



Steric Hindrance and Steric Acceleration
in the
Acylation of Aromatic Amines

1916
1916

By

A. Floyd Whipple

A Thesis Presented in Partial Fulfillment of the
Requirements for the Degree of Master of Science
in the
Oklahoma Agricultural and Mechanical College
Department of Chemistry

Stillwater

1916

66363

Cal

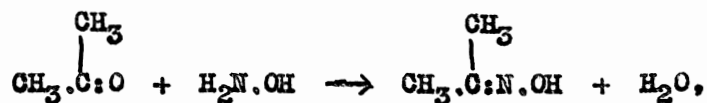
Prefatory

The length of this paper makes it desirable to state at this point that pages 1 to 47 deal with the general subject of steric hindrance in various organic reactions; that pages 48 to 57 treat of the acylation of the amino group in primary bases; and that pages 58 to 73 contain the results and conclusions of the work in hand, together with a description of the experiments as carried out in the laboratory.

Steric Hindrance and Steric Acceleration in the
Acylation of Aromatic Amines, With Special Regard
to Acid-forming Substituents in the Para Position.

By A. Floyd Whipple.

It has long been known that the progress of certain typical reactions is more or less interfered with by the presence of neighboring groups. Thus, it has been found¹ that acetone readily reacts with hydroxylamine to give an oxime, as may be illustrated by the equation:



but that the reaction takes place with less ease if one or more of the methyl hydrogen atoms have been replaced by atoms or radicals of greater weight (and presumably occupying more space); and that if all have been substituted, the normal reaction may be entirely prevented. A study of these and

1. V. Meyer, Ber., 15, 1524, 2776 (1882); 16, 823, 1784 (1883); etc.

many similar cases has shown that the interference is due to the spatial disposition of the substituents, and the phenomena are now usually described under the general head of steric hindrance. The hindrance referred to has been noted in several typical reactions, and the study of the effect has involved the behavior of many different substituents. For the purposes of this paper these reactions will be grouped under the following heads:

I. Formation of Quaternary Ammonium Compounds.

II. Hydrolysis.

A. Conversion of Cyanides into Acids.

B. Conversion of Acid Amides and Acid Chlorides into their Corresponding Acids.

C. Action of Alcohol on Acid Chlorides.

D. Conversion of Esters into Acids and Alcohols.

III. Formation of Imino Ethers.

IV. Reactions of the Carbonyl Group.

A. Formation of Oximes.

B. Formation of Hydrazones.

C. Benzaldehyde on Aromatic Amines. Rosanilines.

V. Esterification.

A. Aromatic Acids.

B. Fatty Acids.

VI. Acylation of Secondary Bases.

VII. Nitrous and Nitric Acid and Diazo Salts on Aromatic Amines.

VIII. Phosphorus Pentachloride on Hydroxy-acids.

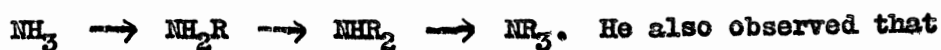
IX. Reduction of Nitro Compounds.

X. Bischoff's Reactions.

XI. Acylation of Primary Amines.

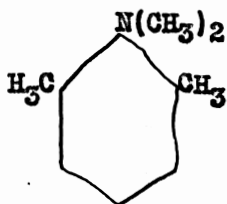
I. The Formation of Quaternary Ammonium Salts
from Tertiary Amines.

In his classical work on the substituted ammonias, Hofmann found that the hydrogen atoms of ammonia could be successively replaced by alkyl to form what is known as a tertiary amine, in accordance with the following scheme:

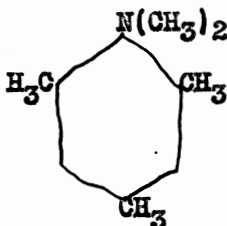


He also observed that the tertiary amine could react once more with alkyl halide to give a compound of the type NR_4X (X = halogen). He made, perhaps, the first observation in steric hindrance when he

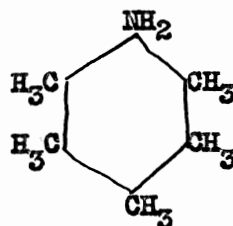
noted¹ that dimethylxylidine, dimethylmesidine, and pentamethylaminobenzene gave little or no quaternary ammonium compounds when heated with methyl iodide to 150°, and concluded that 'this inability to unite with methyl iodide must depend upon some kind of molecular arrangement'. Hofmann gave no further explanation of the inability of these compounds to undergo the usual reaction, but it is clear from the structures of the compounds that this is a well defined case of steric hindrance.



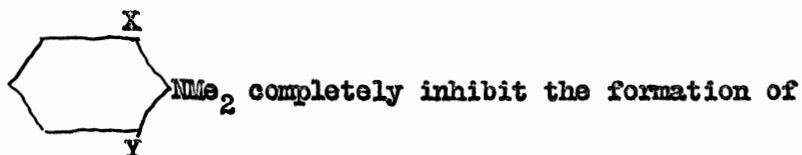
Dimethylxylidine.



Dimethylmesidine.

Pentamethylamino-
benzene.

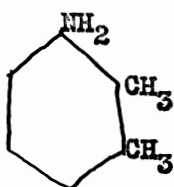
This question was reinvestigated later by Fischer and Windaus² who have shown that the presence of ortho-substituents in a tertiary aromatic amine of the type



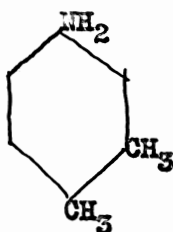
1. Ber., 5, 713, 718 (1872); 8, 61 (1875).

2. Ber., 33, 345, 1967 (1900).

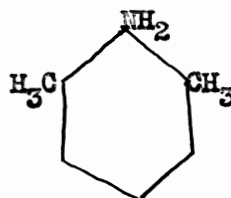
quaternary ammonium compounds. Though all six of the isomeric xylidines can be converted into tertiary bases by Noelting's method (using methyl iodide and sodium carbonate), the 2, 6-



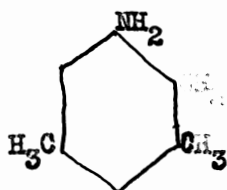
adj.-o-Xylidine.



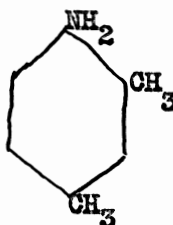
unsym.-o-Xylidine.



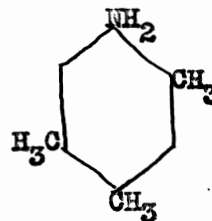
adj.-m-Xylidine.



sym.-m-Xylidine.



unsym.-m-Xylidine.



p-Xylidine.

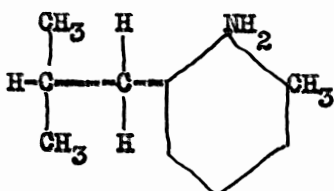
compound, which has the structure given above, gives no quaternary ammonium iodide. The same is true with the different isomeric bromotoluidines and bromoxylidines.

Moreover, Friedlander¹ found that 2, 6-xylidine²

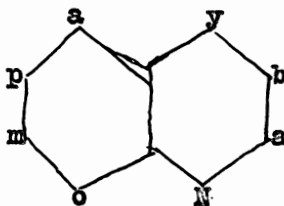
1. Monatsh., 19, 645 (1898).

2. Formula above for adj.-m-xylidine.

can, with difficulty, be converted into the tertiary diethyl compound, whilst Effront¹ could only obtain traces of the dimethyl tertiary base with 2-methyl-6-isobutyl toluidine,



and methyl iodide at 150°. Decker noticed the same phenomenon in *o*- or *a*-substituted quinolines,



which will not combine with alkyl iodides.

II. Hydrolysis.

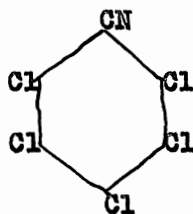
A. Conversion of Cyanides or Nitriles into Acids.

When an alkyl or aryl cyanide or nitrile is boiled

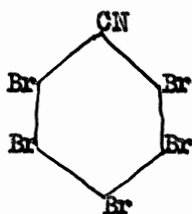
1. Ber., 17, 2317 (1884).

with water to which a little acid or alkali has been added it is decomposed into ammonia and the corresponding acid, in accordance with the following equation:

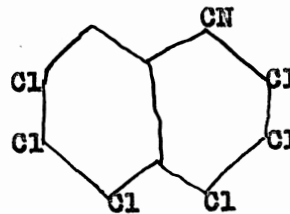
$R.CN + 2H_2O \rightarrow R.COOH + NH_3$. If the cyanide radical is ortho to some group other than hydrogen this reaction is resisted to a noticeable extent; and when it is surrounded by such substituents the reaction may fail entirely. Well known examples are to be had in the work of Merz and Weith,¹ who found that perchloro- and perbromo-benzonitrile and hexachloro- α -naphthonitrile cannot be hydrolysed by the usual reagents, and in the work of Hofmann, who found, in the following year, that tetramethyl- and pentamethyl-benzonitrile behave in a similar manner.



Perchloro-
benzonitrile.

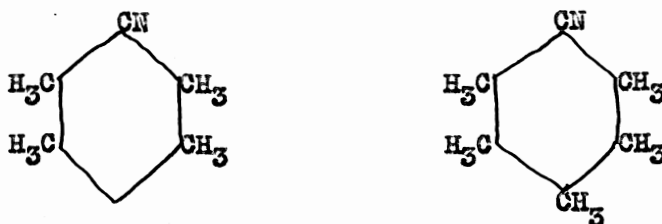


Perbromo-
benzonitrile.



Hexachloro- α -
naphthonitrile.

1. Ber., 16, 2886, 2892 (1883).



Tetramethyl-benzonitrile. Pentamethyl-benzonitrile.

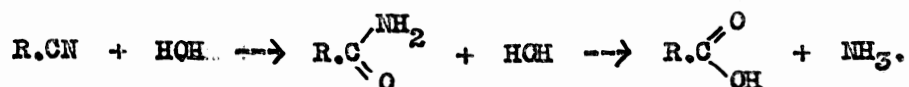
Seven years later, in a more extended investigation, Claus and his pupils showed that resistance to hydrolysis is greatly enhanced if one, and still more if both ortho positions to the cyanogen group are substituted by halogen, alkyl or nitro groups.¹ The influence of the nitro group in this reaction is quite significant, for the presence of one, still more of two nitro groups greatly facilitates hydrolysis. Whilst great difficulty is experienced in hydrolysing *s*-trimethylbenzonitrile the mono- and dinitroderivatives may be completely, though slowly, converted into acids.² This special role of the nitro group in modifying steric hindrance is also evident in the rate of reduction of nitro compounds, as will be shown later.

B. Hydrolysis of Acid Amides and Acid Chlorides.

It was mentioned in the previous section that the

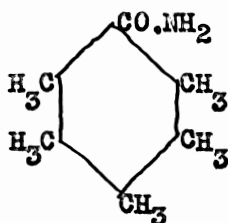
1. Ann., 265, 378 (1891); 266, 225 (1891); 269, 212 et seq (1892).
2. Kuster and Stallberg, Ann., 278, 207 (1894).

nitriles may be hydrolysed to give ammonia and the corresponding acids. The acid amides undergo a similar reaction, and since we may remove water from an acid amide and obtain a nitrile, the acid amide may be regarded as an intermediate product in the passage from the cyanide to the acid. Careful regulation of the experiment sometimes makes it possible to isolate the amide in the hydrolysis. The following equations indicate the relationships:

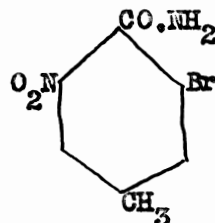


When the position adjacent to the reacting group has been substituted the hydrolysis is retarded. Thus, in 1889, Jacobson¹ noticed that pentamethylbenzamide² completely resists hydrolysis, and Claus³ found that, like the nitriles, many diorthosubstituted derivatives of p-toluyamide exhibit unusual stability. These relationships are clearly indicated by the formulas for the compounds.

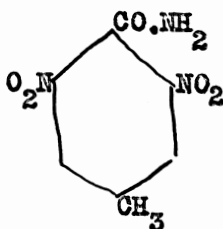
1. Ber., 22, 1219 (1889).
2. Obtained by the action of aluminium chloride on a mixture of chloroformamide and pentamethylbenzene.
3. Ann., 265, 364 (1891); 266, 223 (1891); 269, 208 (1892).



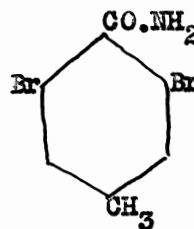
Pentamethylbenzamide.



o-Nitro-o-bromo-p-toluylamide.



o-Dinitro-p-toluylamide.



o-Dibromo-p-toluylamide.

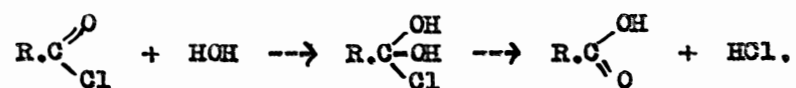
Remsen and Reid¹ studied the relative rates of hydrolysis of ortho-, meta-, and para-substituted benzamides, and obtained results which showed that ortho substituents exerted a retarding influence on the reaction, which was much more than that caused by meta and para substituents.

Acid chlorides react with water in accordance with the equation:

$R.COCl + HOH \rightarrow R.COOH + HCl$. In this, as in the hydrolysis referred to above, it may be assumed that the

1. Am. Chem. J., 21, 340 (1899).

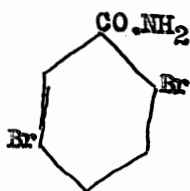
progress of the reaction involves the addition of a molecule of water, and the subsequent splitting off of a molecule of hydrochloric acid, as indicated below:



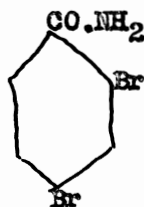
In such a case it is conceivable that the formation of the additive compound might take place less readily, or not at all, if the space adjacent to the reacting group is occupied largely by active radicals. These possibilities have been studied by Sudborough¹ working with V. Meyer, and from his results he concludes that those compounds in which substitution does not occur in either of the ortho positions are readily decomposed by dilute alkalis, whereas those which have a bromine atom in one ortho position are relatively more stable, but where both ortho positions are occupied by bromine atoms the compounds are remarkably stable and are only converted into the corresponding sodium salts of the acids by long continued boiling with an alkali solution.

1. J. Chem. Soc., 67, 601 (1895).

Previous to this time Claus¹ had made some experiments with the hydrolysis of amides and acid chlorides, and had recorded certain facts which indicated differences in the rates of reaction for the different positions of substituents. Meanwhile Victor Meyer's 'esterification law' (which will be referred to later) had been formulated, and this generalization stimulated new interest in Claus' results. To decide the question Sudborough, in conjunction with Jackson and Lloyd,² showed conclusively that in the hydrolysis of benzamides ortho substituents strongly retard the process, so that under conditions which effected almost complete hydrolysis of 2, 5- and 2, 4-dibromobenzamide only 11 per cent of 2, 6-dibromo- and 4.5 per cent of 2, 4, 6-tribromobenzamide were converted.



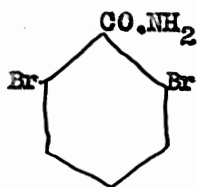
2, 5-Dibromobenzamide.



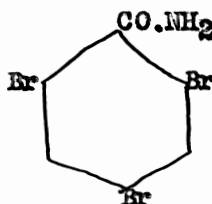
2, 4-Dibromobenzamide.

1. Loc. cit. (See page 8 of this paper.)

2. J. Chem. Soc., 67, 601 (1895); 71, 229 (1897).



2, 6-Dibromobenzamide.



2, 4, 6-Tribromobenzamide.

C. Hydrolysis of Acid Chlorides.

Another reaction which should be mentioned here is the action of alcohols on acid chlorides. Steric influences determine the rapidity of the action, for among the series of menthyl esters of disubstituted benzoyl chlorides Cohen and his collaborators¹ found that the diortho compound invariably required a much higher temperature and more prolonged heating than the other acid chlorides to effect reaction with menthol.

D. The Hydrolysis of Esters.

Under the head of hydrolysis must be mentioned the behavior of esters. With water, and much more rapidly with

1. J. Chem. Soc., 89, 1482 (1906).

alkali, they are converted into alcohols and acids. The esters of the acids of the aromatic series are specially suited for study in this connection, since they give rise to isomers whose substituents are in different positions. Such studies have been made by V. Meyer,¹ and later by Kellas,² who found that substitution in the ortho position hinders the hydrolysis of mono-substituted benzoic esters more than in the meta or para position; yet the effect of halogens and still more of the nitro group in the latter positions is so great as to increase the hydrolysis as compared with that of benzoic ester itself. This would seem to indicate that the chemical character of the group, as well as its position, influences the reaction. Other cases have been noted and will be referred to later.

III. Formation of Imino Ethers.

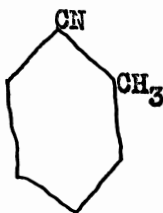
In addition to the hydrolysis of cyanides referred to above, these compounds undergo another important reaction discovered by Pinner many years ago.³ In the presence of

1. Ber., 28, 188 (1895).
2. Z. physik. Chem., 24, 243 (1897).
3. About 1880.

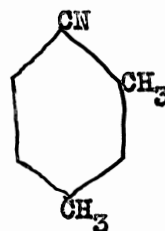
dry hydrogen chloride they absorb alcohol to give a class of substances known as imino ethers, as indicated by the following equation:



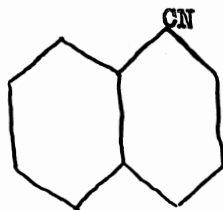
that certain ortho-substituted nitriles failed to undergo this reaction. Neither o-tolunitrile, 2, 4-dimethylbenzonitrile, nor a-naphthoic nitrile (which may be regarded as an ortho-substituted compound) give imino ethers, whereas b-naphthoic nitrile enters readily into the reaction.



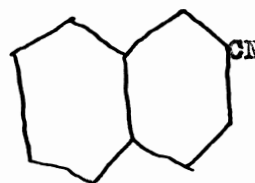
o-Tolunitrile.



2, 4-Dimethylbenzonitrile.



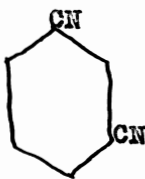
a-Naphthoic nitrile.



b-Naphthoic nitrile.

1. Ber., 23, 2917 (1890).

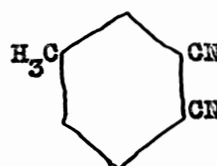
Again, both cyanogen groups in isophthalic and terephthalic nitrile readily react, whereas in homophthalic nitrile only one cyanogen group forms an imino ether.



Isophthalic nitrile.



Terephthalic nitrile.

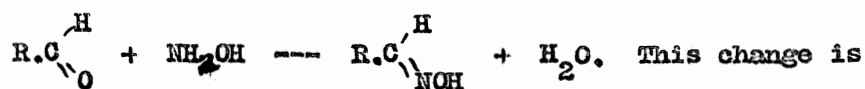


Homophthalic nitrile.

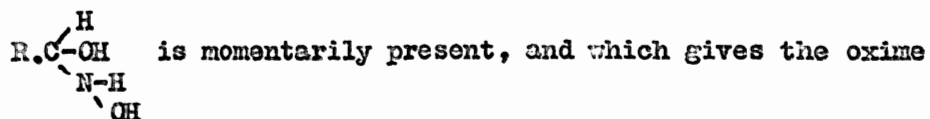
IV. Reactions of the Carbonyl Group.

A. The Formation of Oximes.

One of the most important reactions of the carbonyl group is that with hydroxylamine, by which oximes are formed. Since these substances are not soluble in water and are usually easily crystallized, their preparation forms a favorite method of identifying a carbonyl compound. The reaction takes place in accordance with the equation:

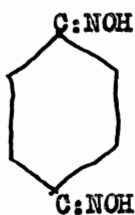


often interpreted as an additive reaction, in which the compound

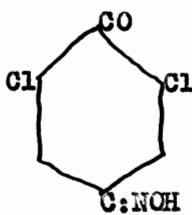


through the loss of water. As might be expected, the reaction is hindered by the presence of substituents of high molecular weight, provided they are near the reacting group, CO.

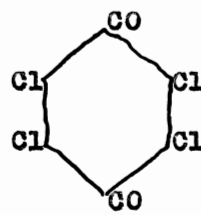
Kehrmann¹ studied a large number of cases, and found that ortho substitution in the quinones retards or inhibits the formation of oximes. Quinone gives a dioxime, *m*-dichloroquinone yields a monoxime, and chloranil gives none.



Quinonedioxime.

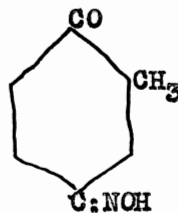
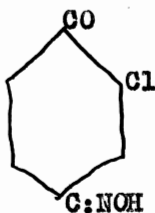


Dichloroquinoneoxime.



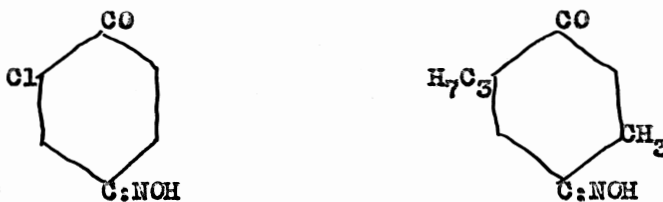
Chloranil.

In monochloroquinone and toluquinone, and other mono-substituted quinones, the oxime group first attacks the oxygen which has no ortho substituent, then the second oxygen reacts:



1. Ber., 21, 3315 (1888); 23, 2557 (1890); J. prakt. Chem., (2) 40, 257 (1889); (2) 42, 134 (1890); see also Nietzki and Schneider, Ber., 27, 1431 (1894).

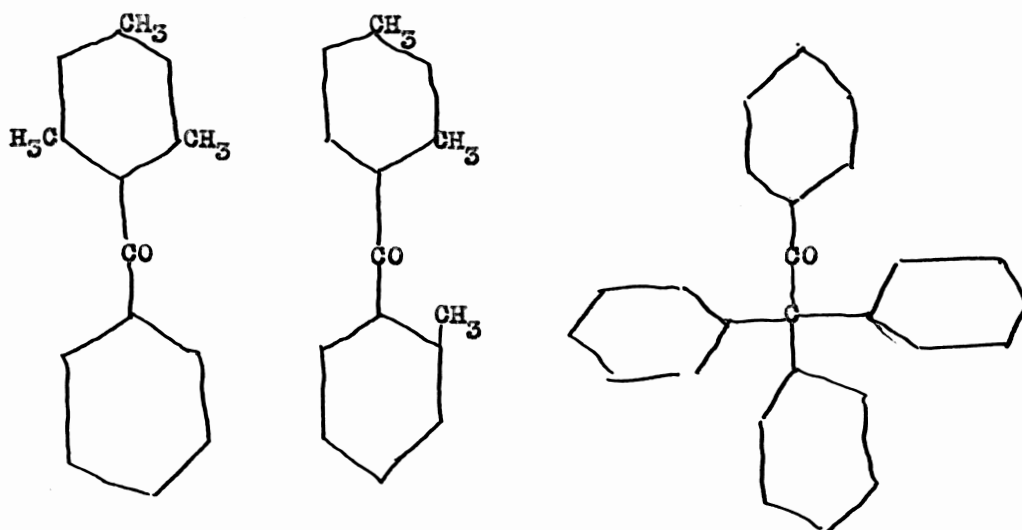
With para-substituted quinones containing a halogen and a methyl group, the oxygen in the ortho position to the alkyl only is replaced by the oxime group; if two alkyls are present, the oxygen in the ortho position to the smaller group reacts.



This behavior led Kehrman to believe that it is less the nature of the substituents (halogen or alkyl) than their presence in the particular (ortho) position to the quinone oxygen which interferes with the reaction. The formation of oximes from aromatic ketones is of the same nature. Neither phenylmesitylketone, xylyl-o-tolylketone nor benzpinacolone react with hydroxylamine (configurations next page).¹ Many similar examples have been mentioned by Baum and V. Meyer.² It should be pointed out, however, that the nature of the second radical attached to the ketone group also influences

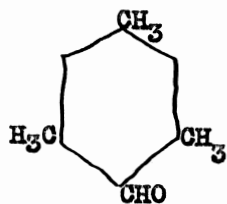
1. Hantzsch, Ber., 23, 2773 (1890); Smith, Ber., 24, 4050 (1891); Beckmann and Wegerhoff, Ann., 252, 14 (1889); Harries and Hubner, Ann., 296, 301 (1897).

2. Ber., 28, 3207 (1895); 29, 836, 2564 (1896).

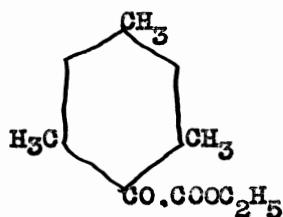


Phenylmesitylketone. Xylyl-o-tolylketone. Benzpinacolone.

the result. Both mesityl aldehyde and mesitylglyoxylic ester readily form oximes.



Mesityl aldehyde.

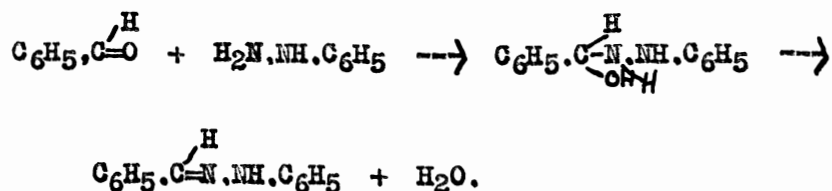


Mesitylglyoxylic ester.

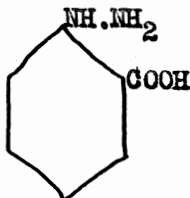
From this it appears that when there is but little "crowding" of the carbonyl group the usual reaction takes place.

B. The Formation of Hydrazones.

When carbonyl compounds, such as aldehydes, ketones, quinones, etc., are allowed to react with phenylhydrazine a class of compounds known as hydrazones is formed. This reaction involves the same principle as that mentioned under oximes, and may be thought of as taking place in two steps, viz., the addition of the hydrazine to the carbonyl group, forming an unstable product which easily loses water:



Many examples of steric retardation of this reaction are known where carbonyl groups are surrounded by ortho substituents. Thus, an ortho substituted quinone will not react with phenylhydrazine. The interference may occur even in those cases where the ortho substituent is in the hydrazine molecule, rather than in the carbonyl compound. Thus, o-hydrazine benzoic acid,



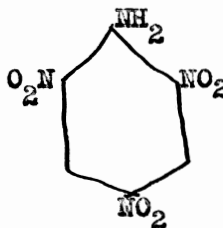
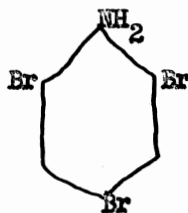
will not react with benzaldehyde, but if carboxyl is in the meta position, the reaction takes the usual course. This could hardly have been anticipated since the substituent is so far from the reacting group.

**C. The Interaction of Aromatic Aldehydes
and Aromatic Amines.**

It is well known that benzaldehyde will react with aromatic amines in such a way that the amino hydrogen and the carbonyl oxygen are eliminated as water to form the products known as benzalanilines, as indicated by the equation:

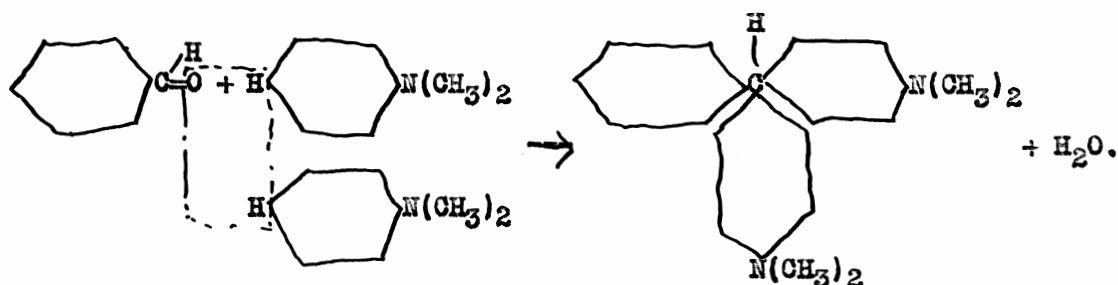


To test the effect of steric hindrance in such cases, Hantzsch¹ studied the reaction with substituted amines. He found that it does not take place in the case of *s*-tribromo- and *s*-trinitroaniline.



1. Ber., 23, 2776 (1890).

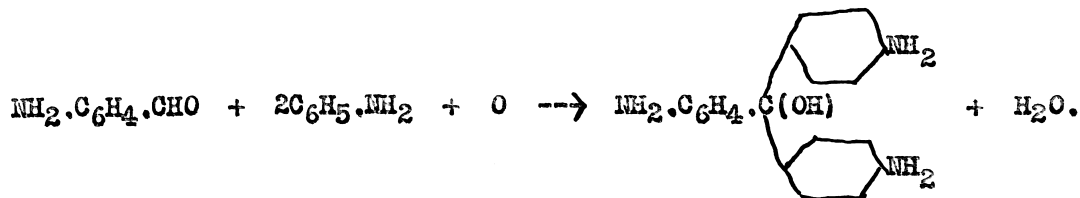
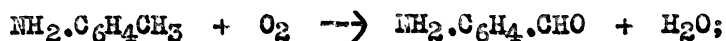
There is, however, another type of reaction which aldehydes and amines may undergo, and this¹⁵ is indicated by the preparation of the leuco-base of malachite green, which takes place in accordance with the following equation:



But it has been found that this reaction is prevented if the tertiary bases have ortho substituents, and this has been interpreted to mean that the reaction involves an intermediate additive compound in which the nitrogen takes a part. This view, though, is in striking contrast to that which appears to be necessary in the case of primary amines, where it is the meta substituents that cause the hindrance. In view of the fact that in the final product the aldehyde carbon is attached to the other nuclei by means of the carbon atoms para to the amino groups, the hindrance caused by meta substituents makes it necessary to assume that in these cases, at least, the reaction is direct, and does not involve the nitrogen. This difference caused by the difference in the positions of substituents is well shown by the fact that *o*-toluidine readily reacts with *p*-nitrobenzaldehyde, while

m-toluidine does so with difficulty.¹

A reaction of very great commercial importance is that involved in the preparation of rosaniline and its derivatives. The reaction is carried out by oxidizing a mixture of *p*-toluidine and other aromatic amines, and gives a triphenylmethane derivative. The change may be assumed to proceed in two steps; the first one involving the oxidation of *p*-toluidine to the corresponding aldehyde, and the second the reaction of this aldehyde with the bases present as indicated by the equations given below:



Now Noelting has observed that if, in place of aniline, meta-amines like *m*-toluidine and *s-m*-xylylidine are substituted, the reaction does not occur. From the stereochemical standpoint the methyl group in the meta position to the amino group stands in the ortho position to the para carbon with which the aldehyde always interacts.

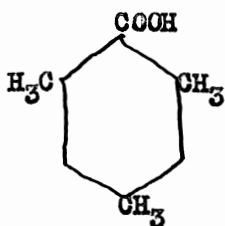
1. This would hold only when it is shown that the effect of the nitro group, which seems to cause irregularities in some cases, has been eliminated.

V. Esterification.

B. Aromatic Acids.

The most extended researches made in attempting to find out the causes for abnormalities in certain characteristic type reactions are those of V. Meyer and his pupils upon the interference in the formation of esters, from which has arisen the 'esterification law'.

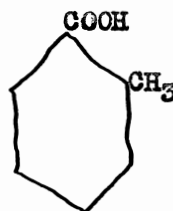
In 1894, V. Meyer found that a mixture of mesitylene carboxylic acid and alcohol in the presence of hydrochloric acid did not unite in the cold to form an ester, whilst the same process gave an nearly theoretical yield in the case of benzoic acid and its monomethyl (toluic acid), 3, 5-dimethyl (mesitylenic acid), and 3, 4, 6-trimethyl (durylic acid) derivatives!



Mesitylene
carboxylic acid.

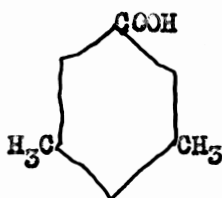


Benzoic acid.

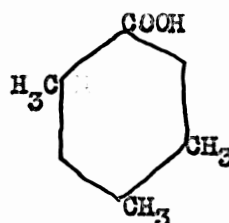


Toluic acid.

1. Ber., 27, 510, 1580 (1894); 28, 1255, 2774, 3197 (1895); see also Gattermann, Ber., 32, 1117 (1899).

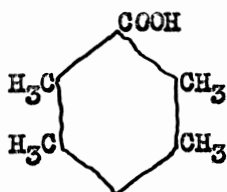


Mesitylenic acid.

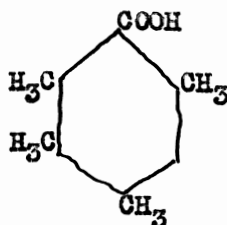
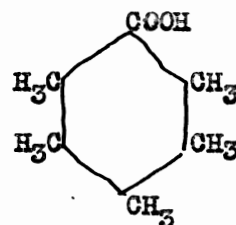


Durylic acid.

He then pointed out that the following acids, all containing methyl groups in both ortho positions to carboxyl, like mesitylenic acid, yielded no ester with hydrochloric acid in the cold:



Durene carboxylic acid.

Isodurene
Carboxylic acid.Pentamethyl
benzoic acid.

The evidence just given was strengthened by a study of the diortho-substituted chloro-, bromo-, and nitro-benzoic acids which formed no ester, whilst similar compounds with at least one free ortho position readily yielded the ester.

V. Meyer next undertook to decide between the chemical character of the substituent and its position. To do this he studied the esterification of acids whose ortho substituents

varied widely in their chemical character. The *o*-methyl-, *o*-chloro-, *o*-bromo, *o*-iodo-, and *o*-nitro-benzoic acids were subjected to the reaction under identical conditions of time, temperature, and concentration. In this and subsequent work, V. Meyer adopted the method of Fischer and Speier,¹ and determined the relative rate of esterification in cases where the process was not prevented, but merely retarded.

Kellas² found the relative amount of ester of ortho-, meta-, and para-isomers of mono-substituted benzoic acids formed at different temperatures. At any definite temperature, the ortho compound always yielded the smallest amount of ester and, curiously, the para slightly less than the meta.

	CH ₃	Cl	Br	I	NO ₂
<i>o</i> .	48.3	50.9	43.4	20.5	8.6
<i>m</i> .	77.1	72.0	66.6	57.6	57.1
<i>p</i> .	75.6	70.5	60.1	52.9	57.1

Benzoic acid = 82.5

From these observations it is apparent that the ortho substituents affect the reaction to a very marked extent.

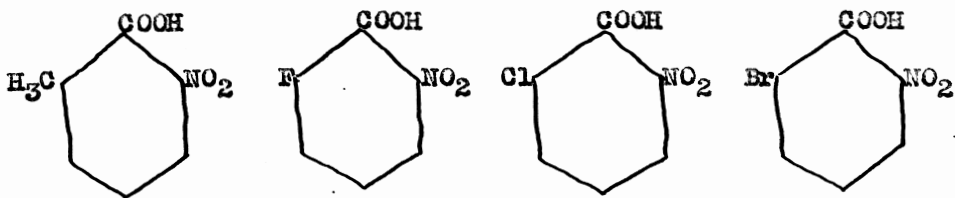
1. Consists in heating the acid with methyl alcohol containing 2 or 3 per cent of hydrogen chloride for a definite time at a definite temperature.

2. Z. physik. Chem., 24, 221 (1897).

But if the hindrance is due entirely to space relations, it might be expected that the substituent having the highest molecular weight, and presumably occupying the greatest space, would cause the most noticeable retardation. It is interesting, therefore, to consider the figures below, which indicate the order of increase in molecular weight, and in retardation, respectively, when ortho compounds were employed:

CH ₃	Cl	NO ₂	Br	I	Order of increasing molecular weight.
15	35.5	46	80	127	
Cl	CH ₃	Br	I	NO ₂	Order of increasing hindrance.

To decide finally whether this irregularity was due to the chemical character of the substituents or to space relations, V. Meyer subjected the following named acids to the esterification experiment above described:

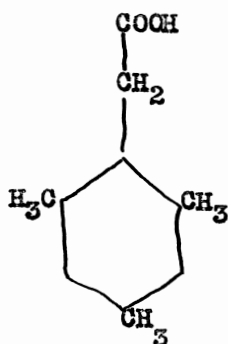


- (1) *o*-Methyl-*o*-nitro-benzoic acid. (2) *o*-Fluoro-*o*-nitro-benzoic acid. (3) *o*-Chloro-*o*-nitro-benzoic acid. (4) *o*-Bromo-*o*-nitro-benzoic acid.

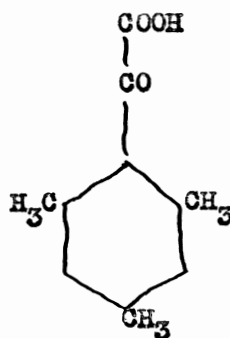
Under the same conditions (1) and (2) gave esters, while

(3) and (4) failed to react, from which it was concluded that the chemical character of the group is a secondary consideration, and is outweighed by the spatial relations.

That the interference of the ortho substituents arises from their position rather than from their chemical nature is further shown by the similar effect produced by both positive alkyl and negative halogen and nitro groups. Furthermore, the behavior of both mesityl acetic and mesityl glyoxylic acid (in which the carboxyl is removed from the proximity of the two methyl groups), which, unlike mesityl carboxylic acid, readily yield esters, clearly points toward the fact that it is steric conditions which cause the interference with ester formation.



Mesityl acetic acid.



Mesityl glyoxylic acid.

The velocity constants (K) of esterification determined by Goldschmidt,¹ upon the basis that in large excess of alcohol and only 2 per cent of catalyst the reaction between alcohol and acid is practically unimolecular, are of a similar nature.

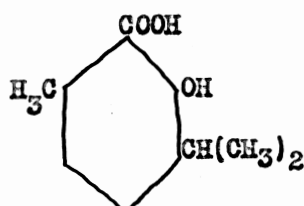
	CH ₃	Br	NO ₂
o.	0.0111	0.0203	0.0028
m.	0.0470	0.0553	0.0296
p.	0.0241	0.0450	0.0261

Benzoic acid = 0.0428

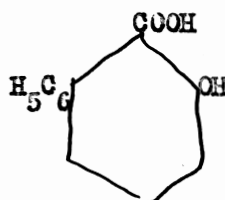
Again, the effects of meta and para substitution are not equivalent, and the greater values in the case of the meta compounds indicate the existence of other factors in the phenomena of interference which cannot be disregarded.

V. Meyer also studied² the relative amount of esterification of different diortho-substituted acids. No esterification took place in twelve hours at 0°, or by Fischer and Speier's method in the case of thymotic, o-phenylsalicylic, mesitylene carboxylic, and other diortho-acids in which both ortho hydrogen atoms are replaced by

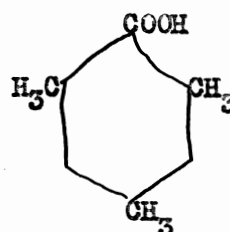
1. Ber., 28, 3218 (1895).
2. Ber., 28, 1254 (1895).



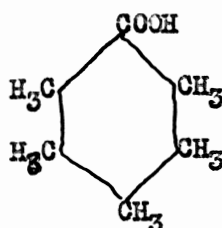
Thymotic acid.



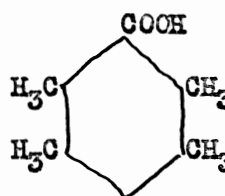
o-Phenylsalicylic acid.



Mesitylene carboxylic acid.



Pentamethyl benzoic acid.

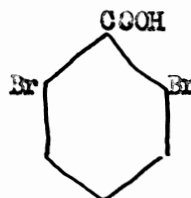
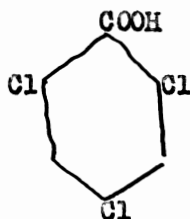


Durene carboxylic acid.

hydroxyl or methyl groups; but when hydrochloric acid gas was passed into the boiling alcoholic solution for several hours, the following percentages of ester were formed:

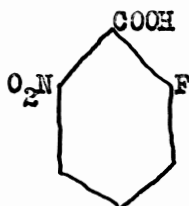
Thymotic acid	23.3
o-Phenylsalicylic acid	76.5
Mesitylene carboxylic "	64.5
Pentamethyl benzoic "	70.0
Durene carboxylic "	60.0

whereas s-trichloro-, s-tribromo-, s-trinitro-, and 2, 6-dibromo-benzoic acid under similar conditions remained unchanged.



s-Trichloro-benzoic acid. 2, 6-Dibromo-benzoic acid.

Furthermore, Van Loon and V. Meyer¹ found that 2-fluoro-6-nitro benzoic acid gives 2 per cent of ester in twelve hours at 0°, while under the same conditions benzoic acid yields



2-Fluoro-6-nitrobenzoic acid. Benzoic acid.

97 per cent of ester. And V. Meyer has shown that even the ortho hydrogen atoms in benzoic acid diminish the amount of ester formed: phenyl acetic acid is more rapidly esterified than benzoic acid.



Phenylacetic acid.

1. Ber., 29, 839 (1896).

It would seem that whilst hydrogen, fluorine, hydroxyl, and methyl retard esterification it is only completely arrested by chlorine, bromine, iodine and nitro groups. V. Meyer concludes that the atomic weights or sizes of the substituents which prevent esterification in the hot liquid are much larger than those which produce this effect only in the cold.¹

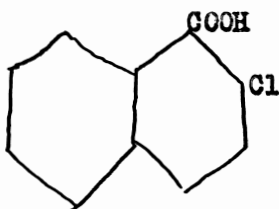
Retard.	Prevent.
H = 1	Cl = 35.4
CH ₃ = 15	NO ₂ = 46
OH = 17	Br = 80
F = 19	I = 127

The objection to this view is the fact that there is little difference effected by substituting a larger alkyl radical for methyl; and that the nitro group has a much greater effect than the larger bromine and iodine atoms.² It would seem that the latter objection, as well as the usual remarkably greater influence of the nitro group in retardation and acceleration, might be met by the argument that the nitro group, being a combination of atoms, will naturally occupy more room, due to intramolecular space, than would a single atom of the same or even greater molecular weight.

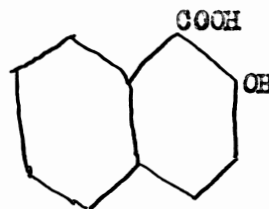
1. Ber., 28, 1260 (1895).

2. Kellas, Loc. cit. (See page 26 of this paper.)

An interesting case in steric hindrance is the effect produced by an adjoining nucleus. *b*-Chloro and *b*-hydroxy-*a*-naphthoic acid cannot be esterified in the cold, whilst

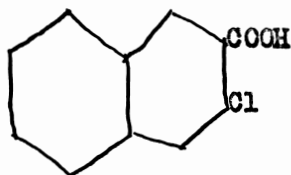


b-Chloro-*a*-naphthoic acid.

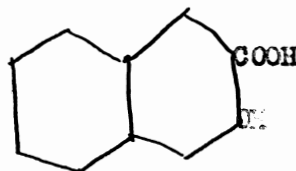


b-Hydroxy-*a*-naphthoic acid.

b-chloro- and *b*-hydroxy-*b*-naphthoic acid yield a high percentage of ester under the same conditions. The CH group



b-Chloro-*b*-naphthoic acid.



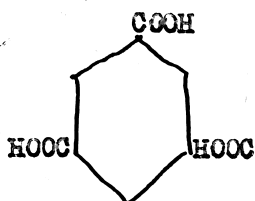
b-Hydroxy-*b*-naphthoic acid.

of the adjoining nucleus behaves like an ortho substituent.¹

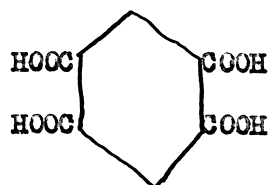
Ortho carboxyl groups produce a similar effect to that of an adjoining nucleus.² Trimesic and pyromellitic acid give a nearly quantitative yield of ester in the cold,

1. V. Meyer, *Loc. cit.* (See page 29 of this paper.)

2. V. Meyer and Sudborough, *Ber.*, 27, 1580 (1894).

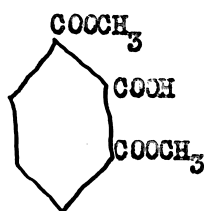


Trimesic acid.

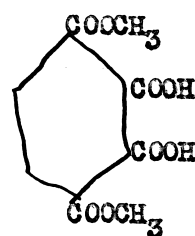


Pyromellitic acid.

whilst hemimellitic and premitic acid give a dimethyl ester only.

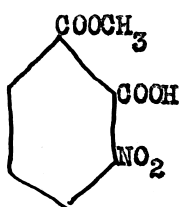


Hemimellitic ester.

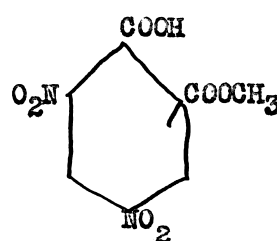


Prehmitic ester.

3-Nitro and 4, 6-dinitrophthalic acid yield chiefly monoalkyl



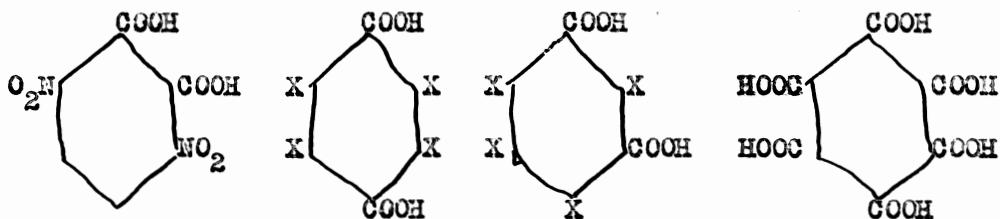
3-Nitrophthalic ester.



4, 6-Dinitrophthalic ester.

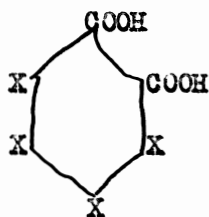
esters, but 3, 6-dinitrophthalic acid, the tetrahalogen derivatives of terephthalic and isophthalic acid, and also mellitic acid form no ester at all.¹

1. V. Meyer., Ber., 27, 3146 (1894).

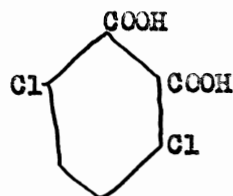


3, 6-Dinitro-phthalic acid. Tetrahalogen (X) derivatives of terephthalic and isophthalic acid. Mellitic acid.

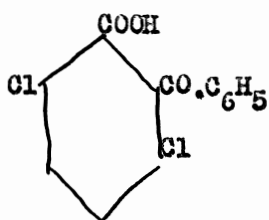
On the other hand, the tetrahalogen derivatives of phthalic acid, 3, 6-dichlorophthalic acid, and 3, 6-dichloro-2-benzoylbenzoic acid and tetrachloro-2-benzoylbenzoic acid,



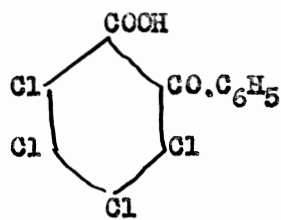
Tetrahalogen (X) derivative of phthalic acid.



3, 6-Dichlorophthalic acid.



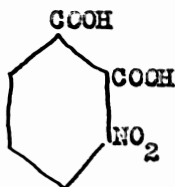
3, 6-Dichloro-2-benzoylbenzoic acid.



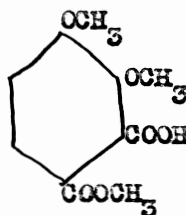
Tetrachloro-2-benzoylbenzoic acid.

do not follow the 'esterification law' (see below), as they

form monoalkyl esters.¹ Also, 3-nitrophthalic acid² forms with amyl alcohol some a-monomethyl ester besides the b-compound.



3-Nitrophthalic acid.



Hemipinic acid ester.

Furthermore, hemipinic acid, which first forms an acid ester, can, by long esterification, be converted into the neutral compound.³ Since the effect of the carboxyl or carbalkoxyl group is to retard rather than prevent esterification, it must, in spite of its atomic weight, be classed with the members of the alkyl and hydroxyl series.

These investigations led V. Meyer to formulate the following law: 'When the hydrogen atoms in the two ortho positions to the carboxyl group in a substituted benzoic acid are replaced by radicals, such as, Cl, Br, NO₂, CH₃, COOH, an acid results which can only be esterified with difficulty or not at all.'

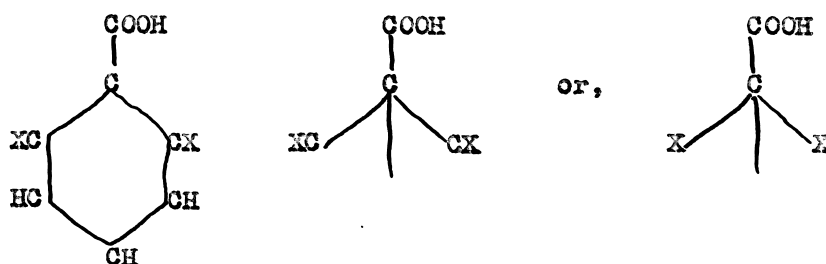
1. Grebe, Ber., 33, 2026 (1900).

2. Marckwald and McKenzie, Ber., 34, 486 (1901).

3. It should be noted at this point that the diortho-substituted benzoic acids which V. Meyer and his co-workers failed to esterify by the methods described may be esterified in other ways, viz., by the action of alcohol on the acid chloride, and the action of alkyl iodide on the silver salt of the acid, or of methyl sulphide on the alkali salt of the acid. This is important because it shows that the failures cannot be due to any inherent inability of the acid group to react in the usual way.

B. Esterification of Fatty Acids.

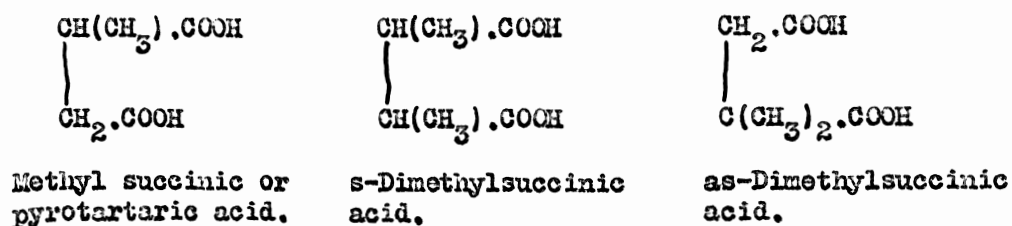
The interesting results with aromatic acids suggested the possibility of similar interference in the esterification of substituted fatty acids possessing a structure analogous to the diortho compounds of the aromatic series.



In 1879 Menschutkin¹ observed that upon heating mono-, di-, and trimethyl acetic acids with alcohol in the absence of hydrogen chloride (autocatalysis) the rate of esterification rapidly decreased in the order given.² A much more extended investigation by Sudborough and his colleagues,³ in which the esterification constants of a long series of substituted acetic acids in the presence of hydrochloric acid were

1. Ann., 195, 334 (1879); 197, 193 (1879).
2. Lichty⁴ reported that the increase in the number of chlorine atoms facilitated esterification.
3. J. Chem. Soc., 75, 467 (1899).
4. Ann. Chem. J., 17, 27 (1895); 18, 590 (1896).

determined, shows clearly that the rate of esterification is retarded in proportion to the number and size of the substituents introduced into the molecule and is independent of the strengths of the acids as determined by the dissociation constants. More recently Bone, Sudborough, and Sprankling¹ have shown that in the esterification of the mono esters of the methyl succinic acids the successive introduction of methyl groups causes additional interference.

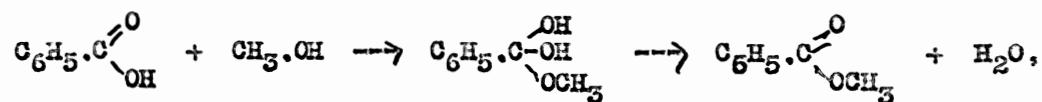


Also, in as-dimethylsuccinic acid the tertiary carboxyl is more difficult to esterify than the primary group.²

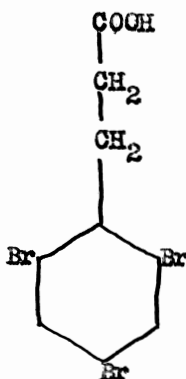
It can hardly be assumed that the process of ester formation depends upon the presence of free ions, inasmuch as there is no relation between the rate of esterification and the dissociation constants found in determining the strengths of acids used. The more generally accepted view is that of Wegscheider³ who assumes that an additive compound of the acid

1. J. Chem. Soc., 87, 534 (1904).
2. Blaise, Compt. rend., 126, 753 (1898).
3. Monatsh., 16, 148 (1895).

and alcohol,

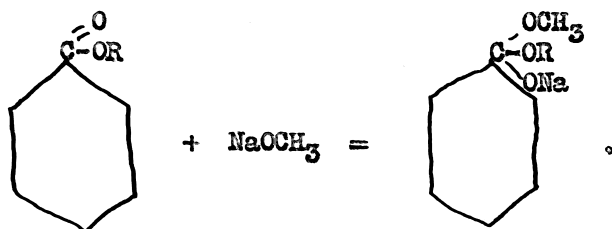


is first formed, and that water is then eliminated giving the ester; and that the spatial arrangements in the compound are such that ortho-substituents are so close to the carboxylic group that they interfere with the formation of the additive compound, thus retarding or preventing esterification. This view is confirmed by the fact that ortho substituents do not exert the same influence when the carboxylic group is removed to some distance, as in *s*-tribromo-hydrocinnamic acid,

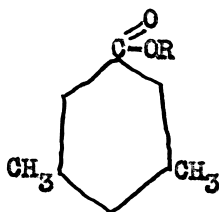


which is readily esterified under the usual conditions.

Also, whilst benzoic ester forms an additive compound with sodium methoxide, which can be isolated, mesitylenic ester



does not.¹

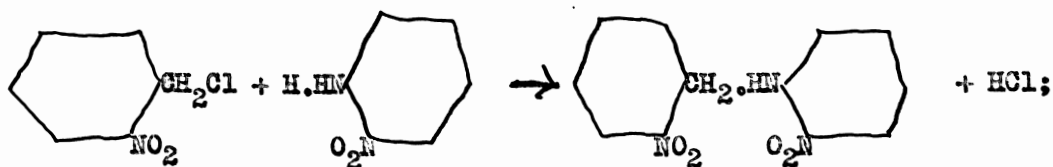


Mesitylenic ester.

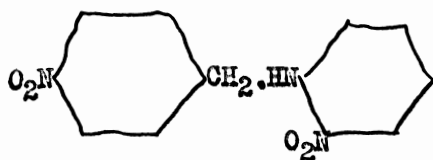
VI. Acetylation of Secondary Amines.

Paal and Kromschroder² have observed two interesting cases of steric hindrance which may be noted briefly here. First, it was found that the reaction between *o*-nitrobenzyl chloride and *o*-nitroaniline took place with difficulty, as indicated in the following equation:

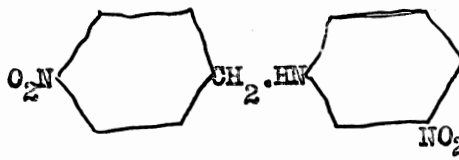
1. V. Peckman, Ber., 31, 501 (1898).
2. J. prakt. Chem., 54, 265 (1896).



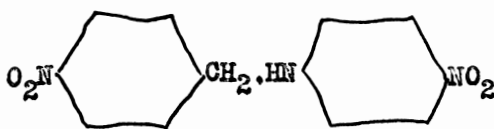
but when the meta and para-compounds were employed the reaction took place readily. Second, the o-nitrobenzyl-o-nitroaniline obtained could not be acetylated. This hindrance was shown to be dependent on the nitro group of the base because, of the three compounds obtained by the action of p-nitrobenzyl chloride on the three isomeric nitroanilines, only the ortho-derivative resists the action of acetylating agents. Furthermore, since



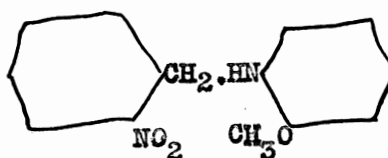
p-Nitrobenzyl-o-nitroaniline.



p-Nitrobenzyl-m-nitroaniline.



p-Nitrobenzyl-p-nitroaniline.

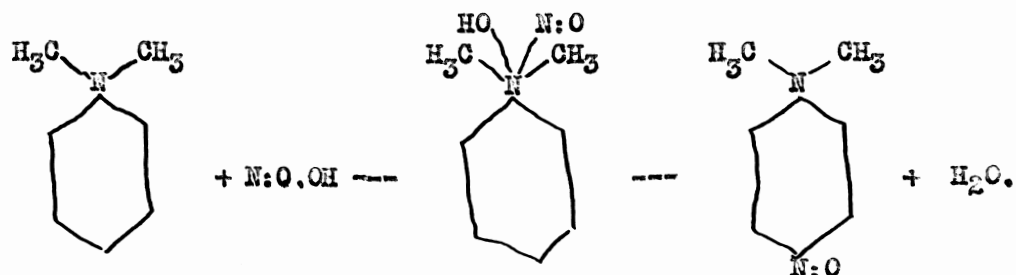


o-Nitrobenzyl-o-anisidine.

o-nitrobenzyl-o-anisidine can be acylated, it follows that the hindrance in the case of the corresponding nitro compound must be dependent on the negative character of the substituent.

VII. Action of Nitrous and Nitric Acid and
Diazo-salts on Aromatic Amines.

When an aromatic amine is treated with nitrous acid a nitroso-derivative is formed in accordance with the following typical equation:



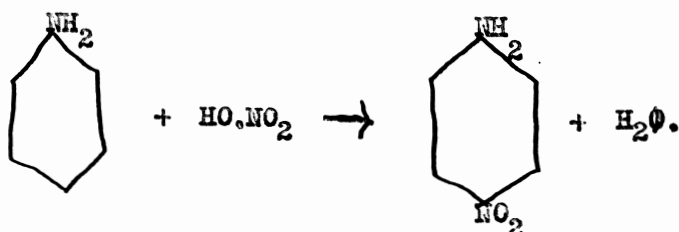
It has been noted that, although the para position is free, dimethyl-o-toluidine and dimethyl-o-methoxyaniline,



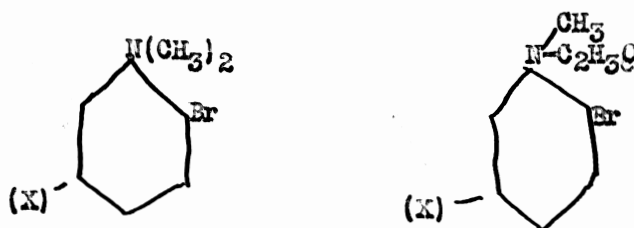
give no nitroso derivatives, whilst dimethylaniline does.

When nitric acid is allowed to act upon an aniline a nitrocompound is formed, as may be illustrated by the equation:¹

1. In this reaction the amino group must be 'protected' by being previously acylated.



But it is well known that ortho-substituted alkyl or acetylalkyl anilines such as dimethyl-o-bromoaniline or acetylmethyl-o-bromoaniline, for instance,



give meta- (X) and not para-nitro derivatives.

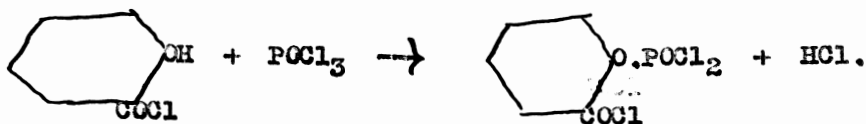
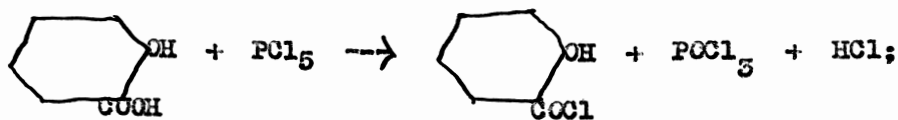
Diazo-salts readily react with aromatic amines to form aminoazo compounds, thus:



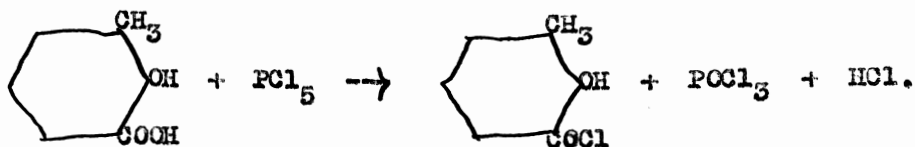
While dimethyl aniline readily follows this reaction, ortho-substituted dialkylanilines react with difficulty. It is supposed that ortho substitution interferes with the initial formation of an additive compound which is assumed to occur between the nitrogen of the tertiary base and the reagent previous to substitution in the nucleus.

VIII. Phosphorus Pentachloride on Hydroxy-acids.

Anschutz¹ and his pupils have shown that the ordinary course of the reaction between phosphorus pentachloride and hydroxy-acids is usually presented by the following two equations:



If, however the two ortho positions to the hydroxyl are occupied, as in *o*-methylsalicylic acid, the phosphorus oxychloride produces no change in the hydroxyl group, and only the first reaction takes place:



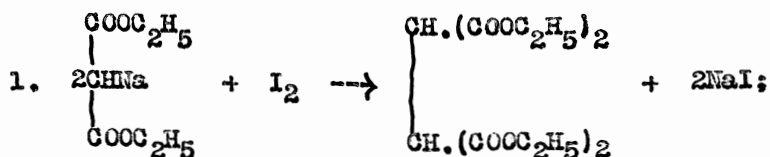
1. Ber., 30, 221 (1897).

IX. Reduction of Nitro-compounds.

Cohen and McCandlish¹ studied the action of ammonium sulphide on a variety of substituted nitro derivatives of benzene. They found that while acidic groups invariably facilitated reduction, the presence of ortho substituents always caused the reduction to proceed more slowly than did the same group in the meta or para position.

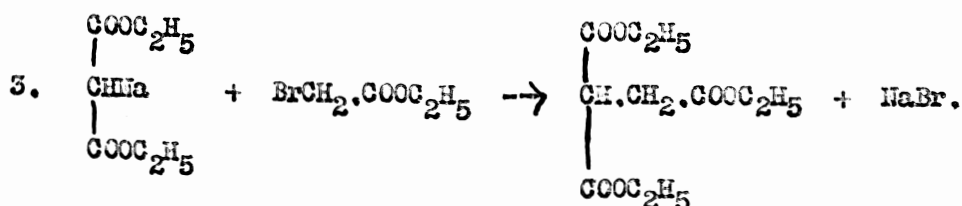
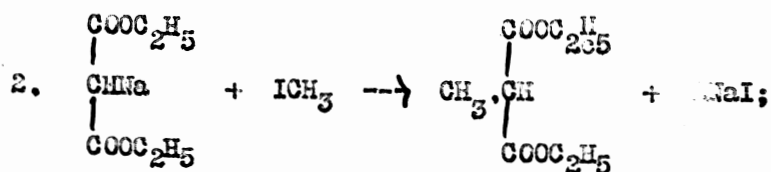
X. Bischoff's 'Verkettungen'.

The subject of steric hindrance cannot be dismissed without brief reference to the work of Bischoff and his collaborators,² in which the steric influences in chain formations were studied. Sodium malonic ester readily reacts with halogens, alkyl halogens, and halogen esters, and the process may often be repeated by introducing a second sodium atom and halogen group:

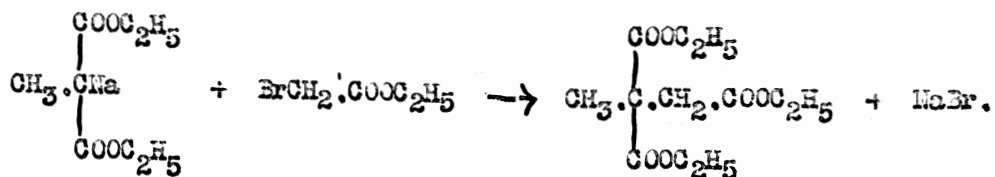


1. J. Chem. Soc., 87, 1257 (1905).

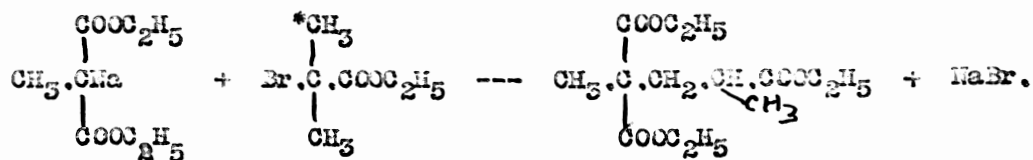
2. Cohen, "Organic Chemistry," Vol. I, p. 241 et seq. (1907)



Nos. 2 and 3 may be combined by introducing an acetic ester group into methyl malonic ester:



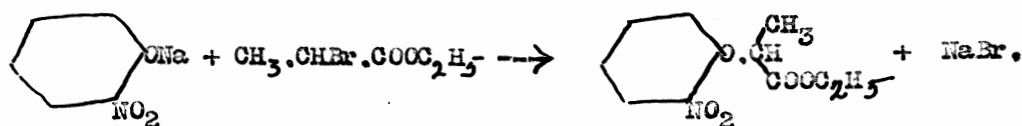
Steric influences begin to assert themselves in the last reaction as soon as larger alkyl groups are introduced into the malonic ester molecule on the one hand, or the α -bromine atom in the halogen ester is replaced by one forming a tertiary group on the other. For example, if sodium methyl malonic ester and α -bromoisobutyric ester are boiled together in alcoholic solution, the reaction proceeds abnormally in the following manner, in which, instead of the α -carbon, $^*\text{C}$ becomes linked to the malonic ester molecule:



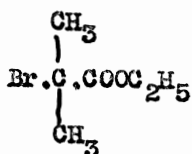
In xylene solution, however, the reaction takes its normal course.

Also, in such a case as the linking of sodium phenates and halogen esters, steric influences may modify the results.

Whilst sodium o-nitrophenate and α -bromopropionic ester combine in a normal fashion,



no reaction occurs with α -bromoisobutyric ester.



α -Bromoisobutyric ester.

XI. Acylation of Primary Amines.

Reference has been made above to the hindrance in the acetylation of secondary bases that contained ortho substituents. Bischoff¹ found that with primary amines (aniline) this retardation was evident, and that it increased with the increase of the mass of the acid radical and was more noticeable with iso acids than with normal ones. He also noticed that ortho substituents interfered to a greater extent than those in the meta and para positions. Substantially the same conclusions were reached by Kusselius,² Menschutkin,³ and Potozki,⁴ while Cybulsky⁵ found the same relationships for certain quinoline and naphthalene derivatives.

Although Remmers⁶ prepared a single diacetyl derivative of aniline, it was perhaps first shown by Bistrzcki and Ulffers⁷ that an ortho substituent might not interfere with the acylation of the amino group, and that the reaction might proceed to the extent of displacing both amino hydrogen

1. Ber., 30, 2321, 2467, 2475 (1897).
2. J. Russ. Phys. Chem. Soc., 32, 29 (1900).
3. Ibid., 32, 46 (1900).
4. Ibid., 35, 339 (1903).
5. Ibid., 35, 219 (1903).
6. Ber., 7, 350 (1874).
7. Ber., 23, 1876 (1890).

atoms with the formation of a diacetyl compound. They prepared a diacetyl derivative by heating o-toluenediamine with acetic anhydride, and assumed that both amino groups were acylated, not considering that possibly both acyl radicals might have entered the same amino group. In 1893 Key¹ obtained diacetyl derivatives by the action of acetyl chloride on phenyl isothiocyanate, acetanilide, and acetyl-o- and acetyl-p-toluidine at 170-180°. The following year, Bistrzyki and Ulfers² obtained a 90 per cent yield of diacetanilide by heating one molecule of acetanilide with two molecules of acetic anhydride in a sealed tube for eight to ten hours at 200-205°. Ulfers and Janson³ investigated a number of substituted anilines, employing six to seven molecules of anhydride to one of base under the conditions mentioned above, and found that acid (or negative) substituents (Cl, Br, NO₂) in the ortho position tend to retard the formation of a monoacetyl compound, but that after the entrance of the first acetyl group the same ortho substituents facilitate in the introduction of a second to form a diacetyl derivative. Thus, s-tribromoaniline is practically unacted on by acetic

1. Ber., 26, 2853 (1893).
2. Ber., 27, 91 (1894).
3. Ber., 27, 93 (1894).

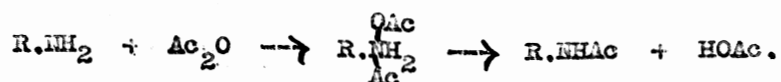
anhydride in the cold, whilst if it is boiled with an excess of anhydride for an hour a good yield of the diacetyl derivative is obtained.

Sudborough¹ noticed that when *a*-naphthylamine trinitrobenzene is warmed a few minutes with an excess of acetic anhydride a monoacetyl derivative, $C_6H_3(NO_2)_3.C_{10}H_7.NH(C_2H_3O)$, results; but upon heating for an hour decomposition ensued, the products being trinitrobenzene and diacetyl-*a*-naphthylamine. The ease with which this took place, in a much shorter time and at a lower temperature than previous investigators had employed, also without the use of sealed tubes, caused him to attempt the acylation of alpha and beta naphthylamine, pseudo cumidine, ortho and para toluidine, and the single 2, 6-dibromoaniline to study the effect of positive ortho substituents in the acylation of aryl amines.² He boiled one molecule of the base with four molecules of acetic anhydride for one hour under a reflux condenser protected by a calcium chloride tube, from which reaction mixture the products formed were recovered and separated by fractional crystallization or distillation under reduced pressure. He found

1. J. Chem. Soc., 79, 523 (1901).
2. Ibid., 79, 533 (1901).

that a positive methyl group (or a neighboring nucleus in the case of the naphthylamines) in an ortho position favors the acylation of an amino group. Experiments with the monoacetyl derivatives and two molecules of anhydride gave similar results, though slightly larger yields of the diacetyl compounds.

In explanation of these facts, Sudborough assumed that the following equation might indicate the course of the reaction, in which an additive compound is formed which subsequently decomposes to give the monoacetyl derivative and one molecule of acetic acid:

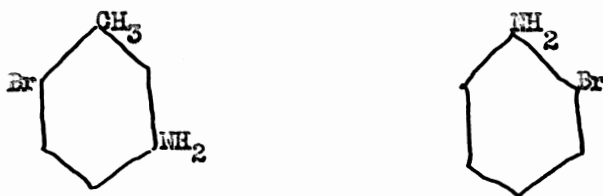


The formation of a diacetyl compound may also be assumed to proceed in a similar manner:

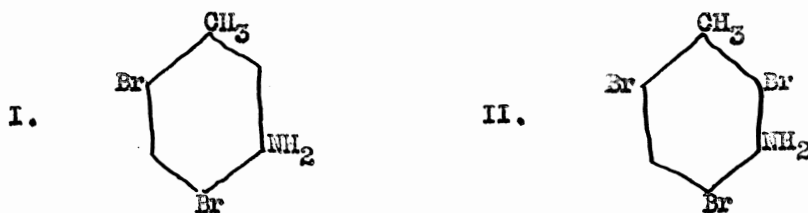


If this actually represents the course of the reaction, then by analogy with other additive reactions the ortho-substituents would be expected to exert an inhibiting influence, whereas, although they do seem to retard it to a certain extent in the first stage, they accelerate it in the second.

The results of Sudborough led Raiford and McBride¹ to make a study of the effects of substituents other than those in the ortho position; and of acid-forming ortho substituents, as compared with Sudborough's "positive" substituents, upon the acylation of the amino group. Their results with *m*-toluidine show that the methyl group in the meta position accelerates the acylation of the amino group. The behavior of monobromo-*m*-toluidine and *o*-bromoaniline,



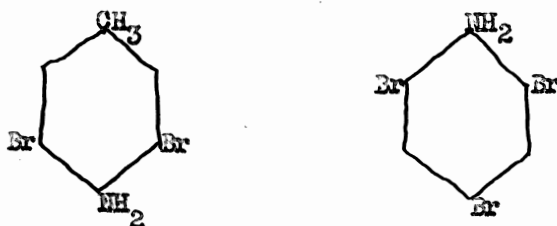
indicate that a single negative substituent in either the para or the meta position accelerates the reaction. With one ortho and the para position occupied by bromine, as in 4, 6-dibromo-*m*-



toluidine (formula I), no diacetyl derivative resulted, but an 86.3 per cent yield of the mono compound; but when both ortho and the para positions were occupied, as in 2, 4-tribromo-*m*-toluidine (formula II),

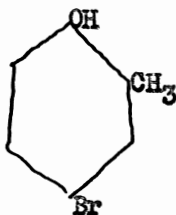
1. Unpublished work, University of Chicago, 1915.

there was formed an 80.5 per cent yield of the diacetyl derivative. Also, other ortho-ortho-para-substituted bases, as 5, 5-dibromo-p-toluidine and s-tribromoaniline,



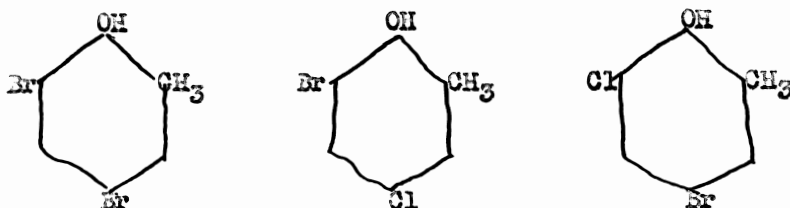
gave larger diacetyl products than the unsubstituted compounds.

Similar cases to that of the failure of 4, 6-dibromo-m-toluidine to react to form the diacetyl derivative have been reported. Claus and Jackson¹ observed that 2-methyl-4-bromophenol,

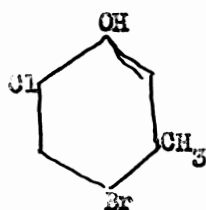


could not be oxidized by chromic acid to the corresponding quinone with loss of the para bromine atom, whilst if the para and both ortho positions (relative to hydroxyl) were substituted oxidation by chromic acid proceeded in the usual way. Thus, 4, 6-dibromo-2-methylphenol, 4-chloro-6-bromo-2-methylphenol, and 4-bromo-6-chloro-2-methylphenol,

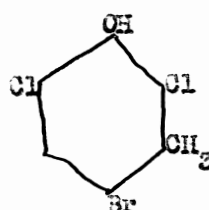
1. J. prakt. Chem., (2) 38, 324 (1888).



were readily oxidized by chromic acid. The behavior of 4-bromo-6-chloro-3-methylphenol, which is isomeric with 4-bromo-6-chloro-2-methylphenol, suggests that the difference in reactivity depends upon the fact that in the one set of compounds both positions ortho to the hydroxyl group had been substituted, whilst in the first only one had been substituted. It was shown by Raiford and Baird¹ that 4-bromo-6-chloro-3-methylphenol was not oxidized by chromic acid to a quinone; then Raiford and Beavell² found that upon



4-Bromo-6-chloro-3-methylphenol.

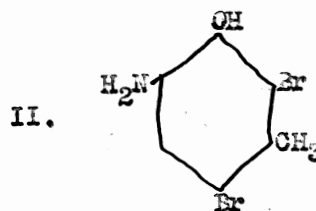
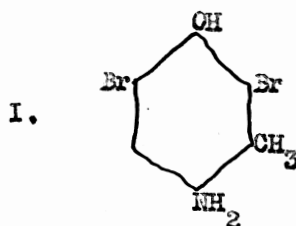


3, 6-Dichloro-4-bromo-5-methylphenol.

1. Unpublished work, University of Chicago, 1913.
2. J. Am. Chem. Soc., 36, 1510 (1914).

converting this compound into 2, 6-dichloro-4-bromo-5-methyl-phenol,¹ both ortho positions (to hydroxyl) being substituted by halogen, a quinone could be formed at once. Other trihalogenated phenols show the same reactions.²

Raiford³ found that when 2, 6-dibromo-4-amino-m-cresol (formula I below) was subjected to the action of acylating agents, only N-acyl derivatives were obtained.

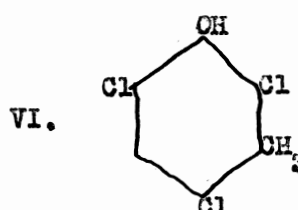
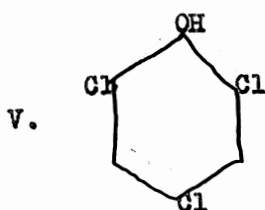
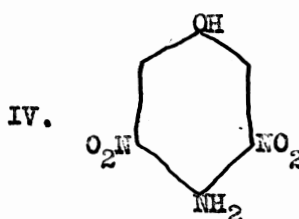
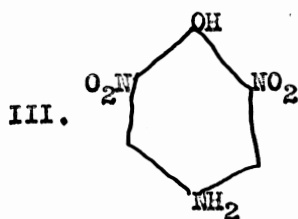


Under the same conditions 2, 4-dibromo-6-amino-m-cresol (formula II) gave diacylated compounds, in which both hydroxyl and amino groups reacted.

The belief that this difference in behavior was due to steric hindrance caused by ortho substituents seemed

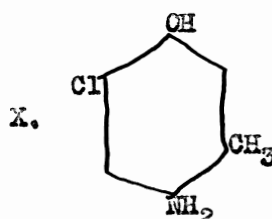
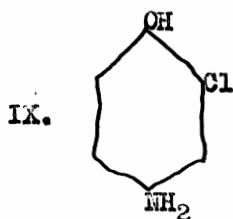
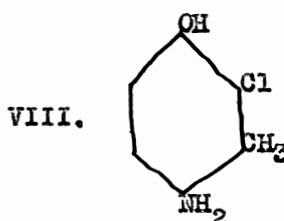
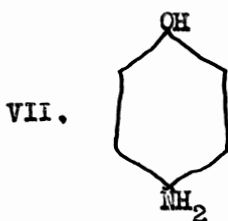
1. See last configuration on preceeding page.
2. Am. Chem. J., 46, 425 (1911); J. prakt. Chem., (2) 39, 370 (1889).
3. Am. Chem. J., 46, 429 (1911).

to be supported by the results of Meldola and Hollely,¹ who found that 2, 6-dinitro-4-aminophenol (formula III) gave only N-acyl derivatives, and that 5, 5-dinitro-4-aminophenol (formula IV) gave only an O-acyl derivative. But the behavior of 2, 4-dibromo-6-amino-m-cresol² (formula II), 2, 4, 6-trichlorophenol³ (formula V), 2, 4, 6-tribromophenol,⁴ 2, 4, 6-triodophenol,⁵ 2, 4, 6-trichloro-m-cresol⁶ (formula VI), and 2, 4, 6-tribromo-m-cresol,⁷ all of which are readily acylated



1. J. Chem. Soc., 105, 410 (1914).
2. Raiford, Loc. cit.
3. Fischer, Ann., spl., 7, 184.
4. Schunk and Marchlewsky, Ann., 278, 347 (1893).
5. Raiford and Heyl, Am. Chem. J., 44, 212 (1910).
7. Claus and Hirsch, J. prakt. Chem., (2) 39, 59 (1889).
6. Crowther and McCombie, J. Chem. Soc., 103, 542 (1913).

in the usual way, showed that the hydroxyl group is not always protected by two ortho substituents. That the failure to give an O-acyl derivative could not be due to the relative positions of the hydroxyl and amino groups seems to be shown by the behavior of p-aminophenol¹ (formula VII), 2-chloro-3-methyl-4-aminophenol² (formula VIII), 2-chloro-4-aminophenol (formula IX), and 6-chloro-3-methyl-4-aminophenol³ (formula X), all of which gave O- and N-acyl derivatives without difficulty.



1. Ladenburg, Ber., 9, 1528 (1876).
2. Raiford, Am. Chem. J., 46, 449 (1911).
3. Kehrman, Ann., 303, 8 and 26 (1898).

Few experiments with the acylation of aromatic amines containing para substituents had been described; and as the work undertaken with ortho and meta-substituted anilines and toluidines¹ showed that increased yields of the diacetyl compounds over those produced by the primary bases were obtained, it seemed advisable to conduct experiments with other bases in order to determine:

(1) The accelerating or retarding effect of acid-forming substituents in the para position upon acylation in experiments conducted under the same conditions employed by Sudborough² in studying the effect of "positive" ortho substituents;

(2) Whether the behavior noted by Raiford³ in the case of the two isomeric dibromo-amino-*m*-cresols is general.

The bases selected for the first consideration were *p*-bromoaniline, *p*-chloroaniline, and *p*-nitroaniline, and for the second consideration 4, 6-dibromo-2-aminophenol and its isomer, 2, 6-dibromo-4-aminophenol; and the action of acetic anhydride upon those, and of benzoyl chloride upon the last two named, has been studied.

1. Raiford and McBride, *Loc. cit.*

3. Raiford, *Loc. cit.* (See page 55 of this paper, Ref. 3.)

2. *Loc. cit.* (Ref. 2, page 50, this paper.)

The results with the substituted anilines clearly indicate that acid-forming substituents in the para position hinder the acylation of the amino group. The largest yield of the diacetyl derivative was in the case of p-bromoaniline, which gave 48.4 per cent, as compared with 53 per cent¹ for the unsubstituted base, aniline, under the same conditions. 54.6 Per cent of the bromoaniline was recovered in the form of the monoacetyl derivative, making a total yield of 85.0 per cent. p-Chloroaniline gave similar results, though the retardation was greater. Only 39.2 per cent of the diacetyl derivative was obtained, with 45.1 per cent of the monoacetyl compound, which together show that 84.3 per cent of the base underwent acylation. The results with p-nitroaniline are very interesting as they are in perfect accord with the general abnormal reactivity of the nitro group.² The greatest retardation was observed in this case, only 13.0 of the diacetyl compound

1. Sudborough, Loc. cit. (p. 50, this paper); Raiford and McBride, Loc. cit. (p. 52, this paper).

2. Cf. Claus, Loc. cit. (p. 8, this paper); Kellas, Loc. cit. (pp. 14, 26 and 32, this paper); Galdschmidt, Loc. cit. (p. 29, this paper); Cohen and McCandlish, Loc. cit. (p. 45, this paper).

being formed. A large amount of the base, 85.5 per cent, was obtained as the monoacetyl derivative, giving the highest total yield, 98.5 per cent.

	Mol. Wt. of Substituent.	Monoacetyl Per cent.	Diacetyl Per cent.	Total Per cent.
Aniline		38.5	53	91.5
p-Bromoaniline	80	34.6	48.4	83.0
p-Chloroaniline	55.5	45.1	39.2	84.3
p-Nitroaniline	46	85.5	13.0	98.5

Reference to the above table shows that chlorine in the para position has a greater retarding effect upon the acylation of the amino group than bromine in the same position, which is not in accord with a similar comparison of the results of Kellas, Meyer and others concerning the effects of these substituents upon esterification.¹ It is also noticeable that the order of increase in the total amounts of acetyl compounds formed in each case is in the opposite order to that of the increase in the percentages of the diacetyl compounds formed; which suggests that those para substituents

1. See page 26 of this paper.

which exert the greatest retardation toward the formation of the diacetyl derivatives show the least hindrance toward the formation of the monoacetyl derivatives. This is interesting in connection with the work of Ulffers and Janson¹ in which it was shown that these same substituents (Cl, Br, NO₂) in the ortho position seemed to hinder the formation of the monoacetyl compound, but to favor the subsequent formation of the diacetyl compound from the mono derivative.

The results with the dibromo-aminophenols seem to indicate that the observation of Raiford² is a general one. 2, 6-Dibromo-4-aminophenol, which corresponds to the 2, 6-dibromo-4-amino-*m*-cresol worked with by Raiford,³ gave *m*-acyl derivatives only, whilst its isomer, 2, 4-dibromo-6-aminophenol, corresponding to 2, 4-dibromo-6-amino-*m*-cresol, gave both a diacetyl and a dibenzoyl derivatives, in which, in each case, the hydroxyl and the amino group reacted.

The experimental evidence upon which the immediately foregoing conclusions are based will now be given.

1. See page 49 of this paper.
2. See page 55 of this paper.
3. Compare with formulas on page 55 of this paper.

Acylation of p-Chloroaniline.

The material used in this experiment was Kahlbaum's purest product, which melted at 70° , in accordance with the record given in Beilstein.¹ 10 G. (one molecule) were mixed with 31 g. (four molecules) of acetic anhydride, and the mixture vigorously boiled for one hour under a reflux condenser protected by a calcium chloride tube. Upon cooling a brittle, colorless, crystalline solid separated out. This was removed by filtration, and the filtrate (see below) was reserved. The crystals melted sharply at 175° , and dissolved readily in alcohol, ether, carbon disulphide, dilute acetic acid, and to a less extent in ligroine, which accord with Beilstein and Kurbatow's description² of acetyl-p-chloroanilide. Analysis³ for chlorine and nitrogen are in accord with the formula for the monoacetyl derivative. The compound was analysed for chlorine by the method of Robertson:⁴

1. Handbuch der Organischen Chemie, Vol. II.

2. Ann., 182, 98.

3. The reason for analysing the monoacetyl compounds obtained in each case was the fact that in some instances it had been observed that the melting points, as well as general solubilities, of the diacetyl and monoacetyl derivatives were identical. Cf. Raiford and McBride, Loc. cit.

4. J. Chem. Soc., 107, 902 (1915).

0.1617 g. subs. required 10.59 cc. 0.1 N AgNO_3 . Calc.
for $\text{C}_8\text{H}_8\text{ONCl}$: Cl, 20.94; found: 20.30.

Analysis for nitrogen (Kjeldahl):

0.4006 g. subs. required 23.5 cc. 0.1 N H_2SO_4 . Calc.
for $\text{C}_8\text{H}_8\text{ONCl}$: N, 8.2; found, 8.2.

The filtrate mentioned above was poured into four volumes of water, whereupon a heavy colorless oil separated out, which solidified in two hours to a brittle mass of colorless crystals, almost identical in appearance with the first product obtained. These crystals melted at 65° , and dissolved freely in alcohol and in 10 per cent acetic acid, and very readily in cold acetone, but were best purified by recrystallization from ligroine. Repeated fractions melted sharply at 64.5° , and were regarded as pure.¹ Analysis for chlorine conforms to the formula for diacetyl-p-chloranilide,

1. In treating 6.6 g. of the second product with hot ligroine in order to purify same by recrystallization, a residue of some 1.5 g. was obtained which would not dissolve readily in ligroine, and was found to have a melting point of $175-176^\circ$. These facts may mean that a portion of the diacetyl-p-chloranilide was hydrolysed to the mono-compound during solution for recrystallization.

which, so far as we are aware, has not been described in the literature. Analysis for chlorine:

0.2017 g. subs. required 9.46 cc. 0.1 N AgNO_3 . Calc. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{NCl}$: Cl, 16.78; found, 16.65.

The yields, based upon the amounts theoretically possible, were:

	Grams.	M.p.	Per cent.
Monoacetyl . . .	6.0	173°	45.1
Diacetyl	6.5	64.5°	39.2

Acylation of p-Bromoaniline.

This substance was prepared as follows: p-bromoacetanilide was made in accordance with the method of Remmers¹ and hydrolysed by boiling the compound with two and one-half times its own weight of concentrated hydrochloric acid under a reflux condenser for two hours. The hydrochloride which

1. Ber., 7, 346 (1874).

separated out upon cooling was removed by filtration, dissolved in water, and the free base precipitated by the addition of a slight excess of ammonium carbonate solution. 10 G. (one molecule) of the dry substance, melting at 65° , were treated with 23.7 g. (four molecules) of acetic anhydride. Interaction began at once with the evolution of considerable heat, and a dark, reddish-brown solution was formed. The mixture was then vigorously boiled for one hour under a reflux condenser as above. Upon cooling a mass of fine greyish-brown crystals separated out, which was removed by filtration. These crystals soon dried when exposed to the air, and were found to have a melting point of 165° . They dissolved very readily in alcohol, but were practically insoluble in cold water. The melting point given by Korner¹ for acetyl-p-bromocinnilide is 165.4° , and the solubilities found for the product in question are the same as those given in Beilstein's description for that substance. Analysis for bromine gave the following figures:

0.2255 g. subs. required 10.64 cc. 0.1 N AgNO_3 . Calc.
for $\text{C}_8\text{H}_8\text{ONBr}$: Br, 37.39; found: 37.74.

1. Jahresber., 542 (1875).

Analysis for nitrogen (Kjeldahl):

0.6192 g. subs. required 29.0 cc. 0.1 N H_2SO_4 . Calc. for C_8H_8ONBr : N, 6.54; found: 6.56.

The mother liquor from the above was poured into four volumes of water, whereupon a heavy slightly reddish-brown oil settled out, and solidified in two hours to greyish-brown crystals, identical in appearance to the first product obtained. They dried at once in the air, and melted sharply at 68° . Analysis for bromine is in accord with the formula for diacetyl-p-bromoanilide:

0.2671 g. subs. required 10.49 cc. 0.1 N $AgNO_3$. Calc. for $C_{10}H_{10}O_2NBr$: Br, 31.35; found: 31.42.

The yields were:

	Grams.	M.p.	Per cent.
Monoacetyl	4.3	165°	54.6
Diacetyl	7.2	68°	48.4

Acylation of p-Nitroaniline.

This base was prepared in accordance with the method of Bender and Erdmann,¹ being purified by recrystallization from boiling water. 10 G. (one molecule) of the substance, melting at 147°, were mixed with 29 g. (four molecules) of acetic anhydride and boiled for one hour under a reflux condenser fitted with a calcium chloride tube. Upon cooling very fine, light, colorless crystals separated out which soon dried in the air and melted sharply at 207°. Rudnev² gives the melting point for acetyl-p-nitroanilide as 207°. Analysis for nitrogen is in accordance with the formula for the monoacetyl derivative of p-nitroaniline. Analysis for nitrogen (Kjeldahl):

0.2987 g. subs. required 32.9 cc. 0.1 N H_2SO_4 . Calc. for $\text{C}_8\text{H}_8\text{O}_3\text{N}_2$: N, 15.5; found: 15.4.

The mother liquor was poured into four volumes

1. Chemische Präparatenkunde, II, 438.
2. Zeitschrift für Chemie, 7, 202 (1871).

of cold water, whereupon a heavy, light-yellow-colored oil separated out which solidified in less than an hour to a mass of fine, almost colorless crystals. These crystals dried quickly in the air and had a melting point of 120° . In keeping with the results obtained in the two former cases it is highly probable that this material is diacetyl-p-nitroanilide.¹

The weights were:

	Grams	M.p.	Per cent.
Monoacetyl	11.15	207°	85.5
Diacetyl	2.1	120°	15.0

Reactions of 2, 6-Dibromo-4-aminophenol.

The starting point for obtaining this base was Kahlbaum's purest p-nitrophenol, 10 g. (one molecule) of which, melting at 114° , were dissolved by a mechanical stirrer in 5 liters of water and slowly treated, with constant stirring,

1. Scarcity of material and lack of time prevented further study of this substance.

with 25 g. (two molecules) of bromine dissolved in a liter of water. 15 G. of the dried precipitate, 2, 6-dibromo-4-nitrophenol, melting sharply at 141° and decomposing a few degrees above this temperature, in agreement with the results of Brunck and Korner,¹ were dissolved in 65 cc. of alcohol and to the boiling liquid was gradually added a solution of 90 g. of stannous chloride in 90 cc. of concentrated hydrochloric acid. When reduction was complete one volume of concentrated acid was added and the mixture allowed to come to the room temperature. The amino hydrochloride which separated out was removed by filtration, washed with a little concentrated hydrochloric acid, drained as well as possible, and then dissolved in water and decomposed by adding a slight excess of ammonium carbonate solution. The free amine was promptly precipitated, and after a few minutes it was collected upon a filter, washed several times with cold water, pressed out on filter paper, and dried in vacuum over sulphuric acid. It had a melting point of 190° , in agreement with Lellmann and Grothmann,² and readily dissolved in dilute alkalies.

1. Zeitschrift für Chemie, 323 (1868).

2. Ber., 17, 2731 (1884).

Monoacetyl Derivative.--The monoacetyl derivative was formed as follows: a mixture of 3 g. of the free base, 1 g. of sodium acetate, and 8 cc. of acetic anhydride was gently boiled for a few minutes in a test tube. Upon cooling no product separated out, but upon addition to six volumes of water a mass of colorless crystals was obtained. These crystals were found to be slightly soluble in 50 per cent alcohol, ligroine, chloroform, and acetone, but were best recrystallized from benzene, giving fine, colorless leaves melting at 174° . Holz¹ gives the melting point as $175-174^{\circ}$. The substance was readily soluble in dilute alkalis, showing it to be the N-compound, $\text{HO.C}_6\text{H}_2\text{Br}_2.\text{NH}(\text{C}_2\text{H}_5\text{O})$. No further product could be obtained from the reaction mixture.²

Benzoyl Derivative.--Attempts to benzoylate this base according to the Schotten-Baumann reaction, were not all satisfactory. Several trials seemed to show that a single benzoyl derivative, melting at 116° , can be formed.

1. J. prakt. Chem., (2) 32, 68.
2. The amount worked with was small. It would seem desirable to study this point further, working with larger quantities.

Reactions of 4, 6-Dibromo-2-aminophenol.

This base was prepared in an analogous manner to that for its isomer just described. 5.5 G. of o-nitrophenol, melting at 45° , were dissolved in 50 cc. of glacial acetic acid, and 12.6 g. (two molecules) of bromine dissolved in 20 cc. of glacial acetic acid slowly added with shaking. After standing over night the mixture was poured into five times its volume of water with stirring. After settling the liquid was decanted off and the 4, 6-dibromo-2-nitrophenol purified by recrystallization from alcohol. 5 G. of the gold-yellow crystals, melting at 117° ,¹ were dissolved in 25-30 cc. of alcohol and to the boiling liquid was added a solution of 30 g. of stannous chloride in 30 cc. of concentrated hydrochloric acid. The amino hydrochloride was purified by treatment of its dilute (1-20) alcoholic solution with excess of concentrated hydrochloric acid. The crystals of hydrochloride separated promptly upon allowing the liquid to cool, and were free from tin compounds. The free base was obtained by mixing ammonium carbonate solution with an aqueous solution of the hydrochloride and filtering off the precip-

1. in agreement with the literature.

itate. The latter was recrystallized from water, and had a melting point of about 94° . Holz¹ gives the melting point as $91-92^{\circ}$.

Monoacetyl Derivative.--To a mixture of 0.5 g. of base and a few crystals of sodium acetate were added about 6 cc. of acetic anhydride and the mixture gently warmed for a few minutes. Upon cooling a mass of colorless crystals separated out. These melted at 196° . Holz¹ gives the melting point of the monoacetyl derivative as 186° , and states that the compound is soluble in alcohol, ether and benzene, and readily dissolves in alkalis, the latter showing it to be the N-compound. The product in question is probably identical with that of Holz.

Diacetyl Derivative.--The mother liquor from the above was poured into four volumes of water and vigorously shaken, whereupon an oil separated out which soon gave a mass of fine greyish-brown crystals. These had a melting point of 145° , and, in keeping with results noted elsewhere in this paper, were believed to be diacetyl-4, d-dibromo-2-aminophenol, which, as far as we know, has not been described in the literature. Analysis for bromine confirmed this view:

1. Loc. cit. (See page 20 of this paper.)

0.1809 g. subs. required 9.85 cc. 0.1 N AgNO_3 . Calc.
for $\text{C}_{10}\text{H}_9\text{O}_2\text{NBr}_2$: Br, 45.6; found: 45.6. (Calc. for
 $\text{C}_8\text{H}_7\text{O}_2\text{NBr}_2$: Br, 51.8.)

Benzoyl Derivatives.--Benzoylation was attempted by the Schotten-Baumann reaction. A small amount of the aminophenol was dissolved in 10 cc. of water to which had been added a drop of sodium hydroxide solution in a test tube. A few drops of benzoyl chloride were added, the mixture made alkaline with sodium hydroxide solution, and then gently warmed to the boiling temperature. Upon cooling under the tap, with shaking, a pinkish-brown mass of crystals separated out, which had a melting point of about 112° . The product was partly soluble in dilute sodium hydroxide solution, and from this solution acids precipitated a colorless product probably identical with the original material. It was believed that both an N- and an O-benzoyl derivative were thus obtained, but further study was impossible at the time.

1. Although the analysis is not close, it distinguishes at once between the mono and the diacetyl derivatives.