Preparation and Properties of S-Acetyl-N-benzoylcysteamine[1]

HERBERT T. NAGASAWA AND HELMUT R. GUTMANN

Received August 16, 1957

The acetylation of aromatic amines in a physiological system is known to proceed through the intermediate acetyl coenzyme A,[2] a molecule in which the acetyl group is attached to coenzyme A through a thioester linkage.[3] The known susceptibility of thioesters to nucleophilic agents in general,[4] and particularly to aminolysis, has led Tarbell *et al.* to study the kinetics of the acetylation of the aliphatic amine, *n*-butylamine, by model thioesters related to acetyl coenzyme A.[5,6] However, the *enzymatic* acetylation of aromatic amines in a system in which the acetyl group is transferred to the acceptor amine from a model acetyl thioester instead of from acetyl coenzyme A has not been studied. We became interested in this problem in the course of experiments concerned with the effect of structure of the aromatic amine on the rate of *in vitro* acetylation. It was hoped that a simple, stable acetyl thioester could be synthesized which might replace the rather complex and relatively unstable acetyl coenzyme A as the acetylating agent. *S*-Acetyl-*N*-benzoylcysteamine was selected because it was thought that this compound, unlike most of the model thioesters employed by Tarbell *et al.*[5,6] would be a solid. This expectation was fully realized and the compound proved to be a stable solid melting at 91.5–92°.

Ethyleneimine was benzoylated and the intermediate, benzoylethyleneimide,[7] prepared *in situ*, was converted to the thioester by reaction with thioacetic acid. *S*-Acetyl-*N*-benzoylcysteamine was found to exhibit only feeble acetylating activity in the standard enzymatic test.[2] As these rate studies are no longer being pursued, we wish to report the preparation and properties of this new thioester.

EXPERIMENTAL

A solution of 42.2 g. (0.30 mole) of benzoyl chloride in 35 ml. of benzene was added dropwise to an ice cold, stirred mixture of 12.9 g. (0.30 mole) of ethyleneimine, prepared by the modifications[8,9] of the procedure of Wenker,[10] and 30.4 g. (0.30 mole) of triethylamine in 250 ml. of anhydrous benzene. After stirring for 1 hr., the precipitate of triethylamine hydrochloride was removed by filtration. The benzene filtrate was then added rapidly to a cooled (ice bath), stirred solution of 22.8 g. (0.30 mole) of thioacetic acid in 100 ml. of benzene. After 1 hr., the benzene was removed by distillation *in vacuo* at room temperature to incipient precipitation of the product. The product was collected after stirring the mixture with 500 ml. of ligroin, and the crude material was dissolved in approximately 750 ml. of a mixture of benzene and ethyl acetate (4:1). The solution was washed three times with 50 ml. portions of distilled water and dried over anhydrous sodium sulfate. The solution was then concentrated *in vacuo* to 400 ml., warmed slightly, and diluted to 800 ml. with ligroin. On standing at room temperature, the product precipitated as fine, flocculent clusters (needles). There was obtained 52.1 g. of material melting at 90–91° (corr.); 78% yield. An analytical sample was recrystallized from ethyl acetate:ligroin, m.p. 91.5–92.0° (corr.).

Anal. Calcd. for $C_{11}H_{13}O_2NS$: C, 59.2; H, 5.87; S, 14.4. Found: C, 59.4; H, 5.89; S, 14.2.

The ultraviolet absorption spectrum of the compound in ethanol showed an absorption maximum at 230 mμ (ϵ = 15,100). The infrared spectrum showed the characteristic thioester band at 5.90 μ.[11] Hydrolysis of the thioester was accomplished with 0.5*N* sodium hydroxide. The hydrolysis was followed spectrophotometrically by the decrease in absorption at 230 mμ and was essentially complete in 30 min., but was allowed to proceed for 4 hr. Calculation of the molar extinction coefficient of the thioester bond based on the difference spectrum gave a value of 4.54×10^3. This is in excellent agreement with the values for ethyl thioacetate and β-acetaminoethyl thioacetate (4.57×10^3 and 4.51×10^3 respectively) reported by Hawkins and Tarbell.[5]

RADIOISOTOPE SERVICE
VETERANS ADMINISTRATION HOSPITAL AND
DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF MINNESOTA,
MINNEAPOLIS, MINN.

(1) This work was supported by Grant C-2571, National Cancer Institute, U. S. Public Health Service.

(2) N. O. Kaplan and F. Lipmann, *J. Biol. Chem.*, **174**, 37 (1948).

(3) F. Lynen, *Federation Proc.*, **12**, 683 (1953).

(4) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

(5) P. J. Hawkins and D. S. Tarbell, *J. Am. Chem. Soc.*, **75**, 2982 (1953).

(6) D. S. Tarbell and D. P. Cameron, *J. Am. Chem. Soc.*, **78**, 2731 (1956).

(7) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(8) P. A. Leighton, W. A. Perkins, and M. L. Renquist, *J. Am. Chem. Soc.*, **69**, 1540 (1947).

(9) W. A. Reeves, G. L. Drake, Jr., and C. L. Hoffpauir, *J. Am. Chem. Soc.*, **73**, 3522 (1951).

(10) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).

(11) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York 1954, p. 160.

p,p′-Nitro and Amino Derivatives of 1,3-Diphenylpropane

FREDERICK D. GREENE AND BEN E. EDWARDS

Received August 17, 1957

Nitration of 1,3-diphenylpropane by fuming nitric acid has been reported to yield a dinitro derivative of m.p. 139°.[1] Investigation of a variety of nitrating conditions has shown that the *p,p′*-dinitro derivative, m.p. 140–141°, may be obtained in 22% yield by use of acetic anhydride, nitric, and sulfuric acids. The proof of structure lies in the oxidation to *p*-nitrobenzoic acid in substantially greater than 50% yield. Reduction of the

(1) A. Michaelis and A. Flemming, *Ber.*, **34**, 1293 (1901).