[Contribution from the Laboratory of Organic Chemistry of the State University of Iowa]

BEHAVIOR OF MIXED O-ACYL-N-ACYL DERIVATIVES IN WHICH THE REACTING GROUPS ARE NOT ON ADJACENT CARBON ATOMS[1]

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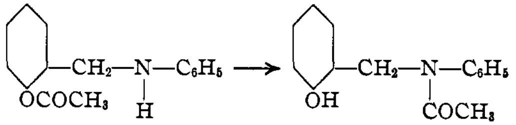
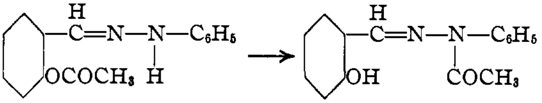
Work in this Laboratory has shown that the benzoylation of 2-acetylaminophenol and the acetylation of 2-benzoylaminophenol lead to the same product, 2-benzoylaminophenyl acetate, which indicates that the relative weights of the acyl radicals play a role in this rearrangement.[2] Further study of this question showed that the relative acidity of these radicals is also an important, though not always decisive, factor in this change.[3] In this work, however, the migration was observed only where the reacting groups (amino and hydroxyl) were attached to adjacent carbon atoms.[4]

The work of Auwers and collaborators[5] with somewhat different compounds having these groups situated on carbon atoms that are not adjacent showed that acyl might shift its position from oxygen to nitrogen. Thus, when an O-acyl derivative of *o*-hydroxybenzyl bromide was heated with aniline, not only was the bromine atom replaced by the phenylamino residue but at the same time acyl wandered to the β-atom (nitrogen) of the side chain. When the O-acetyl derivative of salicylaldehydephenylhydrazone was boiled with glacial acetic acid, acyl migrated to the γ atom of the side chain to give the N-acyl isomer.[6] The same change occurred with the corresponding ketone derivative unless the hydrocarbon radicals were large enough to cause steric hindrance. These workers did not, apparently, study the effect of introducing a second (and different) acyl radical into these products.





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[1] Abstract of a portion of a thesis presented by E. P. Clark to the Graduate College of the State University of Iowa in partial fulfilment of the requirements for the degree of Doctor of Philosophy. Reported in abstract at the Ithaca meeting of the American Chemical Society, September, 1924.

[2] Raiford and Couture, This Journal, **46,** 2305 (1924).

[3] Raiford and Lankelma, *ibid.*, **47,** 1111 (1925).

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

[5] Auwers and others, *Ber.*, **33,** 1923 (1900); *Ann.*, **332,** 159 (1904).

[6] *Ann.*, **365,** 284, 314 and 343 (1909).

Derivatives of *o*-Hydroxybenzyl Amine

In the present work it has been shown that the introduction of a heavier radical into the N-acyl derivative of an *o*-hydroxybenzyl-aniline does not cause migration. Thus, when 2-hydroxy-3,5-dibromobenzylacetanilide, prepared as directed by Auwers, Anselmino and Richter,[7] is benzoylated, there is obtained an acetyl-benzoyl derivative that shows no tendency to rearrange and that readily loses the latter radical on hydrolysis to give the original material.

Since these results were obtained with compounds in which the amino radical was substituted it seemed necessary in our work to study the behavior of acetyl-benzoyl derivatives prepared from a phenolic compound having an unsubstituted amino radical attached to a side chain adjacent to the hydroxyl group. Such derivatives were prepared from *o*-hydroxybenzyl amine by Raiford and Clark,[8] and although the acyl radicals were introduced in both possible orders, no migration was observed. This failure to rearrange raised the question as to whether the result was determined by the specific chemical character of the group on the side chain. It will be shown below that this is probably not the case, since the introduction of the acetyl and benzoyl radicals into the isomeric base, *o*-aminobenzyl alcohol, leads to isomeric substances without the migration of acyl.

Derivatives of *o*-Aminobenzyl Alcohol

o-Aminobenzyl alcohol[9] readily gives the di-acetyl derivative[10] and hydrolysis of this product causes the loss of acyl from oxygen; benzoylation of this hydroxyl compound gives *o*-acetylaminobenzyl benzoate, m. p. 110°, which loses the benzoyl radical on hydrolysis.

Introduction of the radicals in the reverse order gives a different diacyl derivative. Benzoylation of the free base with 2.25 molecular proportions of benzoyl chloride gives a quantitative yield of the dibenzoyl derivative. Hydrolysis of this gives a 95% yield of a substance that melts[11] at 95° and

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[7] Auwers, Anselmino and Richter, *Ann.*, **332**, 177 (1904).

[8] Raiford and Clark, This Journal, **45**, 1738 (1923).

[9] Mettler, *Ber.*, **38**, 1751 (1905).

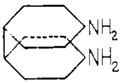
[10] The tri-acetyl derivative of Söderbaum and Widman [(a) *Ber.*, **22**, 1667 (1889)] was avoided by following the suggestion of Raiford and Couture [(b) This Journal, **44**, 1792 (1922)].

[11] A product reported to have this composition was obtained by Auwers [*Ber.*, **37**, 2261 (1904)] who prepared it by Claisen's method [*Ann.*, **277**, 196 (1893)], by digestion of an ethereal solution of the base and benzoyl chloride with potassium bicarbonate. He records that after many recrystallizations from ligroin, the substance melted constantly at 132–133°. As the melting point of the material here under consideration, as indicated above, is 95°, while the melting point of the product Auwers reported upon was so near the melting point of the dibenzoyl derivative, it was thought desirable to repeat his work to find, if possible, the discrepancy. Therefore, 1 g. of the base was benzoylated, following as closely as possible Auwers' directions. Much

which is shown by analysis to be *o*-benzoylaminobenzyl alcohol. Acetylation of this material gives an acetyl-benzoyl derivative; m. p., 115°. A mixture of this and the one described above, m. p. 110°, melts between 80° and 105°. Evidently migration does not occur.

Derivatives of 4′-Amino-4-hydroxydiphenyl

There were reasons, however, for testing the possibility of this rearrangement in derivatives from other bases. Raiford and Colbert[12] found that but one acetyl-benzoyl derivative of 3-amino-4-hydroxydiphenyl can be prepared regardless of the order of introduction of the groups, which shows that the phenyl radical as a *para* substituent neither prevents nor hinders noticeably the migration of acyl from nitrogen to oxygen. The work of Borodine,[13] Michler and Zimmermann,[14] Koller,[15] Kaufler,[16] and Cain and collaborators[17] indicates that the amino radicals of benzidine may approach each other to such a degree that their distances apart are the same as in *o*-phenylenediamine. To account for this behavior benzidine was represented by the formula



More recent work by Adams, Bullock and Wilson[18] indicates that these relative positions cannot be fixed, and that the tendency of the benzene nuclei to approach each other as required by the Kaufler-Cain formula depends on the characters of the substituents.

This view was tested further in the present work by the study of the

gummy material was obtained from which, by the use of petroleum ether, a small amount of white product was secured which melted from 90° to 105°. When this was recrystallized from alcohol, a fraction was obtained which melted at 124°. When this was mixed with a known sample of dibenzoyl derivative, the mixture melted at 129°. From the mother liquors, a second fraction was obtained, which melted at 131–132°. This, when mixed with the dibenzoyl derivative, caused no depression in melting point. By dissolving some of the crude product (m. p., 90–105°) in hot benzene and allowing the solution to cool, a product crystallized which melted at 94°. When this was mixed with the N-benzoyl compound (m. p., 95°) the mixture began to soften at 91° and melted sharply at 95°. Taking into account these facts, it is evident that benzoylation of the base as carried out by Auwers gives two products, namely, the monobenzoyl derivative, m. p. 95°, and the dibenzoyl compound, m. p. 131–132°. It seems probable that Auwers determined the melting point of one fraction of his product and analyzed the other.

[12] Raiford and Colbert, THIS JOURNAL, **47,** 1454 (1925).

[13] Borodine, *Jahresber.*, **1860,** 356.

[14] Michler and Zimmermann, *Ber.*, **14,** 2178 (1881).

[15] Koller, *Ber.*, **37,** 2881 (1904).

[16] Kaufler, (a) *Ber.*, **40,** 3250 (1907); (b) *Ann.*, **351,** 151 (1907).

[17] Cain and Micklethwait, *J. Chem. Soc.*, **105,** 1437 (1914) and other papers there cited.

[18] Adams, Bullock and Wilson, THIS JOURNAL, **45,** 521 (1923).

acetyl-benzoyl derivatives of 4′-amino-4-hydroxydiphenyl. A supply of this base, prepared according to the general method of Täuber,[19] was carefully purified. Treatment of the base in pyridine solution with 2.25 molecular proportions of benzoyl chloride gave a product that melted at 273–274°, which was identified as 4′-benzoylamino-4-benzoyloxydiphenyl. Hydrolysis of this substance with alcoholic potassium hydroxide gave a benzoylaminophenol melting at 284°; acetylation of this phenol in the usual way gave a compound that melted sharply at 227° and which was shown by analysis to contain both a benzoyl and an acetyl radical. When this was hydrolyzed the acetyl radical was lost and the N-benzoyl derivative mentioned above, m. p. 284°, was recovered in 98.5% yield.

To learn whether migration could occur, the radicals were introduced in the reverse order. The aminophenol was converted in nearly quantitative yield into a diacetyl derivative that melted at 219–220° and which, upon hydrolysis, lost the acyl connected to oxygen and gave an N-acyl aminophenol that melted at 224–225°. This was shown by analysis and other properties not to be an impure sample of the starting material. Benzoylation of this compound gave a substance that melted at 254–255°. Analysis showed that this contained both the benzoyl and the acetyl radical, but the difference in melting point and the behavior on hydrolysis prove that the material here under consideration cannot be identical with the acetyl-benzoyl derivative melting at 227° and which had acetyl on oxygen. Hydrolysis of the one here in question caused the loss of benzoyl, which shows that the mixed diacyl derivatives were isomeric and that migration did not occur.

Derivatives of 8-Amino-1-hydroxynaphthalene

In a similar way, it seemed desirable to test naphthalene derivatives. Amstrong,[20] working in this Laboratory, found it possible to prepare but one acetyl-benzoyl derivative from 1-amino-2-naphthol and one from the 6-bromo substituted base, which shows that the migration characteristic of *o*-aminophenol derivatives takes place here. But the behavior of certain other naphthalene derivatives indicates that Positions 2,6 and 2,7 are more closely related than the plane surface formula suggests. Thus, 2,7-naphthalenedisulfonic acid is converted by long heating completely into the 2,6 acid.[21] On the assumption that these substituents render each other labile and that this effect is a measure of the relative distance between them, the substituents in the 2,7 compound are more closely related than in the 2,6 isomer. Again, Kaufler and Karrer[22] were able to diazotize but one amino radical of 2,7-diaminonaphthalene, although

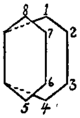
[19] Täuber, *Ber.*, **27**, 2629 (1894).

[20] Armstrong, *Thesis*, University of Iowa, **1922**.

[21] Ref. 16 b, p. 154.

[22] Kaufler and Karrer, *Ber.*, **40**, 3262 (1907).

they used an excess of reagent, and treatment of the base with chlorodinitro- and chlorotrinitrobenzene, respectively, caused condensation with only one amino group. The failure of the second group to react was said to be due to steric hindrance caused by the proximity of the radicals in the 2,7 positions, and this view was supported by the formation of a monophthalyl-naphthalenediamine. This behavior is accounted for by supposing the napthalene molecule to have the structure



On this theory, Positions 1 and 8 should approach each other closely, and it seemed that the question might be tested by the study of the acetyl-benzoyl derivatives of 8-amino-1-naphthol.

As will be indicated below, it was found difficult to obtain the free base from the 8-amino-1-naphthalenesulfonic acid;[23] consequently the acyl derivatives were prepared directly from the alkali fusion mixture.[24] The dibenzoyl derivative thus obtained, m. p. 207–208°, when heated rapidly,[25] was hydrolyzed to give benzoylaminonaphthol; m. p., 216°, with decomposition.[26] Acetylation of this product gives an acetyl-benzoyl derivative, m. p. 180°, which upon hydrolysis loses acetyl and gives the phenolic starting material.

The possibility of migration was tested by introduction of the radicals in reverse order. When the diacetylated compound, m. p. 118°, as found by Fichter and Gageur, was hydrolyzed by alcoholic potassium hydroxide, a phenolic product was isolated which melted[27] at 181°. Benzoylation of this substance gave an acetyl-benzoyl derivative, m. p. 180–181°, which was identical with that obtained by the action of acetic anhydride on

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[23] Portions of this material were freely supplied by the National Aniline Co. and by E. I. du Pont de Nemours and Co., to whom we wish to express here our thanks.

[24] Thirty g. each of sodium and potassium hydroxide were melted with 50 cc. of water, 10 g. of the aminosulfonic acid was added and the mixture gradually heated to 250–260°. At this temperature a black frothy scum rose to the surface of the brick-red liquid. The scum was removed as fast as formed and all that was obtained was mixed with 150 cc. of water, the mixture filtered, most of the alkali neutralized by sulfuric acid and the mixture benzoylated by the Schotten-Baumann method.

[25] Fichter and Gageur [*Ber.*, **39**, 3335 (1906)] found 206–207°.

[26] Fichter and Gageur [Ref. 25] reported 193–194° for a product obtained by heating *peri*-aminonaphthol hydrochloride, benzoic anhydride, glacial acetic acid and sodium acetate, which they reported as having the composition of ours.

[27] Friedländer and Silberstern [*Monatsh.*, **23**, 513 (1902); *Sitzb. Akad. Wiss. Wien*, **111**, 365 (1902)] recorded 138° for a product in which they found 68.79% of carbon instead of 71.58% (they calculated 69.26%) required by the formula and which was probably impure. Fichter and Gageur (Ref. 25) reported 168–169° for a product that gave a satisfactory analysis, and which should be identical with ours.

8-benzoylamino-1-naphthol. The position of acetyl in the product here in question was confirmed by hydrolysis. Acetyl was lost and the phenolic compound left was identified as the N-benzoyl derivative; m. p., 216°. Apparently rearrangement occurred when the acetylaminonaphthol was benzoylated, which indicated that Positions 1 and 8 have a relationship approaching that of an *ortho* compound.

Experimental Part

Methods of Work.—The general methods of acylation and hydrolysis found most suitable in this work have been described in previous papers[28] from this Laboratory, and need not be repeated here. The results obtained in the present study have been summarized in Table I.

TABLE I

COMPOSITION AND PROPERTIES OF ACYL DERIVATIVES

Substance	Solvent	Form	M. p., °C.	Analysis Subs.	 0.1 N acid Cc.	 N, calcd., %	 N, found, %
2-Benzoyloxy-3,5-dibromobenzylacetanilide	chloroform and petroleum ether	colorless needles	150	0.6034 .3009	12.0 18.82 0.1 N $AgNO_3$	2.78 31.80 (Hal)	2.78 31.61
o-Acetylaminobenzyl acetate	benzene and ligroin	colorless rods	95	.3103	14.98	6.76	6.76
o-Acetylaminobenzyl alcohol	benzene	colorless needles	116	.3003	18.4	8.48	8.58
o-Acetylaminobenzyl benzoate	benzene and ligroin	colorless leaflets	110	.4300	15.8	5.20	5.15
o-Benzoylaminobenzyl benzoate	alcohol	colorless needles	131–132	.6008	18.04	4.23	4.21
o-Benzoylaminobenzyl alcohol	benzene	colorless rods	95	.4006	17.5	6.16	6.15
o-Benzoylaminobenzyl acetate	ligroin	needles	115	.4996	18.5	5.20	5.20
4′-Benzoylamino-4-benzoyloxydiphenyl	pyridine and alcohol	diamond-shaped	273–274	.6018	15.12	3.56	3.52
4′-Benzoylamino-4-hydroxydiphenyl	amyl alcohol	plates	284	.2054	7.05	4.84	4.81
4′-Benzoylamino-4-acetyloxydiphenyl	amyl alcohol	fine needles	227	.3545	10.75	4.23	4.25
4′-Acetylamino-4-acetyloxydiphenyl	chloroform	slender rods	219–220	.1766	6.4	5.20	5.08
4′-Acetylamino-4-hydroxydiphenyl	dil. alcohol	prisms	224–225	.3009	12.84	6.16	5.98
4′-Acetylamino-4-benzoyloxydiphenyl	butyl alcohol	colorless leaflets	254–255	.4442	13.18	4.23	4.16
8-Benzoylamino-1-benzoyloxynaphthalene	alcohol	colorless needles	207–208	.4982	13.51	3.81	3.80
8-Benzoylamino-1-hydroxynaphthalene	absolute alcohol	plates	216	.4350	16.38	5.32	5.28
8-Benzoylamino-1-acetoxynaphthalene	absolute alcohol	rosets of short needles	180	.4129	13.4	4.59	4.55
8-Acetylamino-1-acetoxynaphthalene	alcohol and water	long narrow plates	118	...[a]	....	...	...
8-Acetylamino-1-hydroxynaphthalene	alcohol	diamond-shaped plates	181	....[a]	....	...	...

[a] Analytical data for these compounds have been published.

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[28] Ref. 10 b, p. 1794; Ref. 2, p. 2311.

Summary

1. The acetyl-benzoyl derivatives of certain bases having one reacting group on a side chain have been tested for the possibility of migration of acyl.

A. Benzoylation of 2-hydroxy-3,5-dibromobenzylacetanilide gave a stable O-benzoyl-N-acetyl derivative.

B. When the acetyl and benzoyl radicals were introduced in both orders into *o*-aminobenzyl alcohol, isomeric mixed diacyl derivatives were obtained and no rearrangement was observed.

2. The acetyl-benzoyl derivatives of 4′-amino-4-hydroxy-diphenyl were obtained in isomeric forms that showed no tendency to rearrange. This behavior opposes the theory that Positions 4 and 4′ of diphenyl derivatives are fixed relatively as suggested by the Kaufler-Cain formula.

3. Only one acetyl-benzoyl derivative of 8-amino-1-naphthol was obtained although the radicals were introduced in both possible orders, which shows that a molecular rearrangement occurred in one case and indicates that Positions 1 and 8 have a relationship approaching that of an *ortho* compound.

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[Contribution from the Chemical Laboratories, Columbia University, No. 499]

THE BEHAVIOR OF DEAMINIZED COLLAGEN. FURTHER EVIDENCE IN FAVOR OF THE CHEMICAL NATURE OF TANNING[1]

By Arthur W. Thomas and Stuart B. Foster

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Studies on vegetable tanning have focused attention on the important part played by the amino groups of the collagen molecule in vegetable tanning, and considerable evidence in support of a chemical theory of vegetable tanning has been accumulated.[2] Briefly stated, this theory holds in part, that in the vegetable tanning process the conversion of raw hide to leather is due to chemical combination between the amino (and possibly imino) groups of the complex collagen cations and the anions of the complex weak organic acids, the tannins, the rate of combination being a function of the Sörensen (P_H) value of the tannin solution.

It was thought that additional evidence in behalf of the chemical theory of tanning might be acquired through an investigation of the behavior of collagen in whose molecular structure the free amino groups had been replaced by less reactive groups such as hydroxyl. Granting the validity

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[1] Read before the Division of Leather and Gelatin Chemistry, 69th Meeting of the American Chemical Society, April 6–10, 1925, Baltimore, Md.

[2] (a) Procter and Wilson, *J. Chem. Soc.*, **109,** 1327 (1916). (b) Wilson, *J. Am. Leather Chem. Assoc.*, **12,** 108 (1917); (c) **15,** 374 (1920). (d) Thomas and Kelly, *Ind. Eng. Chem.*, **15,** 1148 (1923); (e) **16,** 800, (f) 925 (1924).