in nature and in the form of a cyclic hemiacetal that is resistant to acid hydrolysis but is capable of existing in anomeric forms. In dihydrostreptobiosamine, a carbonyl group has been reduced to an alcohol group.

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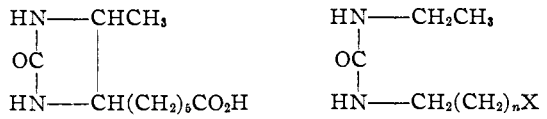
[FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

The Reaction of Aminoesters with Ethyl Isocyanate: Open Chain Models of Desthiobiotin

BY EVERETT M. SCHULTZ

It has been proposed that in order for a compound to resemble biotin in avidin combinability, two structural features are essential: an imidazolidone nucleus and an ω-alkylcarboxylic acid side-chain.[1] It has been demonstrated also that for certain organisms pimelic acid acts as a precursor[2] in the biosynthesis of biotin. More recently, Tatum has shown that for some organisms pimelic acid may act as the precursor for desthiobiotin.[3]

The work described in this paper is the preparation of some 1,3-disubstituted ureas (II) that may be considered as open chain analogs of desthiobiotin (I). When $n = 4$ (IIA) the urea has the carboxyl side chain that occurs in desthiobiotin. When $n = 5$ (IIB), the urea becomes a true acyclic model of desthiobiotin. In view of the



I II

IIA ($n = 4$, X = CO_2H)
IIB ($n = 5$, X = CO_2H)
IIC ($n = 3$, X = H)
IID ($n = 4$, X = $CO_2C_2H_5$)
IIE ($n = 4$, X = $CONH_2$)
IIF ($n = 5$, X = $CO_2C_2H_5$)

biosynthesis of biotin and desthiobiotin from pimelic acid, it was thought possible that the same organisms that can bring about such transformations might also utilize such a compound as IIB as precursor. It also seemed of interest to test such open chain desthiobiotin analogs for avidin combinability.

None of the ureas described in this paper showed either biotin or antibiotin activity when tested microbiologically against *Lactobacillus casei* or *Lactobacillus arabinosis*. None was avidin combinable nor did any one act as a precursor for the biosynthesis of desthiobiotin or biotin.[3,4]

Since *n*-butylamine combined readily with ethyl isocyanate to give 1-ethyl-3-butyl-urea (IIC), the chosen method of synthesis was the reaction of ω-amino acids with ethyl isocyanate. It was found that, while the free acids were inert to ethyl isocyanate, their ethyl esters reacted vigorously. The 1-ethyl-3-(ω-carbethoxyalkyl)-ureas were easily saponified by cold dilute sodium hydroxide solution to form the free acids and could be converted to amides by shaking with cold concentrated aqueous ammonia. The stability of the urea linkage is such that the compounds are completely unchanged by autoclaving at 120° for fifteen minutes in water, in which all are sufficiently soluble for microbiological assay.

For the synthesis of IIF, 7-aminoheptanoic acid was required. It was prepared by the reduction of 6-cyanocaproic acid (III), a compound that apparently has not been reported in the literature. The cyanoacid was prepared from cyclohexanone through ethyl 6-hydroxycaproate (V) and 6-bromocaproic acid (VI). The structure of III was demonstrated by hydrolysis to pimelic acid.

Experimental

6-Cyanocaproic Acid (III).—6-Bromocaproic acid,[5a,b,c] m. p. 32°,[6] (71.17 g., 0.37 mole) was suspended in water (125 cc.) and sodium carbonate (22.6 g., 0.185 mole) was added slowly with stirring. Then sodium cyanide (96%) (121 g., 0.409 mole) was added with shaking. The mixture was heated to 54° and the reaction flask was wrapped with a cloth. The internal temperature rose to 57° over a period of one-half hour. The mixture was then heated quickly to 100° and boiled for five minutes. The black opaque reaction mixture was cooled to 30° and acidified (hydrogen cyanide evolved) with concentrated hydrochloric acid. The free hydrogen cyanide was removed under reduced pressure at room temperature. After saturating the aqueous mixture with ammonium sulfate, the product was extracted with ether. The ether solution was filtered and dried over anhydrous sodium sulfate. Upon evaporation of the ether, there remained an oily residue that was distilled to give a liquid boiling at 158–160° (2.5–3 mm.) The yield was 56%.

One gram of the above nitrile was added to a solution of 13 g. of potassium hydroxide in 107 cc. of ethanol and the mixture was refluxed for twenty hours. Upon working up the reaction mixture there was obtained a good yield of pimelic acid, identified by melting point and mixed melting point.

7-Aminoheptanoic Acid (IV).—Dry potassium 6-cyanocaproate (17 g., 0.095 mole) (prepared by adding the calculated amount of 40% potassium hydroxide solution to an aqueous suspension of 6-cyanocaproic acid, and evaporating the water in a vacuum desiccator over solid potassium

(1) Dittmer and du Vigneaud, *Science*, **100**, 130 (1944).

(2) du Vigneaud, Dittmer, Hague and Long, *ibid.*, **96**, 186 (1942); Eakin and Eakin, *ibid.*, 187 (1942).

(3) Tatum, *J. Biol. Chem.*, **160**, 455 (1945).

(4) Tests were carried out by Dr. Lemuel D. Wright, of these laboratories.

(5) (a) Robinson and Smith, *J. Chem. Soc.*, 373 (1937); (b) Barger, Robinson and Smith, *ibid.*, 722 (1937); (c) Brown and Partridge, THIS JOURNAL, **66**, 839 (1944).

(6) Marvel, *et al.*, *ibid.*, **46**, 2838 (1934).

TABLE I

PHYSICAL PROPERTIES AND ANALYTICAL DATA ON SUBSTITUTED UREAS

Compound	Yield, %	M. p., °C.	Formula	Nitrogen, %[f] Calcd.	Found
(IIA) 1-Ethyl-3-(5-carboxyamyl)-urea[a]	74	117–118	$C_9H_{18}N_2O_3$	13.85	13.87
(IIB) 1-Ethyl-3-(6-carboxyhexyl)-urea[a]	39	120–121.5	$C_{10}H_{20}N_2O_3$	12.95	13.06
(IIC) 1-Ethyl-3-(*n*-butyl)-urea[b]	..	57–58	$C_7H_{16}N_2O$	19.45	19.55
(IID) 1-Ethyl-3-(5-carbethoxyamyl)-urea[c]	60	67–68	$C_{11}H_{22}N_2O_3$	12.20	12.18
(IIE) 1-Ethyl-3-(5-carbamylamyl)-urea[d]	55	148.5–149.5	$C_9H_{19}N_3O_2$	20.90	20.89
(IIF) 1-Ethyl-3-(6-carbethoxyhexyl)-urea[e]	50	74–75.5	$C_{12}H_{24}N_2O_3$	11.48	11.65

[a] Needles from water. [b] Needles from ethyl ether. [c] Needles from *i*-propyl ether. [d] Prepared by shaking IID with concentrated ammonium hydroxide for five days. Needles from acetone. [e] Needles from 1:2 benzene–benzine. [f] Analysis by Miss Thelma Plank of this Laboratory.

hydroxide) was dissolved in 145 cc. of dry methanol containing 16.5 g. of ammonia. The solution was placed in an autoclave with 6 g. of Raney nickel and shaken at 100° under hydrogen at an initial pressure of 1590 lb. for two hours.

The catalyst was removed by filtration and the solvent was removed by vacuum distillation at 30–50° The white pasty residue was dissolved in a minimum amount of water. Acetic acid (6.7 g.) was added and the solvent was again removed ***in vacuo*** at 30–50°. Dry ethanol (10 cc.) was added to the pasty residue. The amino acid separated as a white flocculent solid that was collected by filtration and washed with absolute ethanol. There was obtained 2.75 g. of white solid that melted at 185°. The reported melting point is 186–187°.[7] An additional amount (1.4 g.) of product melting at 185° was obtained by evaporating the filtrate and washings and adding absolute alcohol to the pasty residue.

Preparation of Substituted Ureas.—The preparation of 1-ethyl-3-(6-carbethoxyhexyl)-urea (IIF) illustrates the general preparation of the carbethoxy ureas. A suspension of 7-aminoheptanoic acid (4.15 g.) in absolute alcohol (40 cc.) was saturated with hydrogen chloride and refluxed for one-half hour. The volatile components were removed by vacuum distillation at about 35°. The residue was taken up in a little water, ether was added and, while cooling and shaking, 20% sodium hydroxide was added until the aqueous layer was strongly basic. The ether layer was separated and dried over anhydrous sodium sulfate, concentrated to 30 cc., and cooled. To the cold solution ethyl isocyanate (3 g.)[8] was added slowly. After addition was complete, the mixture was refluxed for a half-hour. The ether and excess ethyl isocyanate were removed by heating on a steam-bath. The residue was recrystallized from a benzene–benzine mixture (1:2) from which the product separated in fine tangled needles.

The saponification of the carbethoxy alkyl-ureas was carried out by shaking at room temperature with 0.5 *N* sodium hydroxide (10 cc. per g. of ester) until solution was complete. This required two to three hours. The solution was made weakly acidic with dilute hydrochloric acid. The precipitated solid was collected by filtration and recrystallized.

(7) (a) Manasse, *Ber.*, **35**, 1369 (1902); (b) Wallach, *Ann.*, **312**, 206 (1900).

(8) Slotta and Lorenz, *Ber.*, **58**, 1323 (1925).

Summary

Some open chain models of desthiobiotin have been prepared by the addition of ω-amino-carboxylic acid esters to ethyl isocyanate.

Certain ω-amino-carboxylic acids have been found to be inert toward ethyl isocyanate, whereas the corresponding esters add readily to ethyl isocyanate.

1-Ethyl-3-(6-carboxyhexyl)-urea, an open chain analog of desthiobiotin, does not act as a precursor in the biosynthesis of desthiobiotin nor is it avidin combinable. The same is true of 1-ethyl-3-(5-carboxyamyl)-urea, a compound that has the same acid side-chain as desthiobiotin. These findings appear to agree with the theory of Dittmer and du Vigneaud[1] that an imidazolidone nucleus and an ω-carboxyalkyl side-chain are essential in order that a molecule have avidin combinability.

GLENOLDEN, PENNSYLVANIA RECEIVED JANUARY 6, 1947

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

Inhibition and Retardation of the Peroxide Initiated Polymerization of Styrene

BY SAUL G. COHEN

The polymerization of vinyl compounds appears, under certain commonly applying conditions, to be a radical propagated chain reaction,[1] and, as such, is markedly influenced by compounds which may be present at low concentrations. While certain compounds accelerate these reactions,[2] others lead to diminished rates or molecular weights, or both, and may inhibit the reactions completely.[3,4,5] Halogenated compounds,[3] quinones,[4] phenols,[4a] aromatic nitro compounds[4a,5] and amines[4a] show such effects.

The reactions which interfere with the chain growth process may be divided into two major classes. In chain transfer, a chain is terminated

(1) (a) H. Staudinger, *Trans. Faraday Soc.*, **32**, 97 (1936); (b) *cf.* H. Mark and R. Raff, "High Polymeric Reactions," Interscience Publishers, Inc., New York, N. Y., 1941, pp. 155 ff.

(2) For references see C. S. Marvel and E. C. Horning in H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 771–778.

(3) (a) H. Suess, K. Pilch and H. Rudorfer, *Z. physik. Chem.*, **A179**, 361 (1937); (b) H. Suess and A. Springer, *ibid.*, **A181**, 81 (1937).

(4) (a) S. G. Foord, *J. Chem. Soc.*, 48 (1940); (b) J. W. Breitenbach and H. L. Breitenbach, *Z. physik. Chem.*, **A190**, 361 (1942).

(5) C. C. Price and D. A. Durham, THIS JOURNAL, **65**, 757 (1943).