

Hypochlorite oxidation¹⁰ of VI to thianaphthene-2-carboxylic acid, m. p. 240–241.5^{21,22} was effected in 75% yield. The infrared absorption spectra of the pure ketones V and VI as well as the spectrum of the mixture are found in Fig. 1. Quantitative analysis of the mixture by infrared analysis showed it to consist of 75% V and 25% VI.

Acylation of Thiophene with Acetic Anhydride. (a) **Stannic Chloride as the Catalyst.**—The addition of 1.3 g. of stannic chloride to the solution of thiophene and acetic anhydride at room temperature caused the temperature to rise slowly to 81°. Stirring was continued for one-half hour after which the reaction was worked up in the regular way to give 52.2 g. (83%) of methyl 2-thienyl ketone, b. p. 86–87° at 10 mm., semicarbazone, m. p. 188–189°. ⁶

(b) **Anhydrous Ferric Chloride as the Catalyst.**—Ferric chloride (0.8 g.) was added to the thiophene-anhydride solution at room temperature. This caused a rapid rise in temperature to 113°, after which the reaction was completed by stirring for one-half hour to give 55.2 g. (88%) of methyl 2-thienyl ketone, b. p. 76–77° at 5 mm.

Acetylation of Benzofuran with Acetic Anhydride. (a) **Boron Fluoride Etherate as the Catalyst.**—To 0.25 mole (29.5 g.) of benzofuran, prepared by the decarboxylation of coumarilic acid,^{13,14} and 0.29 mole of acetic anhydride at room temperature was added 3.5 g. of boron fluoride etherate. The mixture was heated to 50° and then the heat was removed. The reaction temperature rose spontaneously to 76° and the reaction was completed by stirring for one-half hour and worked up in the regular way. There were obtained 10.0 g. of unreacted benzofuran, b. p. 50–60° at 8 mm., and 14.8 g. (37%) of methyl 2-benzofuryl ketone, b. p. 118–119° at 5 mm., m. p. 69–71°. After one recrystallization from petroleum ether, b. p. 60–70°, this product melted at 71–72°¹³; semicarbazone, m. p. 206–207° (from ethanol). *Anal.* Calcd. for C₁₁H₁₁N₃O₃: N, 19.34. Found: N, 19.63. Hypochlorite oxidation¹⁰ of the ketone gave benzofuran-2-carboxylic (coumarilic) acid, m. p. 195–196°¹² alone and when mixed with an authentic sample.

(b) **Stannic Chloride as the Catalyst.**—To the solution of benzofuran and acetic anhydride was added 3.25 g. of

stannic chloride all at once. The temperature of the mixture rose to 65–70° at which point the flask was cooled in a cold-water-bath. Stirring was continued for one-half hour and then worked up as described above to give 6.0 g. of unreacted benzofuran, b. p. 52–60° at 8 mm., and 16.4 g. (40%) of methyl 2-benzofuryl ketone, b. p. 118–119° at 5 mm., m. p. 67–70°. After one recrystallization from petroleum ether, b. p. 60–70°, this product melted at 71–72°.¹³

Acknowledgment.—The authors gratefully acknowledge the financial support of the Atomic Energy Commission during the course of this investigation and the assistance of Dr. Robert Friedel of the U. S. Bureau of Mines, Bruceton, Pennsylvania, in interpreting the infrared data.

Summary

2,5-Dimethylthiophene has been successfully acylated with three aliphatic anhydrides in high yields by the boron fluoride etherate method but 2,5-dichlorothiophene could not be acylated by this method.

Thianaphthene has been acetylated using seven Lewis acids as condensing agents. In every case, a mixture of methyl 3-thianaphthenyl and methyl 2-thianaphthenyl ketones was obtained. However, when benzofuran was acetylated only one compound, methyl 2-benzofuryl ketone, was obtained. An explanation of these apparently anomalous results is offered.

Thiophene has been acetylated using catalytic amounts of anhydrous ferric chloride or stannic chloride to effect the condensations but trace amounts of the aluminum chloride-diethyl ether or nitromethane complexes can apparently not be used in this reaction.

(22) Weissberger and Krider, *Ber.*, **53**, 1551 (1920).

PITTSBURGH 13, PENNA.

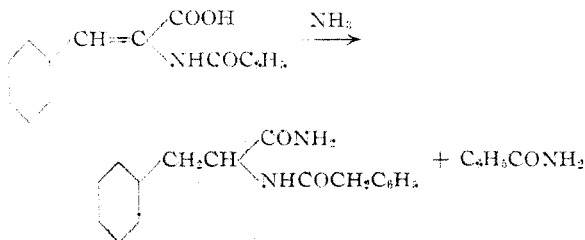
RECEIVED MARCH 18, 1950

{CONTRIBUTION FROM THE GALAT CHEMICAL CORPORATION}

The Reaction of Phenylpyruvic Acid and Related Compounds with Ammonia

BY ALEXANDER GALAT

In 1897 Erlenmeyer reported the formation of the amide of N-phenylacetylphenylalanine as the product of the reaction between α -(N-benzamido)-cinnamic acid and ammonia¹



Since phenylpyruvic acid, the hydrolysis product of α -(N-benzamido)-cinnamic acid, reacted

(1) Erlenmeyer, *Ber.*, **30**, 2976 (1897); **31**, 2238 (1898); *Ann.*, **307**, 71, 146 (1899).

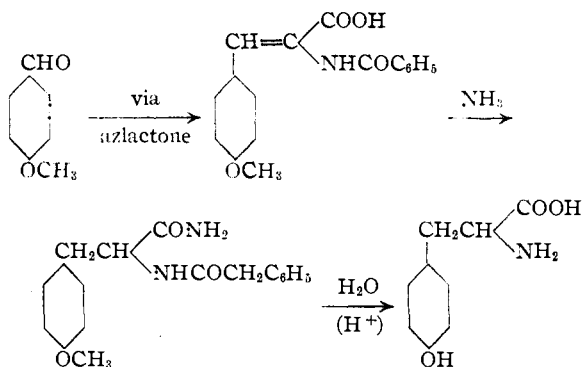
with ammonia in the same manner, Erlenmeyer concluded that the formation of phenylpyruvic acid was the first step in this reaction. Several years later Kropp and Decker found that 3,4-dimethoxy- and 3,4-methylenedioxyphenylpyruvic acids reacted with ammonia in the same way to give the corresponding amides of N-phenylacetylphenylalanines.²

This unusual reaction appeared promising to us as a new route to some of the less accessible amino-acids, phenylacetic acids and isoquinolines and the present communication deals with our work in this direction.

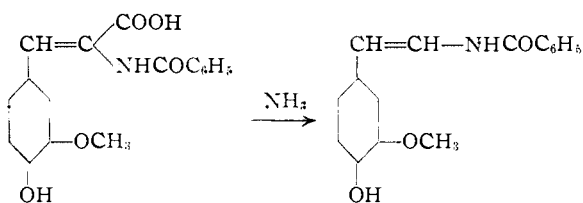
It was found that 4-alkoxy-, 3,4-alkoxy- and 3,4-methylenedioxybenzamidocinnamic acids readily react with ammonia under pressure to give the expected amides of N-phenylacetylphenylala-

(2) Kropp and Decker, *Ber.*, **42**, 1184 (1900).

nines. From these, *dl*-tyrosine and *dl*-dihydroxyphenylalanine or their ethers were obtained on hydrolysis. The synthesis of *dl*-tyrosine from anisaldehyde is represented as

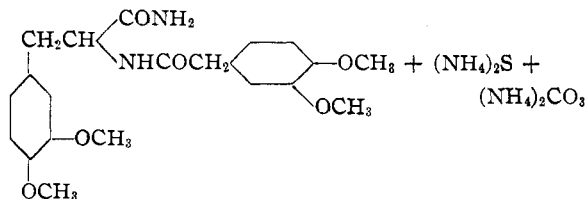
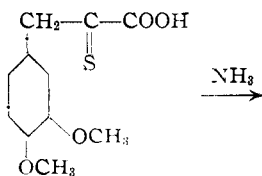


When the para position in the α -(*N*-benzamido)-cinnamic acid is substituted by a free phenolic group the expected reaction with ammonia does not appear to take place, the only isolable product being an α -benzamido-styrene formed by the loss of carbon dioxide. Thus, α -(*N*-benzamido)-3-methoxy-4-hydroxycinnamic acid gave α -(*N*-benzamido)-3-methoxy-4-hydroxy-styrene

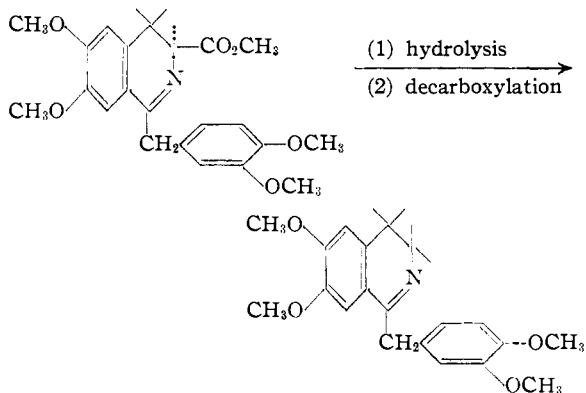
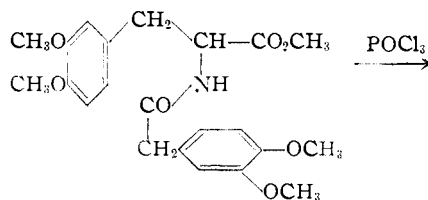
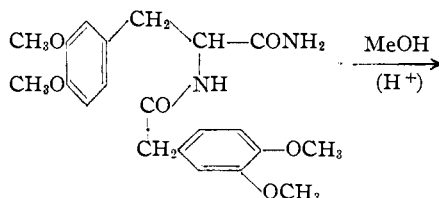


It was observed that phenylpyruvic acids themselves or compounds easily hydrolyzed to phenylpyruvic acids, such as α -*N*-acetamidocinnamic acids, gave the lowest yields of phenylacetylphenylalanines, whereas the difficultly hydrolyzable *N*-benzamidocinnamic acids gave the highest. This observation appears to contradict Erlenmeyer's assumption concerning the mechanism of the reaction.

Compounds related to phenylpyruvic acids, such as phenylthiopyruvic and α -(*N*-acetamido)-cinnamic acids, have been found to undergo the same reaction with ammonia as the corresponding phenylpyruvic acids. Thus, 3,4-dimethoxyphenylthiopyruvic acid gave the amide of *N*-(3,4-dimethoxyphenylacetyl)-3,4-dimethoxyphenylalanine

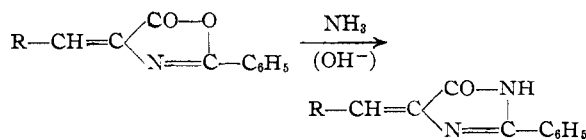


From this di-amide, 3,4-dihydropapaverine, which is an intermediate in the syntheses of papaverine, papaveraldine and laudanosine, was obtained by the sequence

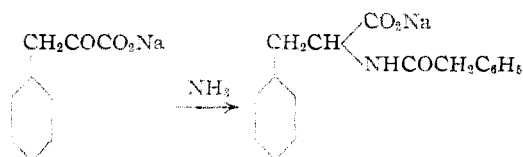


The details of this synthesis and the syntheses of the related isoquinolines will be reported in a subsequent communication.

Since α -*N*-acylamidocinnamic acids and phenylpyruvic acids are prepared by the alkaline hydrolysis of azlactones, an attempt was made to convert the latter directly into phenylacetylphenylalanines by the action of a mixture of alkali and ammonia. However, under these conditions the expected reaction did not take place. Instead, good yields of imidazolones were obtained, thus providing a simple method for the preparation of these compounds



On the other hand, alkaline salts of phenylpyruvic and acylaminocinnamic acids reacted with ammonia to give directly phenylacetylphenylalanines instead of the corresponding amides



We also wish to report an improved method for the synthesis of azlactones. We have found that potassium carbonate (or bicarbonate) is an excellent catalyst for the condensation of aldehydes with hippuric acid and is, in several respects, superior to sodium acetate used in the standard procedure.² In the presence of potassium carbonate the condensation takes place without external heating, is complete in a short period of time and gives appreciably higher yields than those obtained by the standard method.

Experimental

The Preparation of Azlactones.—The preparation of the azlactone from piperonal and hippuric acid illustrates the new procedure. Seventy-five grams (0.5 mole) of piperonal, 45 g. (0.5 mole) of hippuric acid, 80 ml. (1.7 mole) of acetic anhydride and 25 g. (0.5 mole) of potassium bicarbonate (or the equivalent amount of potassium carbonate) were stirred together at room temperature. The internal temperature gradually rose to about 100° and the mixture set into a crystalline mass. It was allowed to stand overnight at room temperature, treated with 150 ml. of hot water, the crude azlactone filtered and washed with dilute acetic acid followed by water. The dry material weighed 60 g. (82%) and melted at 195–197° (lit.³ m. p. 197°, yield 67%).

By the same method, the yield from veratraldehyde was 84–85%, as compared to about 70% by the standard procedure.⁴

N-(3,4-Methylenedioxy-phenylacetyl)-3,4-methylenedioxyphenylalanine Amide.—The preparation of this diamide describes the standard procedure employed for the synthesis of the analogous compounds. Thirty-one and nine-tenths grams of N-benzamido-3,4-methylenedioxy-cinnamic acid, prepared by the usual procedure from the corresponding azlactone,³ was dissolved in 45 ml. of 20% ammonium hydroxide and heated in a pressure bottle at 100–120° for 24 hours. The product partially crystallized during this period. Upon cooling, the diamide was filtered, washed with dilute ammonium hydroxide and the wet product boiled with 79 ml. of isopropyl alcohol, cooled and filtered. The treatment with isopropyl alcohol removes the benzamide formed in the reaction. The product dried at 100° weighed 11.0 g. (59%) and melted at 190° (lit.³ m. p. 190°). The over-all yield based on piperonal was 43–44%. This product was prepared by Kropp and Decker from the less accessible 3,4-methylenedioxyphenylpyruvic acid² with an over-all yield of 28–29% based on piperonal.

N-(4-Methoxyphenylacetyl)-4-methoxyphenylalanine amide was obtained by the same procedure from α -(N-benzamido)-4-methoxycinnamic acid with a yield of 46%. It melted at 183–184°. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{N}_2$: N, 8.18. Found: N, 8.04.

N-(4-Methoxyphenylacetyl)-4-methoxyphenylalanine was obtained by the hydrolysis of the diamide with one

equivalent of aqueous sodium hydroxide. It melted at 139–140°. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_5\text{N}$: N, 4.09; neut. equiv., 342. Found: N, 4.00; neut. equiv., 345.

dl-Tyrosine Methyl Ether and p-Methoxyphenylacetic Acid.—Seven grams of the amide was hydrolyzed with 100 ml. of 20% hydrochloric acid. After refluxing for 3.5 hours the solution was evaporated to near dryness and cooled. The precipitated p-methoxyphenylacetic acid was removed by filtration, washed with water and recrystallized from the same solvent. The yield of the product melting at 85–86° was 2.6–2.7 g. (80%), (lit.⁵ m. p. 85–86°).

The filtrate was made weakly alkaline with ammonium hydroxide and allowed to crystallize overnight. The product was filtered, washed with water and methanol and dried. The yield was 3.3–3.4 g. (83%) of the product melting at 295° (dec.) (lit.⁶ m. p. 295° with dec.). The recrystallized material showed the same melting point.

dl-Tyrosine was prepared from its methyl ether or directly from the diamide by hydrolysis with hydrobromic acid. Nine-tenths of a gram of the diamide (or an equivalent amount of the methyl ether), 6 ml. of hydrobromic acid (48%) and 6 ml. of acetic acid was refluxed for four hours, diluted with water and made slightly alkaline with ammonia. The mixture was allowed to crystallize overnight, the product filtered, washed with water and methanol and dried; yield, 0.4 g. (84%). The product melted at 315–318°. The recrystallized material melted at 315–320° (lit.⁷ 316–320°). *Anal.* Calcd. for $\text{C}_9\text{H}_{11}\text{O}_3\text{N}$: N, 7.7. Found: N, 7.8.

N-(3-Methoxy-4-ethoxy-phenylacetyl)-3-methoxy-4-ethoxyphenylalanineamide was prepared by the method described above and had a melting point of 180°. It separated from water or alcohol as a gelatinous precipitate and an analytical sample could not be prepared. The corresponding phenylacetylphenylalanine was prepared by hydrolysis with one equivalent of aqueous sodium hydroxide and had a melting point of 160–161°. An analytical sample was prepared by recrystallization from water. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{29}\text{O}_7\text{N}$: N, 3.25; neut. equiv., 431. Found: N, 3.1; neut. equiv., 430.

N-(3,4-Dimethoxyphenylacetyl)-3,4-dimethoxyphenylalanine Amide.—The standard procedure described for the corresponding methylenedioxy compound gave the following yields of this diamide: 60% from α -benzamido-3,4-dimethoxycinnamic acid, 35% from 3,4-dimethoxypyruvic acid, 30% from α -acetamido-3,4-dimethoxycinnamic acid and 20% from 3,4-dimethoxy-phenylthiopyruvic acid. The product melted at 176–177° (lit.² 176–177°).

3,4-Dimethoxyphenylalanine and 3,4-Dimethoxyphenylacetic Acid.—Twenty grams of N-(3,4-dimethoxyphenylacetyl)-3,4-dimethoxyphenylalanine and 300 ml. of concentrated hydrochloric acid was heated under reflux for two hours, the mixture reduced to a small volume *in vacuo* and extracted with chloroform. The aqueous solution was evaporated to dryness, dissolved in alcohol and treated with an excess of pyridine. After several hours the crystals were filtered, washed with alcohol and purified by redissolving in dilute hydrochloric acid, treating with charcoal, filtering and reprecipitating with ammonium hydroxide; yield, 4.4 g. (40%); the product had a melting point of 255–260° (cor.) (dec.), (lit.⁸ 249–250°, dec.). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_4\text{N}$: N, 6.22. Found: N, 6.15. The chloroform extract was dried, reduced to a small volume *in vacuo* and gradually treated with petroleum ether. The precipitate was filtered, washed with petroleum ether and air-dried. The yield of a product melting at 80–82° was 5 g. (lit.⁹ m. p. 80°).

α -Benzamido-4-hydroxystyrene.—Ten grams of α -benzamido-4-hydroxycinnamic acid, 12 ml. of concentrated ammonium hydroxide and 6 ml. of water was heated

(3) Mauthner, *Ann.*, **370**, 374 (1909).

(4) Dakin, *J. Biol. Chem.*, **3**, 20 (1910).

(5) Fisher, *Ber.*, **32**, 3039 (1899); Harrington and McCurtney, *Biochem. J.*, **21**, 854 (1927).

(6) Johnson and Bengis, *This Journal*, **35**, 1606 (1913).

(7) Pictet and Finkelstein, *Ber.*, **42**, 1979 (1909).

(3) Carter, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. 3, p. 198.

(4) Buc and Ide, "Organic Syntheses," Coll. Vol. 11, John Wiley and Sons, Inc., New York, N. Y., p. 35.

in a pressure bottle at 100° for 18 hours. The mixture was allowed to cool, the precipitate filtered, washed with dilute ammonium hydroxide and dried. The product melted at 210°; yield 1.5 g. (18%). The same product was obtained by heating under reflux 5 g. of α -benzamido-4-hydroxycinnamic acid with 5 ml. of pyridine and 20 ml. of water for ten hours. *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.67; H, 5.30; N, 5.70. On hydrolysis with hydrochloric acid the product gave benzoic acid, ammonium chloride and a gum which could not be purified, apparently a polymer of the unstable and easily resinifiable *p*-hydroxyphenylacetaldehyde. On methylation with dimethyl sulfate a product analyzing correctly for the expected methyl ether was obtained (*Anal.* Calcd. for $C_{16}H_{15}O_2N$: N, 5.54. Found: N, 5.45). This melted at 190–193°, which is appreciably higher than the melting point reported for this compound in the literature (169°).¹⁰ However, discrepancies in the melting points of benzamidostyrenes have been noted by several investigators and the existence of the *cis-trans* isomerism has been suggested.¹¹

α -Benzamido-4-hydroxy-3-methoxystyrene was obtained by heating 32 g. of 3-methoxy-4-hydroxybenzamido-cinnamic acid,¹² 32 ml. of concentrated ammonium hydroxide and 10 ml. of water in a pressure bottle for 24 hours at 105°. The product isolated in the usual manner and recrystallized from isopropyl alcohol melted at 173–174°, yield 9 g., 65%. *Anal.* Calcd. for $C_{16}H_{15}O_3N$: C, 71.3; H, 5.57; N, 5.2; mol. wt., 269. Found: C, 71.6; H, 5.30; N, 5.3; mol. wt. (Rast), 262, 265. The hydrolysis with hydrochloric acid gave benzoic acid, am-

monium chloride and a gum having a weak vanillin odor. Methylation with dimethyl sulfate gave a product melting at 137–138°, whose analysis corresponded to that of the expected methyl derivative (*Anal.* Calcd. for $C_{17}H_{17}O_3N$: N, 4.9; Found: N, 5.0). The melting point reported in the literature for this compound is 138°.¹¹ However, on recrystallization from dilute acetic acid the melting point rose to 150–151° while the analytical value did not change.

2-Phenyl-4-(3,4-dimethoxybenzal)-imidazolone-5.—Sixteen grams of the azlactone from veratraldehyde, 5.5 g. of sodium carbonate, 16 ml. of ammonium hydroxide and 30 ml. of water was heated in a pressure bottle for thirty hours at 110–120°. The mixture was allowed to cool, the crystals filtered, washed with dilute ammonium hydroxide and dried. The product melted at 265–266°, yield 12.5 g. (78%). The melting point did not change on recrystallization from acetic acid. *Anal.* Calcd. for $C_{18}H_{16}O_5N_2$: N, 9.1. Found: N, 9.0. 2-Phenyl-4-(3-methoxy-4-ethoxy-benzal)-imidazolone-5 was prepared in the same manner with a yield of 81% and had a melting point of 260–262°.

Summary

Alkoxy and methylenedioxy substituted α -(*N*-acylamido)-cinnamic, phenylpyruvic and phenylthiopyruvic acids react with ammonium hydroxide to yield *N*-phenylacetyl-phenylalanines. Para-substituted acids, under the same conditions, give acylamidostyrenes. An improved procedure for the synthesis of azlactones and 2-phenyl-4-benzalimidazolones-5 is described.

126 BUCKINGHAM ROAD
YONKERS, N. Y.

RECEIVED FEBRUARY 2, 1950

(10) Rosenmund, Nothnagel and Riesenfeldt, *Ber.*, **60**, 392 (1927).

(11) Sugasawa, *J. Pharm. Soc. Japan*, **55**, 58 (1935).

(12) Harrington and McCartney, *Biochem. J.*, **21**, 854 (1927).

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

Polyamides from Azelaonitrile and Formaldehyde

By DAVID T. MOWRY AND EUGENE L. RINGWALD

The normal addition of alcohols or their derivatives to nitriles under acidic conditions leads to the formation of iminoester salts or esters. Certain secondary and tertiary alcohols or related olefins, however, add abnormally to give *N*-substituted amides.¹ Recently Buc² has shown that *N*-methylolamides reacted with nitriles in a similar abnormal fashion to give amides of methylene diamine. A related reaction of two moles of an aromatic nitrile with one of formaldehyde to give methylene bisamides in the presence of excess mineral acids has been known for many years.³

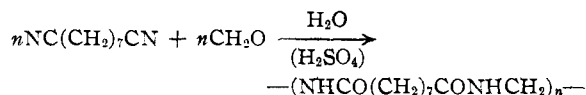
A preliminary extension of this reaction to aliphatic mononitriles indicated that the reaction was rapid and essentially quantitative. Studies

(1) Wieland and Dorner, *Ber.*, **63**, 404 (1930), obtained *N*-cyclohexylformamide from cyclohexene and hydrogen cyanide in the presence of aluminum chloride. See also Ritter, Minieri and Kalish, *THIS JOURNAL*, **70**, 4045, 4048 (1948); Benson and Ritter, *ibid.*, **71**, 4128 (1949). The products obtained from cyclohexanone and nitriles by Bruson, Riener and Riener, *ibid.*, **70**, 483 (1948), are probably better formulated as *N*-substituted amides rather than as iminoesters.

(2) Buc, *THIS JOURNAL*, **69**, 254 (1947).

(3) Hepp and Spiess, *Ber.*, **9**, 1424 (1876); **10**, 1649 (1877); Kraut, *Ann.*, **258**, 109 (1890); Thiesing, *J. prakt. Chem.*, [2] **44**, 570 (1891); Duden and Scharff, *Ann.*, **288**, 247 (1895); Riedel, *J. prakt. Chem.*, [2] **54**, 533 (1896).

were then initiated in an effort to produce polyamides of high molecular weight from a number of aliphatic dinitriles from three to ten carbon atoms. The formaldehyde-azelaonitrile reaction was selected for detailed study since the thermal (m. p. 245–250°) and solubility (soluble only in phenols and formic acid) characteristics of the resultant polymethylene azelamide approximated those of commercial polyhexamethylene adipamide. As



expected, methylene polyamides having a lower carbon to nitrogen ratio, prepared from lower straight chain aliphatic dinitriles, melted at higher temperatures and were less soluble. After a systematic study of reaction variables it was possible to prepare polymethylene azelamide having specific viscosities of 0.9 to 1.2 for a 1% solution in 90% phenol. These values are comparable to those found for samples of commercial flake Nylon which have been shown to have molecular weights of approximately ten thousand.⁴

(4) Taylor, *THIS JOURNAL*, **69**, 635 (1949).