

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

STERIC RELATIONS IN THE ACYLATION OF AROMATIC AMINES AND AMINOPHENOLS

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The behavior of aromatic amino compounds toward acylating agents has frequently been observed to exhibit steric hindrance¹ when the reaction is carried out in the direct way. It was long ago observed, however, that the acetylation of cellulose is accelerated² by the addition of a small portion of concd. sulfuric acid to the reaction mixture; and later work³ has shown that any one of several concentrated acids may be used, and that the amino radical and acyls other than acetyl are subject to the effect.

In the replacement of both amino hydrogen atoms by acetyl there are many cases on record which show not only that *ortho* substituents do not necessarily retard the reaction, but that they frequently accelerate it. The experiments of various workers⁴ prove that diaceto-anilides of *ortho* substituted anilines can be obtained when the base and acetic anhydride

¹ The theory that the failure of dimethylxylylidine and its homologs to give more than traces of quaternary ammonium salts [(a) Hofmann, *Ber.*, **5**, 718 (1872)] and the difficulty in acetylating the *o*-nitro and -bromo-anilines [(b) Remmers, *Ber.*, **7**, 350 (1874)] is due to the presence of neighboring atoms or radicals which, by reason of the space they occupy, protect the reacting group, was first clearly formulated by Kehrman [(c) *Ber.*, **21**, 3315 (1888)]. In a series of studies [listed in *Ber.*, **41**, 4357 (1908)] he and his collaborators found that *ortho* substitution in quinones retards or inhibits the formation of oximes. Paal and Kromschröder [(d) *J. prakt. Chem.*, [2] **54**, 265 (1896)] found that *o*-nitrobenzyl-*o*-nitro-aniline could not be acetylated, while Bischoff's work [(e) *Ber.*, **30**, 2321, 2467, 2475 (1897)] showed that in the acetylation of aniline hindrance increased with the increase of the mass of the acid radical, and was more noticeable with *iso* acids than with normal ones. *Ortho* substituted bases reacted much less readily than *meta* and *para* compounds. Similar results were obtained by Musselius [(f) *J. Russ. Phys.-Chem. Soc.*, **32**, 29 (1900)], Menschutkin [(g) *ibid.*, **32**, 46 (1900)], Potoski [(h) *ibid.*, **35**, 339 (1903)], and Cybulsky [(i) *ibid.*, **35**, 219 (1903)]. Bogert and Hand [(j) *THIS JOURNAL*, **25**, 938 (1903)] were unable to acetylate 2-amino-3,5-dibromobenzonitrile by boiling it for a long time with acetic anhydride, while Kaufmann and Frank [(k) *Ber.*, **40**, 3999 (1907)] found that 2-aminoresorcinoldimethyl ether could not be acetylated by the usual methods. Attempts to convert it into the corresponding thiocarbonyl and benzylidene derivatives were likewise unsuccessful. Failure to acetylate the amino radical in 3,5-dinitro-*p*-aminophenol by boiling it with acetic anhydride dissolved in acetic acid was reported by Meldola and Holley [(l) *J. Chem. Soc.*, **105**, 410 (1914)].

² Franchimont, *Ber.*, **12**, 1941 (1879).

³ Smith and Orton, *J. Chem. Soc.*, **93**, 1242 (1908). Blanksma, *Chem. Weekblad*, **6**, 717 (1909). Ref. 11. Reverdin, *Helvetica chim. Acta*, **1**, 205 (1918).

⁴ Ref. 1 b, Kay, *Ber.*, **26**, 2853 (1893). Bistrzycki and Ulfers, *Ber.*, **27**, 91 (1894). Ulfers and von Janson, *Ber.*, **27**, 93 (1894).

are heated together under pressure. Later work⁵ has shown that a methyl (positive) group, or a second hydrocarbon residue, as in the case of α -naphthylamine, in the *ortho* position to the amino group favors the formation of a diacyl derivative, when the base is boiled for an hour in an open vessel with four molecular proportions of acetic anhydride without a catalyst. Sudborough, however, studied but a single example of an amine containing an acid-forming substituent, though Montagne found⁶ that when 4-iodo-aniline was heated for six hours with 10.75 molecular proportions of acetic anhydride the corresponding diaceto-anilide only was obtained.

A certain interest attaches to the study of compounds containing acid-forming substituents, especially the nitro radical, since it has been shown that this group exercises an unexpected influence both in the esterification of substituted benzoic acids and in the hydrolysis of the corresponding nitriles. When it occupies the *ortho* position in benzoic acid, it retards esterification to a degree out of proportion to its molecular weight,⁷ while in the hydrolysis of benzonitrile⁸ the action is facilitated by the presence of one and still more by two nitro radicals.

In order to learn whether the acceleration indicated is general, 13 substituted anilines were acetylated in accordance with Sudborough's directions, care being taken to observe as nearly as possible the same precautions in each case. The results seem to indicate (1) that one negative

TABLE I
EFFECT OF ORTHO SUBSTITUENTS AS SHOWN BY THE RESULTS OF ACETYLATION ACCORDING TO SUDBOROUGH'S METHOD
(Taft)

Amino compound	Percentage of base recovered as acetylated product	
	Mono-acetyl derivative	Diacetyl derivative
Aniline.....	39.9	48.0
2-Chloro-aniline.....	10.5	77.7
2-Bromo-aniline.....	..	90.0
2-Iodo-aniline.....	7.0	72.3
4-Bromo-aniline.....	86.0	6.7
2-Nitro-aniline.....	30.0	65.6
4-Nitro-aniline.....	92.0	6.2
2,5-Dichloro-aniline.....	31.0	69.0
2,4-Dibromo-aniline.....	49.7	12.7
2,4-Dinitro-aniline.....	43.7	21.6
4,6-Dibromo- <i>m</i> -toluidine.....	75.0	6.0
3,5-Dibromo- <i>p</i> -toluidine.....	..	75.9
2,4,6-Tribromo-aniline.....	4.4	69.7
2,4,6-Tribromo- <i>m</i> -toluidine.....	24.1	66.0

⁵ Sudborough, *J. Chem. Soc.*, **79**, 533 (1901).

⁶ Montagne, *Ber.*, **51**, 1489 (1918).

⁷ Kellas, *Z. physik. Chem.*, **24**, 221 (1897).

⁸ Küster and Stallberg, *Ann.*, **278**, 207 (1894).

substituent in the *ortho* position in an aniline greatly facilitates the formation of a diacetyl derivative under the conditions of these experiments; (2) that such a substituent in the *para* position retards the reaction, and (3) that when both are present one offsets the effect of the other. It is noticeable, also, that in those cases which are most comparable, namely, where a single *ortho* substituent is present, the order of increase of acceleration is NO₂, I, Cl, Br, which is not in accordance with the relative weights of these radicals. Table I gives a summary of these results.

The failure to acetylate hydroxyl in many cases where it is adjacent to radicals heavier than hydrogen has also been explained by the theory of steric hindrance.⁹ And although it is stated that, in general, tertiary alcohols¹⁰ are not readily acetylated, there are on record many cases where an hydroxyl group somewhat similarly situated has been acetylated without difficulty. Thus, many phenols in which both *ortho* positions are occupied by halogen atoms or nitro groups give acetates under the usual conditions, and while the yields are not always given, no mention is made of steric hindrance.¹¹

⁹ α -Dihydroxyquinoline [La Coste and Valeur, *Ber.*, **20**, 1822 (1887)] gave a mono-acetyl derivative only when heated in a sealed tube with acetyl chloride; camphor pinacone [Beckmann, *Ann.*, **292**, 5 (1896)], α -hydroxy-benzalacetophenone [Wislicenus, *Ann.*, **308**, 232 (1899)], and the polymerization product of dimethyl-1,3-cyclohexenone-5, [Knoevenagel and Reinecke, *Ber.*, **32**, 420 (1899)] which was regarded as an hydroxyl compound, all resisted the action of boiling acetic anhydride for many hours, while benzylidene-anhydracetone benzil [Japp and Findlay, *J. Chem. Soc.*, **75**, 1018 (1899)] failed to react when heated with the anhydride in a sealed tube at 150°. 2-Hydroxy-3-methyl-5-nitrobenzaldehyde could not be acetylated in any way [Auwers and Bondy, *Ber.*, **37**, 3914 (1904)], and while 2-chloro-4-iodophenol was readily benzoylated by the Schotten-Baumann method, when both *ortho* positions were occupied by chlorine atoms, no benzoyl derivative could be obtained in this way [Brazier and McCombie, *J. Chem. Soc.*, **101**, 970 (1912)].

¹⁰ Schmidt and Weiling, *Ber.*, **39**, 654 (1906).

¹¹ *s*-Trichlorophenol [(a) Fischer, *Ann. Spl.*, **7**, 184 (1870)] is readily converted into the acetyl derivative by gentle boiling with acetyl chloride. The corresponding bromine [(b) Schunck and Marchlewski, *Ann.*, **278**, 347 (1894)] and iodine [(c) Raiford and Heyl, *Am. Chem. J.*, **44**, 212 (1910)] derivatives are obtained by heating a mixture of the phenol with acetic anhydride and anhydrous sodium acetate. 2,4,6-Trichloro-*m*-cresol can readily be acetylated by treatment with acetic anhydride and a drop of sulfuric acid [(d) Crowther and McCombie, *J. Chem. Soc.*, **103**, 546 (1913)], or with the anhydride and sodium acetate [(e) Raiford, *Am. Chem. J.*, **46**, 424 (1911)], while the tribromo compound is equally easily obtainable [(f) Claus and Hirsch, *J. prakt. Chem.*, [2] **39**, 59 (1889)]. *o*-Nitrophenyl-nitro-ethanol [(g) Thiele, *Ber.*, **32**, 1293 (1899)] was quickly acetylated by acetic anhydride and a trace of concd. sulfuric acid. 2,4,6-Trinitrophenol was acetylated [(h) Tomassi and David, *Ann.*, **169**, 167 (1873)] by boiling the phenol with 9 molecular proportions of acetic anhydride for two hours. The benzoyl derivative was obtained by heating the acid and benzoyl chloride [(i) Laurent and Gerhardt, *Ann.*, **75**, 78 (1850); (j) Kym, *Ber.*, **32**, 1428 (1899)]. The yield of the trinitro compound is not given, but the last-named author records a quantitative yield from 2,4-dinitrophenol under the same conditions.

In the acylation of *p*-aminophenols where both positions *ortho* to hydroxyl are occupied by halogen atoms, experiments have been recorded¹² in which only N-acyl derivatives were isolated, which indicated that the hydroxyl radical was completely protected or that the amount of O-acyl-N-acyl derivative was so small that it escaped detection. To test the second possibility with the hope of learning whether the observations cited represented isolated cases or the general behavior of such compounds, the question has been further studied. Four *p*-aminophenols in which one or both positions *ortho* to hydroxyl were occupied by halogen atoms, the symmetrical trihalogenated phenols, and 2,4,6-tribromo-aniline were acylated with benzoyl chloride,¹³ and with *p*-nitrobenzoyl chloride.

To insure comparable results, all acylations were conducted under as nearly uniform conditions as possible. In every case where benzoyl chloride was used, with the exception noted in the experimental part, the substance to be acylated was mixed with ten times its weight of a solution of alkali containing 1.25 molecular proportions of sodium hydroxide for each hydroxyl or amino radical present. To the resulting solution or suspension 1.25 molecular proportions of the acyl chloride for each of these radicals was added at once, and the whole shaken until the odor of the acid chloride could no longer be detected. The solid that separated was filtered off by suction, washed with a little cold water and weighed. Acylation with *p*-nitrobenzoyl chloride was carried out in pyridine solution following, in general, the method first employed by Deninger¹⁴ for amino compounds studied in more detail by Walther and Wlodkowski,¹⁵ and found to apply equally well to hydroxyl derivatives by Einhorn and Hollandt and Fischer.¹⁶ By a slight modification of this method, to the extent that the acid chloride was sometimes dissolved in chloroform before being added to the aminophenol solution and the resulting mixture allowed to stand until the chloroform had evaporated, the reaction went smoothly in our work. The residue was usually treated with a large quantity of water, the solid removed by filtration and washed with ice-cold, very dil. sulfuric acid to remove pyridine, then with a very dilute solution of sodium bicarbonate finally with a little cold water and dried.

The N-acyl derivative was separated from the O-acyl-N-acyl compound by treatment with a cold dilute solution of caustic alkali. Five g. of the pulverized material obtained as indicated was shaken for ten minutes with 50 cc. of water containing the calculated quantity of alkali required to convert the material into a soluble salt on the assumption that only the

¹² Raiford, Ref. 11 c, p. 429; *THIS JOURNAL*, **36**, 676 (1914).

¹³ Schotten-Baumann, *Ber.*, **17**, 2544 (1884); **19**, 3218 (1886).

¹⁴ Deninger, *Ber.*, **28**, 1322 (1895).

¹⁵ Walther and Wlodkowski, *J. prakt. Chem.*, [2] **59**, 266 (1899).

¹⁶ (a) Einhorn and Hollandt, *Ann.*, **301**, 95 (1898). (b) Fischer, *Ber.*, **53**, 1621 (1920).

N-acyl compound was present, the mixture filtered and the residue washed with a little cold water.¹⁷ Treatment of the filtrate with acid precipitated the N-acylated product.¹⁸

As a result of these experiments it may be stated that in the acylation of phenols and substituted *p*-amino-phenols with benzoyl and *p*-nitrobenzoyl chlorides, the presence of halogen atoms in the 2,6-positions protects the hydroxyl radical to a noticeable degree in every case, but that the protection is not complete in any case, not even with 2,4,6-tri-iodophenol.¹⁹ This is more clearly indicated by the figures shown in Table II.

TABLE II
EFFECTS OF ORTHO SUBSTITUENTS IN THE ACYLATION OF PARA-AMINOPHENOLS
(Lankelma)

Substance tested	Acylating agents			
	Benzoyl chloride Products ^a		<i>p</i> -Nitrobenzoyl chloride Products ^c	
	Monoacyl derivative	Diacyl derivative	Monoacyl derivative	Diacyl derivative
Phenol.....	77.5 ^b	...	54.00	..
Aniline.....	62.9 ^b	...	75.00	...
2-Chloro-4-aminophenol.....	49.08	42.96	38.24	60.94
2,6-Dichloro-4-aminophenol.....	58.05	34.64	28.12	71.62
2-Bromo-4-aminophenol.....	37.64	61.05	35.22	53.81
2,6-Dibromo-4-aminophenol.....	58.17	38.93	7.61	83.52
2,6-Di-iodo-4-aminophenol.....	48.93	38.15	5.69	84.98
2,4,6-Trichlorophenol.....	10.92	...	84.89	...
2,4,6-Tribromophenol.....	12.27	...	80.81	...
2,4,6-Tri-iodophenol.....	none	...	76.97	...
2,4,6-Tribromo-aniline.....	none	...	none	...

^a From Claisen's work, *Ber.*, **27**, 3183 (1894), carried out under conditions similar to ours.

^b Schotten-Baumann method, Ref. 13.

^c Fischer method, Ref. 16 b.

Experimental Part

The diacyl derivatives in which both radicals are attached to nitrogen, and which are indicated in Table III, were obtained by the method employed by Sudborough,⁵ from materials that were purified until their properties agreed with those recorded in the literature. The aminophenol derivatives were prepared in accordance with the general directions given above.

¹⁷ It was found that the material obtained by acylation of the trihalogenated phenols required three extractions with alkali to remove all unchanged phenol.

¹⁸ In certain cases where benzoyl chloride was the acylating agent it was found that this precipitate was contaminated with benzoic acid. To remove this the dried material was extracted two or three times with small portions of cold benzene which readily dissolved the acid but not the acylaminophenol.

¹⁹ Here a reaction took place, but a pure product could not be isolated from the material produced.

TABLE III
COMPOSITIONS AND PROPERTIES OF ACYL DERIVATIVES
(Lankelma and Taft)

Substance	Solvent	Crystalline form	M. p. °C.	Analysis			
				Subs.	Ag hal.	Calc.	Found
<i>o</i> -Chlorodiaceto-anilide.....	86-87	0.5015	0.3321	16.76	16.39
<i>o</i> -Iododiaceto-anilide.....	dil. acetic acid	needles	64-65	.4939	.3147	41.88	42.11
2,5-Dichlorodiaceto-anilide..	alcohol	plates	91-92	.4318	.5075	28.84	28.67
2 - Chloro - 4 - benzoylamino-phenol.....	dil. alcohol	colorless needles	178	.1535	.0909	14.32	14.65
2 - Chloro - 4 - benzoylamino-phenyl benzoate.....	dil. alcohol	colorless needles	206	.1856	.0763	10.09	10.17
2 - Chloro - 4 - (<i>p</i> - nitro-benzoylamino-phenol).....	dil. alcohol	yellow needles	242	.1824	.0906	12.14	12.29
2 - Chloro - 4 - (<i>p</i> - nitro-benzoylamino-phenyl) <i>p</i> -nitrobenzoate.....	acetone	leaflets	253	.1787	.0567	8.04	7.85
2,6 - Dichloro - 4 - benzoylamino-phenol.....	dil. alcohol	colorless needles	198	.1814	.1855	25.18	25.30
2,6 - Dichloro - 4 - benzoylamino-phenyl benzoate...	dil. alcohol	needles	177	.2037	.1507	18.39	18.30
2,6 - Dichloro - 4 - (<i>p</i> - nitro-benzoylamino-phenol)...	alcohol	yellow needles	265	.1360	.1195	21.71	21.74
2,6 - Dichloro - 4 - (<i>p</i> - nitro-benzoylamino-phenyl) <i>p</i> -nitrobenzoate.....	acetone	colorless needles	246	.2035	.1247	14.91	15.16
2 - Bromo - 4 - benzoylamino-phenol ^a	dil. alcohol	gray needles	193	.1735	.1098	24.70	26.93
2 - Bromo - 4 - benzoylamino-phenyl benzoate.....	dil. alcohol	colorless needles	199	.2107	.0983	20.20	19.86
2 - Bromo - 4 - (<i>p</i> - nitro-benzoylamino-phenol)...	dil. alcohol	yellow needles	237	.1824	.1027	23.73	23.86
2 - Bromo - 4 - (<i>p</i> - nitro-benzoylamino-phenyl) <i>p</i> -nitrobenzoate.....	acetone	colorless fibers	255	.1658	.0647	16.46	16.61
2,6 - Dibromo - 4 - benzoylamino-phenol.....	dil. alcohol	colorless needles	208	.1724	.1762	43.12	43.49
2,6 - Dibromo - 4 - benzoylamino-phenyl benzoate...	dil. alcohol	scales	172	.1410	.1132	33.68	34.16
2,6 - Dibromo - 4 - (<i>p</i> - nitro-benzoylamino-phenol)...	alcohol	lemon needles	268	.0452	.0412	38.46	38.79
2,6 - Dibromo - (4 - <i>p</i> - nitro-benzoylamino-phenyl) <i>p</i> -nitrobenzoate.....	acetone	colorless	237	.2297	.1530	28.31	28.34
2,6-Di-iodo-4-nitrophenol ^b ...	dil. alcohol	yellow needles	155-6	.1907	.2280	64.95	64.63
2,6-Di-iodo-4-aminophenol ^c ...	dil. alcohol	yellow needles	169-71	.2131	.2754	70.34	69.86
2,6 - Di-iodo - 4 - benzoylamino-phenol.....	dil. alcohol	cotton-like masses	222	.2420	.2465	54.60	55.06
2,6 - Di-iodo - 4 - benzoylamino-phenyl benzoate...	dil. alcohol	colorless scales	210-11	.1964	.1632	44.62	44.92
2,6 - Di-iodo - 4 - (<i>p</i> - nitro-benzoylamino-phenyl) <i>p</i> -nitrobenzoate.....	chloroform	short needles	277	.1556	.1112	38.52	38.63
Phenyl <i>p</i> -nitrobenzoate ^d	alcohol	colorless needles	129	.1608	8 cc. of N	5.74	5.55
2,4,6-Trichlorophenyl benzoate.....	alcohol	colorless needles	74	.0646	.0930	35.32	35.61
2,4,6 - Trichlorophenyl <i>p</i> -nitrobenzoate.....	alcohol	colorless needles	105-6	.1504	.1854	30.73	30.50
2,4,6 - Tribromophenyl benzoate.....	alcohol	colorless needles	81	.2756	.3578	55.17	55.25

TABLE III (Concluded)

Substance	Solvent	Crystalline form	M. p. °C.	Analysis		
				Subs.	Ag hal.	Calc. Found
2,4,6 - Tribromophenyl <i>p</i> -nitrobenzoate.....	dil. alcohol	colorless needles	153-4	.2456	.2873	50.00 49.78
2,4,6-Tri-iodophenyl <i>p</i> -nitrobenzoate.....	dil. alcohol	colorless needles	181	.1694	.1911	61.33 60.98
2-Nitrobenzanilide ^d	acetone	colorless scales	212	.1814	18.6 cc.	11.57 11.48 of N ₂

^a Meldola and Hollely [*J. Chem. Soc.*, **103**, 182 (1913)] prepared this product by brominating 4-benzoylaminophenol and recorded 184-185° as the melting point.

^b Busch [*Ber.*, **7**, 462 (1874)] obtained what he regarded as a mono-iodonitrophenol, melting at 154-155°, and which is recorded by Beilstein as having the structure 2-iodo-4-nitrophenol, by treatment of *p*-nitrophenol in glacial acetic acid solution with one molecular proportion of iodine and the subsequent addition of 1/2 molecular proportion of mercuric oxide. He recorded no analysis for his product. Schall [*Ber.*, **16**, 1899 (1883)] studied the action of iodine on sodium phenolate and obtained *o*-iodophenol, tri-iodophenol, and a di-iodophenol for which he gave no configuration. Brenans [*Compt. rend.*, **134**, 359 (1902)] repeated Schall's work and converted the di-iodophenol in question into a derivative of *p*-hydroxybenzaldehyde, the structure of which had previously been established by Paal [*Ber.*, **28**, 2412 (1895)] thus showing that the di-iodo compound was 2,6-di-iodophenol. When this product was nitrated it gave a substance that had the composition of a mononitrodi-iodophenol [compare Weselsky, *Ann.*, **174**, 108 (1874) and Post, *ibid.*, **205**, 91 (1880)]. Our product was a di-iodo compound and no mono compound was obtained in this way.

^c Seifert [*J. prakt. Chem.*, [2] **28**, 437 (1843)], recorded a melting point of 221.5°, with loss of iodine, for his product.

^d Determinations of nitrogen were made by the absolute method.

Summary

1. A negative substituent in the *ortho* position in an aniline facilitates the formation of a diacetyl derivative under the conditions of these experiments.
2. Such a substituent in the *para* position hinders the formation of a diacetyl derivative.
3. In the acylation of *p*-aminophenols with benzoyl chloride and *p*-nitrobenzoyl chloride, respectively, halogen atoms in the 2,6-positions (OH=1) protect the hydroxyl group to a noticeable degree in every case, though the protection does not seem to be complete in any case.
4. In the acylation of the symmetrical trihalogenated phenols the hindrance was much more pronounced with benzoyl chloride than with the *p*-nitro compound.
5. Under the conditions of these experiments *s*-tribromoaniline yielded no acyl derivative.²⁰

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²⁰ Though this compound is known, it was obtained by a method different from that used in this work.