[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Mixed Diacyl Derivatives of 2-Aminophenol Containing the Phenoxyacetyl Radical

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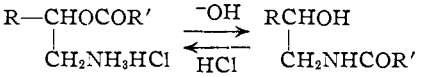
The preparation of 2-phenoxyacetylaminophenyl acetate, 2-phenoxyacetylaminophenol, 2-phenoxyacetylamino-4-methyl-6-bromophenyl acetate and 2-phenoxyacetylamino-4-methyl-6-bromophenol has been described. A study of mixed diacyl derivatives of 2-aminophenol and 2-amino-4-methyl-6-bromophenol in which one of the acyls was acetyl and the other was phenoxyacetyl has been made. The given pair was introduced into the respective aminophenols in both possible orders, and their purified products subjected to hydrolysis with dilute alkali. In both instances, migration of acetyl from nitrogen to oxygen took place when the N-acetyl compounds were treated with phenoxyacetyl chloride.

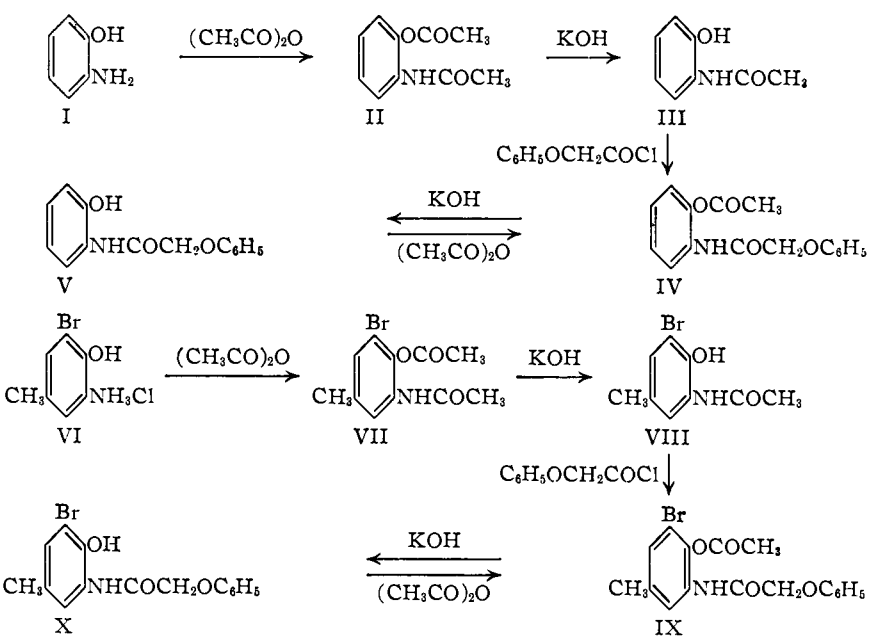
It has been reported by Raiford and his students[3,4] that attempts to prepare mixed diacyl derivatives of 2-aminophenols in which the acyl radicals bound to oxygen and nitrogen, respectively, were different, that the heavier and more acidic of these radicals was usually attached to nitrogen regardless of the order of introduction of these groups, and that migration of acyl from nitrogen to oxygen occurred somewhere in the reaction. Similar results were obtained by these workers[5] with variously substituted 2-aminophenols. The same type of migration of acyl groups has been observed in 8-amino-1-naphthol and in 1-amino-2-naphthol[6]; however, similar experiments with 2-aminocyclohexanol and *o*-aminobenzyl-2-naphthol[6] showed no migration of acyl groups. By using more refined analytical methods, LeRosen and Smith[7] showed, contrary to earlier reports, that the expected isomeric mixed diacyl derivatives of *o*-aminophenol, with the acetyl and benzoyl radicals were formed and could be isolated pure. In each instance these workers observed some migration. Therefore, from many observations, Raiford concluded that the migration of acyl radicals in 2-aminophenols was a general reaction, but that the reaction did not apply to aminoalkanols. Under different conditions, however, the migration of acyl radicals has been observed in 2-aminoalkanols and in some instances in 3-aminoalkanols by several workers.[8]

The rearrangement is general for 2-aminoalkanols and is more or less reversible, the rate greatly depending on structure.



R = alkyl or phenyl; R′ = phenyl

Since several factors are involved in the rearrangement of acyl radicals in 2-aminophenols, and that this rearrangement might be of value in the identification and synthesis of mixed diacyl derivatives of this class of bases, it seemed important to test the phenoxyacetyl and acetyl radicals in the preparation of mixed diacyl derivatives of 2-aminophenols.



The bases used in this work were 2-aminophenol (I) and 2-amino-4-methyl-6-bromophenol hydrochloride (VI). The hydrochloride was much more stable. These bases were treated with acetic anhydride, and the resultant diacetylated derivatives II and VII were hydrolyzed with dilute KOH to give the respective N-acetylaminophenols III and VIII. These compounds were treated with phenoxyacetyl chloride in pyridine and the resultant mixed diacyl derivatives IV and IX were hydrolyzed with dilute KOH. In both cases the respective N-phenoxyacetylaminophenols V and X were produced.

When the N-phenoxyacetylaminophenols V and X were treated with acetic anhydride, the mixed di-

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(3) L. C. Raiford, THIS JOURNAL, **41**, 2068 (1919).

(4) L. C. Raiford and J. R. Couture, *ibid.*, **44**, 1792 (1922).

(5) L. C. Raiford and C. M. Woolfolk, *ibid.*, **46**, 2246 (1924).

(6) L. C. Raiford and F. C. Mortensen, *ibid.*, **50**, 1202 (1928).

(7) A. L. LeRosen and E. D. Smith, *ibid.*, **70**, 2705 (1948); **71**, 2815 (1949).

(8) (a) F. Wolfheim, *Ber.*, **47**, 1447 (1914); (b) S. Gabriel, *Ann.*, **409**, 326 (1915); (c) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 403 (1915); (d) W. H. Hartung, J. C. Munch and E. B. Kester, THIS JOURNAL, **54**, 1526 (1932); (e) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940); (f) A. C. Cope and E. M. Hancock, THIS JOURNAL, **66**, 1448 (1944); (g) J. R. Reasenberg and G. B. L. Smith, *ibid.*, **66**, 991 (1944); (h) H. R. Reasenberg and S. D. Goldberg, *ibid.*, **67**, 933 (1945).

acyl derivatives IV and IX were produced. The results of these reactions show that migration of acetyl from nitrogen to oxygen occurred.

Experimental

2-Phenoxyacetylaminophenyl Acetate (IV).—Three and nine-tenths grams of 2-acetylaminophenol[9] was dissolved in 3 g. of pyridine and to this liquid 4.5 g. of phenoxyacetyl chloride was added slowly. The mixture was shaken well and allowed to stand for six hours at room temperature. The solid mass that formed was broken into small pieces and mixed with cold water to decompose unchanged acid chloride and to dissolve salts. The mixture was filtered and the yellow solid that remained was dissolved in the smallest possible quantity of boiling alcohol, treated with norite and filtered. The filtrate was cooled; 6 g. of colorless needle-like crystals deposited, m.p. 80–82° (81%). Analysis for nitrogen gave results that required a phenoxyacetyl and acetyl radical.

Anal. Calcd. for $C_{16}H_{15}O_4N$: N, 4.91. Found: N, 5.15.

Hydrolysis of 2-Phenoxyacetylaminophenyl Acetate (IV).—To 4 g. of IV there was added 2.2 g. of KOH dissolved in 50 ml. of alcohol. The mixture was warmed on a steam-bath for 30 minutes; the resulting solution was cooled to room temperature, acidified with dilute hydrochloric acid and allowed to stand for two hours at room temperature. A yellowish precipitate separated and was collected on a filter. The precipitate was washed with distilled water and dried. The product weighed 3 g. (88%), and melted at 144–146°. Repeated recrystallization from alcohol gave a product which melted constantly at 144–146°. The product was found to be soluble in cold dilute alkali solution, and treatment of this liquid with dilute acid precipitated a solid that melted at 144–146°. A mixture of this and the original material melted without depression. Its solubility in alkali solution indicated a phenolic compound. Determination of nitrogen gave results which were in agreement with a formula that contains a phenoxyacetyl radical and a free hydroxyl group.

Anal. Calcd. for $C_{14}H_{13}O_3N$: N, 5.75. Found: N, 5.59.

The facts presented indicated that the migration of the acetyl radical from nitrogen to oxygen occurred somewhere during the above described reactions. To further substantiate these facts, 2-phenoxyacetylaminophenol was synthesized directly from 2-aminophenol by an entirely different method.

2-Phenoxyacetylaminophenol (V).—In 5.2 g. of pyridine there was dissolved 6.6 g. of 2-aminophenol and to this solution there was added 5.2 g. of phenoxyacetyl chloride with rapid stirring. The mixture was allowed to stand for six hours at room temperature. A solid separated which then was broken into small pieces, stirred with cold water and collected on a filter. Crystallization from alcohol gave slightly yellow colored needle-like crystals which melted at 144–146°. A mixture of this product and that obtained by the hydrolysis of IV melted without depression.

2-Phenoxyacetylamino-4-methyl-6-bromophenyl Acetate (IX).—To a solution containing 5.7 g. of 2-acetylamino-4-methyl-6-bromophenol (VIII)[10] dissolved in an equal weight of pyridine there was slowly added 4.3 g. of phenoxyacetyl chloride. The mixture was allowed to stand for six hours at room temperature. The solid mass which separated was broken into small pieces, mixed with cold water, stirred for several minutes and filtered. Repeated crystallization of the pale brown solid from alcohol gave colorless crystals with a very brilliant sheen. The product melted at 134–136° and weighed 4.2 g. (77.7%).

Determination of bromine gave results which agreed with a formula that required a phenoxyacetyl and an acetyl radical.

Anal. Calcd. for $C_{17}H_{16}O_4NBr$: Br, 21.14. Found: Br, 21.23.

2-Phenoxyacetylamino-4-methyl-6-bromophenol (X).—To 4.5 g. of 2-phenoxyacetylamino-4-methyl-6-bromophenyl acetate (IX) there was added 50 ml. of alcoholic KOH containing 0.18 g. of alkali; the mixture was warmed on a steam-bath until solution was complete. The solution was cooled to room temperature, acidified with dilute hydrochloric acid and allowed to stand for two hours. The product was collected on a filter, washed with water and purified by crystallization from alcohol from which it separated in faintly yellow colored needles that melted at 165–167°. The product weighed 2 g. (52.5%). The compound was soluble in dilute alkali solution; from this liquid it was precipitated by dilute hydrochloric acid. The melting point of a mixture of the starting material (X) with the product precipitated by acid was not lowered.

Analysis for bromine gave results that were in agreement with a formula that required a phenoxyacetyl radical and a free hydroxyl group.

Anal. Calcd. for $C_{15}H_{14}O_3NBr$: Br, 23.67. Found: Br, 23.69.

The facts presented above show that compound X had the composition assigned and that migration of the acetyl radical from nitrogen to oxygen occurred during the reaction of phenoxyacetyl chloride with 2-acetylamino-4-methyl-6-bromophenol (VIII). To support this view, the product in question (X), m.p. 165–167°, was prepared directly from the hydrochloride of 2-amino-4-methyl-6-bromophenol (VI). Five and one-tenth grams of the latter was dissolved in 4.2 g. of pyridine, and to this liquid 3.5 g. of phenoxyacetyl chloride was added. The mixture was allowed to remain at room temperature for 24 hours. The light brown solid that separated was broken into small pieces, mixed well with cold water and finally separated by filtration. Crystallization from alcohol gave slightly yellow colored needles that melted at 165–167°. A mixture of this and the product (X) obtained by the hydrolysis of the diacyl derivative IX melted at 165–167°.

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