-Chloro-6-bromo-*m*-cresol behaved in the same way. (c) Chlorine is not replaceable by the nitro group under the conditions here studied. (d) Further evidence has been obtained to support the views previously recorded, *viz.*, that, in general, only one acetyl-benzoyl derivative can be prepared from an *o*-aminophenol regardless of the order of introduction of the acyl radicals.

2. Further work is in progress.

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