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The Nitration of Para-Cresol and of Para-Cresyl Carbonate in the Presence of Sulfuric Acid¹

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The addition of sulfuric acid during the nitration of some aromatic compounds is known to influence the ratio of meta to ortho-para substitution. This is especially true of aromatic amines such as aniline, of which the ortho-para directing NH₂ group is converted, by salt formation, into the meta directing NH₃ group. An explanation has been advanced³ for this behavior on two grounds, *viz.*, (1) the addition of the proton to the lone electron pair of the nitrogen atom greatly increases the electron attraction of the entire group, and (2) the blocking off of the lone pair prevents any possibility of addition formation at this point with the reagent and therefore of subsequent rearrangement to ortho and para positions on the ring.

According to Vorländer, Robinson, Ingold and others⁴ the most strongly meta-directing groups are the positive poles directly attached to the benzene ring. Thus phenyltrimethylammonium nitrate is nitrated exclusively in the meta position⁵ and many other compounds of similar type yield meta derivatives almost exclusively on nitration; among these may be mentioned diphenyl idonium nitrate,⁶ triphenylantimony dinitrate,⁷ triphenylbismuth dinitrate⁸ and diphenyllead dinitrate.⁹

The change in the ortho-para directive influence of the NH₂ group to the meta orienting influence of the NH₃X group through salt formation has been ascribed to the ionization of the salt to give a positive ion in which substituents take the meta position because of the positive charge carried by the NH₃⁺ group. Flürscheim and Holmes^{4d} found that the addition of ammonium sulfate to the nitrating mixture of nitric and sulfuric acid decreased the yield of the meta isomeride formed during the nitration of benzyldiethylamine while Pollard and Robinson¹⁰ observed similar effects in the nitration of benzylpiperidine. In these cases the added salts depress the ionization of the salt undergoing nitration and thus cause a decrease in the meta directive power of the positive pole.

Since the oxygen atom resembles the nitrogen atom in the formation of

(1) Paper presented at the Denver Meeting of the American Chemical Society, August, 1932.

(2) China Foundation Fellow.

(3) Lucas, *THIS JOURNAL*, **48**, 1827 (1926).

(4) (a) Vorländer, *Ber.*, **52**, 262 (1919); (b) Allan, Oxford, Robinson and Smith, *J. Chem. Soc.*, 401 (1926); (c) Goss, Ingold and Wilson, *ibid.*, 2440 (1926); (d) Flürscheim and Holmes, *ibid.*, 1562 (1926); (e) Ingold, *Annual Reports Chem. Soc.*, **23**, 130 (1926).

(5) Vorländer and Siebert, *Ber.*, **52**, 283 (1919).

(6) Vorländer and Büchner, *ibid.*, **58**, 1898 (1925).

(7) Morgan and Micklethwaite, *J. Chem. Soc.*, **99**, 2286 (1911).

(8) Vorländer and Schroedter, *Ber.*, **58**, 1900 (1928).

(9) Vorländer and Spreckels, *ibid.*, **58**, 1900 (1928).

(10) Pollard and Robinson, *J. Chem. Soc.*, 2770 (1927).

TABLE I
EFFECT OF SULFURIC ACID UPON NITRATION OF *p*-CRESOL IN GLACIAL ACETIC ACID (24 G.)

Expt.	<i>p</i> -Cresol, g.	HNO ₃ , 1.42 g.	H ₂ SO ₄ , 1.84 g.	Molal ratio H ₂ SO ₄ / <i>p</i> -Cresol	Temp., °C.	Time, min.	<i>p</i> -Cresol	Products in grams			<i>p</i> -Cr	Percentage of yield			Total	Ratio <i>m</i> / <i>o</i>
								<i>o</i> -NO ₂ ^a	<i>m</i> -NO ₂ ^b	di-NO ₂ ^c		<i>o</i> -NO ₂ ^a	<i>m</i> -NO ₂ ^b	di-NO ₂ ^c		
I	2.7	1.5	0	0	-15 to -20	5-10	1.1550	1.947	trace	0.0186	42.8	51.0	trace ^d	0.40	94.2	0
II	2.7	1.0	1.0	0.41	0	30	1.1840	0.3893	0.1144	.0188	43.9	10.2	3.1 ^e	.40	57.6	.28
III	2.73	1.0	2.0	0.81	-15 to -20	3-5	1.9450	.3654	.1131	.0129	71.3	9.5	2.9	.30	84.0	.29
IV	2.72	1.0	3.0	1.22	-15 to -20	3-5	1.6990	.3214	.1226	.0080	62.5	8.4	3.2	.20	74.3	.36
V	2.7	1.0	4.0	1.63	-15 to -20	3-5	1.4540	.4147	.1512	.0006	53.9	10.9	4.0	.02	68.8	.36
VI	2.7	1.0	6.0	2.45	-15 to -20	30	1.1562	.3729	.1631	.0019	42.8	9.8	4.3	.04	56.9	.43
VII	2.7	1.0	7.0	2.70	-15 to -20	3-5	2.1180	.2730	.1258	.0042	78.5	7.1	3.3	.10	89.0	.45
VIII	2.7	1.5	8.0	3.27	-15 to -20	3-5	1.7655	.2737	.1263	.0049	65.4	7.2	3.3	.10	76.0	.45
IX	2.7	1.5	9.0	3.50	-15 to -20	3-5	1.8205	.2603	.1385	.0043	67.4	6.8	3.6	.10	77.9	.52
X	2.7	1.5	10.0	4.08	-15 to -20	3-5	2.2015	.2408	.1686	.0017	81.5	6.3	4.4 ^f	.03	92.2	.69
XI	2.7	1.5	12.0	4.70	-15 to -20	3-5	1.8740	.2484	.1818	.0012	69.4	6.5	4.8	.02	80.7	.73
XII	2.7	1.5	25.0	9.80	-15 to -20	60	1.4041	.7520	.5880	.0010	52.1	19.7	15.4	.02	87.2	.78

^a Nitro group ortho to the hydroxyl. ^b Nitro group meta to the hydroxyl. ^c Nitro groups ortho to the hydroxyl. ^d No benzoate of *m*-nitro-*p*-cresol obtained. ^e Benzoate of *m*-nitro-*p*-cresol obtained in 61% yield. ^f Benzoate of *m*-nitro-*p*-cresol obtained in 84% yield.

onium salts, the nitration of a phenol in the presence of varying amounts of sulfuric acid might be expected to yield different ratios of meta derivatives. It has been shown recently that the addition of sulfuric acid in the nitration of benzaldehyde and of ethyl benzoate leads to increased production of the meta derivative.¹¹

For this work *p*-cresol was selected since it is known to form two addition compounds with sulfuric acid, *viz.*, $2C_7H_8O \cdot H_2SO_4$, m. p. 11.0° , and $C_7H_8O \cdot 2H_2SO_4$, m. p. 93.5° .¹² If these compounds are ionized the electronic

formulas are, for the former, $2CH_3C_6H_4 : \overset{H}{\underset{H}{\ddot{O}}} : H^+ , SO_4^-$; and for the latter,

$CH_3C_6H_4 : \overset{H}{\underset{H}{\ddot{O}}} : H^{++} , 2HSO_4^-$. The presence of a positive charge on the

former would presumably increase the proportion of the meta isomer produced on nitration while the presence of a doubly positive charge on the latter would be expected to have an even greater effect. Any influence of added acid, due to salt formation alone, might be expected to carry through to the esters of *p*-cresol, and for that reason the carbonate of *p*-cresol was also nitrated under varying conditions.

The results obtained with *p*-cresol by nitrating in glacial acetic acid solution are shown in Table I, and those with *p*-cresyl carbonate and fuming nitric-sulfuric acid mixture are shown in Table II.

TABLE II
EFFECT OF SULFURIC ACID UPON THE NITRATION OF *p*-CRESYL CARBONATE

Expt.	Carbonate:	Molal ratio		Temp., °C.	Nitration products, per cent.					Total	Ratio <i>m/o</i>
		HNO ₃ : 2.5% N ₂ O ₅	H ₂ SO ₄ : 5% SO ₃		<i>p</i> -Cresol	<i>o</i> -NO ₂	<i>di</i> -NO ₂	<i>o</i> -NO ₂	<i>m</i> -NO ₂		
I	1	1.9	0	-10	39.7	32.8	0.2	33.2	3.8	76.5	0.1
II	1	1.9	1.2	0 to -5	37.4	2.7	14.2	31.1	7.3	61.6	0.2
III	1	2.2	2.9	0	27.7	8.8	4.8	18.4	28.8	70.1	1.6
IV	1	2.2	3.9	0	8.9	14.2	6.7	27.6	44.5	74.3	1.6
V	1	2.2	4.4 ^a	0	19.0	12.0	4.4	20.8	34.3	69.7	1.7
VI	1	2.2	5.5 ^b	0	5.2	9.1	9.8	28.7	52.4	76.5	1.8
VII	1	2.1	6.2	0 to -5	5.8	6.7	11.7	30.1	65.3	89.5	2.2
VIII	1	2.1	8.2	-5 to -10	1.5	5.8	7.2	20.2	48.6	63.1	2.4
IX	1	2.1	10.8	-5 to -10	3.6	6.2	9.9	26.0	61.6	83.3	2.4

^a 95% H₂SO₄. ^b 90% H₂SO₄.

When using fuming sulfuric and nitric acids *p*-cresol undergoes rapid decomposition and satisfactory results cannot be obtained. The addition of glacial acetic acid cuts down the undesirable side reactions so that, by working rapidly, one can obtain a fair amount of nitration products. On the other hand, the nitration of the carbonate proceeds much more smoothly and can be carried out with the nitric and sulfuric acids alone.

The results obtained in these nitration experiments are shown graphically

(11) Baker and Moffitt, *J. Chem. Soc.*, 314 (1931); Baker and Hey, *ibid.*, 1226 (1932).

(12) Kendall and Carpenter, *THIS JOURNAL*, **36**, 2498 (1914).

in the figure where the molal ratio of *m*-nitro to *o*-nitro¹³ isomer is plotted against the ratios of sulfuric acid to the compound undergoing nitration. In the case of *p*-cresol, only the ortho isomer is formed when there is no sulfuric acid present, but when the sulfuric acid-cresol ratio is one-half, the meta-ortho ratio is approximately one-fourth. As more sulfuric acid is added the meta-ortho ratio rises, at first slowly, then more rapidly, and finally reaches a maximum where further addition of acid changes the meta-ortho ratio but little.

In the case of *p*-cresyl carbonate the meta-ortho ratio is 0.1 at zero concentration of sulfuric acid. It changes slowly at first as acid is added, then more rapidly, and finally approaches a maximum.

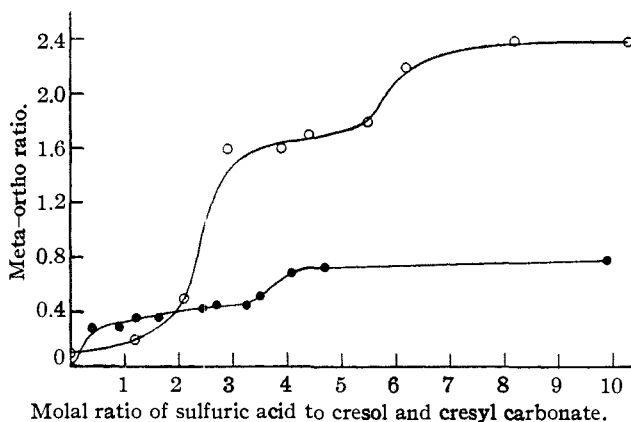


Fig. 1.—O, Nitration of *p*-cresyl carbonate; ●, nitration of *p*-cresol.

Interpretation of the Results.—Increase in the amount of the meta isomer on the addition of sulfuric acid can be accounted for on the basis of oxonium salt formation. It is to be expected that the rate of increase at first would be greater in the case of *p*-cresol since the weakly basic properties of its oxygen atom should exceed the even weaker basic properties of the carbonate. The initial rapid increase in the meta-ortho ratio during the nitration of *p*-cresol corresponds to its conversion into the addition compound, $2\text{CH}_3\text{C}_6\text{H}_4\text{OH}\cdot\text{H}_2\text{SO}_4$. Additional sulfuric acid has little effect until the second addition compound, $\text{CH}_3\text{C}_6\text{H}_4\text{OH}\cdot 2\text{H}_2\text{SO}_4$, is formed. Since the latter is partly dissociated, an excess of sulfuric acid is necessary for the complete conversion of the first into the second. The break in the curve after three moles of sulfuric acid have been added probably corresponds to this change. Finally, the maximum value of 0.8 in the meta-

(13) Since the discussion centers about the hydroxyl group the derivatives are named in reference to it, rather than to the methyl group. Thus 2-nitro-4-hydroxytoluene is here called *m*-nitro-*p*-cresol and 3-nitro-4-hydroxytoluene is called *o*-nitro-*p*-cresol.

ortho ratio indicates that even when completely converted into the disulfate compound more ortho than meta is formed.

In the case of the carbonate the rapid rise in the meta-ortho ratio comes only after approximately two moles of sulfuric acid have been added. Since the carbonate is a weaker base than the cresol the oxonium reaction on each phenolic oxygen should require a higher ratio of sulfuric acid, probably one of acid to each oxygen atom. The resulting compound, $(C_7H_7O)_2CO \cdot 2H_2SO_4$, would probably be unstable and require an excess of sulfuric acid for its complete formation. The rapid rise in the meta-ortho ratio above this point probably corresponds to the conversion of the small amount of uncombined carbonate into the oxonium complex. The second rapid rise above five moles of sulfuric acid probably corresponds to the complete transformation of the first complex into a second, *viz.*, $(C_7H_7O)_2CO \cdot 4H_2SO_4$. Further addition of sulfuric acid brings about little additional change.

The increase in the meta orienting influence of the oxygen atom through salt formation is probably due to its greater attraction for the electron pair which joins it to ring carbon, a condition associated with an increase in the residual kernel charge of the oxygen atom.¹⁴ It is evident that this charge is greater, the greater the degree of ionization of the oxonium complex, since the hydrogen atoms act as bonds in the undissociated molecules. One would expect a progressive increase in the residual kernel charge of the oxygen atom in the following radicals: OH, OH₂X, OH₃X₂, OH₃X⁺, OH₃⁺⁺. On the basis of the positive pole theory the last two should be exclusively meta orienting. The production of the ortho isomer, even in a large excess of sulfuric acid, seems to indicate that a part of the complex is un-ionized and that the nitration of this gives the ortho as well as the meta isomer. It is reasonable to assume, therefore, that on the addition of sulfuric acid the orienting influence of the hydroxyl group suffers modification in the same way as the amino group, but to a less extent.

Experimental

Materials.—Eastman *p*-cresol No. P 449, m. p. 33–34°, was twice distilled under reduced pressure and the portion boiling at 102–102.5° and 22 mm. was collected. It melted at 36.0°. This was converted into the carbonate by dissolving in sodium hydroxide solution and passing in carbonyl chloride.¹⁵ After crystallizing from alcohol it melted at 113°.

3-Nitro-*p*-cresol, 3-nitro-4-hydroxytoluene (called *o*-nitro-*p*-cresol in this paper) was prepared by nitrating 108 g. (1 mole) of *p*-cresol with a mixture of 135 g. of concd. nitric acid (1.4 moles), 200 g. of concd. sulfuric acid (2 moles), and 500 ml. of water at 5–10°. The solution was extracted with ether, the ether was evaporated and the solid was twice steam distilled, m. p. 32.0–32.5°. It analyzed 99.3% pure with standard titanous sulfate and 99.0% pure with standard bromide-bromate solution.

(14) Latimer and Porter, *THIS JOURNAL*, **52**, 206 (1930).

(15) Holleman and Hoeflake, *Rec. trav. chim.*, **36**, 271 (1916).

2-Nitro-*p*-cresol, 2-nitro-4-hydroxytoluene (called *m*-nitro-*p*-cresol in this paper) was prepared by nitrating *p*-cresyl carbonate and saponifying the resulting nitrocarbonate according to the method of Copisarow.¹⁶ The yellow, odorless needles from alcohol melted at 78.5° and analyzed 99.5% pure with standard titanous sulfate and 99.4% pure with standard bromide-bromate.

3,5-Dinitro-*p*-cresol, 3,5-dinitro-4-hydroxytoluene, was prepared by nitrating 36 g. (0.33 mole) of *p*-cresol at 30–40° with a mixture of 135 g. of concd. nitric acid (1.4 mole) and 200 g. of concd. sulfuric acid (2 moles). The reaction mixture was steam-distilled and the residue of crude product was recrystallized from alcohol several times, using norite for decolorizing, m. p. 85.0°. This was found to be 99.3% pure by analysis with standard titanous sulfate and with standard bromide-bromate.

The benzoate of 3-nitro-*p*-cresol was prepared in quantitative yield by the action of benzoyl chloride upon 3-nitro-*p*-cresol dissolved in pyridine. After one crystallization from alcohol the yield of fairly pure crystals was 90%. A second crystallization yielded colorless flakes melting at 96.0°. Reduction with standard titanous solution gave 5.4% N; theoretical for C₁₄H₁₁O₄N, 5.45% N.

The benzoate of 2-nitro-*p*-cresol was prepared as above, in approximately the same yield. It crystallized from alcohol in pale yellow needles melting at 90°. Reduction with standard titanous solution gave 5.42% N; theoretical for C₁₄H₁₁O₄N, 5.45% N.

Nitration.—The operations were carried out in a 20-cm. test-tube provided with a mercury-sealed stirrer, a dropping funnel to admit the nitrating mixture, and an exit tube carrying a calcium chloride tube to prevent moisture from entering. The test-tube was immersed in a freezing mixture of ice and hydrochloric acid at –15 to –20°. To 2.7 g. (0.025 mole) of *p*-cresol dissolved in a mixture of 18 g. of glacial acetic acid and varying amounts of c. p. concd. sulfuric acid was added a mixture of 1 to 1.5 g. of c. p. concd. nitric acid (0.01 to 0.017 mole) and 6 g. of glacial acetic acid, usually during three to five minutes. The mixture was at once poured onto ice and worked up according to the procedure described under purification. It was found that when the cresol was nitrated with a mixture of nitric and sulfuric acids alone only small amounts of nitro-cresols could be obtained since considerable oxidation took place; but in glacial acetic acid the undesirable reactions were so cut down that the nitro compounds could be obtained. However, it was necessary to keep the mixture at –12 to –20° and to shorten the time of addition; otherwise there was a fairly large amount of non-phenolic material produced. Because of the deficiency of nitric acid, only a part of the *p*-cresol was nitrated. The amount of unreacted cresol could be decreased by increasing the time (see Expt. VI, Table I), but more non-phenolic compounds were formed. However, the tendency to undesirable side reactions seemed to drop off at high sulfuric acid ratios since in Expt. XII good yields of products were obtained even though the mixture stood for sixty minutes.

The nitration of the *p*-cresyl carbonate was carried out in the same apparatus, as follows. To 4.83 g. (0.02 mole) of the carbonate dissolved in varying amounts of fuming sulfuric acid containing 5.0% of sulfur trioxide was added 1.9 to 2.2 g. of fuming nitric acid (0.03–0.035 mole) containing 2.5% of nitrogen pentoxide. The temperature was kept at 0 to –10° during the nitration and for three hours afterward; the mixture was then allowed to stand overnight and in the morning it was poured onto a mixture of 30 g. of chopped ice and an amount of sodium carbonate sufficient to neutralize about two-thirds of the sulfuric acid. The precipitated material was filtered onto a Gooch crucible and saponified by refluxing for two to three hours with a solution of 6 g. of sodium carbonate in 60 ml. of water.¹⁸ The solution containing the sodium salts of *p*-cresol and its nitration products was filtered from a small amount of flocculent material, acid was added to the filtrate and this solution was worked up as described under purification

(16) Copisarow, *J. Chem. Soc.*, 251 (1929).

below, except that the solid *o*-nitro-*p*-cresol and *m*-nitro-*p*-cresol were dried to constant weight.

Purification and Separation of Reaction Products.—The aqueous acid solutions resulting from the nitration of *p*-cresol and from the hydrolysis of the nitrated *p*-cresyl carbonate were extracted with ether several times. The ether phase was then extracted with dilute (0.5 to 1.0 *N*) sodium hydroxide. Following this extraction the ether phase was usually colored by the presence of non-phenolic compounds resulting from oxidation. This was discarded. Dilute sulfuric acid was added to the aqueous phase, another ether extraction followed, and after evaporation of the ether the residue was steam distilled, unchanged *p*-cresol and *o*-nitrocresol coming over, *m*-nitro- and dinitrocresol remaining behind. The distillate was extracted with ether, the ether phase was dried with anhydrous sodium sulfate and then evaporated. The residue was dissolved in 100 ml. of glacial acetic acid. Solutions resulting from the nitration of *p*-cresol were analyzed by titration with standard titanous sulfate solution¹⁷ and those from the carbonate, with standard bromide-bromate solution.¹⁷ The residue of *m*-nitro- and dinitrocresol, along with some non-phenolic material, was dissolved in ether, which was then extracted with dilute sodium hydroxide solution. This phase was filtered, dilute sulfuric acid was added, and the cresols dissolved out by ether. The ether phase, after drying with anhydrous sodium sulfate, was evaporated off and the residue was dissolved in 100 ml. of glacial acetic acid. Solutions coming from the nitration of *p*-cresol were analyzed by reduction with standard titanous solution, followed by titration with standard bromide-bromate solution. Those from the nitration of the carbonate were analyzed with bromide-bromate.

The separation by steam distillation of *p*-cresol and *o*-nitro-*p*-cresol from *m*-nitro- and di-nitro-*p*-cresol under the conditions used gave satisfactory results with a known mixture, as shown below:

	Distillate		Residue	
	<i>p</i> -Cresol g.	<i>o</i> -nitro- <i>p</i> -cresol, g.	<i>m</i> -nitro- <i>p</i> -cresol, g.	dinitro- <i>p</i> -cresol, g.
Weight taken	0.3001	2.0011	0.2466	0.0214
Weight recovered	.2981	1.9871	.2478	.0215

Analysis.—The determination of *p*-cresol and of *o*-nitro-*p*-cresol in a mixture of these two obtained by the steam distillation of the reaction product from the nitration of *p*-cresol was done by titrating one aliquot of the glacial acetic acid solution with standard titanous sulfate, following the procedure described by Francis and Hill¹⁷ for the use of titanous chloride in determining nitro compounds in alcoholic solution, and by titrating a second aliquot first with an excess of titanous sulfate and second with standard bromide-bromate, following again the procedure of Francis and Hill. The use of glacial acetic acid is preferable to alcohol since the latter slowly reacts with the bromide-bromate solution.¹⁸ From the amount of titanous solution required the amount of nitro compound can be calculated readily, and from the titanous and bromate titrations the amount of unchanged cresol is easily calculated. The data below show the results obtained with a known mixture:

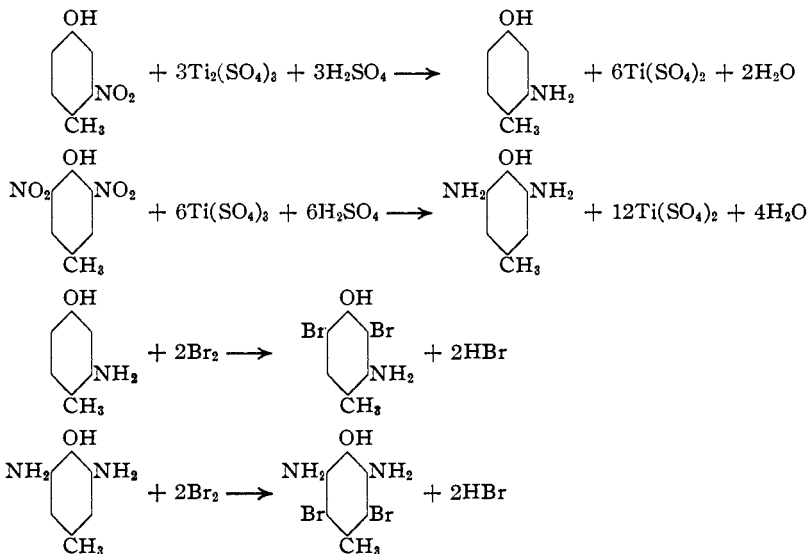
ANALYSIS OF *p*-CRESOL (1.5250 G.) AND *o*-NITRO-*p*-CRESOL (0.3650 G.) DISSOLVED IN 100.0 ML. OF GLACIAL ACETIC ACID, BY REDUCTION AND BROMINATION

Soln., ml.	Ti ₂ (SO ₄) ₃ (0.00528 <i>N</i>), ml.	KBrO ₃ (0.1022 <i>N</i>), ml.	<i>o</i> -Nitro- <i>p</i> -cresol		Error, %	Taken, g.	<i>p</i> -Cresol Found, g.	Error, %
			Taken, g.	Found, g.				
2	9.01	13.73	0.00730	0.00727	-0.83	0.0305	0.03021	-1.0
2	9.04	13.78	.00730	.00729	- .50	.0305	.03028	-0.7

(17) Francis and Hill, *THIS JOURNAL*, **46**, 2498 (1924).

(18) Buxton and Lucas, *ibid.*, **50**, 249 (1928).

In the same way the mixture of *m*-nitro- and dinitro-*p*-cresol can be analyzed, the calculations being based upon the equations



When a is equivalents of titanous sulfate and b is equivalents of bromine used up, the weight of *m*-nitro- (x) and of dinitro-*p*-cresol (y) can be calculated by means of the two equations

$$x = 76.5b - 153a; \quad y = 198a - 49.5b$$

The data below show the results obtained with a known mixture.

ANALYSIS OF *m*-NITRO-*p*-CRESOL (0.2025 G.) AND DINITRO-*p*-CRESOL (0.0200 G.) DISSOLVED IN 50.0 ML. OF GLACIAL ACETIC ACID, BY REDUCTION AND BROMINATION

Soln., ml.	Ti ₂ (SO ₄) ₃ (0.00528 N) ml.	KBrO ₃ (0.0536 N), ml.	<i>m</i> -Nitro- <i>p</i> -cresol			Dinitro- <i>p</i> -cresol		
			Taken, g.	Found, g.	Error, %	Taken, g.	Found, g.	Error, %
2	11.62	4.28	0.00310	0.00814	+0.5	0.00080	0.00079	-1.2
2	11.60	4.27	.00310	.00814	+ .4	.00080	.00079	-1.2

The reaction products from the nitration of *p*-cresyl carbonate were analyzed by bromination alone. In this case it was necessary to know the weight of solid material and this was obtained by complete evaporation of the ether solutions, followed by desiccation over concd. sulfuric acid for one or two days. With known mixtures bromination gave fairly satisfactory results.

ANALYSIS OF *p*-CRESOL (1.0835 G.) AND *o*-NITRO-*p*-CRESOL (2.1406 G.) DISSOLVED IN 250 ML. OF GLACIAL ACETIC ACID, BY BROMINATION ALONE

Soln., ml.	KBrO ₃ (0.1346 N), ml.	Taken, g.	<i>p</i> -Cresol		Taken, g.	<i>o</i> -Nitro- <i>p</i> -cresol		Error, %
			Found, g.	Error, %		Found, g.	Error, %	
10	20.15	0.04334	0.04279	-1.3	0.08562	0.08601	+0.5	
10	20.18	.04334	.04290	-1.0	.08562	.08590	+ .4	

The calculations above were based upon the fact that *p*-cresol reacts with two moles of bromine and the *o*-nitro derivative with only one. In the equations x is amount of *p*-cresol, y is amount of *o*-nitro-*p*-cresol, a is equivalents of bromine used and w is weight of the sample in grams.

$$x = 41.80a - 0.547w$$

$$y = 1.548w - 41.80a$$

ANALYSIS OF *m*-NITRO-*p*-CRESOL (0.3621 G.) AND DINITRO-*p*-CRESOL (0.1284 G.) IN 50 ML. OF GLACIAL ACETIC ACID; BY BROMINATION ONLY

Soln., ml.	KBrO ₃ (0.1346 N), ml.	Taken, g.	<i>m</i> -Nitro- <i>p</i> -cresol Found, g.	Error, g.	Taken, g.	Dinitro- <i>p</i> -cresol Found, g.	Error, %
10	14.16	0.07242	0.07304	+0.8	0.02568	0.02506	-2.4
10	14.14	.07242	.07302	+ .8	.02568	.02508	-2.4

These calculations are based upon the fact that *m*-nitro-*p*-cresol reacts with two moles of bromine and the dinitro compound with none. The calculations are made according to the equations below in which x is weight of *m*-nitro- and y is weight of dinitro-*p*-cresol.

$$x = 38.25a$$

$$y = w - 38.25a$$

Experimental Results.—The results of the nitration of *p*-cresol in glacial acetic acid solution and of the nitration of *p*-cresyl carbonate are given in Tables I and II. It is from these data that the curves shown earlier were constructed.

In the nitration of *p*-cresol there was always a deficiency of nitric acid. The small amount of dinitro compound was assumed to be the isomer in which both nitro groups were ortho to the hydroxyl. Benzoylation of the residue non-volatile with steam from Experiment II gave an amount of the benzoate of *m*-nitro-*p*-cresol equivalent to 61% of the meta compound found by analysis and the residue from Experiment X gave 84%. None of this benzoate could be obtained from Experiment I.

Since *p*-cresyl carbonate undergoes nitration with greater difficulty, it was necessary to use a mixture of fuming nitric and fuming sulfuric acid. Here again the dinitro-*p*-cresol was assumed to be 3,5-dinitro-4-hydroxy-toluene. Such an assumption probably involves an error, since the dinitro compound may in part be the 2,5- or even the 2,6- isomer. If the former is present then the meta-ortho ratio should be less than the one calculated, while if the latter is present this ratio should be greater. It is possible that the error from this source is not great since these two effects counteract each other.

Summary

Nitrations of *p*-cresol and of *p*-cresyl carbonate have been carried out in the presence of sulfuric acid in amounts varying from 0 to 10 moles of acid per mole of organic compound. It was found in the case of *p*-cresol that the ortho directive power of the hydroxyl group decreased as sulfuric acid

increased, and that more and more of the entering nitro group took up a position meta to the hydroxyl. However, a maximum value of about 0.8 was reached for the meta-ortho ratio. This change in directive power is ascribed to the salt-forming property of the oxygen atom of *p*-cresol. The predominating tendency toward ortho substitution, even when a large excess of acid is present, probably arises from the fact that the oxonium salt is in part un-ionized.

In the case of *p*-cresyl carbonate, increase in the amount of sulfuric acid likewise increased the meta-ortho ratio. It is assumed that here also oxonium salt formation is responsible for the change.

These changes in orientation are entirely analogous to the modification in the orientation of amino and substituted amino groups by the addition of sulfuric acid.

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The Preparation of Some Structurally Related Monoguanidines

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Introduction

In a study of the relationship between guanidine structure and hypoglycemic activity it became necessary to prepare the following series of structurally related monoguanidines: α -phenylguanidine sulfate, benzylguanidine sulfate, phenylaminoguanidine hydrochloride, *p*-aminophenylguanidine sulfate, *n*-hexylguanidine sulfate, cyclohexylguanidine hydrochloride, *o*-tolylguanidine hydrochloride, *m*-tolylguanidine sulfate, *p*-tolylguanidine hydrochloride, α -methyl α -phenylguanidine hydrochloride and β -phenylethylguanidine sulfate. The first four were prepared as described by previous investigators.¹

The detailed syntheses of the latter seven are recorded here for the benefit of those interested in the field. While the nitrate salts of *o*-tolylguanidine and *p*-tolylguanidine have been described,² no record of their hydrochlorides could be found.

Since the compounds were synthesized for the purpose of studying their physiological reactions, special emphasis was placed upon purity, and no attempts were made to produce maximum yields. The hydrochloride and sulfate salts were selected to obtain greater water solubility than might be expected with the free bases or the nitrate salts. The results of the physiological investigation of these compounds, which is in progress, will be reported separately.

(1) Smith, *THIS JOURNAL*, **51**, 476 (1929); Davis and Elderfield, *ibid.*, **54**, 1499 (1932); Pellizzari, *Gazz. chim. ital.*, **21**, 330 (1891); Braun, *THIS JOURNAL*, **54**, 1511 (1932).

(2) Meister, Lucius and Bruning, German Patent 172,979; Kampf, *Ber.*, **37**, 1683 (1904).