activity goes down to less than one—less than if no side chain were present: *p*-hydroxylphenyl *n*-propyl ether 5, *p*-hydroxyphenyl *n*-γ-hydroxypropyl ether 0; *o*-cresol 2.2, saligenin 0.

Summary

While it is true that no concise "rules" can result from such limited data, certain conclusions are perhaps permissible.

1. The mass of a group substituted into a phenol has little relation to the germicidal activity of the resulting compound.
2. Position isomerism has little effect on the bactericidal activity of alkyl and alkoxy substituted phenols.
3. Side chain isomerism affects the activity of alkyl phenols markedly. The more compact the group, the lower the activity.
4. The group CH_2R is much more effective than OR in enhancing the activity of a phenol.
5. The carbomethoxy and acetoxy groups are ineffective in enhancing the activity of phenol.

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THE NITRATION OF PHENYLACETIC ACID

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Latimer and Porter have shown that the directive influence of a group substituted for hydrogen in the benzene ring depends upon the residual charge of the atom attached to the ring.[1] The method of determining the residual charge is based upon the unequal sharing of electrons between two unlike atoms. It was found that if the residual charge on the atom attached to the ring has a high positive value, the substituent directs the incoming group mainly to the meta position and if the residual charge is zero or negative the substituent is ortho–para in its orienting influence. The method used in calculating the residual charge does not take into account the influence of atoms beyond those directly connected with the key atom. In order to evaluate the influences of remote atoms it is necessary to have exact data on the behavior of border-line groups. As a start in this direction we have studied the nitration of phenylacetic acid.

Radziszewski[2] found that the nitration of phenylacetic acid yielded mostly the para isomer, which is quite insoluble, and a small amount of the ortho isomer, which remained behind in the mother liquor. Maxwell,[3]

[1] Latimer and Porter, THIS JOURNAL, **52**, 206 (1930).

[2] Radziszewski, *Ber.*, **2**, 207 (1869); **3**, 648 (1870).

[3] Maxwell, *ibid.*, **12**, 1764 (1879).

Bedson[4] and later Borsche[5] also studied the nitration of phenylacetic acid, but in no case is any mention made of the formation of the meta derivative. The nitration of the ethyl ester of phenylacetic acid was carried out qualitatively by Radziszewski[2] and quantitatively by Baker and Ingold[6] and by Flürscheim and Holmes.[7] Baker and Ingold found that approximately 9% of the meta derivative was formed whereas Flürscheim and Holmes obtained about 12% of the meta derivative. Baker and Ingold state that undissociated phenylacetic acid should yield an even higher proportion of the meta derivative, but the effect of ionization might be a large contrary factor. The negative charge induced by ionization would tend to make the effective residual charge on the key atom more negative, and hence more ortho–para in its orienting power. The similar case of the benzoate ion has been discussed by Flürscheim and Holmes.[8] From the results of Holleman[9] and Zaki,[10] who found that benzoic acid yields more of the meta compound than do its esters, we should expect phenylacetic acid to yield a higher proportion of the meta isomer than would be obtained from its esters. Actually we obtained 14.4% of the meta derivative upon the nitration of phenylacetic acid.

Analytical Method.—The nitro bodies obtained from phenylacetic acid by nitration were oxidized with alkaline permanganate to the corresponding nitrobenzoic acids. The total quantity of nitrobenzoic acid (ortho, meta and para) obtained in this way was determined by titration with titanium trichloride. The nitrobenzoic acids were converted into aminobenzoic acids by reduction and the amino acids were treated with bromine water. By this process the ortho and para aminobenzoic acids were converted into tribromoaniline which precipitated and the meta compound was converted into 2,4,6-tribromo-3-aminobenzoic acid, which remained in solution. The tribromoaniline was filtered off and weighed to obtain the quantity of the ortho and para nitrobenzoic acids present. The meta isomer was determined by the difference between the total quantity of nitrobenzoic acids formed and the quantity of mixed ortho and para nitrobenzoic acids. This procedure is a modification of the method used by Flürscheim and Holmes[11] for the analysis of a mixture of aminobenzoic acids.

Each step of our entire process was checked by isolating the products at all the intermediate stages and by repeating each step with known syn-

[4] Bedson, *J. Chem. Soc.*, **37**, 90 (1880).
[5] Borsche, *Ber.*, **42**, 3596 (1909–1910).
[6] Baker and Ingold, *J. Chem. Soc.*, 832 (1927).
[7] Flürscheim and Holmes, *ibid.*, 1607 (1928).
[8] Flürscheim and Holmes, *ibid.*, **128**, 1565 (1926).
[9] Holleman, *Rev. trav. Chim.*, **18**, 267 (1899).
[10] Zaki, *J. Chem. Soc.*, 983 (1928).
[11] Flürscheim and Holmes, *ibid.*, 448 (1928).

thetic mixtures. Finally, artificial mixtures consisting of the three nitrophenylacetic acids, phenylacetic acid and nitric acid were put through the procedure and the percentage of the meta derivative found was well within 1% of that calculated.

Experimental Section

Reagents.—*Meta*-nitrophenylacetic acid was prepared from *m*-nitrotoluene. The nitrotoluene (68 g. or 0.5 mole) was kept at 135–145° while 84 g. of bromine (5% excess) was slowly added from a dropping funnel (compare Wachendorff)[12] while the mixture was mechanically stirred. Reaction occurred readily as shown by a steady bubbling of the mixture with a constant evolution of hydrogen bromide. The addition of the bromine took approximately an hour and the mixture was kept at the above temperature for half an hour longer and then allowed to cool. When the temperature is allowed to rise above 145°, resinous substances are produced and the yield is poor. A saturated solution of 32.5 g. of potassium cyanide (0.5 mole) in water and 300 cc. of alcohol was then added to the impure nitrobenzyl bromide and the reaction mixture was refluxed for three hours on a water-bath. The alcohol was distilled off and the nitrobenzyl cyanide was hydrolyzed by refluxing with 350 cc. of concentrated hydrochloric acid for three hours (see Gabriel and Borgmann).[13] The hydrolyzed mixture was filtered through glass wool while still hot and then allowed to cool. The cooled solution deposited crystals of *m*-nitrophenylacetic acid after a few hours. A second crop of crystals was obtained by evaporating the mother liquor to half of its volume. The crude *m*-nitrophenylacetic acid was repeatedly recrystallized from water and dried under reduced pressure over calcium chloride (m. p. 119.5–120°). On the basis of the nitrotoluene used a 62% yield (56 g.) of the purified product was obtained.

Phenylacetic acid, *o*-nitrophenylacetic acid and *p*-nitrophenylacetic acid were available on the market. The commercial products were purified by fractional crystallization. Kahlbaum's nitric acid was freed from oxides of nitrogen by bubbling dry air through it under reduced pressure for three to four hours. At the end of this time the resulting liquid had only a very pale yellow color.

Procedure

Nitration.—Dried and finely pulverized phenylacetic acid (approximately 5 g.) was added in small portions to 30 cc. of nitric acid free from oxides of nitrogen and having a density of 1.495. The temperature was kept at 0° and the flask was shaken thoroughly after each small addition of the phenylacetic acid. The mixtures were then allowed to stand for three hours at 0°. At the end of this time the mixture was poured onto cracked ice and the precipitated nitro bodies were filtered off. The precipitate was freed from nitric acid by washing with water until the wash water no longer gave a test with diphenylamine and sulfuric acid.[9] The washings and filtrate were combined and extracted with ether and the ether extracts were washed with water. All of the ether extracts were combined, dried over anhydrous sodium sulfate and the solvent was distilled off. The nitro bodies obtained from the filtrate and from the precipitate were then combined and subjected to analysis. Equivalent weight determinations showed that neither dinitration nor oxidation occurred with nitric acid of density 1.495 when the reaction mixture was kept at 0°.

Oxidation of Nitrophenylacetic Acids.—The oxidation of the $-CH_2COOH$ group with alkaline permanganate goes in steps[14] through $-CHOHCOO^-$, $-COCOO^-$ and

[12] Wachendorff, *Ann.*, **185**, 277 (1887).

[13] Gabriel and Borgmann, *Ber.*, **16**, 2064 (1883).

[14] Prjevalsky, *J. Russ. Phys.-Chem. Soc.*, **49**, 567 (1917–1918).

finally to $-COO^-$ and CO_3^{--}. To be of value the oxidation in this case must proceed to the last step without changing the ratio between the isomers present. Synthetic mixtures composed of the ortho, meta and para-nitrophenylacetic acids were oxidized under varying conditions. The equivalent weights of the oxidation products, the percentage recovery and the percentage of the *m*-derivative present in each mixture were determined.

The oxidation conditions were varied as follows: (1) time of reaction, 4, 8, 10 and 12 hours; (2) excess of permanganate, 10, 20, 30 and 50%; (3) hydroxide-ion concentration, 0.01, 0.1, 0.25 and 0.50 normal. The following procedure was finally adopted. The theoretical amount of solid permanganate was added all at once, the volume of the solution being adjusted so that a 2% permanganate solution resulted. The hydroxide-ion concentration was kept at 0.1 normal. The temperature was maintained at 95–100°. Samples were withdrawn from the oxidation vessels every hour, and the manganese dioxide was allowed to settle. If the clear liquid above the manganese dioxide was not violet, additional permanganate was added and the mixture was heated again. The process was continued until permanganate was still present after two hours of continuous heating. Usually the reactions were over in four to six hours. Under these conditions the recovery of the oxidation products was about 90% of the theoretical and with artificial mixtures of known composition the percentage of the meta compound found was within 1% of the actual value.

After the oxidation had been completed, the manganese dioxide was filtered off and extracted with three 250 cc. portions of boiling water. The aqueous extracts and the original filtrate were combined and evaporated to about 500 cc. The clear solution was then acidified with sulfuric acid and the precipitated nitrobenzoic acids were filtered off. The precipitate was washed with water and the washings and filtrate were combined and extracted with three 150 cc. portions of ether. The ether extracts were combined and dried, and the solvent was distilled off. The residue thus obtained was combined with the originally precipitated acids, the benzoic acid present was sublimed off and equivalent weight determinations were made with titanium trichloride.

Reduction of the Nitrobenzoic Acids.—A weighed amount of the mixed nitrobenzoic acids was dissolved in a known volume of standardized sodium hydroxide solution and the resulting alkalinity of the stock solution was then calculated. Samples (50 cc. portions) were pipetted from the stock solution and a sufficient quantity of concentrated hydrochloric acid was added to give a four normal solution for a 300-cc. volume. A measured excess of titanium trichloride was added and the mixture was gently boiled for ten minutes. If the solution became colorless during boiling, a small amount of titanium trichloride was added and the boiling continued until a slight violet color remained after ten minutes' boiling. (For methods of using titanium trichloride see Knecht and Hibbert.[15])

Bromination of the Aminobenzoic Acids.—By a series of experiments with known mixtures of ortho, meta and para-aminobenzoic acids we were able to modify the methods of Francis and Hill[16] and of Flurscheim and Holmes[11] so as to obtain a nearly quantitative bromination and we were able to apply a systematic correction for the difference between the theoretical yield and the quantity obtained. The following technique was adopted: (a) a sample of the mixed nitrobenzoic acids (approximately 2.5 g.) was dissolved in 500 cc. of 0.1 *N* sodium hydroxide. (b) A 50 cc. portion of this solution was acidified by the addition of 95 cc. of 12 *N* hydrochloric acid and heated with a measured excess of titanium trichloride. (c) To the clear cooled solution 30 cc. of 95% alcohol

[15] Knecht and Hibbert, "New Reduction Methods in Volumetric Analysis," Longmans, Green and Co., New York, 1925.

[16] Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).

was added and the solution was warmed to 40°. (d) Bromine water was added until the solution had a permanent pale yellow color. (e) The mixture was diluted to 300 cc. and the acidity was adjusted to exactly four normal. (f) The precipitate was allowed to stand in contact with the mother liquor for twenty-four hours. (g) The residue was filtered, washed and then dried over calcium chloride in a vacuum desiccator and weighed.

Under these conditions *m*-aminobenzoic acid is brominated in the 2,4,6-positions, yielding tribromo-*m*-aminobenzoic acid, which is soluble in water. The ortho and para-aminobenzoic acids are converted into tribromoaniline, the carboxyl group being replaced by bromine. An addition of 0.036 g. is made to the weight of the precipitate to cover the loss due to the solubility of the product and possibly due in part to incomplete bromination. This correction is the average of many determinations made on equivalent quantities of known mixtures.

Estimation of the Total Nitrobenzoic Acids.—Samples of the stock solution (50-cc. portions of the solution described under bromination) were withdrawn, acidified and mixed with a measured excess of standardized titanium trichloride. The mixture was placed in a water-bath at 90° for twenty minutes. A continuous stream of carbon dioxide was passed over the surface of the liquid to avoid oxidation of the reagent by the air. After cooling, the excess of titanium trichloride was back-titrated with a solution of ferric alum, using ammonium thiocyanate as the indicator.

The results for the last group of nitrations are given in Table I, where the figures for the molecular weights, the titrations and the brominations represent averages of three determinations.

TABLE I

RESULTS OF EXPERIMENTS

Nitration number	1	2	3
Weight nitrated in grams	5.13	5.05	5.65
Weight of nitro bodies obtained in grams	6.68	6.67	7.45
Percentage nitration yield	98	99	99
Molecular weight of nitration product	181.6	182.2	181.0
Weight oxidized in grams	5.54	5.47	5.54
Weight of oxidation product obtained in grams	4.55	4.58	4.70
Percentage oxidation yield	89	91	92
Weight of benzoic acid sublimed in grams	0.031	0.009	0.042
Percentage of benzoic acid present in product	0.7	0.2	0.8
Molecular weight of oxidation products	166.8	166.4	166.7
0.2485 *N* $TiCl_3$, cc.	28.14	29.60	29.81
Total nitrobenzoic acids present in grams	0.1946	0.2048	0.2062
Grams of tribromoaniline +0.036	.329	.345	.350
o-p-Nitrobenzoic acids present in grams	.1666	.1747	.1773
Percentage of meta compound	14.4	14.7	14.0

The molecular weight calculated for a mono-nitrophenylacetic acid is 181.1; that for a mono-nitrobenzoic acid is 167.05.

Summary

The nitration of phenylacetic acid has been studied quantitatively. A method of analysis developed by Flürscheim and Holmes has been modified to meet the requirements of this investigation. Optimum conditions

have been established for the nitration of phenylacetic acid, the oxidation of nitrophenylacetic acids, the reduction of these compounds to amino acids and the bromination of aminobenzoic acids. Using this procedure, which yields reproducible results, it was found that 14.4% of the meta isomer is formed when nitric acid at 0° acts upon phenylacetic acid.

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[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN & FINK, INC.]

BACTERICIDAL PROPERTIES OF MONOETHERS OF DIHYDRIC PHENOLS. III. THE MONOETHERS OF PYROCATECHOL. COMPARATIVE NOTES ON THE THREE SERIES OF MONOETHERS

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The third and last group of monoethers studied in this series of investigations[1] comprises the derivatives of pyrocatechol.

The antibacterial action of the parent compound pyrocatechol and of its methyl ether, guaiacol has been studied by many investigators in the past. It is not intended to give a complete tabulation of these findings; the general conclusion may be drawn from them, that as a bactericidal agent, pyrocatechol is less effective than phenol while guaiacol shows practically the same potency as phenol. This is not true, however, of the inhibitory action. Thus according to Cooper and Mason[2] the minimum concentration of pyrocatechol required to inhibit the growth of *B. coli* at 37° is almost one-half that of phenol, while in the case of *B. fluorescens liquefaciens* it is even less.

The preparation of certain higher alkyl monoethers of pyrocatechol from the corresponding diethers is referred to in the German patents Nos. 78,910, 92,651 and 94,852.[3] However, the antibacterial efficacy of these ethers does not appear to have been determined. In addition to these compounds the phenyl monoether is also known. It has been prepared by Ullmann and Stein[4] by treating the solution of the methyl phenyl ether of pyrocatechol in benzene with aluminum chloride.

The series of monoethers of pyrocatechol prepared and studied by us comprises the straight chain aliphatic derivatives up to and including the *n*-heptyl ether, the *sec.*-amyl ether, the phenyl ether and the alphyl aromatic derivatives up to and including the phenyl propyl ether.

In preparing these compounds we followed generally the methods applied

[1] Klarmann, Gatyas and Shternov, THIS JOURNAL, **53**, 3397 (1931); **54**, 298 (1932).

[2] F. A. Cooper and J. Mason, *J. Hygiene*, **26**, 118 (1927).

[3] Friedländer, *Fortschritte der Teerfarbenfabrikation*, **4**, 122–124.

[4] F. Ullmann and A. Stein, *Ber.*, **39**, 623 (1906).