to pull electrons from the positions in which they function as valence electrons. The significance of this fact in hydrogenation has been considered.

Facts too numerous to recapitulate here have been discovered in an extensive and comparative study of the behavior of ethanol, acetic acid, ethyl acetate, ethyl ether, acetal and acetaldehyde at the surface of some 20 nickel, iron, copper, zinc and magnesia catalysts.

MADISON, WISCONSIN

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

THE ROLE OF WEIGHT OF ACYL IN THE MIGRATION FROM NITROGEN TO OXYGEN. II[1]

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Introduction

Previous reports from this Laboratory have shown (1) that when an *o*-acetylaminophenol is benzoylated by the Schotten-Baumann method, the benzoyl radical goes to nitrogen while acetyl migrates to oxygen;[2] (2) that this migration takes place also when acid-forming substituents are attached to the nucleus of the aminophenol;[3] (3) that the acetyl-benzoyl derivatives of *p*-aminophenols do not suffer this rearrangement;[4] (4) that the migration does not take place when one of the reacting groups is situated on a side chain;[5] (5) that the presence of bromine and other heavy radicals occupying positions *ortho* to the reacting groups (amino and hydroxyl), which in many reactions have been found[6] to cause marked retardation and in some instances, complete inhibition, does not prevent the rearrangement;[7] (6) that these observations seem to hold with bases derived from condensed and multinuclear hydrocarbons, namely, 1-amino-2-napththol[8] and halogenated derivatives, and 3-amino-4-hydroxydiphenyl[9] and (7) that in the diacylated compounds studied up to this point the heavier acyl was always found on nitrogen.[10] But, in view of the fact that none of these radicals contained any substituent except hydrogen,

[1] Condensed from a thesis presented by J. R. Couture to the Graduate College of the State University of Iowa in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1923.

[2] Raiford, THIS JOURNAL, **41**, 2068 (1919).

[3] Raiford and Couture, *ibid.*, **44**, 1793 (1922). Glavincheff, unpublished research.

[4] Raiford and Iddles, *ibid.*, **45**, 469 (1923).

[5] Raiford and Clark, *ibid.*, **45**, 1738 (1923).

[6] Stewart, "Stereochemistry," Longmans, Green and Co., 2nd ed., 1919, p. 261.

[7] Raiford and Woolfolk, THIS JOURNAL, **46**, 2246 (1924).

[8] Armstrong, unpublished research.

[9] Colbert, unpublished research.

[10] Raiford and Greider, THIS JOURNAL, **46**, 430 (1924)

it was still a question whether weight or some chemical characteristic of the radical was responsible for the displacement of acetyl by benzoyl.[11]

Earlier Work

Previous studies in this general field have been made by several other workers. Ransom[12] found in the derivatives he prepared from *o*-aminophenol and certain acyl and carboxyl radicals that the lighter of the groups present was always attached to nitrogen, and this observation was confirmed by subsequent study[13] when the diacyl derivatives contained radicals from these particular classes and were used in the combinations specified by the authors. Einhorn and Pfyl[14] found that the reduction of the O-acyl derivatives of the *o*-nitrophenols they studied gave regularly, through the rearrangement of the normal reduction product, a mixture of the N-acylaminophenol and the corresponding anhydrobase. Auwers[15] allowed aniline to react with 2-acetyloxy-3,5-dibromobenzyl bromide and found that not only was the bromine atom of the side chain replaced by the aniline residue, but that acetyl had wandered from oxygen to nitrogen although the latter was attached to a side chain. In subsequent work with several collaborators it was found that this rearrangement took place when various substituted anilines and primary aliphatic amines were used, and also when benzoyl and other heavy acyl radicals were employed.[16] Further work indicated that the O-acetyl derivatives of the phenylhydrazones of aromatic *o*-hydroxy aldehydes were stable under ordinary conditions, but that several reagents caused the acyl to wander to the γ-atom (nitrogen) of the side chain.[17] Similarly, when an attempt was made to prepare the free base of the O-benzoate of the enol form of β-aminopropiophenone, the benzoyl radical wandered from oxygen to nitrogen, while the enol rearranged to the keto form.[18] This difference in attraction between oxygen and nitrogen is not always so pronounced, for it was found[19] that when only one acetyl radical was introduced into the molecule of α'-methyl-α-ethylolpiperidine it attached to oxygen, and that it did not wander to nitrogen.

In later work Auwers and Eisenlohr[20] studied the behavior of acetyl-

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[11] The displacement from nitrogen of a lighter by a heavier acyl radical was noted by Paal and Otten [*Ber.*, **23**, 2590 (1890)], Pictet [*Ber.*, **23**, 3011 (1890)] and Freundler, [*Bull. soc. chim.*, **31**, 622 (1904)], while the opposite behavior was observed by Cohen [*J. Chem. Soc.*, **59**, 71 (1891)] and Heller and Jacobsohn [*Ber.*, **54**, 1110 (1921)].

[12] Ransom, (a) *Ber.*, **31**, 1060 (1898); **33**, 199 (1900); (b) *Am. Chem. J.*, **23**, 1 (1900).

[13] Ransom and Nelson, THIS JOURNAL, **36**, 390 (1914).

[14] Einhorn and Pfyl, *Ann.*, **311**, 34 (1900).

[15] Auwers, *Ber.*, **33**, 1923 (1900).

[16] *Ann.*, **332**, 159 (1904).

[17] *Ber.*, **37**, 3904 (1904).

[18] Gabriel, *Ann.*, **409**, 312 (1915).

[19] Löffler and Remmler, *Ber.*, **43**, 2058 (1910).

[20] Auwers and Eisenlohr, *Ann.*, **369**, 209 (1909).

benzoyl derivatives obtained from 2-amino-4-methylphenol. When the N-acetyl derivative of this phenol was subjected to the Schotten-Baumann reaction, using five molecular proportions of benzoyl chloride and seven of sodium hydroxide, the same diacyl derivative was obtained as that formed by reduction of 2-nitro-4-methylphenyl benzoate with zinc dust and acetic acid in the presence of acetic anhydride, and was regarded as the O-benzoyl-N-acetyl compound. When this derivative was hydrolyzed by aqueous alkali it gave only N-benzoylate, which was interpreted to mean that the heavier of these radicals had migrated from nitrogen to oxygen during hydrolysis. The isomeric diacyl derivative, 2-benzoylamino-4-methylphenyl acetate was saponified normally to the N-benzoylaminophenol only.

In continuation of their research with other combinations of acyl radicals on this base, Auwers and Eisenlohr made the tacit assumption that in all the diacylated derivatives prepared, the radical last introduced is bound to oxygen without, in each case, comparing the derivative with its supposed isomer, made by introducing the radicals in reverse order. The rearrangements they observed were attributed to the influence of the alkali, and they arrived at the conclusion that "only when there is a considerable difference in the weights of the two radicals, as for example, between benzoyl and acetyl was there a complete displacement, during saponification, of the lighter by the heavier group. When the difference is less pronounced part of the mixed ester is saponified normally and one obtains a mixture of two different acylamino derivatives in varying proportions or only the normal saponification product." In no case was such a rearrangement observed with *m*- and *p*-aminophenols.

Purpose of this Study

In general, as will appear, while our results are in accord with those of Auwers and Eisenlohr, we have regarded the whole problem from a somewhat different standpoint. In every instance we have attempted to obtain the two possible isomeric mixed diacyl derivatives by introducing the two radicals in reverse order. The two derivatives, whether isomeric or identical, were saponified separately and the products carefully examined and compared.

The work of these authors on the acetyl-benzoyl derivatives of the aminophenol in question has been repeated in this Laboratory and somewhat different results have been obtained. Two different mixed diacyl derivatives were secured from the base in question and these had melting points that differed but slightly (see Experimental Part) from those found by Auwers and Eisenlohr. But each of them upon hydrolysis with dilute alkali gave a mixture of the two mono-N-acylated derivatives, namely, 2-acetylamino-4-methylphenol and 2-benzoylamino-4-methylphenol, which indicated that a partial rearrangement had occurred during the saponification of each.[21]

Effect of Increasing the Weight of the Fatty Acyl.—When 2-propionylamino-4,6-dibromophenol was benzoylated, a product which appeared to be identical with that formed by the action of propionyl chloride on 2-benzoylamino-4,6-dibromophenol was obtained. Hydrolysis of separate portions of the material thus prepared by introduction of the acyl radicals in different orders gave, in each instance, a mixture of 2-propionylamino-4,6-dibromophenol and 2-benzoylamino-4,6-dibromophenol. These results may be explained in two ways. The diacylated material may have been a mixture of the two possible isomerides produced by a partial rearrangement during the introduction of the second acyl in each case; or the rearrangement may have occurred during hydrolysis. The first possibility was indicated by the fact that repeated crystallization of the diacyl derivative from each source caused a lowering of the melting point; and since the formation of the diacyl compound may be regarded as a competition of the two acidic radicals for the most basic position in the molecule, it seems likely that a mixture might be formed.

To test this effect further it was decided to examine the caproyl-benzoyl derivatives of the base under consideration. When 2-caproylamino-4,6-dibromophenol was benzoylated, a diacyl derivative melting at 137° was obtained. The action of caproyl chloride on 2-benzoylamino-4,6-dibromophenol gave a diacyl derivative that also melted at 137°, while a mixture of the two products melted at 120–125°. On the assumption that the acyl last introduced went to oxygen, the first product should be 2-caproylamino-4,6-dibromophenyl benzoate, and the second 2-benzoylamino-4,6-dibromophenyl caproate. Each of these derivatives gave, on hydrolysis, a mixture of the two N-mono-acyl derivatives, 2-benzoylamino-4,6-dibromophenol and 2-caproylamino-4,6-dibromophenol. Evidently, the rearrangement was only partial, and occurred during the saponification. This case is significant in that we are here dealing with two acyl radicals, one aliphatic and the other aromatic, having nearly the same weight. Apparently, in such a case, there is little tendency for one acyl to replace another during the introduction of these radicals, though the migration may occur in either direction during hydrolysis.

The introduction of the acetyl and caproyl radicals into the base under consideration gave derivatives that melted at 120° and 133°, and which were regarded as 2-acetylamino-4,6-dibromophenyl caproate and 2-

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[21] This is the only case in which we have been able to prepare isomeric acetyl-benzoyl derivatives from an *o*-aminophenol. It is, likewise, the only case in which an N-acetyl compound has been found among the saponification products of an acetyl-benzoyl derivative, although more than twenty such compounds have been examined. The remainder of the work here described was done with other bases.

caproylamino-4,6-dibromophenyl acetate, respectively. Hydrolysis of each of these products gave a mixture of 2-acetylamino-4,6-dibromophenol and 2-caproylamino-4,6-dibromophenol. The caproyl radical has nearly the same weight as benzoyl but it does not, as does the latter, readily displace acetyl in the formation of the diacyl derivatives, which suggests that the characters of the groups, as well as their relative weights, may have a bearing on the rearrangement.

Effect of Varying the Weight of the Aromatic Acyl.—To determine what effect would be produced by a variation in the weight of the aromatic radical used in connection with acetyl, a number of acetyl substituted benzoyl derivatives were studied. Compounds containing various pairs of these aromatic radicals were also considered. The action of *p*-nitrobenzoyl chloride on 2-acetylamino-4-methyl-6-bromophenol gave a product that melted at 206°, and the introduction of the acyl radicals in the reverse order gave the same substance. Hydrolysis of this material gave only 2-acetylamino-4-methyl-6-bromophenol and *p*-nitrobenzoic acid, from which it was concluded that the diacyl derivative was 2-acetylamino-4-methyl-6-bromophenyl *p*-nitrobenzoate, and that no rearrangement occurred when the *p*-nitrobenzoyl radical was introduced last. This behavior is remarkable in that acetyl, which is both lighter in weight and less acidic than *p*-nitrobenzoyl, as shown by the ionization constants of the respective acids (see Table I), nevertheless completely displaces the latter radical from its position on nitrogen. If difference in weight of the pair of acyls used were the determining factor in the migration, acetyl should be completely displaced by *p*-nitrobenzoyl as it usually is by benzoyl. Likewise, if the migration were determined by the relative acidity of these radicals, the more acidic should be found on nitrogen. Exactly the reverse was observed in this case.

The marked difference in their ability to cause the migration of acetyl shown by the benzoyl and *p*-nitrobenzoyl radicals made it a matter of much interest to examine the behavior of a diacyl derivative containing these two aromatic ones. When they were introduced successively into 2-amino-4,6-dibromophenol, the same diacylated product was obtained, regardless of the order of introduction. The only products of hydrolysis were 2-benzoylamino-4,6-dibromophenol and *p*-nitrobenzoic acid, which indicated that this diacyl derivative was 2-benzoylamino-4,6-dibromophenyl *p*-nitrobenzoate. This required the migration of the *p*-nitrobenzoyl radical from nitrogen to oxygen when that group was the first of the two introduced. In this case, also, a lighter and less acidic radical has displaced a heavier and more acidic one from nitrogen.

The acetylation of 2-(*m*-nitrobenzoylamino)-4-methyl-6-bromophenol gave a product which seemed to be identical with that obtained by the action of *m*-nitrobenzoyl chloride on the acetylamino derivative of the same base. Hydrolysis of this material gave two different acylaminophenols, indicating either that it was an equilibrium mixture of the two isomeric mixed diacyl compounds resulting from partial rearrangement during acylation of each form, or that complete rearrangement had occurred in one direction during acylation and was followed by partial rearrangement in the opposite sense during saponification. The former explanation seems the most probable one.

TABLE I

FORMATION AND BEHAVIOR OF DIACYL DERIVATIVES

Pairs of acyls used	Ionization constant[a] $= k \times 10^5$ at 25°	Aminophenol used	Diacyl derivatives	Hydrolysis products
Acetyl	1.86	2-Amino-4-methylphenol	Different	Mixture[b]
Benzoyl	6.6			
Benzoyl	6.6	2-Amino-4,6-dibromophenol	Identical	Mixture
Propionyl	1.35			
Benzoyl	6.6	2-Amino-4,6-dibromophenol	Different	Mixture
Caproyl	1.46			
Acetyl	1.86	2-Amino-4,6-dibromophenol	Different	Mixture
Caproyl	1.46			
Acetyl	1.86	2-Amino-4-methyl-6-bromophenol	Identical	Acetyl on nitrogen
p-Nitrobenzoyl	40.1			
Benzoyl	6.6	2-Amino-4,6-dibromophenol	Identical	Benzoyl on nitrogen
p-Nitrobenzoyl	40.1			
Acetyl	1.86	2-Amino-4-methyl-6-bromophenol	Identical	Mixture
m-Nitrobenzoyl	34.5			
Acetyl	1.86	2-Amino-4-methyl-6-bromophenol	Identical	*p*-Chlorobenzoyl on nitrogen
p-Chlorobenzoyl	9.3			
p-Chlorobenzoyl	9.3	2-Amino-4,6-dibromophenol	Identical	*p*-Chlorobenzoyl on nitrogen
p-Nitrobenzoyl	40.1			

[a] Scudder, "The Electrical Conductivity and Ionization Constants of Organic Compounds," D. Van Nostrand Co., **1914**.

[b] The term "mixture" here refers to the presence of two different N-acylaminophenols.

The products obtained by the action of acetyl chloride on 2-(*p*-chlorobenzoylamino)-4-methyl-6-bromophenol, and *p*-chlorobenzoyl chloride on 2-acetylamino-4-methyl-6-bromophenol, respectively, were identical. Hydrolysis showed that this compound was 2-(*p*-chloro-benzoylamino)-4-methyl-6-bromophenyl acetate. The heavier and more acidic radical had replaced the lighter and less acidic one.

To compare the activity of the *p*-nitrobenzoyl and the *p*-chlorobenzoyl radicals directly they were introduced successively into the base, 2-amino-4,6-dibromophenol. The same substance was obtained regardless of the order in which the process was carried out. Hydrolysis of the compound gave only *p*-nitrobenzoic acid and 2-(*p*-chloro-benzoylamino)-4,6-dibromophenol. To produce such a result, in the case where the *p*-nitro benzoyl is the first of the groups introduced, it must migrate from nitrogen to oxygen as the *p*-chlorobenzoyl group enters the molecule.

These results are summarized in the accompanying table.

Experimental Part

Methods of Acylation.—1. For the preparation of a diacetyl derivative a mixture of equal weights of the hydrochloride of the base and anhydrous sodium acetate was warmed with an excess of acetic anhydride for about 15 minutes. The cooled mass was then triturated with water and the mixture filtered to remove sodium salts. The insoluble residue was then purified by crystallization from a suitable solvent.

2. Acetylation of an N-acetylaminophenol was best accomplished by adding to a concentrated pyridine solution of the compound a considerable excess of acetic anhydride, and allowing the mixture to stand for 15 minutes at room temperature. The diacyl derivative was then precipitated by the addition of water, the solid collected on a filter, washed with very dilute acid and finally with water.

3. The acetyl and propionyl radicals were most easily introduced through the use of the corresponding anhydride as indicated. Derivatives containing higher fatty acyls as well as those containing the benzoyl and substituted benzoyl radicals were prepared by the action of the appropriate acid chloride on a pyridine solution of the starting material, as described by Einhorn and Hollandt.[22] The reaction mixtures were generally allowed to stand for about an hour, after which several volumes of water were added. The solid that was precipitated was collected on a filter, washed with very dilute acid to remove pyridine, and then extracted several times with 5% solution of ammonium carbonate to remove organic acid derived from the excess of acid chloride.[23] When an acylation was carried out in this way, with the hydrochloride of the base as starting material, the O-acyl-N-acyl derivative was obtained. From such material the N-acyl compound was readily prepared by hydrolysis at the O-connection by means of a dilute solution of potassium hydroxide in 95% alcohol.[24]

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[22] Einhorn and Hollandt, *Ann.*, **301**, 101 (1898).

[23] In this work there was usually employed 1.25 molecular proportions of the acid chloride.

[24] In most cases in the present work this method was found to be more convenient and to give a better yield of N-acyl compound than that described by Ransom [Ref. 12 b, p. 17].

Hydrolysis of Derivatives.—1. To determine the structures of the various mixed diacyl derivatives it was necessary to examine the products resulting from hydrolysis with dilute alkali. Such treatment usually caused immediate solution, but the mixture was allowed to stand for at least one hour, after which it was acidified and evaporated on the water-bath to a small volume. After the addition of a little water the mixture was filtered and the residue extracted with dil. ammonium carbonate solution to remove free acid. Such treatment usually left the acylamino derivative unchanged.

1. Acetyl and Benzoyl

A portion of 2-nitro-4-methylphenol[25] was reduced as directed by Noelting and Kohn.[26] The hydrochloride thus obtained was decomposed by ammonium carbonate solution, and gave a free base melting at 133°. Noelting and Kohn recorded 135°. The diacetyl derivative was readily obtained by gently heating the base or its hydrochloride and an equal weight of anhydrous sodium acetate with an excess of acetic anhydride for 15 minutes, although Auwers and Eisenlohr[20] stated that three hours' boiling was necessary. The N-acetyl compound obtained by hydrolysis melted at 158°. Auwers and Eisenlohr found 159°.

Benzoylation of 2-Acetylamino-4-methylphenol.—Benzoylation of this compound by the Schotten-Baumann method gave a quantitative yield of acetyl-benzoyl derivative. Crystallization from alcohol gave fine, white needles that had the general appearance of cotton and that melted[27] at 147°. Saponification of this material gave a product insoluble in water but soluble in alcohol from which it crystallized in small, glittering plates melting at 191°, and which was subsequently found (see below) to be 2-benzoylamino-4-methylphenol. From the liquid left after the separation of the monobenzoyl derivative there was obtained by evaporation a substance which crystallized from water in fine, hairy needles melting at 158°, and which was identified as the N-acetyl derivative.

To learn whether in the acetyl-benzoyl compound melting at 147° the benzoyl group was attached to nitrogen or whether it had migrated to that position during saponification, 2-benzoyl-amino-4-methylphenol, prepared as directed by Auwers and Eisenlohr and melting at 191–192°, as recorded by them, was acetylated. A product melting at 135° was obtained.[28] A mixture of this compound and that (m. p., 147°) obtained by benzoylation of 2-acetylamino-4-methylphenol melted at 115–130°. Hydrolysis of the compound melting at 135° gave a mixture of the two mono-N-acylated derivatives specified above.

2. Benzoyl and Propionyl

2-Propionylamino-4,6-dibromophenyl Propionate.—Fifteen g. of the hydrochloride of the aminophenol was converted into the diacyl derivative by the method described. A quantitative yield was obtained.[29] From alcohol the product crystallized in a mass of very fine, white needles having the general appearance of cotton; m. p., 162°. It did

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[25] Wagner, *Ber.*, **7**, 537 (1874).

[26] Noelting and Kohn, *Ber.*, **17**, 359 (1884).

[27] Auwers and Eisenlohr found 142°, 146° and 149–150°, respectively, for the several portions of this compound that they prepared.

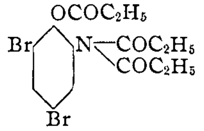
[28] Auwers and Eisenlohr recorded 134°.

[29] When the pyridine method described above was employed, the product was purified more easily, and the yield was but slightly lower, 96.1%.

not dissolve instantly in a solution of caustic alkali, which indicated that it was a diacyl derivative. Analysis for bromine was in accord with this behavior.

Anal. Subs., 0.1745: AgBr, 0.1715. Calc. for $C_{12}H_{13}O_3NBr$: Br, 42.17. Found: 41.82.

When a large excess of propionic anhydride was used in the experiment described above, a substance was obtained which crystallized from benzene in colorless prisms melting sharply at 153°. It was insoluble even on long standing in a dilute solution of sodium hydroxide. It was probably a tripropionyl derivative:



Anal. Subs., 0.0467: AgBr, 0.0406. Calc. for $C_{15}H_{17}O_4NBr_2$: Br, 36.75. Found: 37.00.

2-Propionylamino-4,6-dibromophenol.—To prepare this compound, the dipropionyl *derivative described above was saponified by alkali in the usual way. Three g. of the* product, a 93.9% yield, was obtained. It can be crystallized from benzene or dil. alcohol as colorless needles which develop a pale lilac color on standing. It dissolved readily in caustic alkali solution and was precipitated unchanged by acids; m. p., 88°. Analysis indicated the presence of one propionyl radical.

Anal. Subs., 0.1487: AgBr, 0.1738. Calc. for $C_9H_9O_2NBr_2$: Br, 49.51. Found: 49.74.

Benzoylation of 2-Propionylamino-4,6-dibromophenol.—One g. of this phenol, benzoylated as indicated, gave 1.3 g. of the diacyl derivative, or a yield of 99.4%. In the crude state this material melted at 180–190°, but after two crystallizations from alcohol, from which it separated in a mass of fine, white, cotton-like needles, the melting point was 182°, and further crystallizations did not alter this. Analysis for bromine indicated both a benzoyl and propionyl radical.

Anal. Subs., 0.1555: AgBr, 0.1363. Calc. for $C_{16}H_{13}O_3NBr_2$: Br, 37.44. Found: 37.30.

Hydrolysis of the Benzoyl-propionyl Derivative.—Hydrolysis of 0.5 g. of this substance gave 0.17 g. of a product that softened at 160° and was completely liquid at 175°. One crystallization from alcohol gave fine, colorless needles that melted sharply at 198°, which suggested that it might be 2-benzoylamino-4,6-dibromophenol, first prepared by Raiford[29a] who employed Ransom's method. The product used in the present work was obtained by hydrolysis of the corresponding dibenzoyl derivative. Four g. of the hydrochloride gave 3.7 g. of the pure N-benzoyl compound, a yield of 75.7%.

When the ammonium carbonate extract from the hydrolysis of the benzoyl-propionyl derivative was acidified it gave a white precipitate that weighed 0.11 g. This melted sharply at 88°, and was identified as 2-propionylamino-4,6-dibromophenol.

Benzoic acid was identified in the mother liquor left after removal of the other products of hydrolysis.

Action of Propionic Anhydride on 2-Benzoylamino-4,6-dibromophenol.—Two g. of the phenol, acylated with propionic anhydride in the usual way, gave a quantitative yield of crude product melting at 160–165°. Repeated crystallization from alcohol gave long, white needles, and raised the melting point to 182°. This substance was shown both by analysis and by study of its hydrolysis products to be identical with that obtained by benzoylation of 2-propionylamino-4,6-dibromophenol.

[29a] THIS JOURNAL, **41**, 2078 (1919).

Anal. Subs., 0.1657: AgBr, 0.1456. Calc. for $C_{16}H_{13}O_3NBr_2$: Br, 37.44. Found: 37.39.

3. Benzoyl and Caproyl

2-Caproylamino-4,6-dibromophenyl Caproate.—Six g. of the hydrochloride of the corresponding aminophenol was treated in the usual way with 11 cc. of caproyl chloride,[30] while the mixture was constantly stirred. This large excess of acid chloride was found to be necessary in order to obtain satisfactory yields of the diacylated product. The crude material weighed 7.5 g., a yield of 82.5%. It melted at 110° and was nearly pure. Repeated crystallization from dil. alcohol gave fine, white, cotton-like needles melting at 111°. Analysis indicated the presence of two caproyl radicals.

Anal. Subs., 0.1763: AgBr, 0.1441. Calc. for $C_{18}H_{25}O_3NBr_2$: Br, 34.53. Found: 34.78.

2-Caproylamino-4,6-dibromophenol.—This compound was obtained by hydrolysis of the diacyl derivative just described. A portion weighing 4.85 g. was treated as usual. When the mixture was acidified a grayish oil separated. The supernatant liquid was poured off and the oil washed with a solution of ammonium carbonate, after which the residue solidified to a mass of small granular crystals melting at 70°; yield, 3.70 g., or 96.8%. It was crystallized by cooling its alcoholic solution in ice water and slowly diluting the liquid with water. Fine, white needles were obtained; m. p., 70–71°. The compound is readily soluble in solutions of caustic alkali, and analysis for bromine indicated the presence of but one caproyl radical.

Anal. Subs., 0.1564: AgBr, 0.1614. Calc. for $C_{12}H_{15}O_2NBr_2$: Br, 43.79. Found: 43.94.

2-Caproylamino-4,6-dibromophenyl Benzoate.—This compound was obtained by treatment of 0.5 g. of the caproyl aminophenol described above with benzoyl chloride in the usual manner. A quantitative yield was obtained. The crude product melted at 120–128°, but repeated crystallizations from chloroform gave fine, colorless needles that in masses had the appearance of cotton and that melted at 137°.

Anal. Subs. 0.1510: AgBr, 0.1216. Calc. for $C_{19}H_{19}O_3NBr_2$: Br, 34.09. Found: 34.27.

Hydrolysis of 2-Caproylamino-4,6-dibromophenyl Benzoate.—Two-tenths g. of this derivative was hydrolyzed in the usual way. When the mixture was acidified no precipitate was formed, and the volume was therefore reduced to about 10 cc. by evaporation on a radiator. A brown oil separated, but this solidified on standing overnight. The residue insoluble in ammonium carbonate solution weighed 0.150 g. and melted partly at 70°, after which there was no further change until a temperature of 125° was reached. The cooled material was dissolved in warm benzene, and an equal volume of ligroin (b. p., 70°) was added. Upon standing, a considerable quantity of solid separated in the form of small, white nodules. This material was collected and dried, and was found to melt at 196°. It was identified as 2-benzoylamino-4,6-dibromophenol.

Evaporation of the filtrate left after removal of the benzoylaminophenol gave a pale brown oil which on standing solidified to small granular crystals; m. p., 70°. This was identified as 2-caproylamino-4,6-dibromophenol.

2-Benzoylamino-4,6-dibromophenyl Caproate.—Two g. of the *N*-benzoylaminophenol was treated with 21 cc. of caproyl chloride as described. A quantitative yield of material melting at 129–130° was obtained. Crystallization from a mixture of chloroform and ligroin gave fine, white, cotton-like needles; m. p., 137°. A mixture of this

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[30] Meyer, *Monatsh.*, **22**, 418 (1901).

substance and that obtained by benzoylating 2-caproylamino-4,6-dibromophenol melted at 120–125°. Analysis for bromine showed that they have the same composition.

Anal. Subs., 0.1113: AgBr, 0.0919. Calc. for $C_{19}H_{19}O_3NBr_2$: Br, 34.09. Found: 34.52.

Hydrolysis of this diacyl derivative gave the two N-acylaminophenols obtained from the isomer described above.

4. Acetyl and Caproyl

2-Acetylamino-4,6-dibromophenyl Caproate.—Three and four-tenths g. of the N-acetyl derivative[31] was converted into the caproyl derivative; yield, 4.37 g., or 97.6%. Crystallization from alcohol raised the melting point from 117° to 120°. Analysis showed that it was a diacyl derivative.

Anal. Subs., 0.1884: AgBr, 0.1738. Calc. for $C_{14}H_{17}O_3NBr_2$: Br, 39.28. Found: 39.26.

Hydrolysis of this product gave about equal quantities of the two possible N-acylaminophenols.

2-Caproylamino-4,6-dibromophenyl Acetate.—A portion of the N-caproyl derivative weighing 1.65 g. was converted into the diacylated compound by acetyl chloride in the usual way. The yield was quantitative and the crude product melted at 124–130°. Crystallization from alcohol gave colorless needles, melting at 133°; these depressed the melting point of the previously described acetyl-caproyl derivative to 116–128°. Analysis showed that the products are isomeric. Hydrolysis gave in this case, also, each of the possible N-acylaminophenols.

Anal. Subs., 0.1472: AgBr, 0.1366. Calc. for $C_{14}H_{17}O_3NBr_2$: Br, 39.28. Found: 39.49.

5. Acetyl and *p*-Nitrobenzoyl

Action of *p*-Nitrobenzoyl Chloride on 2-Acetylamino-4-methyl-6-bromophenol.—Seven-tenths g. of the N-acetyl derivative[32] was allowed to react with *p*-nitrobenzoyl chloride. The product, obtained in nearly quantitative yield, began to shrink at 182°, and was melted at about 200°. Crystallization from alcohol gave silky needles melting at 206°. Analysis indicated a diacetyl compound.

Anal. Subs., 0.1495: AgBr, 0.0718. Calc. for $C_{16}H_{13}O_5N_2Br$: Br, 20.34. Found: 20.44.

Hydrolysis of the acetylnitrobenzoyl derivative gave *p*-nitrobenzoic acid and the N-acetylaminophenol.

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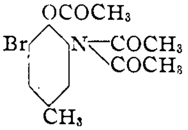
[31] Ref. 2, p. 2075.

[32] This was obtained by hydrolysis of the diacyl derivative. In preparing the latter by the pyridine method, rather than by that previously used, it was found that excess of acetic-anhydride led to a product that crystallized in prisms from benzene, and melted at 109°. Analysis for bromine indicated a triacetyl compound which probably has the structure,



Anal. Subs., 0.1919: AgBr, 0.1160. Calc. for $C_{13}H_{14}O_4NBr$: Br, 24.37. Found: 24.75.

2-(*p*-Nitrobenzoylamino)-4-methyl-6-bromophenol.—This compound was prepared by hydrolysis of the corresponding diacylated product. A yield of 49.3% of pure material melting at 190° was obtained by crystallization from alcohol. The analysis for bromine agrees with the formula assigned.

Anal. Subs., 0.1247: AgBr, 0.0671. Calc. for $C_{14}H_{11}O_4N_2Br$: Br, 22.77. Found: 22.90.

Acetylation of 2-(*p*-Nitrobenzoylamino)-4-methyl-6-bromophenol.—This was carried out by the action of acetyl chloride on the N-(*p*-nitrobenzoyl) compound. The product melted at 206°, and was identified as 2-acetylamino-4-methyl-6-bromophenyl *p*-nitrobenzoate by both analysis and hydrolysis.

Anal. Subs., 0.1307: AgBr, 0.0626. Calc. for $C_{16}H_{13}O_5N_2Br$: Br, 20.34. Found: 20.38.

6. Benzoyl and *p*-Nitrobenzoyl

Action of *p*-Nitrobenzoyl Chloride on 2-Benzoylamino-4,6-dibromophenol.—The product here obtained was nearly insoluble in alcohol, benzene and chloroform. From glacial acetic acid it was obtained in colorless needles that melted at 246°. Analysis showed the presence of both the benzoyl and the nitrobenzoyl radicals.

Anal. Subs., 0.2023: AgBr, 0.1461. Calc. for $C_{20}H_{12}O_5N_2Br_2$: Br, 30.74. Found: 30.75.

When the solid left upon hydrolysis of the above material was extracted with hot water, *p*-nitrobenzoic acid was recovered. The residue was crystallized from 50% alcohol and was identified as 2-benzoylamino-4,6-dibromophenol. No other products were found in the hydrolysis mixture, although the mother liquors left after each crystallization were worked up.

2-(*p*-Nitrobenzoylamino)-4,6-dibromophenol.—To obtain this compound the diacyl derivative was hydrolyzed. Crystallization from alcohol gave tan-colored needles that melted at 214°; yield, 45% of pure material. It showed the usual phenolic properties.

Anal. Subs., 0.1700: AgBr, 0.1546. Calc. for $C_{13}H_8O_4N_2Br_2$: Br, 38.43. Found: 38.70.

Benzoylation of the Phenol.—Treatment of 1 g. of the phenol with benzoyl chloride under the usual conditions gave 1.2 g., or a yield of 94.4%, of a product which was found to be identical with that obtained by the action of *p*-nitrobenzoyl chloride on 2-benzoylamino-4,6-dibromophenol, described above. Hydrolysis gave only *p*-nitrobenzoic acid and the benzoylaminophenol.

7. Acetyl and *m*-Nitrobenzoyl

The Action of *m*-Nitrobenzoyl Chloride on 2-Acetylamino-4-methyl-6-bromophenol.—This reaction gave practically a quantitative yield of a compound which was crystallized from alcohol in silky needles that melted at 190°. Analysis showed the presence of both acyl radicals.

Anal. Subs., 0.1603: AgBr, 0.0759. Calc. for $C_{16}H_{13}O_5N_2Br$: Br, 20.34. Found: 20.15.

Hydrolysis of this substance gave the N-acetyl derivative melting at 129°, and the nitrobenzoyl-aminophenol next to be described.

2-(*m*-Nitrobenzoylamino)-4-methyl-6-bromophenol.—Two g. of the hydrochloride of 2-amino-4-methyl-6-bromophenol was converted in the usual way into the dinitrobenzoyl derivative, which was then hydrolyzed. The product was crystallized from alcohol in pale, tan-colored needles melting at 190°; yield, 59.1%.

Anal. Subs., 0.1358: AgBr, 0.0731. Calc. for $C_{14}H_{11}O_4N_2Br$: Br, 22.77. Found: 22.91.

Acetylation of this phenol gave a product that crystallized in needles from benzene and melted at 190°. It was identical with that obtained by the action of *m*-nitrobenzoyl chloride on 2-acetylamino-4-methyl-6-bromophenol. Hydrolysis gave both possible N-acylaminophenols.

8. Acetyl and *p*-Chlorobenzoyl

2-(*p*-Chlorobenzoylamino)-4-methyl-6-bromophenol.—To prepare this substance the amino hydrochloride was converted by the action of *p*-chlorobenzoyl chloride[33] into the diacyl derivative which was then hydrolyzed. By crystallization from 50% alcohol colorless crystals melting at 166° were obtained. Analysis for halogen showed the presence of one chlorobenzoyl radical.

Anal. Subs., 0.1554: Ag hal., 0.1449. Calc. for $C_{14}H_{11}O_2NClBr$: hal., 33.9. Found: 33.62.

Acetylation of 2-(*p*-Chlorobenzoylamino)-4-methyl-6-bromophenol.—Treatment of the phenol with acetyl chloride in the usual way gave a quantitative yield of material melting before purification at 180–186°. When one volume of ligroin (b. p., 70–80°) was added to a hot saturated solution of the product in absolute alcohol, colorless needles were obtained. These sintered at 180° and melted at 196°.

Anal. Subs., 0.1691: AgBr, 0.1467. Calc. for $C_{16}H_{13}O_3NClBr$: hal., 30.17. Found: 30.42.

Hydrolysis of this compound gave 2-(*p*-chlorobenzoyl)-amino-4-methyl-6-bromophenol, but no *p*-chlorobenzoic acid.

Action of *p*-Chlorobenzoyl Chloride on 2-Acetylamino-4-methyl-6-bromophenol.—When this reaction was carried out as described and the product purified, the latter was found to melt at 196°, and was identical with that obtained by introduction of the acyl radicals in the reverse order.

Anal. Subs., 0.1200: Ag hal., 0.1047. Calc. for $C_{16}H_{13}O_3NClBr$: hal., 30.17. Found: 30.41.

Hydrolysis gave the results noted above.

9. *p*-Chlorobenzoyl and *p*-Nitrobenzoyl

2-(*p*-Chlorobenzoylamino)-4,6-dibromophenol.—This compound was secured by hydrolysis of the corresponding diacyl derivative. After crystallization from alcohol it melted at 209–210°. The yield of pure material was 56.1%.

Anal. Subs., 0.1798: Ag hal., 0.2293. Calc. for $C_{13}H_8O_2NClBr_2$: hal., 48.19. Found: 48.0.

When the substance just described was acylated with *p*-nitrobenzoyl chloride in the usual way it gave a quantitative yield of product that melted at 276°. Crystallization from acetic acid did not change this.

Anal. Subs., 0.0850: Ag hal., 0.0805. Calc. for $C_{20}H_{11}O_5N_2ClBr_2$: hal., 35.58. Found: 35.64.

Hydrolysis of 0.3 g. of this substance gave 0.18 g. of material not soluble in am-

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[33] To obtain this acid chloride, pure *p*-chlorobenzoic acid, prepared as directed by Emmerling [*Ber.*, **8**, 880 (1875)], was refluxed with twice its weight of thionyl chloride for one hour, after which the excess of the latter was removed by distillation, and the high-boiling residue fractionated. The portion boiling at 221–221.5° was regarded as pure and was used throughout these experiments.

monium carbonate solution; after crystallization from alcohol it melted at 208°. It was identified as 2-(*p*-chlorobenzoylamino)-4,6-dibromophenol. The ammonium carbonate extract gave 0.07 g. of a colorless solid which, after crystallization from hot water, melted at 237°. Qualitative tests showed that the material contained nitrogen but no halogen. It was identified as *p*-nitrobenzoic acid.

The Action of *p*-Chlorobenzoyl Chloride on 2-(*p*-Nitrobenzoylamino)-4,6-dibromophenol gave a product that melted at 276° and was identical with that formed by treatment of 2-(*p*-chlorobenzoylamino)-4,6-dibromophenol with *p*-nitrobenzoyl chloride. The hydrolysis products obtained here were identical with those specified above, and nothing else could be isolated.

Summary and Conclusion

1. No general rule can be laid down in regard to the role of weight of the acyl radicals in the migration between nitrogen and oxygen.
2. An increase in the weight of the fatty acyl radical used in conjunction with benzoyl hinders the displacement of the lighter by the heavier radical. This hindering effect is greater, the heavier the fatty radical used.
3. Rearrangement may occur either during acylation or during saponification.
4. Rearrangement may occur in both directions in the same series, either during acylation or during saponification.
5. The introduction of a nitro group into the benzoyl radical in the *meta* or *para* position greatly weakens the power of the radical to replace other radicals from their position on nitrogen in acetylated *o*-aminophenols. This effect is greatest when the nitro group is in the *para* position.
6. The introduction of a chlorine atom into the benzoyl radical in the *para* position does not impair its power to displace other radicals.
7. Neither relative weight nor relative acidity of the acyl radicals is the sole determining factor in this migration.
8. Several new acyl derivatives of *o*-aminophenols have been prepared and their structures established.

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