CONDENSATION PRODUCTS OF 2-PYRIDINECARBOXALDEHYDE WITH VARIOUSLY SUBSTITUTED PHENYLACETONITRILES

Thesis for the Degree of M. S.

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Submitted to the School of Science and Arts of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

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AN ABSTRACT

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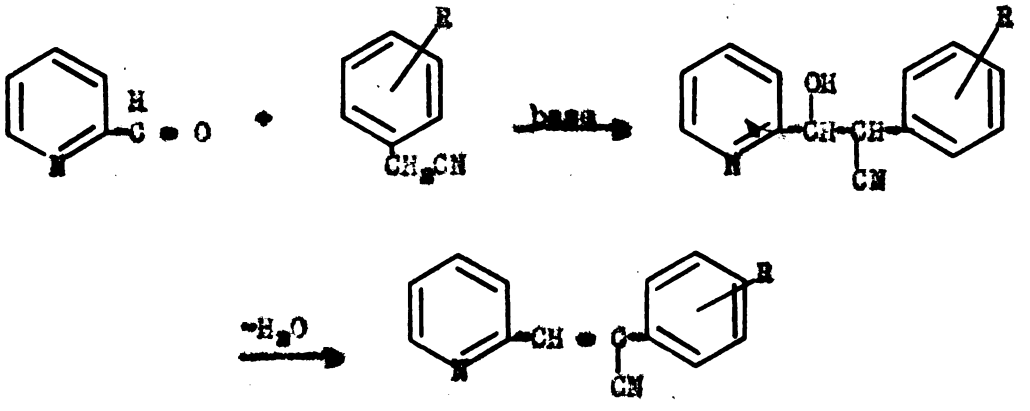
Approved Gordon L. Goerner

ABSTRACT

A series of diaryl acrylonitriles was prepared by condensing 2-pyridinecarboxaldehyde with variously substituted phenylacetonitriles. The condensation reaction proceeds according to the following equation.



The nitriles used were phenylacetonitrile itself, and p-methoxy-, p-hydroxy-, p-amino-, p-dimethylamino-, p-acetamido-, p-nitro-, p-(β-diethylaminoethoxy)-, and o-, m-, and p-chlorophenylacetonitrile.

The α-phenyl-β-(2-pyridyl)-acrylonitriles were found to polymerize readily in polar solvents in the presence of acids.

Attempts to prepare β-phenyl-α-(2-pyridyl)-propylamine by hydrogenating the corresponding acrylonitrile were unsatisfactory due to the resistance to reduction of the double bond between the aromatic rings.

Ethylmagnesium bromide reacted with α-phenyl-β-(2-pyridyl)acrylonitrile by 1,4-addition to give α-phenyl-β-(2-pyridyl)valeronitrile which was fractionated into a solid and a liquid isomer.

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INTRODUCTION

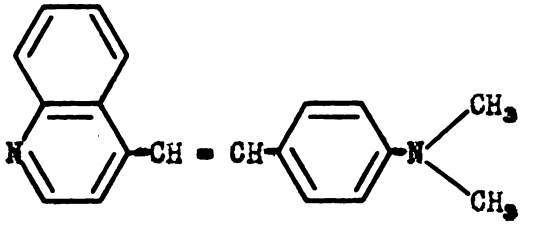
Since the discovery of their cytotoxic action, nitrogen mustards have become the subject of wide investigation as possible chemotherapeutic agents for cancer.

In pursuit of compounds of this type for screening for anti-cancer activity McKay and Brownell (1) prepared N,N-bis(β-chloroethyl)β,γ-diphenyl-n-propylamine and the corresponding dianisyl compound.

$R_1 = R_2 = H, CH_3O$

It was decided to attempt the preparation of similar β,β'-dichlorodiethylamines having a heterocyclic ring in place of the phenyl or anisyl group in the β-position of the propylamine. The preparation of α-phenyl-β-(2-pyridyl)-acrylonitrile was carried out by condensing 2-pyridinecarboxaldehyde and phenylacetonitrile. However, because of unexpected difficulty in reducing the double bond in the acrylonitrile, no propylamines and hence no nitrogen mustards of the desired type could be prepared in this research.

It has been reported by Gilman and Karmas (2) that 4-(p-dimethylaminostyryl)quinoline caused regression of tumors in test animals.



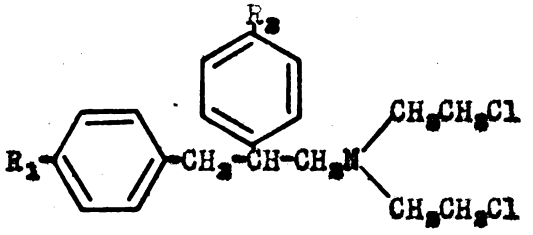
Since the condensation products of 2-pyridinecarboxaldehyde with phenylacetonitriles are similar compounds having a pyridine ring in place of the quinoline group, it was decided to expand the series of substituted diaryl acrylonitriles for study of possible pharmacological properties.

This paper reports the preparation of such a series of diaryl acrylonitriles, some of their chemical properties and the attempts to make β-phenyl-γ-(2-pyridyl)propylamines. The acrylonitriles were made by condensing 2-pyridinecarboxaldehyde with a variety of substituted phenylacetonitriles.

HISTORICAL

The cytotoxic behavior of nitrogen mustards has made these compounds a subject of study in recent years as possible chemotherapeutic agents for cancer.

N,N-bis(β-chloroethyl)-β,γ-diphenyl-n-propylamine and the corresponding dianisyl compound have been prepared by McKay and Brownell (1) for screening for anti-tumor activity.



$R_1 = R_2 = H, CH_3O$

It was decided to attempt the preparation of similar compounds possessing a pyridine ring in place of the phenyl or anisyl group in the β-position.

There are several known routes available for the syntheses of β,γ-diarylpropylamines. The Knoevenagel reaction can be employed for condensing aryl aldehydes with phenylacetonitriles giving arylcinnamonitriles. Subsequent reduction furnishes the β,γ-diarylpropylamine. There are also methods reported for preparing the saturated compounds by alkylating phenylacetonitriles. The resulting α,β-diarylpropionitrile can then be reduced to the amine.

Amines and sodium alcoholates are usually used as catalysts for the Knoevenagel condensation reactions.

Frost (3) showed that benzaldehyde condenses with phenylacetonitrile in the presence of sodium ethoxide, giving an excellent yield of α-phenylcinnamonitrile. Sodium ethoxide was also used to prepare 4-methoxy-α-phenylcinnamonitrile from p-methoxybenzaldehyde and phenylacetonitrile (4). The same method was employed by de Kiewiet and Stephen to prepare the condensation products of 2,4-dimethoxy-, 3,4-dimethoxy- and 2-methoxy-4-acetoxybenzaldehydes with phenylacetonitrile (5). However, poor yields were obtained with 4-hydroxy-2-methoxy- and 4-hydroxy-3-methoxybenzaldehydes when sodium ethoxide was used due to the fact that the sodium salts of the hydroxybenzaldehydes are sparingly soluble in alcohol. Yields were increased to 90% when 6 N alcoholic potassium hydroxide was used. Frost was also able to condense phenylacetonitrile with furfural to give α-phenylfurfuracrylonitrile using sodium ethoxide (6).

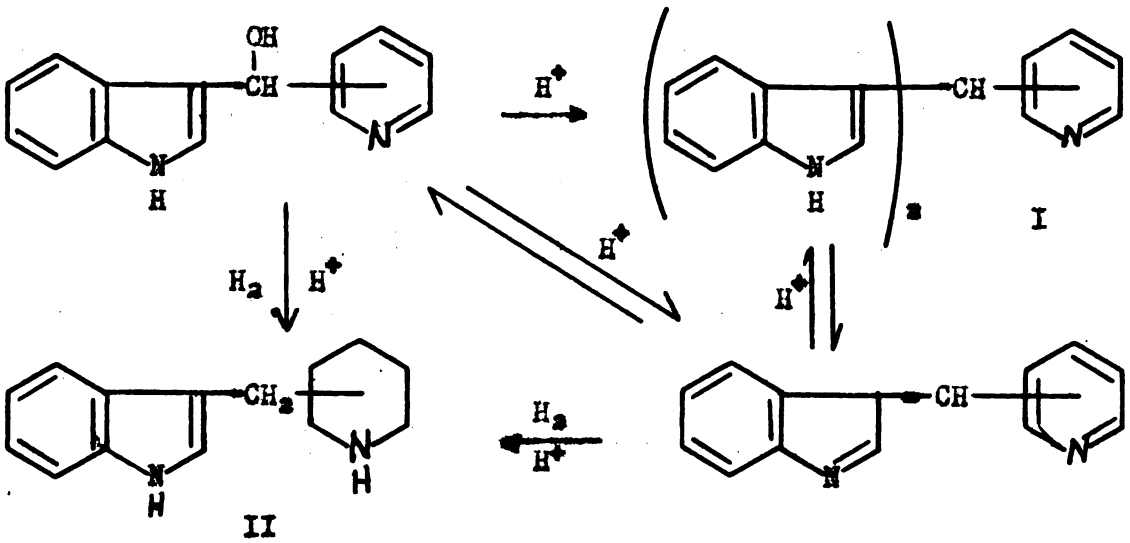
Substituted phenylacetonitriles generally react with aldehydes in the same manner as phenylacetonitrile. Niederl and Ziering (7) have prepared cyanostilbenes from p-methoxyphenylacetonitrile, 3,4-dimethoxy- and 3,4-methylenedioxyphenylacetonitrile and various aromatic aldehydes in yields ranging between 30 and 40% using sodium alcoholates as condensing agents. p-Nitrophenylacetonitrile condenses with p-nitrobenzaldehyde to 4,4'-dinitro-α-cyanostilbene. The m-nitro and o-nitrocompounds react similarly.

McKay and Brownell (1) prepared β, γ-diphenylpropylamine from α-phenylcinnamonitrile [obtained in 95% yield by condensation of benzaldehyde

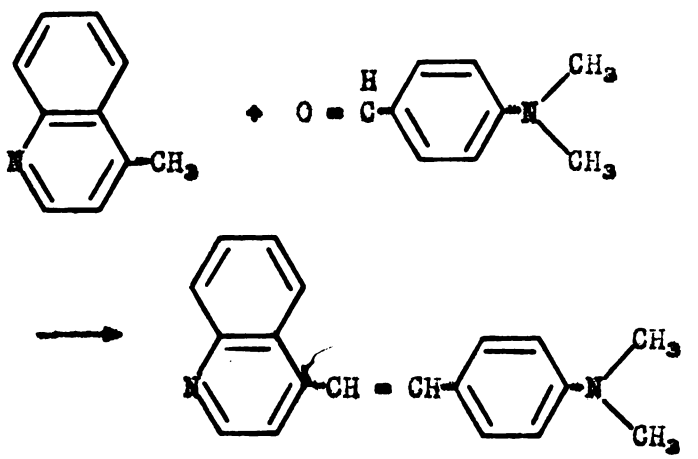
with phenylacetonitrile according to Frost (3)] by catalytic reduction in glacial acetic acid with Adams' platinum oxide catalyst. The reduced product was obtained in 46% yield.

Phillips (8) reported that cinchoninaldehyde reacted rapidly with a variety of substituted phenylacetonitriles to produce the α-(substituted phenyl)-β-(4-quinolyl)-acrylonitriles in 80% or greater yields. Aqueous potassium hydroxide was the usual catalyst, although a more weakly basic catalyst, such as diethylamine or piperidine was used with p-nitrophenylacetonitrile. Apparently the stronger basic catalyst was detrimental with more reactive nitriles.

α,β-Diphenylpropionitrile can be produced in 60-65% yields by alkylating phenylacetonitrile with benzyl chloride using sodium amide (9). Jarrouse (10) reported that α,β-diphenylpropionitrile can be obtained in a 50% yield by the interaction of benzyl chloride and phenylacetonitrile in the presence of aqueous potassium hydroxide and triethylamine. Gray (11) carried out reductive alkylation of indole with 2- and 4-pyridinecarboxaldehydes producing low yields of the respective skatylpiperidines (II) and some diindolyl product (I). The following equilibria would appear to be involved.

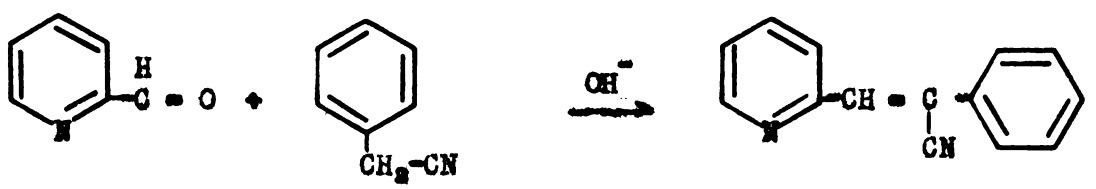


The reactivity of the hydrogen atoms of a methyl group in the α- and γ-positions of a heterocyclic ring has been utilized in a number of condensation reactions. Friedlander (12) was able to prepare γ-styryl-pyridine (stilbazole) by heating a mixture of benzaldehyde and γ-picoline with zinc chloride. Shaw and Wagstaff (13) reported that acetic anhydride, used as the condensing agent for 2- or 4-picoline with aromatic aldehydes, gave purer products and higher yields than did zinc chloride. Gilman and Karmas (2) condensed variously substituted benzaldehydes with picolines, quinaldine and lepidine using either acetic anhydride or zinc chloride. They were able to prepare 4-(p-dimethylaminostyryl)-quinoline according to the following equation.



Bahmer and co-workers (14) reported preparing the isoquinoline analog and variously substituted compounds of this type of the zinc chloride method. Yields from this reaction are occasionally low and often the product must be extracted from the resulting tar.

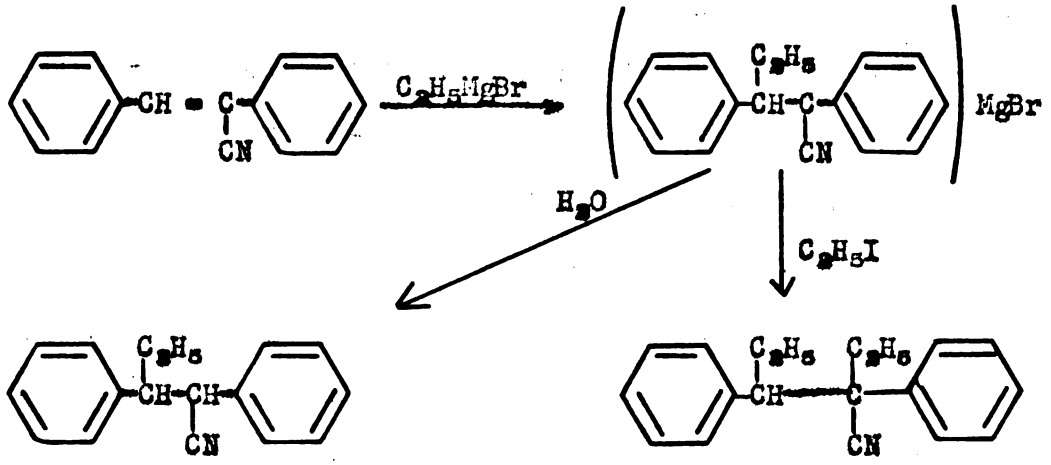
Since the pyridinecarboxaldehydes have recently become available commercially, it was decided to condense 2-pyridinecarboxaldehyde with a number of phenylacetonitriles in the manner employed by Phillips (8). In the course of this investigation it was learned that α-phenyl-β-(2-pyridyl)-acrylonitrile could be prepared in good yield from 2-pyridinecarboxaldehyde and phenylacetonitrile using aqueous potassium hydroxide as the condensing agent. The following reaction illustrates this reaction.



The reduction conditions used by McKay and Brownell (i.e. Adams' platinum oxide catalyst in glacial acetic acid) could not be applied to α-phenyl-β-(2-pyridyl)-acrylonitrile because the vinylpyridine structure is susceptible to polymerization in the presence of acids. The double bond in α-phenyl-β-(2-pyridyl)-acrylonitrile was also found to be very resistant to other methods of reduction and several attempts to hydrogenate the compound gave unsatisfactory results.

Several α-phenyl-β-arylpropionitriles have been obtained in unspecified yields by reduction of the corresponding acrylonitriles with sodium amalgam (10). Avramoff and Sprinzak (15) recently reported the reduction of α,β-diphenylacrylonitriles by refluxing with benzyl alcohol and potassium hydroxide. Although the acid was obtained in most cases, the hydrolysis of the nitrile could be suppressed by distilling out the water from the benzyl alcohol solution before adding the acrylonitrile. These latter methods of reduction were not attempted in this research.

Kohler (16) showed that an equivalent of ethylmagnesium bromide added to α-phenylcinnamonitrile to produce α,β-diphenylvaleronitrile (III).



III IV

If, instead of hydrolyzing the addition product, a slight molar excess of ethyl iodide were added and the mixture refluxed, the resulting product was the disubstituted compound (IV). This disubstituted product, consisting of only a single solid isomer, was obtained by Kohler in 98% yield. Wawzonek (17) doing a reinvestigation of Kohler's work obtained 90% of solid product which could be separated by fractional crystallization and mechanical picking into two isomeric nitriles.

In addition to the nitrogen mustards certain other types of compounds have been reported to possess anti-cancer and anti-tumor activity. Gilman and Karmas (2) reported that 4-(p-dimethylaminostyryl)-quinoline administered in a diet of rats bearing Lymphoma 8 tumors brought about regression of the tumors. Bahner and co-workers (14) stated that a series of 4-(4-aminostyryl)-quinolines and isoquinoline analogs of 4-(p-dimethylaminostyryl)-quinoline showed various degrees of anti-tumor activity.

Since α-phenyl-β-(2-pyridyl)-acrylonitriles are similar to the above compounds, having a pyridine ring in place of the quinoline group and

also possessing the double bond between the aromatic substituents, it appeared desirable to examine this series of compounds for anti-tumor and anti-cancer activity.

This paper therefore, deals with efforts devoted to the preparation of the series of compounds possessing a pyridine ring in a related structure in hopes that they may exhibit similar pharmacological properties.

Hann and Lapworth (18) first formulated the aldol-like mechanism for the Knoevenagel reaction which was later supported by Kohler and Carson (19).

The mechanism probably involves the following steps:

1. Enolization of the methylene compound by dissociation of a hydrogen ion;

$$R'\text{-}CH_2CN \rightleftharpoons H^+ + [R'\text{-}CH\text{-}CN]^-$$

2. Addition of the enol, probably through its ions, to the carbonyl compound;

$$R_2C=O + [R'\text{-}CHCN]^- + H^+ \rightleftharpoons R_2C(OH)\text{-}CH(R')\text{-}CN$$

3. Elimination of water from the aldol-like intermediate.

$$R_2C(OH)\text{-}CH(R')\text{-}CN \rightleftharpoons H^+ + OH^-(\text{or } H_2O) + R_2C=C(R')\text{-}CN$$

Bases produce a higher concentration of the enolate anion in the enolization equilibrium (step 1) by removing the hydrogen ion. The rate

of the addition reaction (step 2) depends upon the degree to which the carbonyl compound is hindered. Reactions similar to step 3 in which water is eliminated are catalyzed by both acids and bases, but generally acids are more effective than bases.

EXPERIMENTAL*

I. REAGENTS

m-Chlorophenylacetonitrile--Prepared by R. Crocker, b. p. 123-126° (5 mm.), n_D^{20} 1.5434, reported (20) m.p. 11.5°, b.p. 261°.

o-Chlorophenylacetonitrile--Prepared by D. Wyman, b.p. 115-116° (5-7 mm.), n_D^{21} 1.6808, reported (20) m.p. 24°, b.p. 251° (242°).

p-Chlorophenylacetonitrile--Prepared by T. Povlock, b.p. 127-128° (8 mm.), n_D^{20} 1.5415, reported (20) m.p. 30°, b.p. 265-267°.

The above chlorophenylacetonitriles were prepared by graduate students in the Organic Preparations Course, Chemistry 543, at Michigan State University. They were prepared from the corresponding chlorobenzyl chlorides and sodium cyanide in aqueous alcohol solution by the method shown in Organic Syntheses (21).

Acetic anhydride--Eastman white label. Used as received.

Anisyl alcohol--Eastman white label. Used as received.

Ethyl bromide--Eastman white label. Used as received.

Lithium aluminum hydride--Metal Hydrides, Inc. Ground to a powder and stored in bottles in a dessicator.

Magnesium shavings--Matheson, Coleman and Bell. Used as received.

Methyl iodide--Eastman white label. Used as received.

Phenylacetonitrile--Eastman white label. Used as received.

Phenyl isothiocyanate--Eastman white label. Used as received.

Pyridine--Matheson, Coleman and Bell. Used as received.

2-Pyridinecarboxaldehyde--Aldrich Chemical Co. Used as received. Stored under nitrogen in the refrigerator until needed.

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*All analyses were by Micro-Tech Laboratories, Skokie, Illinois.

Potassium hydroxide--Baker Analyzed Reagent. Used as received.

5% Palladium on charcoal catalyst.

Mozingo Raney nickel catalyst--Previously prepared by the method described in Organic Syntheses (22).

Sodium Cyanide--Baker Analyzed Reagent. Used as received.

II. PREPARATION OF INTERMEDIATES

p-Methoxyphenylacetonitrile. p-Methoxyphenylacetonitrile was prepared as described in Organic Syntheses(23). In this method anisyl alcohol is converted into the chloride by vigorous stirring with concentrated hydrochloric acid and the resultant chloride is made into the nitrile by heating with sodium cyanide in anhydrous acetone. From 138.2 g. (1.0 mole) of anisyl alcohol there was obtained 114.6 g. (78%) of p-methoxyphenylacetonitrile, b.p. 99-102° (0.4 mm.), n_D^{25} 1.5290. Organic Syntheses reports b.p. 94-97° (0.3 mm.), n_D^{25} 1.5285-1.5291, yields of 74-81%.

p-Hydroxyphenylacetonitrile. This compound has been prepared previously by Yoder and co-workers (24) by the condensation of p-hydroxybenzaldehyde with rhodanine using a modification of the Granacher thio- and oxindine pyruvic acid synthesis (25,26). In this work p-hydroxyphenylacetonitrile was prepared by demethylation of p-methoxyphenylacetonitrile with pyridine hydrochloride.

Twenty-four grams (0.31 mole) of dry pyridine was dissolved in 300 ml. of dry ether and hydrogen chloride gas was passed into the solution until precipitation of the salt was complete. The pyridine hydrochloride was separated by filtration, washed twice with dry ether, and then added

to a 250 ml. flask fitted with an air condenser and thermometer. p-Methoxyphenylacetonitrile (14.7 g., 0.10 mole) was then added and the reaction mixture was heated to 180° on a mantle for four hours. After cooling the melt was taken up in water, about 50 ml. of 6 N hydrochloric acid was added, and the oil was removed by two ether extractions. The combined ether extractions were washed twice with water, dried over sodium sulfate, and the ether was evaporated off on a steam bath. Distillation of the residue gave 9.5 g. (71%) of p-hydroxyphenylacetonitrile, b.p. 148-150° (0.5 mm.). The material solidified in the receiving flask and gave m.p. 69-70°, reported (27) b.p. 330°, m.p. 69-70°.

p-(β-N,N-Diethylaminoethoxy)phenylacetonitrile. Twelve grams (0.09 mole) of p-hydroxyphenylacetonitrile, 4.9 g. (0.09 mole) of sodium methoxide and 100 ml. of methanol were mixed in a 1-liter flask fitted with a stirrer and condenser. After stirring for several minutes 200 ml. of xylene was added and the methanol was then boiled off.

β-Diethylaminoethyl chloride hydrochloride (23.2 g., 0.135 mole) was dissolved in a minimum amount of water in a separatory funnel. Two hundred milliliters of xylene was chilled in a dry ice-acetone bath, and one-third of this was then added to the separatory funnel. Potassium hydroxide (7.6 g., 0.135 mole) was dissolved in a minimum of water and this solution was added to the funnel, the xylene then being used to extract the liberated free amine. Two more extractions were made with the remaining cold xylene. The combined extracts were dried over magnesium sulfate for 30 minutes.

The xylene solution of the amine was added to the reaction flask and refluxed for four hours. When working up the reaction mixture the xylene solution was washed with water, twice with 10% sodium hydroxide solution, and twice again with water. The organic solution was dried a few minutes over magnesium sulfate and the xylene was stripped off under reduced pressure. When the residue was distilled through a four-inch Vigreux column in vacuo, 11.4 g. (55%) of a light yellow oil was collected, b.p. 154-155° (0.5 mm.).

Anal. Calc'd. for $C_{14}H_{20}N_2O$: N, 12.06. Found: N, 11.64.

p-Nitrophenylacetonitrile. p-Nitrophenylacetonitrile was prepared as described in Organic Syntheses (28). Phenylacetonitrile (150.0 g., 1.28 moles) was added dropwise to a chilled mixture of 412.5 ml. of concentrated nitric acid (sp. gr. 1.42) and 412.5 of concentrated sulfuric acid (sp. gr. 1.84) with vigorous stirring. Upon isolation and recrystallization, 110.2 g. (54%) of p-nitrophenylacetonitrile, m.p. 114.5-116.0°, was obtained. Organic Syntheses reports m.p. 115-116°, 50-54% yields.

p-Aminophenylacetonitrile. p-Aminophenylacetonitrile was prepared by a modification of the method reported by Chase and co-workers (29).

Sixty-five grams (0.40 mole) of p-nitrophenylacetonitrile was reduced catalytically in two separate runs of 35.0 g. and 30.0 g. A suspension of the p-nitrophenylacetonitrile in a mixture of 150 ml. of ethyl acetate and 50 ml. of 95% ethanol was shaken at room temperature with 0.3 g. of 5% palladium on activated charcoal at 50 psi. The larger run

absorbed the theoretical amount of hydrogen after four hours; the other run required only two and one-half hours. After filtering off the catalyst the two solutions were combined and the solvent was removed under reduced pressure. The oily residue was distilled in vacuo through a five-inch Vigreux column giving 46.1 g. (90%) of a colorless oil, b.p. 139-140° (0.8 mm.). The hydrochloride melted at 229-230°, reported m.p. 230-231° (29).

p-Acetamidophenylacetonitrile. Eight grams (0.061 mole) of p-aminophenylacetonitrile was dissolved in 5 ml. of concentrated hydrochloric acid in 200 ml. of water. Acetic anhydride (7.5 g., 0.073 mole) was then added to the solution followed immediately by the addition of 9.2 g. of sodium acetate. Within a short time white platelets filled the reaction mixture. The platelets were collected on a filter, washed with cold water and dried. The crude yield was 9.3 g., m.p. 69-73°. This material was recrystallized from water (ca. 200 ml.) with only a few milliliters of ethanol added to aid dissolution. The recovered product weighed 9.1 g. (81%), m.p. 73-74°.

Anal. Calc'd. for $C_{10}H_{10}N_2O$: N, 16.09. Found: N, 16.06.

Trimethyl phosphate. Trimethyl phosphate was prepared by the method described in Organic Syntheses (30), for the preparation of alkyl phosphates.

Sodium metal (34.5 g., 1.50 moles) in small pieces was added slowly to 200 ml. of methanol in a 1-liter flask fitted with a stirrer, condenser and dropping funnel. After all of the sodium had reacted the methanol was boiled off. One hundred milliliters of xylene was added

during the removal of the last of the methanol to prevent caking of the residue. An additional 100 ml. of xylene was then added, the flask was cooled in an ice bath, and 76.6 g. (0.50 mole) of phosphorus oxychloride in xylene (ca. 190 ml.) were added dropwise to the stirred reaction mixture keeping the temperature below 20°. After the addition was complete the reaction mixture was warmed on a steam bath with stirring for 10 hours. The mixture was then filtered and the sodium chloride on the filter was washed several times with ether, the ether wash being added to the filtrate. The solvent was removed under reduced pressure and the product was purified by distillation. The yield of the colorless oil was 31.1 g. (44.4%), b.p. 90-91° (20 mm.), n_D^{25} 1.3950. The reported boiling point is 97° (36 mm.) (31).

p-Dimethylaminophenylacetonitrile. This compound was prepared by the method employed by Billman and co-workers (32,33) for alkylating amines using phosphate esters.

p-Aminophenylacetonitrile (17.1 g., 0.086 mole) was mixed with 12.0 g. (0.086 mole) of trimethyl phosphate in a 1-liter flask fitted with a condenser. The mixture was then cautiously heated with a Bunsen burner until a vigorous reaction set in. A gentle reflux was then maintained for two and one-half hours using a mantle. After the flask cooled the reaction mixture was treated with aqueous potassium hydroxide (15 g. KOH) and the organic material was extracted with three ether washings. The combined extracts were washed with water, dried over potassium carbonate and the ether was evaporated off on the steam bath. The oily residue

was distilled *in vacuo* to give 8.3 g. (40%) of a light yellow oil, b.p. 119-120° (0.5 mm.). The hydrochloride melted at 166-7°.

Anal. Calc'd for $C_{10}H_{13}ClN_2$: N, 14.25. Found: N, 14.47.

III. GENERAL EXPERIMENTAL INFORMATION

Since Phillips (8) reported that cinchoninaldehyde condensed rapidly with various phenylacetonitriles in a base catalyzed reaction, it was reasonable to believe that 2-pyridinecarboxaldehyde would behave in like manner. In order to determine what catalyst would be most suitable for this reaction, a series of condensations were attempted with 2-pyridinecarboxaldehyde and phenylacetonitrile in ethanol using aqueous potassium hydroxide, piperidine, diethylamine and sodium methoxide as the condensing agents. In no case did the product precipitate from the solution as reported by Phillips. It was later learned that phenylacetonitrile was an unfortunate choice, since α-phenyl-β-(2-pyridyl)-acrylonitrile was one of the few condensation products of the series that failed to precipitate from the reaction mixture.

The first effective procedure for the preparation of α-phenyl-β-(2-pyridyl)-acrylonitrile was as follows: Equivalent amounts of 2-pyridinecarboxaldehyde and phenylacetonitrile were mixed in a 5:1 water-ethanol solution. While the suspension was stirred vigorously with a mechanical stirrer a few milliliters of aqueous potassium hydroxide was added. The solid product which formed in a few minutes was isolated, dried, and recrystallized from 50% aqueous ethanol.

A more convenient method later adopted for the preparation of α-phenyl-β-(2-pyridyl)-acrylonitrile involved carrying out the condensation in isopropyl alcohol. The reaction mixture was allowed to stand for approximately an hour to assure completion of the condensation. It was then poured into a beaker of ice with stirring. The product precipitated immediately as a solid. Attempts to cause precipitation of the product by adding water to the isopropyl alcohol solution forced the product out of solution as an oil instead of the desired crystalline material.

Usually the substituted phenylacetonitriles formed condensation products with 2-pyridinecarboxaldehyde which precipitated from isopropyl alcohol solution as crystals within minutes after being catalyzed with aqueous potassium hydroxide.

Aqueous potassium hydroxide was an effective catalyst for most of the condensations. Piperidine was used with p-nitrophenylacetonitrile because benzene was used as the solvent for the reaction. p-Aminophenylacetonitrile was basic enough to self-catalyze its condensation with 2-pyridinecarboxaldehyde.

Isopropyl alcohol proved to be a good solvent for carrying out the reaction and for recrystallization of the products. When isopropyl alcohol and a piperidine catalyst were used to condense p-nitrophenylacetonitrile and 2-pyridinecarboxaldehyde an intense purple color developed in the reaction mixture. When benzene was used as the solvent the solution did not change color appreciably. The acetamido- and

nitro-substituted products were quite insoluble in the alcohols and benzene, and acetonitrile was employed as the solvent for recrystallising these products.

IV. CONDENSATION PRODUCTS

α-Phenyl-β-(2-pyridyl)acrylonitrile. Seventeen grams (0.157 mole) of 2-pyridinecarboxaldehyde and 18.4 g. (0.157 mole) of phenylacetonitrile were dissolved in 150 ml. of isopropyl alcohol in a 500-ml. Erlenmeyer flask. A solution of 5.0 g. of potassium hydroxide in 20 ml. of water was then added, the reaction mixture was swirled a few seconds and allowed to stand overnight. The solution was poured on ice (ca. 500 g.) with stirring, whereupon a white solid precipitated. This material was collected on a filter, washed three times with water to remove traces of alkali, and dried. Recrystallization of the crude product from 150 ml. of isopropyl alcohol yielded 24.8 g. (76.5%) of white crystals, m.p. 63-64°. A second recrystallization gave 23.2 g., m.p. 65-66°.

Anal. Calc'd for $C_{14}H_{10}N_2$: C, 81.52; H, 4.89; N, 13.59.

Found: C, 81.61; H, 5.01; N, 13.50.

α-(p-Chlorophenyl)-β-(2-pyridyl)acrylonitrile. p-Chlorophenylacetonitrile (37.9 g., 0.25 mole) and 26.8 g. (0.25 mole) of 2-pyridinecarboxaldehyde were mixed in 500 ml. of isopropyl alcohol. Within a minute after adding 25 ml. of 20% aqueous potassium hydroxide crystals began precipitating from the solution. After standing overnight the white crystalline product was separated by filtration, washed once with cold

isopropyl alcohol and three times with water. The dried material weighed 55.8 g. (67% yield), m.p. 121-127°. After two recrystallizations from isopropyl alcohol the product melted at 126-127°.

Anal. Calc'd for $C_{14}H_9ClN_2$: C, 69.87; H, 3.77; N, 11.65.

Found: C, 69.56; H, 3.90; N, 11.58.

α-(*m*-Chlorophenyl)-β-(2-pyridyl)acrylonitrile. The condensation of 15.2 g. (0.10 mole) of *m*-chlorophenylacetonitrile and 10.7 g. (0.10 mole) of 2-pyridinecarboxaldehyde was carried out in 175 ml. of isopropyl alcohol using aqueous potassium hydroxide (1 g. in 5 ml. of water) to catalyze the reaction. When the catalyst was added the yellow solution turned slightly darker and crystals precipitated within a minute. After filtration, washing and drying, the product weighed 19.6 g. The yield was 81.6 percent and the white crystals melted at 103-104.5°. Two recrystallizations from isopropyl alcohol did not change the melting point.

Anal. Calc'd for $C_{14}H_9ClN_2$: C, 69.87; H, 3.77; N, 11.65.

Found: C, 70.00; H, 4.01; N, 11.42.

α-(*o*-Chlorophenyl)-β-(2-pyridyl)acrylonitrile. *o*-Chlorophenylacetonitrile (15.2 g., 0.10 mole) and 10.7 g. of 2-pyridinecarboxaldehyde were dissolved in 200 ml. of isopropyl alcohol, followed by the addition of a solution of 1 g. of potassium hydroxide in 5 ml. of water. The reaction mixture was allowed to stand at room temperature for three hours but no precipitation took place. The flask was then placed in the refrigerator overnight, a precipitate being present the following morning. The reaction flask was allowed to stand in the refrigerator two additional

days before the product was isolated. The white crystals were collected on a filter, washed with water and air-dried for several days. The material weighed 16.0 g. (67%) and melted over a 134-152° range. Several recrystallizations from isopropyl alcohol only narrowed the difference to 132-141°. Recrystallizations from benzene and from ethyl acetate failed to improve the melting point.

Anal. Calc'd for $C_{14}H_9ClN_2$: N, 11.65. Found: N, 10.72.

α-(p-Nitrophenyl)-β-(2-pyridyl)-acrylonitrile. Ten grams (0.062 mole) of p-nitrophenylacetonitrile and 6.6 g. (0.062 mole) of 2-pyridinecarboxaldehyde were dissolved in 450 ml. of benzene. Thirty drops of piperidine were added and the reaction mixture was allowed to stand one day. The crystals which formed were collected on a filter and dried. The crude product weighed 11.3 g., m.p. 130-5°. The material was recrystallized from benzene (ca. 800 ml.) and 7.0 g. of tan crystals, (m.p. 198-200°, was recovered in the first crop. The combined mother liquors from the reaction mixture and the recrystallization furnished an additional 6.7 g. when the volume of the solution was reduced. The total yield was 13.7 g., 82.5% of theoretical. The crystals from another recrystallization melted at 198-199.5°.

Anal. Calc'd for $C_{14}H_9N_3O_2$: C, 66.95; H, 3.61; N, 16.73.

Found: C, 67.03; H, 3.77; N, 16.92.

α-(p-Aminophenyl)-β-(2-pyridyl)-acrylonitrile. When 4.8 g. (0.045 mole) of 2-pyridinecarboxaldehyde was added to 8.0 g. (0.045 mole) of

p-aminophenylacetonitrile in 75 ml. of isopropyl alcohol, precipitation of the white crystalline product took place within a minute without the aid of an outside catalyst. After the crystals were collected on a filter and dried, they weighed 8.5 g. (85%) and melted at 94-95°. Recrystallization from isopropyl alcohol gave 7.3 g. of white needles, m.p. 95-96°.

Anal. Calc'd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99.

Found: C, 76.04; H, 5.18; N, 19.07.

One gram of α-(p-aminophenyl)-β-(2-pyridyl)-acrylonitrile was added to a beaker containing 25 ml. of water. Fifteen drops of concentrated hydrochloric acid were added with stirring followed by the addition of 15 drops of acetic anhydride. A water solution of 0.6 g. of sodium acetate was added immediately and the acetylated product formed as a heavy precipitate. Aqueous potassium hydroxide was added until the solution was basic to litmus. The product was collected on a filter, thrice washed with water and dried. The yellow crystalline product melted at 182-197°. Two recrystallizations from acetonitrile raised the melting point to 211.5-212.5°. This is identical with the melting point of α-(p-acetamidophenyl)-β-(2-pyridyl)-acrylonitrile prepared from p-acetamidophenylacetonitrile and 2-pyridinecarboxaldehyde. A mixed melting point of the two products showed no depression.

α-(p-Dimethylaminophenyl-β-(2-pyridyl)-acrylonitrile. Eight grams (0.05 mole) of p-dimethylaminophenylacetonitrile was condensed with 5.3 g. (0.05 mole) of 2-pyridinecarboxaldehyde in 175 ml. of isopropyl

alcohol using aqueous potassium hydroxide (one gram in five milliliters of water) as catalyst. Yellow crystals precipitated from the solution within minutes after the alkali was added. Upon completion of precipitation the product was collected on a filter, washed once with cold isopropyl alcohol and twice with water. The dried yellow crystals weighed 11.7 g., m.p. 130-134°. When the material was recrystallized from isopropyl alcohol 9.3 g. (75%) was recovered, m.p. 135-136.5°. The pure product melted at 135.5-136.5°.

Anal. Calc'd. for $C_{16}H_{15}N_3$: C, 77.09; H, 6.07; N, 16.86.

Found: C, 77.26; H, 6.13; N, 16.95.

α-(p-Acetamidophenyl)-β-(2-pyridyl)-acrylonitrile. p-Acetamidophenylacetonitrile (5.5 g., 0.032 mole) and 3.4 g. (0.032 mole) of 2-pyridinecarboxaldehyde were dissolved in 100 ml. of isopropyl alcohol, followed by the addition of 0.5 g. of potassium hydroxide in 3 ml. of water to the solution. The reaction mixture turned dark purple when the alkali was added. After standing several hours a precipitate formed which was collected on a filter, washed with cold isopropyl alcohol, water, and dried. The yield was 7.0 g. (84.5%) of yellow material, m.p. 208-210°. Two recrystallizations from acetonitrile gave yellow platelets, m.p. 211.5-212.5°.

Anal. Calc'd. for $C_{16}H_{13}N_3O$: N, 15.96. Found: N, 16.18.

α-(p-Methoxyphenyl)-β-(2-pyridyl)-acrylonitrile. This nitrile was obtained as a mixture with β-hydroxy-α-(p-methoxyphenyl)-β-(2-pyridyl)-propionitrile

by the following procedure. Fourteen and seven-tenths grams (0.10 mole) of p-methoxyphenylacetonitrile and 10.7 g. (0.10 mole) of 2-pyridinecarboxaldehyde were mixed in a solution of 75 ml. of isopropyl alcohol in 200 ml. of water. Three grams of potassium hydroxide dissolved in 5 ml. of water was then added and the mixture was swirled vigorously a few minutes until the solid product precipitated. The reaction mixture was then allowed to stand several hours before filtering. After the crude product was washed and air dried it weighed 21.8 g. Recrystallisation from isopropyl alcohol gave two types of crystals. One (the acrylonitrile) melted at 74-75° and the other (shown to be largely the hydroxy nitrile) melted at 118-132°. Separation of the acrylonitrile from the hydroxy nitrile was achieved by redissolving them in the mother liquor and permitting the solution to stand. The acrylonitrile crystallised first and was largely separated from the hydroxy nitrile by decanting to remove the unprecipitated hydroxy nitrile. The acrylonitrile was recrystallised from fresh isopropyl alcohol, 14.2 g. (58%) being recovered, m.p. 71.5-73.0°. Two additional recrystallisations improved the melting point to 72-73°.

Anal. Calc'd. for $C_{15}H_{12}N_2O$: N, 11.86. Found: N, 11.73.

α-(p-Hydroxyphenyl)-β-(2-pyridyl)acrylonitrile. Seven grams (0.053 mole) of p-hydroxyphenylacetonitrile was dissolved in a solution of 3.4 g. (0.06 mole) of potassium hydroxide in 125 ml. of water. 2-Pyridinecarboxaldehyde (5.7 g., 0.053 mole) was then added and the reaction mixture was allowed to stand at room temperature for one day. The product was

precipitated by adding carbon dioxide (dry ice) to the solution. The light brown solid was collected on a filter, washed with water, and dried. The yield of crude product was 6.4 g. (43%), m.p. 155-158°. Recrystallization from isopropyl alcohol gave 5.0 g. of tan crystals melting at 164-165°. A second recrystallization did not change the melting point.

Anal. Calc'd. for $C_{14}H_{10}N_2O$: C, 75.67; H, 4.54; N, 12.61.

Found: C. 75.66; H, 4.70; N, 12.55.

β-Hydroxy-α-(p-methoxyphenyl)-β-(2-pyridyl)propionitrile. p-Methoxyphenylacetonitrile (36.8 g., 0.25 mole) and 28.0 g. (0.25 mole) of 2-pyridinecarboxaldehyde were added to a 2-liter Erlenmeyer flask containing 100 ml. of 95% ethanol and 500 ml. of water. Ten grams of potassium hydroxide pellets was then added and the mixture was swirled several minutes until the pellets dissolved and the solid condensation product formed. After filtering, washing with water and drying, the crude material weighed 58.9 g., m.p. 118-130°. Recrystallization from ethyl acetate furnished 51.2 g. of white crystals. The yield was 88% and the melting point was 148-150°. An additional recrystallization raised the melting point to 149.5-150.5°

Anal. Calc'd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02.

Found: C, 70.74; H, 5.62; N, 10.91.

α-[p-(β-Diethylaminoethoxy)phenyl]-β-hydroxy-β-(2-pyridyl)-propionitrile. Three and one-half grams (0.015 mole) of p-β-diethylaminoethoxy)phenylacetonitrile and 1.6 g. (0.015 mole) of 2-pyridinecarboxaldehyde were

dissolved in 75 ml. of isopropyl alcohol. One pellet of potassium hydroxide was dissolved in a minimum of water and was added to the above solution. After the reaction mixture stood for two days crystals precipitated from the solution. Upon warming the mixture only part of the crystals went into solution. When the warm solution was filtered 0.8 g. of orange crystals, m.p. 156-159°, were obtained. After recrystallization from acetonitrile the resulting orange needles melted at 157-159°. An analysis indicated that the material was α-pyridoin. The reported melting point is 156° (34).

Anal. Calc'd for $C_{12}H_{10}N_2O_2$: C, 67.27; H, 4.71.

Found: C, 67.59; H, 4.72.

The mother liquor from the above product gave a white precipitate upon standing. The crystals were collected on a filter, washed with cold isopropyl alcohol and dried. The yield of α-[p-(β-diethylaminoethoxy)-phenyl]-β-hydroxy-β-(2-pyridyl)-propionitrile was 1.2 g. (25%), m.p. 107-109°. Recrystallization from isopropyl alcohol raised the melting point to 108.5-109°.

Anal. Calc'd. for $C_{22}H_{25}N_3O_2$: C, 70.78; H, 7.43.

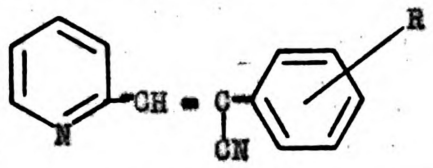
Found: C, 70.68; H, 7.45.

V. DERIVATIVES

α-(p-Chlorophenyl)-β-(2-pyridyl)acrylonitrile Methiodide. Five grams (0.021 mole) of α-(p-chlorophenyl)-β-(2-pyridyl)acrylonitrile was dissolved in 200 ml. of dry benzene, 6 g. of methyl iodide was added and the solution was allowed to stand at room temperature. Precipitation of

TABLE I

CONDENSATION PRODUCTS OF 2-PYRIDINECARBOXALDEHYDE WITH VARIOUSLY SUBSTITUTED PHENYLACETONITRILES



	R	Percent Yield	M.p. °C.
1.	H	75	65-66
2.	p Cl	67	126-127
3.	m Cl	82	103-104.5
4.	o Cl	67	132-141[e]
5.	p NO_2[a]	83	198-199.5
6.	p NH_2[b]	85	95-96
7.	p $NHCOCH_3$	85	211.5-212.5
8.	p $N(CH_3)_2$	75	135.5-136.5
9.	p OCH_3	58[c]	72-73
10.	p OCH_3	88	149.5-150.5
11.	p OH	43	164-165
12.	p $OC_2H_4N(C_2H_5)_2$[d]	25	108.5-109

[a] Piperidine used as catalyst.
[b] No catalyst necessary.
[c] Isolated by fractional crystallization from the crude product which was a mixture of the aldol intermediate and the dehydrated compound.
[d] Stable aldol intermediate.
[e] Repeated recrystallizations from isopropyl alcohol, benzene, and ethyl acetate failed to raise the melting point.

the crystalline methiodide was very slow and the reaction mixture stood for two months before an attempt was made to isolate the orange crystals. After filtration, washing with dry benzene and drying, 4.5 g. (56% yield) of crystals was obtained, m.p. 211-212°. Recrystallization from an isopropyl alcohol-acetonitrile solvent gave orange needles, m.p. 211.5-212° dec.

Anal. Calc'd. for $C_{15}H_{15}ClIN_3$: C, 47.08; H, 3.16.

Found: C, 46.89; H, 3.03.

β-Hydroxy-α-(p-methoxyphenyl)-β-(2-pyridyl)propionitrile Hydrochloride. Six grams (0.024 mole) of β-hydroxy-α-(p-methoxyphenyl)-β-(2-pyridyl)-propionitrile was dissolved in 200 ml. of dry ether with a minimum amount of methanol added to take the material into solution. The hydrochloride was then precipitated by adding a slight excess of ethereal hydrogen chloride. After filtering, washing with dry ether and drying, 7.1 g. of crude product was obtained. When a melting point was attempted the sample in the capillary polymerized around 200°. The melting point of the material was established at 229-230° by the following method. The oil bath was graduated to various temperatures and the melting point of the product tested by immersing the tip of the capillary. By converging on the temperature at which the sample took several seconds to melt and before it polymerized, the melting point was determined. When an attempt was made to recrystallize the hydrochloride by dissolving it in warm methanol, the solution began to darken. Dry ether was quickly added

forcing the salt out of solution. Six grams (88%) of nacreous platelets was recovered, m.p. 231-232° dec.

Anal. Calc'd. for $C_{16}H_{14}N_2O$: C, 61.96; H, 5.21.

Found: C, 62.13; H, 5.26.

β-Phenyl-γ-(2-pyridyl)-propylamine. Twenty and six-tenths grams (0.10 mole) of α-phenyl-β-(2-pyridyl)-acrylonitrile was dissolved in 120 ml. of absolute ethanol and added to the flask for high pressure hydrogenation. The solution was chilled in a dry ice-acetone bath and approximately 20 ml. of liquid ammonia was added. Two grams of Raney nickel was added and the material was then hydrogenated at 1500 psi for four hours at an elevated temperature (ca. 100°). The catalyst was filtered off and the solvent was removed under reduced pressure leaving a red-yellow oil as residue. This material was distilled at 0.5 mm. pressure using a four-inch Vigreux column. A forerun of 0.7 g. of a light yellow oil distilled at 60-61°. Three other fractions were then collected: 5.7 g. at 130-150°; 5.4 g. at 150-155°; and 2.1 g. at 155-165°. The fraction with b.p. 150-155° (0.5 mm.), n_D^{25} 1.5745, was used to identify the product. The oil formed a yellow crystalline salt with picric acid, m.p. 215.5-216.5°. Phenylisothiocyanate was used to prepare the phenylthiourea derivative. This material appeared to have a melting point below room temperature. However, the hydrochloride salt of the phenylthiourea derivative was a white crystalline salt, seemingly non-hygroscopic, which melted at 176-177°. This salt gave the following analysis.

Anal. Calc'd. for $C_{21}H_{22}ClN_3S$: N, 10.94. Found: N, 10.95.

α-Phenyl-β-(2-pyridyl)-valeronitrile. Magnesium turnings (2.9 g., 0.12 gram-atom) were placed in a one-liter flask fitted with a stirrer, condenser capped with a calcium chloride tube, and a dropping funnel, and the entire system was flamed gently. One hundred milliliters of dry ethyl ether was added to the magnesium in the flask. Ethyl bromide (12.7 g., 0.12 mole) was dissolved in 150 ml. of dry ether and poured into the dropping funnel. Ten milliliters of the ethyl bromide solution was then added to the magnesium and the reaction mixture was stirred vigorously. After the reaction began the ethyl bromide solution was then added dropwise to the stirred mixture at such a rate as to maintain a slow reflux (ca. 40 minutes). The stirring was continued one-half hour after the addition was complete. An additional two milliliters of ethyl bromide was added to consume the unreacted magnesium.

α-Phenyl-β-(2-pyridyl)-acrylonitrile (20.6 g., 0.10 mole) was dissolved in 200 ml. of dry benzene and this solution was added dropwise to the Grignard reagent with stirring over a 20-minute period. The reaction mixture was then stirred and refluxed on a steam bath for five hours.

The complex was decomposed by adding slowly a saturated solution (ca. 100 ml.) of ammonium chloride. The organic layer was washed three times with water, dried over potassium carbonate for two hours, and the solvent was evaporated.

The oily residue was distilled in vacuo giving 16.8 g. (79%) of a yellow oil of b.p. 140-142° (0.8 mm.). Several attempts to prepare a suitable crystalline acid salt from hydrogen chloride or picric acid

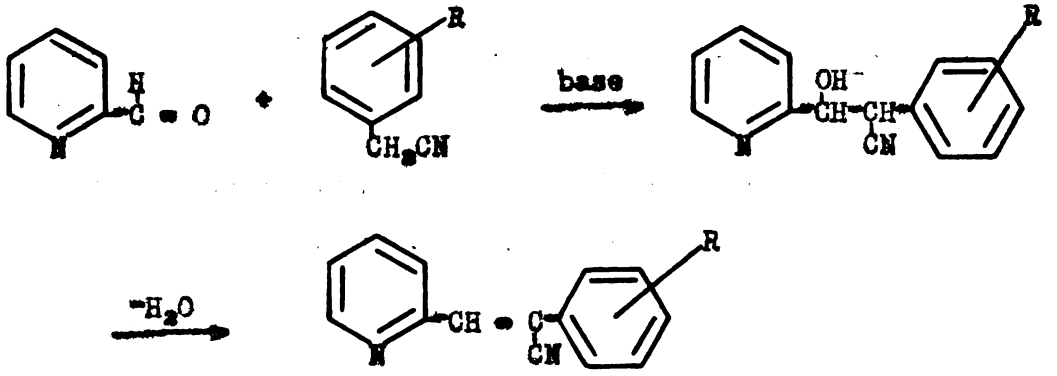
were unsuccessful. The salts may be too hygroscopic to be easily crystallized and purified. The oil was redistilled at 126-128° (0.2 mm.). The distillate solidified upon standing in the refrigerator, m.p. 61-3°, and fractional crystallization from n-hexane gave a solid and a liquid isomer. Six grams of colorless chunky crystals, m.p. 67.5-69°, were obtained from 10.2 g. of distillate. Recrystallization of the solid isomer did not change the melting point.

Anal. Calc'd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82.

Found: C, 81.19; H. 6.83.

DISCUSSION

The condensation of 2-pyridinecarboxaldehyde and ring substituted phenylacetonitriles proceeds according to the following equation.

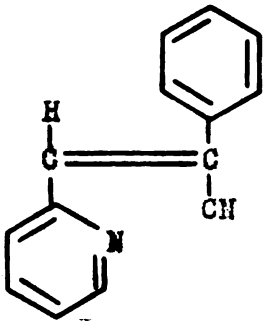


The table on page 28 lists compounds prepared in this manner.

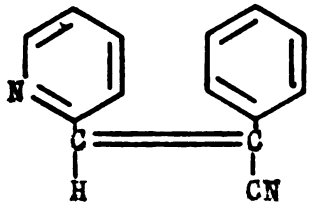
Usually the intermediate aldol compound in this series is unstable and splits out a molecule of water spontaneously during the reaction yielding an acrylonitrile as the final product. However, when p-methoxy phenylacetonitrile was condensed with 2-pyridinecarboxaldehyde the aldol intermediate was stable and was the only product recovered from the reaction mixture. Later, when this condensation was repeated, the crude product was a mixture of the aldol intermediate and the dehydrated compound. p-[(β-Diethylaminoethoxy)-phenyl]-acetonitrile and 2-pyridinecarboxaldehyde also formed a stable aldol compound which was the sole product from the condensation reaction.

Cis and trans isomers of the condensation products are possible, although in no instance was there evidence of more than one isomer produced.

Presumably the isomer isolated from these condensations is the cis-modification where the cyano group lies adjacent to the pyridine ring (the phenyl group and the pyridine group are trans to one another).



Cis-Form



Trans-Form

DeKiewiet and Stephen (5) were unable to hydrolyze nitriles obtained by similar condensations and assumed that the products were the cis-isomers. It had been shown by Pfeiffer (35) that cis forms of certain olefinic nitriles resist hydrolysis whereas the trans isomers can be hydrolyzed without difficulty.

It is possible for two molecules of 2-pyridinecarboxaldehyde to react in a benzoin-type condensation to form 2-pyridoin. In only one of the listed condensations, viz., the preparation of α-[p-(β-diethylamino-ethoxy)phenyl]-β-hydroxy-β-(2-pyridyl)-acrylonitrile, was there any 2-pyridoin recovered from the reaction mixture. 2-Pyridoin may have been formed in this reaction because of the slow precipitation of the hydroxy nitrile, or because fresh 2-pyridinecarboxaldehyde was not used. The condensation product, i.e., the hydroxy nitrile, did not precipitate until after two days, whereas the nitriles from the other condensation reactions precipitated within minutes. If this delay is due to a slower

rate of reaction, perhaps this allows time for free 2-pyridinecarboxaldehyde to condense to form 2-pyridoin. Also, when old 2-pyridinecarboxaldehyde is added to isopropyl alcohol an insoluble material is diffused throughout the solution. Perhaps the insoluble substance is 2-pyridoin which is formed by self-condensation of the aldehyde upon standing. The insoluble material was not in sufficient quantity to be collected on a filter.

If α-phenyl-β-(2-pyridyl)-acrylonitrile or any of the phenyl substituted analogs is dissolved in a polar solvent, such as methanol, and a small amount of acid is added, the solution turns black and a tarry substance covers the bottom and sides of the container. This reaction takes place rapidly, within a matter of seconds under optimum conditions. For this reason it is believed that polymerization is the reaction that occurs rather than any possible oxidation reaction. A polar solvent appears to be essential for the polymerization. The hydrochloride salt of the acrylonitriles can be prepared without difficulty by adding ethereal hydrogen chloride to a solution of the compound in dry ether. The hydrochloride salt, however, cannot be recrystallized since this procedure necessitates dissolving the crystals in a solvent. Strong mineral acids bring about the conversion to the tarry material quickly, whereas acetic acid causes the reaction to take place at a slower rate. An excess of an equivalent of acid is not necessary for polymerization. The reaction is probably an ionic polymerization since a polar solvent and an acid are requisites for the reaction. α,β-Diphenylacrylonitriles

do not behave in this manner, therefore, apparently the pyridine ring in the structure plays a significant role in promoting the polymerization.

The hydrochloride salt of β-hydroxy-β-(p-methoxyphenyl)-β-(2-pyridyl)-propionitrile can be prepared although one must use caution when re-crystallizing the salt in order to avoid dehydration and subsequent polymerization of the compound.

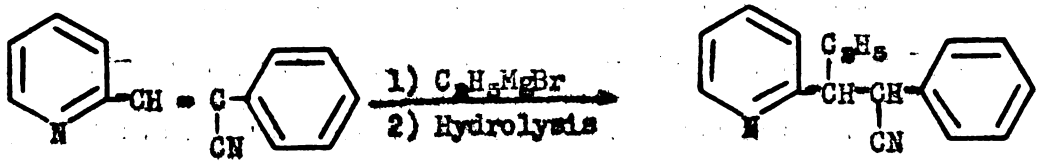
The double bond in α-phenyl-β-(2-pyridyl)-acrylonitriles appears to be very resistant to reduction. When α-phenyl-β-(2-pyridyl)-acrylonitrile was treated with a large excess of lithium aluminum hydride an oil was the resulting product. An infra-red spectrum of the oil indicated that the nitrile group had been reduced. However, apparently the double bond in the vinylpyridine structure remained intact since the oil still polymerized in the presence of an acid and an attempt to distil the oil in vacuo resulted in decomposition. Attempts to hydrogenate the double bond of the acrylonitrile or of the oil derived from the lithium aluminum hydride reduction using platinum oxide or Raney nickel in ethanol at room temperature and 50 psi were unsuccessful. Some β-phenyl-γ-(2-pyridyl)-propylamine was obtained in low yield by reducing α-phenyl-β-(2-pyridyl)-acrylonitrile with Raney nickel at 1500 psi and an elevated temperature.

When p-aminophenylacetonitrile is condensed with 2-pyridinecarbox-aldehyde two different products are possible. The aldehyde can react with the active methylene of the p-aminophenylacetonitrile by the Knoevenagel reaction in the manner common with the other substituted

phenylacetonitriles reported in this work, or the amino group can react with the aldehyde to form the Schiff's base. Since the condensation product formed from p-aminophenylacetonitrile and 2-pyridinecarboxaldehyde precipitated within a minute after merely mixing the two reactants in isopropyl alcohol with no added catalyst, it was reasonable to believe that the Knoevenagel condensation took precedence over the formation of the Schiff's base. However, in order to establish unequivocal proof of which condensation product was obtained, a sample of the material was acetylated. The resulting derivative had the same melting point as did α-(p-acetamidophenyl)-β-(2-pyridyl)-acryonitrile synthesized by condensing 2-pyridinecarboxaldehyde with p-acetamidophenylacetonitrile (page 24). There was no depression in a mixed melting point.

Gray (11, see also page 5) reported reductive alkylation of indole with pyridinecarboxaldehydes in glacial acetic acid using palladium on charcoal catalyst and a low pressure hydrogenator. When Gray's procedure was employed in an attempt to alkylate phenylacetonitrile with 2-pyridine-carboxaldehyde the experiment was unsuccessful, and there was quantitative recovery of the phenylacetonitrile. Gray's reduction was slow and required 72 hours to absorb the theoretical amount of hydrogen; whereas, in this experiment 75% of the theoretical amount of hydrogen was taken up in 45 minutes. Apparently there was no intermediate formed between the 2-pyridinecarboxaldehyde and phenylacetonitrile as was the case with indole, and the absorption of hydrogen was due to hydrogenation of the aldehyde.

α-Phenyl-β-(2-pyridyl)-acrylonitrile was treated with ethylmagnesium bromide in an attempt to prepare α-phenyl-β-(2-pyridyl)valeronitrile.



The resulting oily product was isolated by distilling *in vacuo*. The distillate solidified upon standing a few days in the refrigerator. Fractional crystallization from n-hexane provided a solid and a liquid isomer.

Quaternary salts can be prepared from the acrylonitriles and methyl iodide but the reaction proceeds slowly. If the acrylonitrile and an excess of methyl iodide are dissolved in an inert solvent, such as benzene, and allowed to stand at room temperature, crystals will begin to form after approximately a week. The reported methiodide stood for two months before the product was isolated in order to assure completion of the precipitation.

SUMMARY

2-Pyridinecarboxaldehyde condenses rapidly with phenylacetonitrile and substituted phenylacetonitriles in the presence of an alkaline catalyst to give good yields of α-(substituted phenyl)-β-(2-pyridyl)-acrylonitriles. In two preparations the intermediate aldol compound was sufficiently stable to be isolated.

α-Phenyl-β-(2-pyridyl)-acrylonitriles are polymerised by acids in polar solvents.

The double bond between the aromatic rings in α-phenyl-β-(2-pyridyl)-acrylonitrile is very resistant to reduction. The saturated compound was obtained in a low yield by catalytic hydrogenation at 1500 psi and an elevated temperature.

Ethylmagnesium bromide reacts with α-phenyl-β-(2-pyridyl)-acrylonitrile by 1,4-addition giving α-phenyl-β-(2-pyridyl)-valeronitrile. Fractional crystallisation of the product gave a solid and a liquid isomer.

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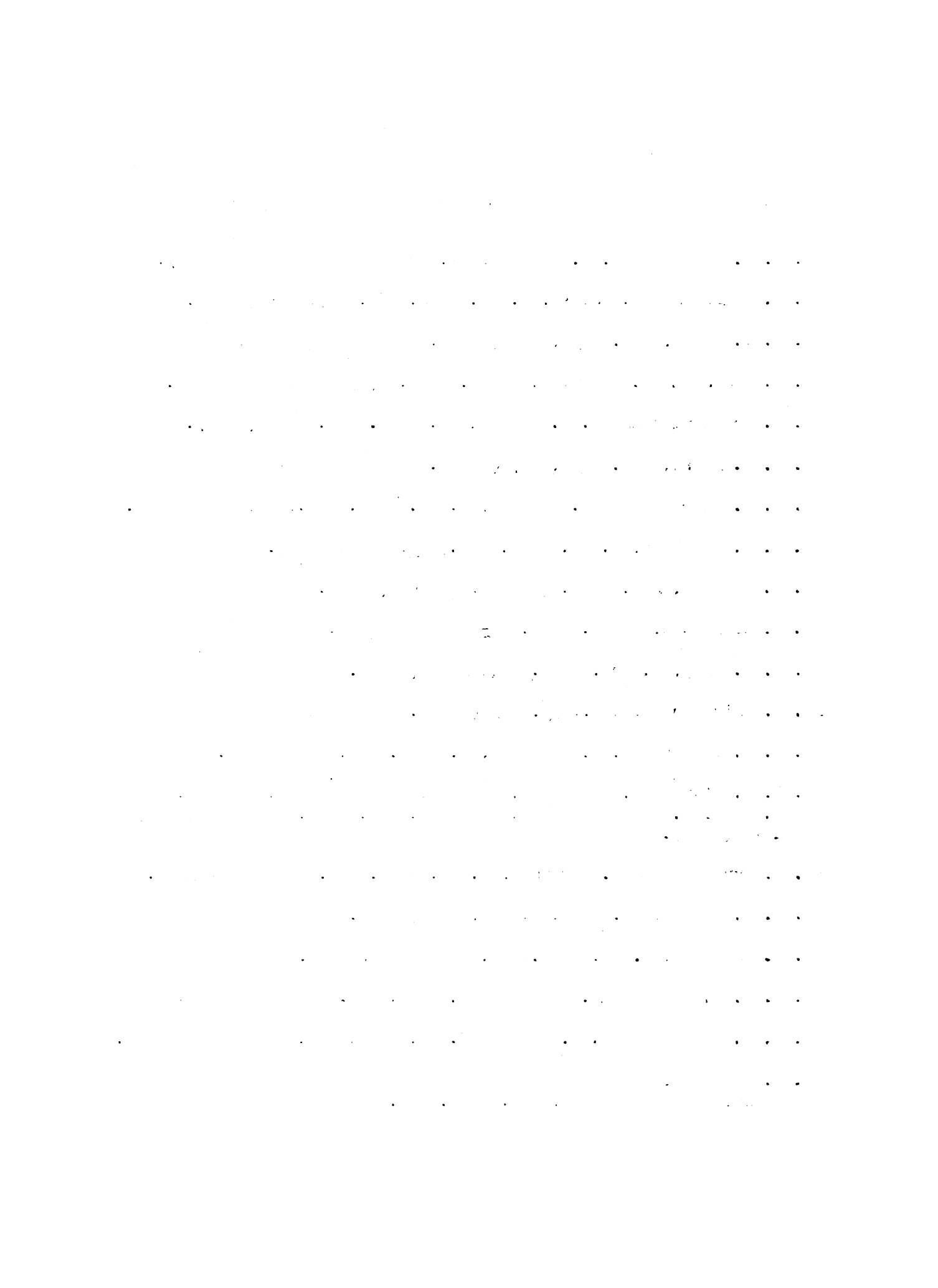

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