[Contribution from the Chemical Laboratory of Purdue University]

ACYL DERIVATIVES OF ORTHO-AMINOPHENOL. IV

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When two acyl groups are introduced into *o*-aminophenol, and then the order of introduction is reversed, identical products are usually obtained, or the product may be an equilibrium mixture of the two isomeric di-acyl derivatives.

The literature on this subject may be reviewed by referring to the work of Ransom,[1] Ransom and Nelson,[2] Nelson and co-workers[3] and Raiford with co-workers.[4]

The evidence of previous work indicates that both the weight and acidity of the acyl groups are factors in determining which acyl group attaches to the nitrogen. While the heavier group, in many cases, attaches itself to the nitrogen, there are definite exceptions to this. The more acidic group would be expected to attach itself to the nitrogen, but Raiford and Lankelma[4i] discovered exceptions.

The purpose of this investigation has been to observe the effect of halogen substituted acyl groups on the molecular rearrangement of di-acyl derivatives of *o*-aminophenol.

The following pairs of groups were used: $—COCH_2Cl$ and $—CO_2C_2H_5$; $—COCH_2Cl$ and $—COCH_3$; $—COCCl_3$ and $—COCH_3$; $—COCCl_3$ and $—COC_6H_5$; $—CO_2CH_2CH_2Cl$ and $—CO_2C_2H_5$.

When ethyl *o*-hydroxycarbanilate was acylated with monochloroacetyl chloride or when *o*-monochloro-acetylaminophenol was acylated with ethyl chlorocarbonate the same di-acyl was obtained. On saponification ethyl *o*-hydroxycarbanilate was formed which showed the compound to have been the monochloro-acetate of ethyl *o*-hydroxycarbanilate. In one case the monochloro-acetyl group had migrated from the nitrogen to the oxygen.

On acylating *o*-monochloro-acetylaminophenol with acetic anhydride a diacyl, *o*-monochloro-acetylaminophenyl acetate was obtained which melted at 113–114°. On reversing the order of introduction of the acyl groups a different diacyl, *o*-acetyl aminophenyl monochloro-acetate was obtained, melting at 128–130°. Each of these isomers on saponification

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[1] Ransom, *Am. Chem. J.*, **23**, 1 (1900).

[2] Ransom and Nelson, This Journal, **36**, 390 (1914).

[3] (a) Nelson and others, *ibid.*, **48**, 1677 (1926); (b) **48**, 1680 (1926); (c) *Indiana Acad. Sci.*, 1921, 201–202.

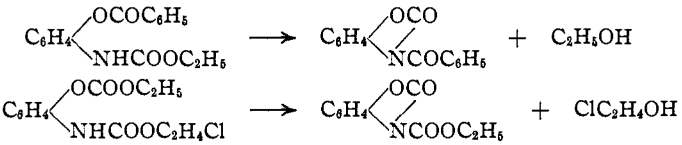
[4] (a) Raiford and others, This Journal, **41**, 2068 (1919); (b) **44**, 1792 (1922); (c) **45**, 469 (1923); (d) **45**, 1728 (1923); (e) **46**, 430 (1924); (f) **46**, 2051 (1924); (g) **46**, 2246 (1924); (h) **46**, 2305 (1924); (i) **47**, 1111 (1925); (j) **47**, 1454 (1925); (k) **48**, 483 (1926).

produced *o*-acetylaminophenol. A molecular rearrangement evidently took place during saponification. In this case the acetyl group, which is the lighter and also the less acidic, attached itself to the nitrogen atom.

When *o*-trichloro-acetylaminophenol was acylated with acetic anhydride a diacyl, *o*-trichloro-acetylaminophenyl acetate was obtained, which on saponification produced *o*-trichloro-acetylaminophenol. Evidently in this case the heavier and more acidic group was attached to the nitrogen. Attempts to prepare this compound or its isomer by introducing the acyls in the reverse order were unsuccessful.

o-Trichloro-acetylaminophenol was acylated with benzoyl chloride, producing the diacyl, *o*-benzoylaminophenyl trichloro-acetate. On saponification this produced *o*-benzoylaminophenol, showing that a rearrangement had taken place and that the formula of the diacyl was $Cl_3COCOC_6H_4NHCOC_6H_5$. Spiegel and Spiegel[5] prepared this diacyl and assigned to it the formula $C_6H_5OCOC_6H_4NHCOCCl_3$. In this case the lighter and also less acidic group was found on the nitrogen atom. Attempts to introduce the acyl groups in reverse order were unsuccessful. One attempt resulted in the formation of benzenylaminophenol.

Attempts were made to acylate *β*-chloro-ethyl-*o*-hydroxycarbanilate with ethyl chlorocarbonate, and ethyl *o*-hydroxycarbanilate with *β*-chloro-ethyl chlorocarbonate, but in both cases a decomposition occurred and carbethoxycarbonyl-*o*-aminophenol was formed. This decomposition probably compares with that observed by Ransom[1] in the dry distillation of benzoyloxyphenylurethan.



$$C_6H_4\left\langle\begin{array}{l}OCOC_6H_5\\NHCOOC_2H_5\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}OCO\\NCOC_6H_5\end{array}\right. + C_2H_5OH$$

$$C_6H_4\left\langle\begin{array}{l}OCOOC_2H_5\\NHCOOC_2H_4Cl\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}OCO\\NCOOC_2H_5\end{array}\right. + ClC_2H_4OH$$

Saponification of the product gave ethyl *o*-hydroxycarbanilate. If the above equation represents the reaction that takes place, it would appear that the heavier and more acidic group attaches itself to the nitrogen atom in each case.

Experimental

β-Chloro-ethyl-*o*-hydroxycarbanilate ($HOC_6H_4NHCO_2C_2H_4Cl$).—This compound was prepared by Groenvik's method.[6] Four and eight-tenths g. of *o*-aminophenol was suspended in 200 cc. of ether and 3.2 g. of *β*-chloro-ethyl chlorocarbonate slowly added. The mixture was filtered and the ether evaporated. After four crystallizations from benzene the white, needle-like crystals melted at 101–103°; yield, 50%.

Anal. Calcd. for $C_9H_{10}NO_3Cl$: N, 6.49. Found: 6.33.

The other monoacyls, which have been described in the literature, were prepared by the same method.

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[5] Spiegel and Spiegel, *Ber.*, **40**, 1737 (1907).

[6] Groenvik, *Bull. soc. chim.*, [2] **25**, 173 (1876).

Monochloro-acetate of Ethyl-*o*-hydroxycarbanilate ($ClCH_2OCOC_6H_4NHCO_2C_2H_5$).—A large excess (5 cc.) of monochloro-acetyl chloride was added to 2.3 g. of ethyl *o*-hydroxycarbanilate and a drop of sulfuric acid added. The mixture was warmed for twenty minutes on a water-bath and then poured into ice water. A dark oil separated. This soon solidified and was recrystallized from dilute alcohol. The crystals were cotton-like and almost white; m. p. 114–115°.

Anal. Calcd. for $C_{11}H_{12}NO_4Cl$: N, 5.44. Found: 5.40.

This diacyl was also prepared by the Schotten-Baumann method by dissolving 1.85 g. of *o*-monochloro-acetylaminophenol in 5.6 cc. of a 10% solution of potassium hydroxide and then adding 1 cc. of ethyl chlorocarbonate. A mixed melting point with the product formed by introducing the acyls in reverse order melted at the same temperature.

It was found necessary to add the ethyl chlorocarbonate immediately upon the solution of the monochloro-acetylaminophenol; otherwise other products precipitated.

Anal. Calcd. for $C_{11}H_{12}NO_4Cl$: N, 5.44. Found: 5.43.

On saponification ethyl *o*-hydroxycarbanilate was formed, proving that the —CO_2-C_2H_5 group had been attached to the nitrogen atom.

***o*-Monochloro-acetylaminophenyl Acetate** ($CH_3OCOC_6H_4NHCOCH_2Cl$).—This compound was prepared by the method described by Jacobs, Heidelberger and Rolf.[7] It melted at 113–114°, as stated in the literature.

On saponification *o*-acetylaminophenol was formed.

***o*-Acetylaminophenyl Monochloro-acetate** ($ClCH_2OCOC_6H_4NHCOCH_3$).—A large excess of monochloro-acetyl chloride was added to 1 g. of *o*-acetylaminophenol. A drop of sulfuric acid was added and the mixture heated on the water-bath for twenty minutes. On pouring into cold water an oil separated and soon solidified. Recrystallization from benzene or dilute alcohol gave a white, crystalline product melting at 128–130°. It was more soluble in benzene than its isomer.

Anal. Calcd. for $C_{10}H_{10}NO_3Cl$: N, 6.16. Found: 6.27.

On saponification a white solid was obtained which after purification melted at 196–197°. A mixture with *o*-acetylaminophenol melted at 200°, showing them to be identical.

A mixture of this product with that produced by the saponification of the isomeric *o*-monochloro-acetylaminophenyl acetate melted at 196–197°, showing them to be identical.

***o*-Trichloro-acetylaminophenyl Acetate** ($CH_3OCOC_6H_4NHCOCCl)_3$ was prepared by the method of Jacobs, Heidelberger and Rolf.[7] Five cc. of acetic anhydride and one drop of sulfuric acid were added to 2.5 g. of *o*-trichloro-acetylaminophenol and the mixture was warmed for ten minutes on the water-bath. On pouring into cold water an oil separated and soon solidified. Recrystallization from dilute alcohol gave a snow white product melting at 85.5°.

Anal. Calcd. for $C_{10}H_8NO_3Cl_3$: N, 4.73. Found: 4.76.

Some trouble was encountered on saponification of this compound. It was finally carried out in this way: 3 g. of *o*-trichloro-acetylaminophenyl acetate was dissolved in 7.8 cc. of 10% ammonium hydroxide. The solution became very dark. This was filtered and acidified. The small amount of dirty white crystals which formed was extracted with ether and the ether solution washed with a dilute solution of sodium carbonate and then with water several times. The ether was evaporated and the resulting crystals melted at 155°. A mixture of this with *o*-trichloro-acetylaminophenol (m. p., 160°)

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[7] Jacobs, Heidelberger and Rolf, THIS JOURNAL, **41**, 458 (1919).

melted at 154–160°, showing the two to be identical. The amount of saponification product obtained did not permit recrystallization.

Attempts to prepare *o*-trichloro-acetylaminophenyl acetate or its isomer from *o*-acetylaminophenol and trichloro-acetyl chloride resulted in failure.

***o*-Benzoylaminophenyl Trichloro-acetate** ($Cl_3COCOC_6H_4NHCOC_6H_5$).—This compound was prepared by the method of Spiegel and Spiegel.[5] The crystals were white, lustrous plates melting at 104°.

On saponification *o*-benzoylaminophenol was formed.

Benzenylaminophenol ($\underbrace{NC_6H_4OC}C_6H_6$).—This compound was formed when an excess of trichloro-acetyl chloride was added to *o*-benzoylaminophenol and allowed to stand on a steam-bath for 72 hours. This was done in an attempt to prepare *o*-benzoylaminophenyl trichloro-acetate. All attempts to prepare that compound from *o*-benzoylaminophenol and trichloro-acetyl chloride were failures. The benzenylaminophenol was purified by steam distillation. The crystals were colorless needles melting at 103°; yield, 73%. They showed all the properties described by Ladenburg.[8]

Anal. Calcd. for $C_{13}H_9NO$: N, 7.18. Found: 7.03.

Carbethoxycarbonyl *o*-Aminophenol ($\underbrace{OCOC_6H_4N}COOC_2H_5$).—This compound was formed in an attempt to prepare ethyl carbonate of β-chloro-ethyl *o*-hydroxycarbanilate as follows: 4.3 g. of β-chloro-ethyl *o*-hydroxycarbanilate was dissolved in 75 cc. of water which contained 1.1 g. of potassium hydroxide, and 2.2 g. of ethyl chlorocarbonate was added dropwise. The brown oil which formed soon solidified and was recrystallized twice from strong alcohol. The crystals were colorless, mica-like plates melting at 80°.

Anal. Calcd. for $C_{10}H_9NO_4$: N, 6.76. Found: 6.87.

On saponification of this product ethyl *o*-hydroxycarbanilate was formed as shown by mixed melting point.

Carbethoxycarbonyl *o*-aminophenol was also formed in the same way, when ethyl *o*-hydroxycarbanilate in alkaline solution was treated with β-chloro-ethyl chlorocarbonate. This was shown by mixed melting point and the fact that the same product was formed on saponification.

In order to confirm the identification of the above products, carbethoxycarbonyl *o*-aminophenol was prepared by a method similar to that used by Ransom[1] for the preparation of benzoylcarbonyl-*o*-aminophenol. One and five-tenths g. of carbonylaminophenol was dissolved in 75 cc. of water containing a chemically equivalent amount of potassium hydroxide. One and two-tenths g. of ethyl chlorocarbonate was slowly added with shaking. The brown oil which formed soon crystallized to lustrous, mica-like plates melting at 79.5°. The melting point remained the same when mixed with the product formed from the action of ethyl chlorocarbonate on β-chloro-ethyl *o*-hydroxycarbanilate, showing the products to be identical.

Summary

1. In three cases out of five of the diacyl derivatives of *o*-aminophenol prepared, it has been found that the lighter and less acidic acyl group attached itself to the nitrogen atom, while the heavier and more acidic group, containing chlorine, attached itself to the oxygen atom. In the other two cases the heavier and more acidic group containing chlorine

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[8] Ladenburg, *Ber.*, 9, 1526 (1876).

attached itself to the nitrogen atom. This demonstrates that neither weight nor acidity is the determining factor.

2. Several new acyl derivatives of *o*-aminophenol have been prepared and studied.

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A QUANTITATIVE STUDY OF THE PHOTOCHEMICAL ACTIVATION OF STEROLS IN THE CURE OF RICKETS

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Recent discoveries in chemical physiology, showing that rickets can be cured by sterols which have previously been exposed to ultraviolet radiation,[1] offer interesting possibilities for photochemical investigations. The study appears attractive because the severity of rickets and its cure can be measured fairly quantitatively and because the antirachitic activation of the curative agent—the sterols—can be effected by such small amounts of energy that monochromatic light obtained with a spectrometer may be used.

In the present investigation an attempt was made to determine quantitatively the amount of energy necessary to secure a demonstrable deposition of calcium in the bones of a rachitic rat. This determination not only gives an idea of the extreme sensitiveness of the physiological reaction but, together with spectrographic evidence, indicates also that while cholesterol of even more than ordinary purity can be activated, the effect is probably due to a contaminant. This, hypothesis is in harmony with the recent suggestions of other investigators.[2]

The absorption spectrum of cholesterol was determined first because it was not available in the literature when the investigation was started. Since it could not be taken for granted that all portions of the absorption region are necessarily concerned in the activation process, cholesterol was exposed in different parts of the spectrum and tested physiologically.

Experimental Procedure

The source of light was a 220-volt quartz mercury vapor lamp loaned by the Hanovia Chemical and Manufacturing Company. It was operated on a 500-volt D. C. current with suitable resistances and a reactance in the circuit. After bringing the lamp to equilibrium by running it for some time, the resistances were so adjusted as to give a current of 2.4 amperes and a potential drop of 130 volts across the lamp terminals. For

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[1] (a) Steenbock, Black, Nelson, Nelson and Hoppert, *J. Biol. Chem.*, **63**, xxv (1925); (b) Hess and Weinstock, *ibid.*, **63**, xxv (1925); (c) Rosenheim and Webster, *Lancet*, **1925**, p. 1025.

[2] Rosenheim and Webster, *Biochem. J.*, **21**, 389 (1927).