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

EFFECT OF RELATIVE POSITIONS OF HYDROXYL AND AMINO RADICALS IN THE MIGRATION OF ACETYL FROM NITROGEN TO OXYGEN

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In previous communications from this Laboratory[1] it has been shown that when the acetyl and benzoyl radicals are introduced into certain *o*-aminophenols the heavier of these two radicals is found attached to nitrogen, regardless of the order in which they are introduced, which shows that in one case the acetyl must have migrated from nitrogen to oxygen. The fact that more than 15 *o*-aminophenols with other substituents in different positions in the molecule, 5 of which have already been reported, were found to behave in this way, indicates that the action is probably general for these two radicals for the class of bases studied. However, in consideration of the known relationships of *ortho* and *para* isomerides in many other reactions, these results made it seem desirable to prepare acetyl-benzoyl derivatives from a series of *p*-aminophenols and thus test the possibility of this migration in *para* compounds.

p-Aminophenol was converted into *p*-acetylaminophenyl acetate in the usual way and this, when hydrolyzed with a solution of sodium hydroxide, gave 4-acetylaminophenol. When the latter was benzoylated by the Schotten-Baumann method there was obtained an acetyl-benzoyl derivative that melted at 170–1°. When, however, 4-benzoylaminophenol, the method of preparation and properties of which showed that the benzoyl radical was attached to nitrogen, was acetylated, an acetyl-benzoyl derivative melting at 169–170° resulted; and this product was entirely different in properties from, but isomeric with, the other one. The results are in agreement with the observations of Reverdin[2] who previously obtained these compounds by a slightly different method. Although known, the compounds indicated were prepared by us in order to test, in the *para* series, the method of acetylation that was found to be so rapid and so satisfactory in obtaining derivatives of *o*-aminophenols.[3]

To learn whether the presence of acid-forming substituents in the aminophenol had any bearing on this behavior, the experiments indicated above were carried through with two other bases, namely, 2,6-dibromo-4-aminophenol[4] which was easily obtainable in pure form, and with 2 hydroxy-3-

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[1] (a) THIS JOURNAL, **41**, 2068 (1919); (b) **44**, 1792 (1922).

[2] Reverdin, *Ber.*, **39**, 3793 (1906).

[3] Ref. 1b, p. 1794.

[4] *J. prakt. Chem.*, [2] **24**, 470 (1881).

bromo-5-aminotoluene[5] which was available to us through the work required to identify and prove the structure of the high-melting isomer obtained by nitration of 2,4-dibromo-*o*-cresol.[6] In each instance, 2 well-characterized isomeric acetyl-benzoyl derivatives were obtained, which indicates that in these cases, also, the compounds had not suffered the migration previously observed in the corresponding *ortho* derivatives.

In addition, it was desired to test the reaction with 2 isomeric dibromoaminocresols, *para* and *ortho*, respectively, the structures of which had previously been determined by one of us by the study of several derivatives of each[7] to be 2,6-dibromo-4-amino-5-methylphenol and 4,6-dibromo-2-amino-5-methylphenol. For the present work these bases were prepared as directed, and after careful purification were found to melt at 176° and 116°, respectively, as previously recorded. In connection with these observations attention should be drawn to the fact that Foster[8] recorded 116° as the melting point of a dibromo-amino-*m*-cresol which he reported as a *para* compound, and from which he obtained a diacetyl derivative that melted at 216°. The weight of more recent evidence, however, is opposed to the view that the *m*-cresol derivatives having the compositions indicated and showing these melting points can be *para* compounds; for the work described in the present paper shows that 116° and 216° are the melting points of the base and diacetyl derivative, respectively, from which was obtained an acetylaminophenol that upon benzoylation by the Schotten-Baumann method readily undergoes the rearrangement here under consideration—behavior that appears to be characteristic of *o*-aminophenols—while the corresponding *para* derivatives have entirely different melting points and other properties (see experimental part). Moreover, one of us has proved by the reduction of the corresponding *o*-nitro-dibromophenylethyl carbonate and the rearrangement of the resulting amino compound into its *o*-hydroxyphenyl urethane—a reaction which has been shown by Stieglitz and his students, especially Ransom and Upson[9] to be characteristic of *ortho* compounds containing these radicals—that the base melting at 116° has an *ortho* structure. Now, the *para* isomeride melts at 176°, and is readily oxidized by the usual reagents to the corresponding quinone. Also, it will be shown below that this base gives a diacetyl derivative that melts at 145–146° and that, in addition, in the preparation of acetyl-benzoyl derivatives from this substance no migration of acetyl was observed but, instead, two isomeric acetyl-benzoyl derivatives were isolated. Taking all facts into account, then, it would appear that the migration of

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[5] Kehrmann, *Ber.*, **48,** 2025 (1915).

[6] Raiford, THIS JOURNAL, **44,** 158 (1922).

[7] *Am. Chem. J.*, **46,** 428 (1911).

[8] Foster, *Dissertation,* Marburg, **1898,** p. 22.

[9] Ransom (a) *Ber.*, **31,** 1055 (1898); (b) **33,** 199 (1900); (c) *Am. Chem. J.*, **23,** 1 (1900). (d) Upson, *ibid.*, **32,** 13 (1904).

acetyl from nitrogen to oxygen, when an *o*-acetylaminophenol is benzoylated by the Schotten-Baumann method, furnishes additional criteria by which *o*- and *p*-aminophenols may be distinguished.

Experimental Part

2,6-Dibromo-4-acetylaminophenyl Acetate.—To obtain this derivative, 2,6-dibromo-4-nitrophenol was prepared as directed by Brunck,[10] and 2 g. of the amino hydrochloride obtained by reduction of the nitro compound was mixed with an equal weight of anhydrous sodium acetate and the theoretical amount of acetic anhydride, after which the mixture was heated on a water-bath for approximately 5 minutes. The cooled mass was extracted with water, and the residue filtered off and crystallized from alcohol. A brownish white powdery material that melted at 172–173° was obtained. Analysis for bromine indicated a diacetyl derivative.

Analysis. Subs., 0.2194: AgBr, 0.2321. Calc. for $C_{10}H_9O_3NBr_2$: Br, 45.54. Found: 45.01.

2,6-Dibromo-4-acetylaminophenyl Benzoate.—To prepare this substance 1.2 g. of 2,6-dibromo-4-acetylaminophenol[11] obtained in this work by hydrolysis of the diacetyl derivative mentioned above, was shaken according to the Schotten-Baumann method with 0.15 g. of sodium hydroxide and 0.54 g. of benzoyl chloride in 50 cc. of water. The precipitate which formed at once was allowed to stand overnight and was then filtered off and dried. It was insoluble in chloroform and benzene, soluble in alcohol and acetone. It was recrystallized from dil. alcohol, and deposited as a light brown, granular solid which melted at 168°. A yield of 0.5 g. was obtained. It was further identified by analysis for bromine.

Analysis. Subs., 0.0951: AgBr, 0.0850. Calc. for $C_{15}H_{11}O_3NBr_2$: Br, 38.70. Found: 38.10.

2,6-Dibromo-4-benzoylaminophenol.—In the preparation of this material 5 g. of the corresponding amino hydrochloride was suspended in ether and 1 g. of benzoyl chloride added, together with the calculated amount of sodium hydroxide necessary to neutralize the hydrochloric acid from the hydrochloride.

After the mixture had been shaken for some time it was allowed to stand until the odor of benzoyl chloride had disappeared. Water was then added and the ether extract separated, from which the benzoyl derivative was obtained by evaporation. The product was purified by dissolving it in hot alcohol and diluting to approximately 50%, when feathery white needles separated. A yield of 2.5 g. or 51% was obtained. The product melted sharply at 208°, as recorded by Forster and Robertson.[12]

2,6-Dibromo-4-benzoylaminophenyl Acetate.—From the monobenzoyl derivative, the acetylated compound was prepared by warming 1 g. of the former, 1 g. of sodium acetate and 1 g. of acetic anhydride until the whole was liquid. After the resulting solid was cool it was triturated with water, the residue collected and redissolved in hot dil. alcohol, from which white crystals separated rapidly as the solution stood. A yield of 0.8 g. or 72% was obtained, and the pure product gave a melting point of 165°. The compound gave an analysis for bromine which corresponds to the presence of both a benzoyl and an acetyl radical.

Analysis. Subs., 0.1078: AgBr, 0.0989. Calc. for $C_{15}H_{11}O_3NBr_2$: Br, 38.70. Found: 39.03.

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[10] Brunck, *Z. Chem.*, **1857**, 204.

[11] Holz, *J. prakt. Chem.*, [2] **32,** 68 (1885).

[12] Forster and Robertson, *J. Chem. Soc.*, **79,** 690 (1901).

To prove that this compound was really an isomer of 2,6-dibromo-4-acetylaminophenyl benzoate, m. p. 168, and not merely an impure specimen of the latter, the melting point of a mixture of the two products was determined. The mixture melted at about 153°. The products are, therefore, different substances.

2-Bromo-4-acetylamino-6-methylphenyl Benzoate.—To prepare this compound 1 g. of 2-bromo-4-acetylamino-6-methylphenol[6] was mixed with 0.6 g. of benzoyl chloride in a solution containing 0.2 g. of sodium hydroxide. The mixture was shaken until the odor of the chloride disappeared and there was formed a very finely divided precipitate that settled slowly. After this had stood overnight it was collected on a filter and dried. Upon crystallization from dil. alcohol, brownish-white scales were formed after standing for some time. When dry the product weighed 0.5 g., a yield of 33%. It melted at 196° and this did not change with subsequent crystallization. Analysis for bromine is in agreement with the formula requiring both a benzoyl and an acetyl radical.

Analysis. Subs., 0.1221: AgBr, 0.0651. Calc. for $C_{16}H_{14}O_3NBr$: Br, 22.96. Found: 22.69.

2-Bromo-4-benzoylamino-6-methylphenol.—In order to show that during benzoylation of the mono-acetyl derivative as described above no rearrangement had occurred, the free base was first benzoylated according to the method described by Ransom,[9] when 1.5 g. of base gave 1.6 g. of monobenzoyl derivative, a yield of 76%. Crystallization of this product from dil. alcohol gave colorless needles that melted sharply at 189°. The compound was soluble in caustic alkali solution, and from such a liquid was precipitated in unchanged form by acids. Analysis for bromine indicated a monobenzoylated product.

Analysis. Subs., 0.1267: AgBr, 0.0784. Calc. for $C_{14}H_{12}O_2NBr$: Br, 26.11. Found: 26.32.

2-Bromo-4-benzoylamino-6-methylphenyl Acetate.—The acetyl derivative was prepared from the monobenzoyl compound by using 1 g. of the latter, and equal weight of dry sodium acetate and 0.33 g. of acetic anhydride. The mixture was heated on a water-bath for about 10 minutes, then allowed to cool, after which the mass was triturated with water to remove the sodium acetate. The remaining solid was filtered out and recrystallized from dil. alcohol, producing a white fluffy mass having the general appearance of cotton. A yield of 0.6 g. or 45% was obtained, and the product melted at 130°. A second crystallization gave silky-white, very fine needles that showed no change in melting point. Analysis for bromine showed that both benzoyl and acetyl radicals are present.

Analysis. Subs., 0.1169: AgBr, 0.0629. Calc. for $C_{16}H_{14}O_3NBr$: Br, 22.96. Found: 22.89.

To show finally that there were 2 isomeric diacyl compounds produced in this case, the N-benzoyl-O-acetyl and the N-acetyl-O-benzoyl compounds, which melted at 130° and 196°, respectively, were melted together. The mixture had a melting point of 121° which proves the presence of 2 individual substances.

This action establishes this isomer, obtained from the nitration of 2,4-dibromo-6-methylphenol, as the *para* variety, which is in agreement with the behavior of its reduction product when oxidized by Raiford.[6]

2,6-Dibromo-4-acetylamino-5-methylphenyl Acetate.—Five g. of the hydrochloride of the corresponding aminophenol, prepared as directed by Raiford[6,7] was mixed with an equal weight of dry sodium acetate and 5 g. of acetic anhydride and warmed for 10 minutes. The solid that resulted on cooling was purified as already described, and the residue dried. This was soluble in alcohol, chloroform, and acetone, and practically insoluble in benzene. It was best crystallized from dil. alcohol from which, after standing for some time, it was deposited in clusters of irregularly shaped, colorless crystals. A yield of 3.5 g. or 61% was thus obtained. The product melted at 145–146°, and its composition was established by analysis for bromine, the results of which agreed with a structure requiring 2 acetyl radicals.

Analysis. Subs., 0.2052: AgBr, 0.2137. Calc. for $C_{11}H_{11}O_3NBr_2$: Br, 43.80. Found: 44.31.

2,6-Dibromo-4-acetylamino-5-methylphenol.—A portion of the diacetyl derivative described above, weighing 2 g., was hydrolyzed by shaking it with 0.5 g. of sodium hydroxide dissolved in 20 cc. of water. The material passed into solution very slowly, and the mixture was allowed to stand overnight, after which it was filtered and the clear liquid faintly acidified with hydrochloric acid. The mono-acetyl derivative which was promptly precipitated was collected on a filter, washed with water and dried. A yield of 1 g. or 55% was obtained. Crystallization from dil. alcohol gave light brown, shining scales that melted at 222°. The compound was readily soluble in a solution of caustic alkali from which it was reprecipitated in unchanged form by acids, indicating a phenolic character, which is in accord with the results of analysis for bromine.

Analysis. Subs., 0.1549: AgBr, 0.1811. Calc. for $C_9H_9O_2NBr_2$: Br, 49.49. Found: 49.74.

2,6-Dibromo-4-acetylamino-5-methylphenyl Benzoate.—Four attempts were made to prepare the above O-benzoyl-N-acetyl compound according to the Schotten-Baumann method, and in each case extremely small yields were obtained, due possibly to the steric hindrance produced by the 2 adjacent bromine atoms. Much better results were obtained by using the method described by Einhorn and Hollandt,[13] in which pyridine was used instead of caustic alkali. Three g. of the dried mono-acetyl compound was dissolved in 10 volumes of pyridine and to this mixture 1.5 moles of benzoyl chloride was added. The mixture was allowed to stand for 6 hours. At the end of that time some precipitate had formed, and when the whole mixture was poured into water, an oil separated. Hydrochloric acid was then added, causing the oil to solidify after some stirring. The precipitate was collected and dried. A yield of 2.7 g. or 70% was obtained. The product was crystallized from dil. alcohol from which it was deposited in the form of a white powder that was crystalline but not well crystallized, and that melted at 182–3°. To show that it was not merely an impure sample of the mono-acetyl derivative, m. p. 222°, from which it was prepared, a mixture of the 2 products was melted. This began to melt at 167° and was completely liquid at 176°, which indicates 2 distinct substances. The composition of the benzoate was still further established by analysis for bromine the results of which agree with a formula requiring both a benzoyl and an acetyl radical.

Analysis. Subs., 0.1441: AgBr, 0.1264. Calc. for $C_{16}H_{13}O_3NBr_2$: Br, 37.43. Found: 37.32.

2,6-Dibromo-4-benzoylamino-5-methylphenyl Acetate.—The starting point in the preparation of this product was 2,6-dibromo-4-benzoylamino-5-methylphenol, first prepared by Raiford,[7] with the purpose of obtaining the corresponding dibenzoyl derivative of the base, but here obtained from the free base by Ransom's method. One g. of the monobenzoylated product was warmed gently for 10 minutes with an equal weight of anhydrous sodium acetate and 1 g. of acetic anhydride. After cooling, the sodium salt was extracted with water and the residue collected and dried; 0.9 g. or a yield of 81% was obtained. After two crystallizations the product melted sharply at 179°. Analysis for bromine indicates the presence of both acetyl and benzoyl radicals.

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[13] Einhorn and Hollandt, *Ann.*, **301**, 95 (1898).

Analysis. Subs., 0.1430: AgBr, 0.1262. Calc. for $C_{16}H_{13}O_3NBr_2$: Br, 37.43. Found: 37.55.

To prove, finally, that we had obtained 2 different acetyl-benzoyl derivatives from 2,6-dibromo-4-amino-5-methylphenol, a mixture of the 2 products described above, and melting at 183° and 179°, respectively, was melted. The mixture was completely liquid at 167°, indicating 2 distinct substances.

2-Acetylamino-4,6-dibromo-5-methylphenyl Acetate.—In the present work this product was obtained by warming a mixture of 5 g. of the hydrochloride of the corresponding amine and an equal weight of anhydrous sodium acetate with 5 g. of acetic anhydride until the whole became liquid. The solid that resulted upon cooling was pulverized and extracted with water, and the residue collected on a filter and dried. A yield of 92% was obtained. Recrystallization from alcohol gave long silky needles that melted at 216°, which is in agreement with the results of one of us.[14]

2-Acetylamino-4,6-dibromo-5-methylphenol.—The mono-acetyl compound was prepared by saponifying 2 g. of the diacetyl derivative with 0.5 g. of sodium hydroxide dissolved in 20 cc. of water. After standing for 3 hours a small amount of brick-colored residue that had not dissolved was filtered off and the filtrate acidified with hydrochloric acid. The flocculent precipitate that formed immediately was collected on a filter, washed and dried. It weighed 1.3 g. which is a yield of 72%. It is soluble in chloroform, acetone and alcohol, not very soluble in benzene and insoluble in ligroin. It dissolves in solutions of caustic alkali, and is precipitated unchanged by acids. It crystallized poorly from alcohol, but from benzene it deposited shining scales which melt at 171°. Analysis for bromine agrees with a formula requiring 1 acetyl radical.

Analysis. Subs., 0.1151: AgBr, 0.1343. Calc. for $C_9H_9O_2NBr_2$: Br, 49.49. Found: 49.47.

Action of Benzoyl Chloride on 2-Acetylamino-4,6-dibromo-5-methylphenol

One g. of the mono-acetylated compound described above was treated with a solution of 0.3 g. of sodium hydroxide in 50 cc. of water; 1 g. of benzoyl chloride was added and the whole shaken until the odor of the acid chloride had disappeared, after which the mixture was allowed to stand overnight. The precipitate which formed was filtered out and recrystallized from dil. alcohol from which it separated as a powdery mass of very fine crystals; 1 g. of pure material or a 77% yield was obtained. The product melted at 195–196° and an analysis for bromine gave results which require both a benzoyl and an acetyl group in the molecule.

Analysis. Subs., 0.1018: AgBr, 0.0897. Calc. $C_{16}H_{13}O_3NBr_2$: Br, 37.43. Found: 37.50.

Proof of the Structure of 2-Benzoylamino-4-6-dibromo-5-methylphenyl Acetate

The monobenzoylated compound in which benzoyl is on nitrogen was first prepared by the method of Ransom[9c] by treatment of 1.6 g. of the free base in ether solution with 0.4 g. of benzoyl chloride. The product was crystallized by dissolving it in hot alcohol and diluting with about an equal volume of water, and gave fawn-colored leaflets that melted at 198–199° with apparent decomposition. A yield of 72% was obtained. The compound is soluble in solution of caustic alkali and from this liquid, acids precipitate the original material, which indicates a phenolic character. An analysis[15] for bromine gave results that agree with the formula assigned.

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[14] Ref. 7, p. 434.

[15] We are indebted to Mr. C. R. Wilcox for this analysis.

Analysis. Subs., 0.1041: AgBr, 0.1199. Calc. for $C_{14}H_{11}O_2NBr_2$: Br, 41.51. Found: 41.01.

To prepare directly the diacyl derivative having benzoyl on nitrogen and acetyl on oxygen the monobenzoyl derivative specified above was acetylated; 1 g. of this substance mixed with an equal weight of dry sodium acetate was treated with 0.4 g. of acetic anhydride, the mixture warmed gently on the water-bath for 5 minutes, and allowed to cool to a hard mass. Sodium salt was removed by extraction with water, and the insoluble residue collected on a filter and dried. Crystallization from alcohol gave a brownish-white powder that melted at 194–195°, which is in agreement with the properties of the product obtained by benzoylating the mono-acetyl compound and described above. A mixture of the 2 products melted at the same temperature as either of them separately which indicates identity, and from which it follows that in the benzoylation of 2-acetylamino-4,6-dibromo-5-methylphenol, the acetyl radical migrates from nitrogen to oxygen, while benzoyl attaches to nitrogen.

Summary

1. Additional evidence has been obtained to indicate that the migration of acetyl from nitrogen to oxygen, when an *o*-acetylaminophenol is benzoylated in accordance with the Schotten-Baumann method, is probably general.
2. It has been shown that under the same conditions benzoylation of a *p*-acetylaminophenol does not cause migration of the acetyl radical.
3. These differences furnish additional criteria for distinguishing *o*-, *p*-aminophenols.

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[Contribution from the Department of Chemical Research of Parke, Davis and Company, No. 15]

URETHANES FROM CHLORINE-SUBSTITUTED SECONDARY AND TERTIARY ALCOHOLS[1]

By Lester Yoder

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Alkyl carbamates of the type represented by urethane, $C_2H_5OCONH_2$, are mild hypnotics with little or no injurious effect. The carbamic esters of secondary and tertiary alcohols are considered stronger hypnotics. Where chlorine atoms are substituted on the β-carbons of a secondary alkyl carbamate, as in Aleudrin, $(CH_2Cl)_2CHOCONH_2$, the hypnotic action is claimed to be still more marked. The action of the carbamate is considerably stronger than that of the alcohol itself unless the latter is too insoluble in water. It was considered of interest, therefore, to prepare the carbamates of the following chlorine-substituted alcohols: (I) trichloromethyl dimethyl carbinol or Chloretone, $CCl_3C(CH_3)_2OH$; (II) trichloromethyl

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[1] Read at the Fall Meeting of the American Chemical Society, Pittsburgh, Pa., Sept. 1922.