

Proceedings of the Iowa Academy of Science

Volume 50 | Annual Issue

Article 20

1943

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Recommended Citation

Bacher, Paul H. and Raiford, L. Chas. (1943) "The use of 2-Chlorophenoxyacetyl Chloride in the Preparation of Mixed Diacyl Derivatives of Ortho Aminophenols," *Proceedings of the Iowa Academy of Science*, 50(1), 247-251.

Available at: <https://scholarworks.uni.edu/pias/vol50/iss1/20>

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THE USE OF 2-CHLOROPHENOXYACETYL CHLORIDE IN THE PREPARATION OF MIXED DIACYL DERIVATIVES OF ORTHO AMINOPHENOLS

PAUL H. BACHER AND L. CHAS. RAIFORD

Raiford and coworkers (1) have proved by a long series of experiments that when two acyl radicals, $R-\dot{C}=O$ and $R'-\dot{C}=O$, are introduced into an ortho aminophenol only one mixed diacyl derivative can generally be obtained, regardless of the order of introduction of the radicals; and in this product the heavier and more acidic of these groups is usually found attached to nitrogen. To meet this requirement the migration of acyl from nitrogen to oxygen must occur in one of these reactions. If the acyls are $R-\dot{C}=O$ and $R-O-\dot{C}=O$ the latter is most frequently found on nitrogen.

Some previous inconclusive experiments by Auwers and Eisenlohr (2) led Raiford and Couture (3) to examine further the question of the relative weights of the acyl radicals involved in this change. They showed that when two aliphatic acyls, acetyl and caproyl, of weights 43 and 99, respectively, were introduced in both possible orders into 2-amino-4, 6-dibromophenol, quantitative yields of isomeric mixed diacyl derivatives were obtained, which indicated that no migration occurred during acylation. It was surprising to find that alkaline hydrolyses of each of these substances gave a mixture of the related N-acetyl- and N-caproylaminophenols. Evidently, partial rearrangement of each diacyl derivative occurred during hydrolysis. Exactly similar results were obtained when the caproyl and benzoyl radicals of weights 99 and 105, were introduced into the same aminophenol. Rearrangement during hydrolysis of such a product has since been observed in other cases by Raiford and Scott (4) who introduced the acetyl and benzoyl radicals, respectively, into 2, 4-dibromo-3-methoxy-6-aminophenol, and by Raiford and Alexander (5) who tested the behavior of 2-acetylaminophenyl diphenylcarbamate toward hydrolysis with caustic alkali solution. Their results show that the characters of the acyl radicals, as well as their relative weights, may have a bearing on the migration in question.

In view of the above observations it was desired to test further the question of relative weight of acyl in these changes. The announcement some months ago of the availability of o-chlorophenoxyacetic acid as a commercial product suggested the opportunity of doing more work in this field. It was proposed to convert a portion of this acid into the related acyl chloride, and to test this against the acetyl and benzoyl radicals in the preparation of mixed diacyl derivatives of certain ortho aminophenols.

EXPERIMENTAL

A. Preparation and characteristics of the acid chloride.

2-Chlorophenoxyacetyl chloride. One hundred grams of 2-chloro-

phenoxyacetic acid supplied by the Dow Chemical Company* was put into a round-bottom flask which was placed on a steam bath and attached to a reflux condenser. One hundred and fifty grams of thionyl chloride was added, the mixture was refluxed for three hours, unchanged thionyl chloride was distilled off, and the residue was fractionated under partial vacuum. The portion that passed over at 147-150° and 20 mm. was reserved. The yield was 62%.

Before using this acid chloride in the particular changes involved in the rearrangement specified above, it seemed desirable to characterize it by the preparation of a number of related compounds. To do this several derivatives were synthesized.

2. *Chlorophenoxyacetamide*.— In the first preparation 10.25 g. of the required acid chloride was slowly added to somewhat more than two molecular proportions of powdered ammonium carbonate while the latter was being stirred continuously in a mortar. The mixture foamed and became warm, and within ten minutes it solidified. The mass was pulverized, triturated with 2-3 cc. of water to dissolve ammonium chloride, then filtered by suction, and the solid residue washed with about 10 cc. of water. The yield was nearly quantitative. Analytical data for this and related compounds are tabulated below.

AMIDES DERIVED FROM 2-CHLOROPHENOXYACETIC ACID

Substituents in the amide radical	Yield percent	Solvent	Crystal Form	M.P. °C.	Formula	ANALYSES			
						HALOGEN		NITROGEN	
						Calc'd	Found	Calc'd	Found
Unsubstituted.....	nearly quant.	Methanol	Colorless plates	145	C ₈ H ₆ Cl NO ₂	19.13	19.24	7.51	7.36
Phenyl.....	nearly quant.	Ethanol	Yellow needles	124	C ₁₄ H ₁₂ Cl NO ₂	13.57	13.73		
4-Tolyl (a).....	nearly quant.	Methanol	Long colorless silky needles	129—130	C ₁₅ G ₁₄ Cl NO ₂	12.88	12.92		

(a) The acid chloride was slowly added with shaking to a benzene solution of two molecular proportions of 4-toluidine.

*Additional quantities of this acid were synthesized in the Iowa Laboratory by C. M. McCloskey, who obtained it in yields of 44-60%, by following the general suggestions of Koelsch [J. Am. Chem. Soc., 53, 304 (1931)]. A mixture of 102 g. of 2-chlorophenol and 1.5 molecular proportions of chloroacetic acid was melted, 300 cc. of 30% solution of sodium hydroxide was slowly added with rapid mechanical stirring while the liquid became successively reddish, then opaque and finally colorless. The mixture was heated to the boiling point, boiling was continued for fifteen minutes, and the cooled liquid was acidified by hydrochloric acid which precipitated most of the new acid. Sodium bicarbonate was added with stirring as long as carbon dioxide was evolved, the resulting mixture was distilled with steam for two hours to remove 2-chlorophenol, the hot liquid in the reaction flask was acidified with hydrochloric acid and the mixture set aside to crystallize. The product melted at 144-145°.

B. Preparation and properties of diacyl derivatives.

2-(2-chlorophenoxyacetyl) amino-4-methyl-6-bromophenyl acetate. To a pyridine solution of 8.76 g. of 2-acetylamino-4-methyl-6-bromophenol, m.p., 129°, there was slowly added with stirring 7.35 g. of 2-chlorophenoxyacetyl chloride, the mixture was allowed to stand for twenty-four hours and was then poured into ice water containing hydrochloric acid. The precipitate that formed was collected on a filter, washed and dried. A yield of 83% was obtained. After four crystallizations from alcohol the product was obtained in the form of colorless blunt needles that melted at 110-111°.

Hydrolysis of 2-(2-chlorophenoxyacetyl)-amino-4-methyl-6-bromophenyl acetate.- Seven-tenths gram of the mixed diacyl derivative was shaken occasionally for a period of about forty minutes with 25 cc. of water containing 0.17 g. (2.5 equivalents) of sodium hydroxide, and the mixture was allowed to stand overnight. The small amount of solid that remained was removed by filtration and the yellow filtrate was acidified with dilute hydrochloric acid. The pale yellowish solid that separated weighed 0.4 g., a yield of 63%. This product was readily soluble in caustic alkali solution and from this liquid it was precipitated in unchanged form by acids. It was soluble in alcohol, chloroform and ether, but was most easily purified by crystallization from alcohol. From this it separated in the form of colorless needles that softened about 186° and melted at 187°. Analysis for halogen indicated the presence of the 2-chlorophenoxyacetyl radical.

0.2092 g. substance required 11.28 cc. .1 N AgNO ₃	
Calculated for C ₁₆ H ₁₃ O ₃ NCIBr	Found
Halogen, 31.17	31.31

The hydrolysis product just described was also obtained by treatment of a pyridine solution of the required aminophenol with one molecular proportion of 2-chlorophenoxyacetyl chloride.

2-(2-Chlorophenoxyacetyl)-amino-4-methyl-6-bromophenyl benzoate. To mixture of 1.85 g. of the required N--acetylaminophenol and 1 cc. of pyridine, which had been rubbed into a thin paste in a mortar, there was added 0.6 cc., or one molecular proportion, of benzoyl chloride, the mixture was triturated for five minutes and allowed to stand overnight. Next a mixture of 1.5 cc. of concentrated hydrochloric acid and 4 cc. of water was added, the semi-solid was rubbed to a smooth paste, filtered by suction and the residue washed well and dried. The yield was nearly quantitative. Crystallization from a mixture of 8 volumes of ethanol and 2 volumes of ethyl acetate gave colorless rectangular plates that melted at 169-70. Analysis for halogen indicated the presence of two acyl groups. 0.2174 g. substance required 9.86 cc. N .0963 AgNO₃.

Calculated for	Found
C ₂₂ H ₁₇ O ₄ NCIBr	
Halogen, 25.08	25.20

2-Benzoylamino-4-methyl-6-bromophenyl 2-chlorophenoxyacetate.

Three grams of the required benzoylamino-4-methyl-6-bromophenol was rubbed in a mor-

tar with 3cc. of pyridine to give a smooth paste, 2 grams of the necessary acid chloride was added, and the mixture was stirred for a few minutes to complete the reaction. After some hours the solid was triturated with dilute hydrochloric acid and filtered. The yield was almost quantitative. Crystallization from chloroform gave nearly colorless fibrous masses of irregular shape that melted at 170°. To show that the product here in question was not identical with that, m.p., 169-170°, obtained by the action of benzoyl chloride on 2-(2-chlorophenoxy)-acetyl-amino-4-methyl-6-bromophenol, a mixture of the two was melted. A range of 155° to 165° was observed, which shows non-identity of products. This indicates that in the formation of these two diacyl derivatives migration of acyl did not take place.

0.2117 g. substance required 9.34 cc. N .0963 AgNO₃

Calculated for C ₂₂ H ₁₇ O ₄ NC1Br	Found
Halogen, 25.08	25.32

Hydrolysis of 2-benzoylamino-4-methyl-6-bromophenyl. 2-chlorophenoxyacetate.—Fifty-nine hundredths gram of the diacyl derivative was mixed with 15 cc. of $\frac{N}{10}$ alcoholic solution of potassium

hydroxide, the flask was heated on a steam bath until all was in solution, the flame was withdrawn and the yellow liquid was allowed to remain until the whole had reached room temperature. The mixture was then acidified with dilute hydrochloric acid, and the solid that separated was collected on a filter, washed and dried. The yield was 92%. Crystallization from benzene gave nearly colorless needles that melted at 185-186° and became faintly lavender colored on standing. They did not depress the melting point of a known sample of 2-benzoylamino-4-methyl-6-bromophenol. A mixture of the hydrolysis product under consideration and 2-(2-chlorophenoxyacetyl)-amino-4-methyl-6-bromophenol, m. p., 186-187°, showed a melting range of 155-165°.

SUMMARY

1. 2-Chlorophenoxyacetic acid, which was not found on record, but which has recently appeared as a commercial product in small quantities, has been characterized, in part, by preparation from it of several derivatives.

2. The acid chloride obtained from it has been used in the further study of the migration of acyl from nitrogen to oxygen in the preparation of mixed diacyl derivatives of ortho aminophenols.

3. It was found that the 2-chlorophenoxyacetyl radical reacts with 2-acetylaminophenol to cause the migration of the acetyl radical from nitrogen to oxygen.

4. When 2-chlorophenoxyacetyl and benzoyl, respectively, were introduced in both possible orders into 2-amino-4-methyl-6-bromophenol isomeric mixed diacyl derivatives were obtained and no rearrangement took place on acylation.

5. When these products were hydrolyzed by caustic alkali solution the acyl attached to oxygen was removed, but migration of acyl was not observed during this change.

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