

of δ -aminovaleric acid- δ -C¹⁴ obtained was 0.55 g. This represents a yield of 59% after taking into account the recovered cyanide. After trituration with a little cold absolute ethanol, 25 ml. of acetone was added and the product was obtained by filtration. Paper chromatography both with collidine-lutidine-water and phenol-water yielded only one ninhydrin reactive spot which corresponded in each case to that obtained with authentic δ -aminovaleric acid (Eastman Kodak Co.). From the radioactive preparation only one radioactive spot was obtained which coincided exactly with the ninhydrin reactive spot of δ -aminovaleric acid. The product was halogen free and melted at 155–156° (reported for δ -aminovaleric acid, 156°).

DEPARTMENT OF RADIATION BIOLOGY
SCHOOL OF MEDICINE AND DENTISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK

Polyphosphoric Acid as a Reagent in Organic Chemistry. V. Conversion of Acids to Substituted Amides; Further Observations on the Lossen Reaction

BY H. R. SNYDER AND CLAYTON T. ELSTON¹

RECEIVED JANUARY 21, 1954

In an earlier paper² it was postulated that the reaction of hydroxylamine with aromatic carboxylic acids in the presence of polyphosphoric acid proceeds to the amine by way of an intermediate hydroxamic acid. In agreement with this postulate it has been found that carboxylic acids react with weakly basic amines under similar conditions to yield the corresponding amides.

The yields of substituted amides formed from benzoic acid and various amines increase markedly as the basic strength of the amine decreases (Table I). Thus aniline was found to be unreactive while 2,4-dinitroaniline reacts almost quantitatively. The reaction is not limited to aromatic acids since acetic acid and 2,4-dinitroaniline give a 92% yield of 2,4-dinitroacetanilide.

The acylation of *p*-nitroaniline with various carboxylic acids was investigated. In these reactions, the ease of amide formation appears to increase as acid strength decreases. However, as shown in Table I, the correlation is not so clearly defined as that pertaining to the basic strength of the amines. Of the nitrobenzoic acids only the *meta* isomer reacts to give the amide and the yield is very low (8%). Neither *o*-nitrobenzoic acid nor the *para* isomer reacts with 2,4-dinitroaniline.

Further attempts were made to extend the amine synthesis² to aliphatic acids. With slightly modified conditions it was found that aliphatic acids do react with hydroxylamine to give low yields of the expected amines. *n*-Amylamine and cyclohexylamine were obtained in yields of 25 and 36%, respectively. The reaction, in contrast with that of aromatic acids, is difficult to control and gives considerable amounts of dark ether-insoluble oil.

Experimental

Table I gives the yields of crude amides obtained. The melting points are given as an indication of purity.

A. Amide Formation.—The preparation of *p*-nitroacetanilide is typical of the method used.

(1) Visking Corporation Fellow, 1953–1954.

(2) H. R. Snyder, C. T. Elston and D. B. Kellom, *THIS JOURNAL*, **78**, 2014 (1953).

TABLE I

Acid	Amine	Amide		Reported m.p., °C.
		Yield, %	M.p., °C.	
Benzoic	Methoxyamine	0		
Benzoic	Aniline	0		
Benzoic	<i>o</i> -Chloroaniline	39	98–99	99
Benzoic	<i>p</i> -Nitroaniline	54	196–197	199
Benzoic	<i>o</i> -Nitroaniline	71	90–92	94
Benzoic	2,4-Dinitroaniline	98	196–200	200–202
Acetic	2,4-Dinitroaniline	92	119–120	121
Acetic	<i>p</i> -Nitroaniline	67 ^a	213–214	214
<i>o</i> -Chlorobenzoic	<i>p</i> -Nitroaniline	64	180–182	180
<i>p</i> -Toluic	<i>p</i> -Nitroaniline	60	201–203	206.5
<i>m</i> -Nitrobenzoic	<i>p</i> -Nitroaniline	8 ^b	248–249	249
<i>o</i> -Nitrobenzoic	<i>p</i> -Nitroaniline	0		
<i>p</i> -Nitrobenzoic	<i>p</i> -Nitroaniline	0		
Monochloroacetic	<i>p</i> -Nitroaniline	7 ^b	184–185	185
<i>o</i> -Nitrobenzoic	2,4-Dinitroaniline	0		
<i>p</i> -Nitrobenzoic	2,4-Dinitroaniline	0		

^a Recrystallized from a mixture of dimethylformamide and water. ^b Recrystallized from ethanol.

To a mixture of 3.5 g. of acetic acid and 4.0 g. of *p*-nitroaniline in a three-necked flask, fitted with a reflux condenser and stirrer, was added 70 g. of polyphosphoric acid. The flask was placed in an oil-bath and the temperature was raised to 160° in the course of 20 minutes. The mixture was then hydrolyzed by pouring it over 200 g. of crushed ice. The precipitated amide was filtered off, washed with water and then recrystallized from a mixture of dimethylformamide and water. The *p*-nitroacetanilide was obtained in the form of fluffy white crystals melting at 213–214°. The yield was 3.5 g. (67%).

B. Amine Synthesis.—*n*-Amylamine and cyclohexylamine were prepared by essentially the same procedure.

A mixture of 7.0 g. of hydroxylamine hydrochloride and 85 g. of polyphosphoric acid was placed in a three-necked flask fitted with a reflux condenser and a stirrer. The mixture was heated to 135°, held at that temperature until the evolution of hydrogen chloride had ceased and then 10.0 g. of cyclohexanecarboxylic acid was added. The vigorous evolution of carbon dioxide which occurred was complete in about ten minutes. The mixture was hydrolyzed by pouring it over 200 g. of crushed ice and the resulting brown solution was made strongly basic with potassium hydroxide. This caused the separation of a brownish-black oil. The mixture was then extracted continuously with ether for 15 hours. The extract was dried over potassium hydroxide and then distilled through a Holtzmann column. The fraction boiling at 136° was collected. The yield was 2.8 g. (36%). The identity of the amine was confirmed by its conversion to the corresponding phenylthiourea, melting point 148°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

Polyphosphoric Acid as a Reagent in Organic Chemistry. VI.¹ The Hydrolysis of Nitriles to Amides

BY H. R. SNYDER AND CLAYTON T. ELSTON²

RECEIVED FEBRUARY 1, 1954

The use of 100% phosphoric acid in the hydrolysis of nitriles to acids has been known for some time.³ Recently, however, the effectiveness of polyphosphoric acid in the Beckmann rearrangement⁴ and in the acylation of amines¹ indicated the rather exceptional stability of amides in this reagent. The reaction of polyphosphoric acid with various nitriles was therefore investigated.

(1) For the preceding paper, see H. R. Snyder and C. T. Elston, *THIS JOURNAL*, **76**, 3039 (1954).

(2) Visking Corporation Fellow.

(3) G. Berger and S. C. J. Olivier, *Rec. trav. chim.*, **46**, 600 (1927).

(4) E. C. Horning, V. L. Stromberg and H. A. Lloyd, *THIS JOURNAL*, **74**, 5153 (1952).

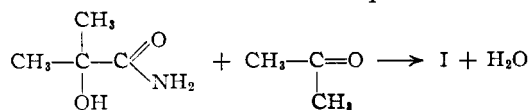
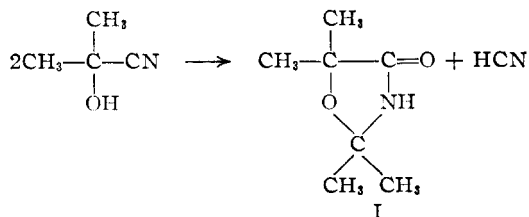
TABLE I

Nitrile	Temp., °C.	Time, hr.	Product	Yield, %	M.p., °C.	Reported m.p., °C.
Benzonitrile	110	1	Benzamide	96	125-126	125-126 (128)
<i>o</i> -Tolunitrile	115	1.5	<i>o</i> -Toluamide	95	137-140	139-140
<i>p</i> -Tolunitrile	120	1	<i>p</i> -Toluamide	94	159-160	159-160
α -Naphthonitrile	110	2	α -Naphthamide	95	198-200	202
Phenylacetoneitrile	115	1	Phenylacetamide	96	155-157	156-157
Ethyl cyanoacetate	100	2	Ethyl malonamate	65	49.5-50	50
2,4-Dimethylbenzoylacetoneitrile	80	2.5	2,4-Dimethylbenzoylacetamide	78 ^a	104-104.5 ^b	
α -Hydroxyisobutyronitrile	25	18	α -Hydroxyisobutyramide	31	93-94	94 (98)
α -Hydroxyisobutyronitrile	85	0.5	2,2,5,5-Tetramethyl-4-oxazolidone	47	165-166 ^c	
Cyanomesitylene	120	2	No reaction			
Cyanomesitylene	155	1	Mesitylene	79	B.p. 158-160 n_D^{20} 1.4993	
2,4,6-Triisopropylbenzonitrile	155	1	No reaction			
1-Hydroxy-2-cyano-3-methylnaphthalene	155	1	No reaction			

^a Recrystallized once from water. ^b *Anal.* Calcd. for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.74; H, 6.96; N, 7.23. ^c Recrystallization from ethyl acetate raised the m.p. to 166-166.5°. *Anal.* Calcd. for C₇H₁₁NO₂: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.79; H, 9.62; N, 9.69.

It has been found that simple aromatic and aliphatic nitriles are hydrolyzed to the corresponding amides in high yields by reaction with polyphosphoric acid for approximately one hour at 110° (Table I). Benzonitrile, for example, was converted to benzamide in a yield of 96%. With water-soluble amides, however, the difficulty involved in isolation usually lowers the yield obtainable. Ethyl malonamate was isolated in only 65% yield from the hydrolysis of ethyl cyanoacetate. The method was not found to be suitable for the hydrolysis of sterically hindered nitriles. 2,4,6-Triisopropylbenzonitrile and 1-hydroxy-2-cyano-3-methylnaphthalene were inert even at 160°, while at this temperature, cyanomesitylene underwent both hydrolysis and decarboxylation to give mesitylene.

The only α -hydroxynitrile studied was α -hydroxyisobutyronitrile. A 31% yield of α -hydroxyisobutyramide was obtained by allowing the nitrile to remain in contact with polyphosphoric acid at room temperature for 18 hours. At a higher temperature (85°) the product was 2,2,5,5-tetramethyl-4-oxazolidone (I). The structure of this compound was confirmed by its synthesis from α -hydroxyisobutyramide and acetone.



Experimental^{5,6}

Table I gives the yields and melting points of the crude amides obtained.

The preparation of *o*-toluamide illustrates the method used when the expected amide was sparingly soluble in

water while the synthesis of ethyl malonamate is typical of the procedures used for water-soluble amides.

***o*-Toluamide.**—A mixture of 5.0 g. of *o*-tolunitrile and 65 g. of polyphosphoric acid was heated with stirring at 115° for 1.5 hours. The colorless solution was diluted with ice-water to a volume of 125 ml., the precipitated solid was filtered off, washed with water, dilute sodium carbonate solution and then again with water. The dried solid weighed 4.8 g. and melted at 137-140°. Neutralization of the cooled filtrate with potassium hydroxide yielded an additional 0.7 g. of solid of the same melting point. The over-all yield was 5.5 g. (95%). One recrystallization from a mixture of ethanol and water gave colorless crystals, melting at 140°.

Ethyl Malonamate.—A solution of 10.0 g. of ethyl cyanoacetate in 80 g. of polyphosphoric acid was heated with stirring at 100° for a period of two hours. The addition of 150 ml. of ice-water gave a clear colorless solution. The solution was neutralized with potassium hydroxide and then extracted continuously with ether for 48 hours. The ether layer was extracted with three 30-ml. volumes of water. Evaporation of the water solution gave beautiful, colorless crystals, m.p. 49.5-50°. The yield was 7.5 g. (65%).

2,2,5,5-Tetramethyl-4-oxazolidone.—A mixture of 15.0 g. of α -hydroxyisobutyronitrile and 85.0 g. of polyphosphoric acid was stirred at room temperature until the mixture became homogeneous (about five minutes). The temperature was then raised to 85° and maintained at that point for 25 minutes. Hydrogen cyanide was evolved and the solution became a clear, pale orange color. Addition of 200 ml. of ice-water caused the separation of a colorless crystalline solid. It was filtered off, washed with water and air-dried. The solid melted at 165-166° and weighed 0.4 g. Neutralization of the cold filtrate caused an additional 5.5 g. of colorless crystals to separate, also melting at 165-166°. Recrystallization from ethyl acetate gave beautiful, colorless crystals, melting point 166-166.5°.

Anal. Calcd. for C₇H₁₃NO₂: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.79; H, 9.62; N, 9.69.

This compound was also prepared by the general method outlined by Fischer, *et al.*,⁷ for the synthesis of 4-oxazolidones. A solution of 0.50 g. of α -hydroxyisobutyramide in 20 ml. of dry acetone was saturated with dry hydrogen chloride, stoppered and allowed to stand at room temperature for 48 hours. The solution was neutralized with sodium carbonate, filtered and then evaporated to dryness. The residue was recrystallized from ethyl acetate (Darco) to give colorless crystals, melting point 166-166.5°. The yield was 0.25 g. (36%). A mixed melting point with the product obtained from α -hydroxyisobutyronitrile showed no depression.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

(7) H. O. L. Fischer, G. Dangschat and H. Stettinger, *Ber.*, **65B**, 1032 (1932).

(5) All melting points are corrected.

(6) The authors are indebted to Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth for the microanalyses.