A similar procedure with the reaction mixture of 1-(*p*-tolylsulfonyl)-2-propyl *p*-toluenesulfonate and triethylamine gave a 75% yield of crystals, m.p. 90–97°. Recrystallization from hexane gave crystals, m.p. 93–100°, reported[20] for propenyl-*p*-tolysulfone, m.p. 102–103°. The infrared absorption spectrum of the product isolated was different than that of allyl-*p*-tolylsulfone[20] and had a peak at 10.58 μ corresponding to a *trans* disubstituted double bond.

Other experiments of this type are reported by Bordwell and Kern.[19]

Other Materials.—The trimethylamine used in the buffer solution was Eastman Kodak White Label Anhydrous which was distilled into water to give a concentrated stock solution. The triethylamine used in the buffer solution was a middle constant-boiling fraction obtained by distilling the Matheson, Coleman and Bell product. The *p*-toluenesulfonic acid used in the buffers was prepared by boiling an approximately 2.5 *N* water solution of the Matheson, Coleman and Bell product with a generous quantity of charcoal and filtering. "Baker Analyzed" ammonium hydroxide solution and redistilled Matheson piperidine were also used for the preparation of buffers. The dioxane used as a solvent in the kinetic runs was purified by the method described in Fieser.[21]

Buffer Solutions.—The buffer stock solution used in the kinetic runs were prepared by pipetting the proper quantities of standardized amine and *p*-toluenesulfonic acid stock solution into a volumetric flask, adding an amount of pure dioxane equal in volume to the combined volumes of the acid and amine stock solutions and diluting to the mark with 50% by volume dioxane–water. An aliquot was titrated with standard acid to the methyl orange end-point and the value obtained in this manner taken as the concentration of amine in the buffer. The buffer stock solutions were in general about 0.64 *N* in free amine and about 0.05 *N* in amine salt.

The kinetic solution containing buffers were prepared by diluting aliquots of the buffer stock solution with 50% by volume dioxane–water, pipetting 20 ml. of this solution into one arm of a "Y" tube and pipetting 20 ml. of a 50% by volume dioxane–water solution of the sulfone tosylate into the other arm. The sulfone tosylate solution was always made exactly 0.01 *N* so that the experimental infinity readings could be checked both by calculations from an initial reading and by comparison with other runs.

Kinetic Procedures for Amine Rates.—Resistances were measured using an Industrial Instruments, Inc., Model RC16 Conductivity Bridge set at 1000 cycles per second. A modified Jones and Bollinger[22] conductance cell was used with the electrodes coated with platinum black. The reactions were timed with an electric timer. The constant temperature bath was maintained at 25 ± 0.03°. The conductance cells were always rinsed with water, acetone and methanol in that order, dried in a stream of dry nitrogen and equilibrated in the constant temperature bath for at least 5 minutes before being used. The kinetic solutions prepared as previously described were equilibrated in separate arms of the "Y" tube at least 10 minutes before mixing. To start a run the solutions were mixed as the timer was started and the solution poured into the conductance cell. The first reading could usually be obtained within 30 seconds of mixing. The calculations were made as described earlier.

(20) R. S. Schiefelbein, Ph.D. Thesis, Northwestern University, 1949.

(21) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 368.

(22) F. Daniels, J. H. Mathews and J. W. Williams, "Experimental Physical Chemistry," 3rd. Ed., McGraw–Hill Book Co., Inc., New York, N. Y., 1941, p. 368.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NOTRE DAME]

Chichibabin Reactions with Phenylacetaldehyde. II[1]

BY CHARLES P. FARLEY[2] AND ERNEST L. ELIEL

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The condensation of phenylacetaldehyde, acetaldehyde and ammonia under pressure is shown to give rise to a mixture of 3,5-diphenylpyridine, 3,5-diphenyl-2-methylpyridine and 2-methyl-5-phenylpyridine. Phenylacetaldehyde, propionaldehyde and ammonia give 3,5-diphenylpyridine, 3,5-diphenyl-2-ethylpyridine, 2-ethyl-3-methyl-5-phenylpyridine and 3-methyl-5-phenylpyridine in addition to a benzyldiphenylpyridine, probably the 2-benzyl-3,5-diphenyl isomer. Phenylacetaldehyde, isobutyraldehyde and ammonia give the same benzyldiphenylpyridine, 3,5-diphenylpyridine and what appears to be 2-isopropyl-3,5-diphenylpyridine. Phenylacetaldehyde, benzaldehyde and ammonia give 3,5-diphenylpyridine, a triphenylpyridine which appears to be the 2,3,5-isomer and another compound of unassigned structure. The course of these condensations is discussed.

Introduction

In a previous publication[1] it was shown that the condensation of phenylacetaldehyde with ammonia under pressure gives mainly 3,5-diphenylpyridine and toluene (Fig. 1, scheme B, R = C_6H_5, R′ = $C_6H_5CH_2$) instead of the expected 3,5-diphenylphenyl-2(or -4)-benzylpyridine (Fig. 1, scheme A or C, R = C_6H_5, R′ = $C_6H_5CH_2$). 3,5-Diphenylpyridine was also the major product isolated from phenylacetaldehyde and ammonia in the presence of isobutyraldehyde, but in the presence of acetaldehyde different bases were obtained.

It was the objective of the present study to condense phenylacetaldehyde and ammonia in the presence of a series of other aldehydes, isolate as many of the products as possible and determine their approximate mole ratios. It was hoped that some correlation could be found between the nature and yield of the products on the one hand and the nature of the added aldehyde on the other.

Results

From the reaction of phenylacetaldehyde, acetaldehyde and ammonia, three products were isolated. One was the previously encountered[1] 3,5-diphenylpyridine. The second one had the correct analysis for a methylphenylpyridine. Condensation with benzaldehyde to the corresponding stilbazole (II) followed by oxidation gave a phenylpyridinecarboxylic acid (III) the carboxyl function of which occupies the α-position, since the acid gave a red coloration with ferrous sulfate.[3] Decarboxylation of the acid yielded 3-phenylpyridine, identified with an authentic specimen prepared by coupling 3-(N-nitrosoacetamido)-pyridine with

(1) First paper in this series: E. L. Eliel, R. T. McBride and S. Kaufmann, THIS JOURNAL, **75**, 4291 (1953).

(2) From the Ph.D. dissertation of Charles P. Farley, National Institutes of Health fellow, 1953–1954, du Pont teaching fellow, 1954–1955.

(3) H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 569.

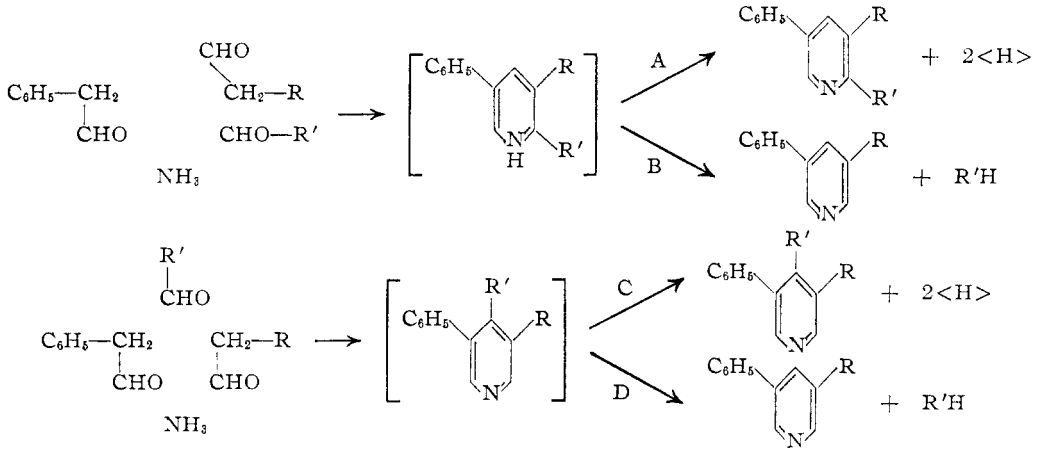

Fig. 1.

benzene.[4] This left 2-methyl-3-phenylpyridine and 2-methyl-5-phenylpyridine as possible structures for the reaction product. The 2-methyl-5-phenylpyridine structure (I) was proved to be the correct one by synthesis of authentic material from 2-methyl-5-carboxypyridine[5] (IV) as outlined in Fig. 2.

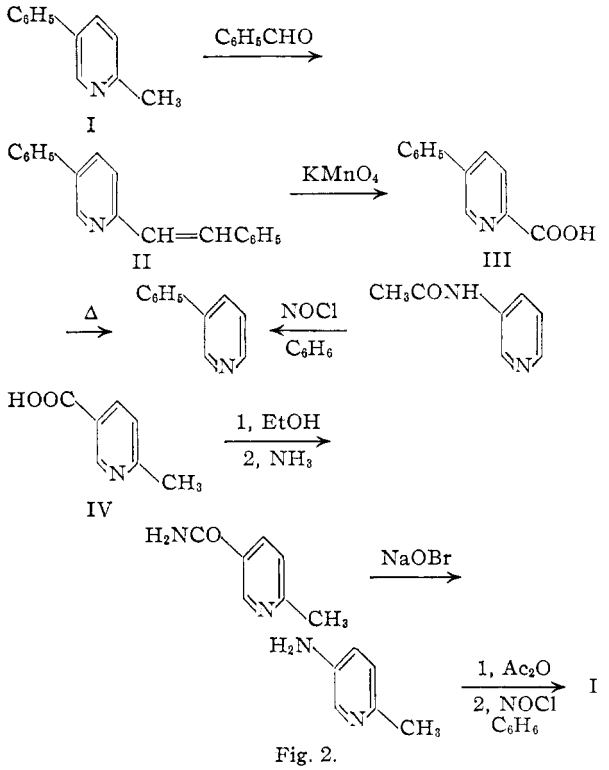

Fig. 2.

The third product of the reaction of phenylacetaldehyde, acetaldehyde and ammonia had the composition of a diphenylmethylpyridine. Oxidation *via* the stilbazole gave a diphenylpyridinecarboxylic acid whose carboxyl group was in the α-position, since it gave a red color with ferrous sulfate. Decarboxylation of this acid led to the known 3,5-diphenylpyridine. Thus the third reaction product is 3,5-diphenyl-2-methylpyridine (V) (*cf.* Fig. 3). The proportions of this compound and 2-methyl-5-phenylpyridine (I) in the condensation product depended on the ratio of phenylacetaldehyde to acetaldehyde. As might be expected, a phenylacetaldehyde to acetaldehyde ratio of 2:1 favors V while a 1:4 ratio favors I.

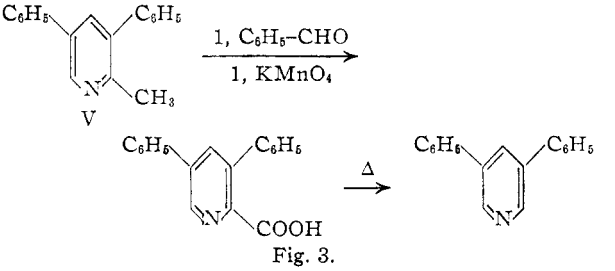

Fig. 3.

Isolation of pure products from the condensation of phenylacetaldehyde, propionaldehyde (2:1 ratio) and ammonia proved difficult. While in the condensation with acetaldehyde removal of the bulk of the 3,5-diphenylpyridine by crystallization followed by fractional distillation and preparation of picrates had led to pure products, in the propionaldehyde case chromatography had to be resorted to. Five products were thus isolated. Of the two intermediate-boiling ones, one was 3,5-diphenylpyridine and the other an ethyldiphenylpyridine. Oxidation of the latter gave the same 2-carboxy-3,5-diphenylpyridine encountered previously; therefore, the compound is 2-ethyl-3,5-diphenylpyridine (VI). The oxidation of VI was carried out *via* the N-oxide VII, acetate VIII and carbinol IV (see Fig. 4),[6] though these intermediates were not isolated.

The lower-boiling material from the condensation also yielded two products, a methylphenylpyridine and a methylethylphenylpyridine. The methylphenylpyridine could be oxidized readily to a phenylpyridinecarboxylic acid which did not give

(4) H. Rapoport, M. Look and G. J. Kelly, THIS JOURNAL, **74**, 6293 (1952), report a 39% yield of 3-phenylpyridine from the 3-isobutyramido derivative but state that the corresponding acetamido derivative is unsuitable for the coupling reaction because of excessive water solubility of its nitroso derivative. We encountered no difficulty in coupling the acetamido derivative using rather concentrated solutions of the reagents, the yield of coupling product being 48%.

(5) Kindly supplied by Dr. Frank Cislak of the Reilly Tar & Chemical Corporation.

(6) *Cf.* V. Boekelheide and W. J Linn, THIS JOURNAL, **76**, 1286 (1954); O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

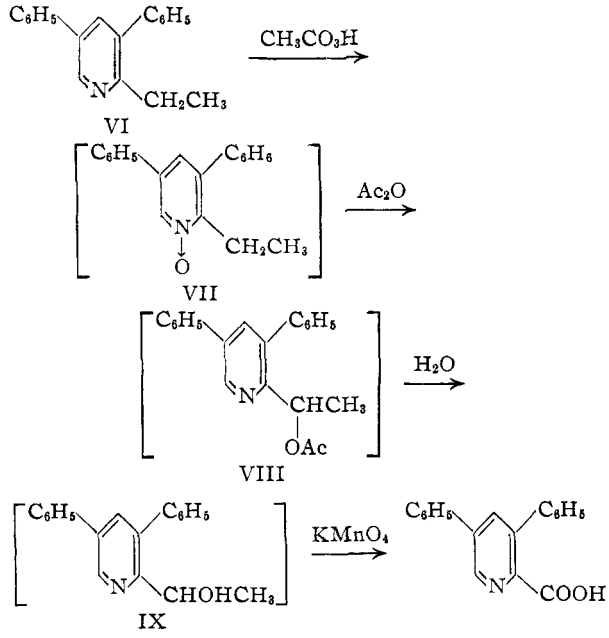

Fig. 4.

a red color with ferrous sulfate indicating absence of an α-carboxyl group. Decarboxylation proceeded with great difficulty and led to 3-phenylpyridine suggesting the acid to be either 3-phenyl-4-carboxypyridine or 3-phenyl-5-carboxypyridine (XI), with preference for the latter in view of its resistance to decarboxylation.[7] This structural assignment was confirmed as explained below and the condensation product which gave rise to the acid is therefore 3-methyl-5-phenylpyridine (X) (*cf.* Fig. 5).

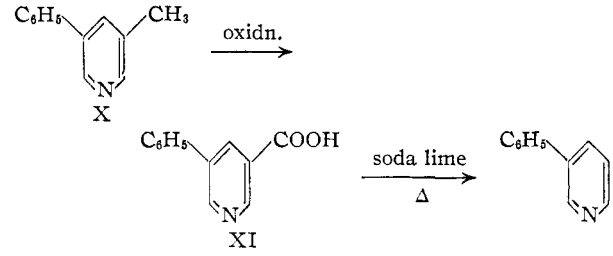

Fig. 5.

Oxidation of the methylethylphenylpyridine (XII) gave two acids. The less soluble of these was the same 3-phenylpyridinecarboxylic acid (XI) obtained from the methylphenylpyridine (X). The more soluble one (XIII) imparted a red color to ferrous sulfate solution and therefore contained an α-carboxyl group. Because of its high solubility, this acid was isolated as its ammonium salt. Treatment of this salt with acetic anhydride gave rise to the corresponding imide XIV, characterized by analysis and infrared spectrum. This proves that the two carboxyl groups in the water-soluble acid are vicinal. Since one of these groups is alpha and since the 3-phenylpyridinecarboxylic acid isolated in this oxidation undoubtedly resulted from decarboxylation of the dicarboxylic acid, it follows that the latter acid is 5-phenylquinolinic acid (XIII). The monocarboxylic acid XI is therefore 5-phenylnicotinic acid (XI) (*cf.* Fig. 6). The methylethylphenylpyridine precursor of the acid XIII could be either 2-methyl-3-ethylpyridine or 2-ethyl-3-methylpyridine (XII). In view of its method of formation (see Discussion) the latter structure is preferred.

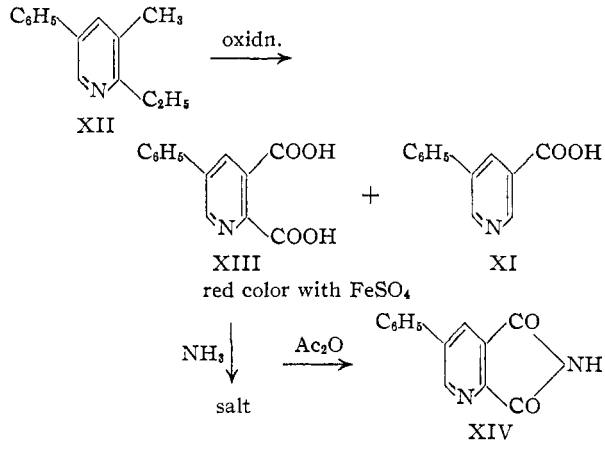

Fig. 6.

The highest-boiling fraction yielded a crystalline solid which had the composition and molecular weight of a benzyldiphenylpyridine. Presence of a benzyl group was confirmed by oxidation to the corresponding benzoyl compound. The position of the benzyl group was not established, but on the basis of analogy and similarity of the ultraviolet spectrum of the compound with those of other 2-alkyl-3,5-diphenylpyridines, the benzyl compound was assigned the 2-benzyl-3,5-diphenylpyridine structure.

Condensation of phenylacetaldehyde, isobutyraldehyde and ammonia gave 3,5-diphenylpyridine and an isopropyldiphenylpyridine. A small amount of the above benzyldiphenylpyridine was also isolated in this reaction. Attempts to oxidize the isopropyldiphenylpyridine to a diphenylpyridinecarboxylic acid, either directly or *via* the carbinol failed. The 2-isopropyl-3,5-diphenylpyridine structure was assigned to the condensation product on the basis of its method of formation and by analogy with the corresponding 2-alkyl compounds isolated in the condensations involving acetaldehyde and propionaldehyde. This assignment is supported by the similarity of the ultraviolet spectrum of the compound with the spectra of 2-methyl- and 2-ethyl-3,5-diphenylpyridine. The only reasonable alternative structure, on the basis of the method of formation of the compound, would be 4-isopropyl-3,5-diphenylpyridine, but it seemed unlikely that the bulky isopropyl group would enter the 4-position when the less bulky methyl and ethyl groups apparently had shunned that position.

Condensation of phenylacetaldehyde, benzaldehyde and ammonia gave 3,5-diphenylpyridine, a triphenylpyridine and a third, high-melting product. The triphenylpyridine was probably the 2,3,5-isomer, in analogy with the products from the other condensations. Its ultraviolet spectrum showed marked differences from those of the 2-alkyl-3,5-diphenylpyridines. This might be ex-

(7) Pyridine 2- and 4-carboxylic acids decarboxylate much more readily than the 3-acids, *cf.* ref. 3, p. 567.

pected, since 2,3,5-triphenylpyridine contains a *p*-terphenyl type as well as *m*-terphenyl type chromophore while the 2-alkyl compounds contain only the *m*-terphenyl type chromophore. The high-melting product, according to its analysis and that of its picrate, was either a triphenylpyridine or a diphenylbenzylpyridine. This compound is likely to be either 3,4,5-triphenylpyridine or 3,5-diphenyl-4-benzylpyridine. Its ultraviolet spectrum closely resembled that of 3,5-diphenylpyridine and the 2-alkyl-3,5-diphenylpyridines, but this would probably be compatible with either of the structures suggested, since the central phenyl ring in 3,4,5-triphenylpyridine is probably inhibited sterically from contributing to the resonating system of the molecule.

Discussion

In the condensation of phenylacetaldehyde and acetaldehyde or propionaldehyde with ammonia, both 2:1 and 1:2 products were isolated, where the ratios refer to the number of phenylacetaldehyde and aliphatic aldehyde molecules, respectively, entering into the product. In the case of isobutyraldehyde and benzaldehyde, only the 2:1 products are possible, since these aldehydes do not contain α-methylene groups available for condensation (see Fig. 1).

In principle, four 2:1 products of a normal "mixed" Chichibabin reaction can be envisaged, a 2-alkyl-3,5-diphenylpyridine, a 4-alkyl-3,5-diphenylpyridine, a 2-benzyl-3-alkyl-5-phenylpyridine and a 4-benzyl-3-alkyl-5-phenylpyridine. (The latter two products require the presence of an α-methylene group in the added aldehyde component.) Only the first of these was formed consistently in all the cases studied. Its method of formation is outlined in Fig. 1, scheme A, where R is phenyl and R′ is methyl, ethyl, isopropyl, phenyl or benzyl. The second product (scheme C) may have been formed in the case where R and R′ were phenyl, but even in this case its identification was only tentative and in no other case was the 4-substituted product isolated. The third and fourth possible products were never isolated. In addition to schemes A and C an "abnormal" Chichibabin reaction[1] involving loss of alkane instead of loss of hydrogen from the intermediate dihydropyridine is possible. Such a reaction (Fig. 1, schemes B and D) leads to a 3,5-disubstituted pyridine regardless of whether the alkane is extruded from position 2 (scheme B) or position 4 (scheme D). Since a 3,4,5-trisubstituted pyridine was usually not found in this work, one is led to believe that once a 3,4,5-trisubstituted dihydropyridine is formed it tends to stabilize itself by scheme D rather than by scheme C. Scheme D may account for most or all of the products of the "abnormal" Chichibabin reactions observed here.

The alkyl group R′ eliminated as alkane in the abnormal reaction *via* scheme B or scheme D may be either benzyl (derived from phenylacetaldehyde) or it may be derived from the other aldehyde component (R′ = methyl, ethyl, isopropyl, phenyl). Experimental evidence suggests that both these possibilities are realized. While in the condensation of phenylacetaldehyde alone with ammonia the amount of toluene isolated was approximately equivalent to the amount of 3,5-diphenylpyridine formed,[1] in the present work the toluene found was always substantially *less*. This implies that other alkyl groups were eliminated as well, in the form of methane, ethane, propane or benzene,[8] though attempts to isolate the latter in the condensation of phenylacetaldehyde, benzaldehyde and ammonia were unsuccessful. There were other indications however, summarized in Table I, that the 3,5-diphenylpyridine obtained was not all formed from phenylacetaldehyde and ammonia alone. *More* 3,5-diphenylpyridine was obtained in the presence of other aldehydes than in their absence, despite the fact that in the presence of other aldehydes, substantial amounts of the phenylacetaldehyde are diverted into products other than 3,5-diphenylpyridine. It is particularly interesting that both the actual yield of 3,5-diphenylpyridine and the ratio 3,5-diphenylpyridine to 2-alkyl-3,5-diphenylpyridine increase as the alkyl group is changed from methyl to ethyl to isopropyl. The enhanced tendency to elimination of the isopropyl group may be due to steric or electronic factors. Until the mechanism of the elimination step is ascertained, the relative importance of these factors remains uncertain.

Only two of the possible 1:2 products (one mole of phenylacetaldehyde and two of aliphatic aldehyde entering the pyridine) were found in the condensations. One, corresponding to scheme A (Fig. 1) was found both with acetaldehyde (R = H, R′ = CH_3) and with propionaldehyde (R = CH_3, R′ = C_2H_5). The other one, an "abnormal" reaction product formed *via* scheme B or D, was found only in the case of propionaldehyde (R = CH_3, R′ = C_2H_5, alternatively explained as a 2:1 product with R = CH_3, R′ = $C_6H_5CH_2$).

TABLE I

NUMBER OF MOLES OF 2:1 CONDENSATION PRODUCTS FORMED FROM ONE MOLE PHENYLACETALDEHYDE, ONE-HALF MOLE ALIPHATIC ALDEHYDE AND AMMONIA

Product	None	Acetaldehyde	Propionaldehyde	Isobutyraldehyde
Toluene	0.032	0.017	Trace	0.0075
3,5-Diphenylpyridine	0.049[a]	.065	0.083	.156
2-Alkyl-3,5-diphenylpyridine	...	.064	0.052	.030
Ratio: line 2/line 3	...	1.0	1.6	5.2

[a] Corrected value.

Experimental[9]

Condensation. General Method.—One mole (120 g.) of phenylacetaldehyde and one-half mole of the other aldehyde component were dissolved in 350 ml. of a saturated solution of ammonia in absolute ethanol. The solution was sealed in a one-liter stainless steel bomb and heated at 225–230°

(8) That the abnormal reaction is not confined to the loss of a benzyl group in particular is indicated by the work of A. E. Chichibabin, *J. prakt. Chem.*, [2] **107**, 122 (1924), and A. E. Chichibabin and M. P. Oparina, *ibid.*, [2] **107**, 145 (1924).

(9) All melting and boiling points are uncorrected. Microanalyses by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet spectra recorded on a Beckman model DU spectrophotometer. Infrared spectra recorded by Mr. Rolland Ro on a Baird double beam instrument. Equivalent weights were determined by the method of K. G. Cunningham, W. Dawson and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

for 6 hr. with constant rocking. The pressure was about 1000 p.s.i. The bomb was then cooled, opened and the contents transferred to a distilling flask. As much ethanol as possible was distilled on the steam-bath at atmospheric pressure. The residue was subjected to a preliminary distillation in which everything boiling up to about 280° (1 mm.) was collected; except in the case of the acetaldehyde condensation where a preliminary distillation with superheated steam at 200° was resorted to. (Omission of this preliminary treatment led to difficulties in the subsequent extraction step.) The distillate was taken up in ether and extracted fifteen times with 2 *N* hydrochloric acid. The residual ether layer was discarded and the aqueous layer plus a third layer which invariably formed were made basic with excess concentrated ammonium hydroxide. The bases liberated were extracted with ether, dried over potassium carbonate and the solution concentrated. The residue was then treated further as described for each individual case.

The original alcohol distillate was poured into an excess of 20–30% aqueous calcium chloride and extracted with pentane. The pentane solution was dried over magnesium sulfate and then carefully concentrated through a glass helix column. The residue (toluene) was distilled from a small modified Claisen flask and derivatized as the 2,4-dinitro compound, m.p. 69–70° in all cases, undepressed by admixture of authentic 2,4-dinitrotoluene.

Condensation of Phenylacetaldehyde, Acetaldehyde and Ammonia.—The crude basic reaction product (60.5 g. see above) on standing overnight deposited 15.0 g. of 3,5-diphenylpyridine which was collected after diluting the mixture with 50 ml. of ligroin (b.p. 60–71°). The material melted at 136–138° (lit.[1] 136–137°) and did not depress the melting point of an authentic sample. The remaining material was distilled to give three arbitrary fractions. The first fraction, b.p. up to 174° (13 mm.), $n^{20}D$ 1.5758–1.6010, weighed 3.95 g. This material yielded[10] 3.06 g. of picrate melting at 189–190° dec. Decomposition of the picrate by means of ethanolamine[11] followed by distillation gave 1.08 g. of 2-methyl-5-phenylpyridine, collected at 143–145° (13 mm.), $n^{20}D$ 1.6062. When exposed to moist air this material formed an unstable hydrate, m.p. 49.5–52°, which reverted to the oil when stored in a desiccator. The material was therefore not analyzed but reconverted to the picrate, m.p. 189–190° dec.

Anal. Calcd. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54. Found: C, 54.63; H, 3.68.

The equivalent weight of the base was found to be 173 by the picrate method (see above), calculated 169. The ultraviolet spectrum of the base showed a maximum at 246 mμ (ε 16,800) and a shoulder at 274 mμ (ε 8,050).

The second fraction, b.p. 174–230° (13 mm.), $n^{20}D$ 1.6158–1.6383, weighed 27.65 g. A 15.63-g. aliquot of this fraction gave 23.2 g. of picrate, m.p. 200–204°. Recrystallization from glacial acetic acid raised the melting point to 205–207° (recovery 88%). Decomposition of 13.0 g. of picrate[11] yielded 5.72 g. of 2-methyl-3,5-diphenylpyridine boiling at 226–228° (13 mm.), $n^{20}D$ 1.6450, which slowly crystallized to a solid melting at 50–52°.

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.13; H, 6.16; equiv. wt., 245. Found: C, 88.31; H, 6.16; equiv. wt., 249.

The ultraviolet spectrum showed a maximum at 238 mμ (ε 25,000) and a shoulder at 277 mμ (ε 8,750).

The picrate melted at 206–208° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{18}N_4O_7$: C, 60.76; H, 3.82. Found: C, 61.10; H, 4.13.

The third fraction, b.p. 230–250° (13 mm.), had $n^{20}D$ 1.6363 and weighed 4.33 g. It yielded[10] 4.42 g. of picrate (after recrystallization from acetic acid) which melted at 202–205° and did not depress the melting point of 2-methyl-3,5-diphenylpyridine picrate described above.

From the original alcohol distillate there was isolated 1.60 g. of toluene boiling at 109–111°, $n^{20}D$ 1.4957 (lit. b.p. 111°, $n^{20}D$ 1.4962).

When the same condensation was effected using 0.5 mole of phenylacetaldehyde and 2 moles of acetaldehyde, the major fractions had b.p. 62–65° (14 mm.), $n^{20}D$ 1.4990 (2.11 g.); b.p. 65–170° (14 mm.), $n^{20}D$ 1.5493 (17.31 g.) and b.p. 170–220°, $n^{20}D$ 1.6071 (8.55 g.).

Fraction 1 yielded a picrate, m.p. 163–165°, undepressed by admixture of authentic 2-methyl-5-ethylpyridine picrate, m.p. 166–168° (literature constants for 2-methyl-5-ethylpyridine[12]: b.p. 68–73° (22 mm.), $n^{20}D$ 1.4959–71, picrate m.p. 167–168°).

Fraction 2 was dissolved in acetone and treated with concentrated hydrochloric acid. The hydrochloride so precipitated was collected, washed with ether and dried, wt. 15.4 g., m.p. 90–93°. The salt was treated with dilute ammonium hydroxide and the liberated base extracted with ether, dried over potassium carbonate and distilled. The 2-methyl-5-phenylpyridine so obtained boiled at 141–145° (12 mm.), $n^{20}D$ 1.6060, and weighed 8.58 g. The picrate melted at 187–189° (dec.).

2-Styryl-5-phenylpyridine (II).—Since direct oxidation of 2-methyl-5-phenylpyridine (I) with permanganate was unsuccessful, this oxidation was effected *via* the styryl derivative.

A mixture of 7.3 g. (0.043 mole) of 2-methyl-5-phenylpyridine (I), 4.2 g. of potassium acetate, 4.4 g. of acetic anhydride, 10.6 g. of freshly purified benzaldehyde and a crystal of iodine were boiled under reflux for 40 hr. While still warm the mixture was treated with 25 ml. of concd. hydrochloric acid and exhaustively steam-distilled to remove excess benzaldehyde. The suspension was then cooled and the product filtered and washed with 100 ml. of ether. The yellow solid so obtained was dissolved in hot ethanol and the solution treated with concentrated ammonium hydroxide and an equal volume of water. The 2-styryl-5-phenylpyridine so crystallized weighed 5.0 g. (45%) and melted at 136–139°. A small sample crystallized for analysis melted at 137.5–138.5°.

Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88. Found: C, 88.73; H, 5.85.

5-Phenylpicolinic Acid (III).—To a well-stirred solution of 3.10 g. (0.012 mole) of 2-styryl-5-phenylpyridine (II) in 250 ml. of acetone maintained at 0–5°, 5.20 g. of potassium permanganate was added in small portions over a period of 3 hr. The reaction mixture was cooled, filtered and the residual manganese dioxide washed four times with 100-ml. portions of 1:1 aqueous acetone. The combined filtrate was concentrated to 200 ml., filtered again and acidified with concd. hydrochloric acid. The precipitated acids were collected, dried and washed with cold ether to remove benzoic acid. The residue was dissolved in hot water, the *p*H adjusted to about 3.5 (congo red) and the solution evaporated to dryness. Two crystallizations of the residue from ligroin (b.p. 93–130°) gave 1.85 g. (77%) of 5-phenylpicolinic acid (III), m.p. 156–157°. The acid gave a red color with aqueous ethanolic ferrous sulfate.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 72.35; H, 4.55. Found: C, 72.71; H, 4.70.

3-Phenylpyridine. (a) By Decarboxylation of III.—The acid III (0.597 g.) was heated at 200° for 45 minutes and the residual oil was converted to the picrate, m.p. 158–160° (lit.[4] 159–160°), undepressed by admixture of an authentic specimen of 3-phenylpyridine picrate prepared as described below.

(b) From 3-Aminopyridine.—A mixture of 5.20 g. (0.055 mole) of 3-aminopyridine[13] and 20 ml. of acetic anhydride was heated on the steam-bath for 1 hr., concentrated by distillation *in vacuo* and the residue crystallized from chloroform–ligroin (b.p. 60–71°). The 3-acetamidopyridine so obtained (4.77 g., 63%) melted at 132–136°, lit.[14] 133°. To a solution of 4.7 g. (0.035 mole) of 3-acetamidopyridine dissolved in 40 ml. of acetic acid and 20 ml. of acetic anhydride was added 10 g. of fused potassium acetate and 0.1 g. of phosphorus pentoxide. The mixture was stirred at 5–10°, and a solution of 4 g. of nitrosyl chloride[15] in 4 g. of acetic anhydride was added dropwise. The reaction mixture was then poured onto crushed ice and the yellow material extracted with benzene. The water layer was made slightly

(10) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

(11) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949).

(12) R. L. Frank and R. P. Severn, THIS JOURNAL, **71**, 2629 (1949).

(13) C. F. H. Allen and C. N. Wolf, *Org. Syntheses*, **30**, 3 (1950).

(14) H. Maier-Bode, *Ber.*, **69**, 1534 (1936).

(15) Prepared from commercial nitrosylsulfuric acid and sodium chloride by the method of J. Sudborough and J. H. Millar, *J. Chem. Soc.*, **59**, 73 (1891).

basic with solid sodium carbonate, sufficient ice being added to keep the mixture cool and maintain the sodium acetate in solution. The solution was then extracted four more times with benzene (100-ml. portions) and the combined benzene extracts were washed once with aqueous sodium carbonate and once with water and dried over sodium sulfate. After 36 hr. the benzene was distilled and the residue made basic with sodium hydroxide (10%) and steam distilled. The distillate was saturated with sodium chloride, extracted with four 75-ml. portions of ether and the ether extracts were dried over potassium carbonate. Concentration followed by distillation gave 2.56 g. (48%) of 3-phenylpyridine collected at 137–138° (13 mm.), $n^{20}D$ 1.6170; lit.[4] b.p. 117–118° (5 mm.), $n^{25}D$ 1.6123. The picrate melted at 162–163° when freshly prepared; the melting point dropped on storage.

2-Methyl-5-phenylpyridine (I).—This was prepared from 2-methyl-5-aminopyridine[16] in a manner entirely analogous to the preparation of 3-phenylpyridine from 3-aminopyridine described above, except that the use of a saturated aqueous potassium carbonate solution was found preferable to solid sodium carbonate. From 4.50 g. of the amine there was thus obtained 2.51 g. (45%) of 2-methyl-5-phenylpyridine, $n^{20}D$ 1.6050, b.p. 146–147° (14 mm.). The infrared spectrum of this compound was identical with that of material isolated from the condensation of phenylacetaldehyde, acetaldehyde and ammonia. 2-Methyl-5-phenylpyridine picrate melted at 188–190° and did not depress the melting point of the picrate of the methylphenylpyridine obtained in the condensation.

2-Styryl-3,5-diphenylpyridine.—From 3.02 g. of 2-methyl-3,5-diphenylpyridine there was obtained, by a method analogous to that used for the lower homolog II, 2.10 g. (51%) of 2-styryl-3,5-diphenylpyridine melting at 144–145° after recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{19}N$: C, 90.06; H, 5.74. Found: C, 90.33; H, 5.75.

3,5-Diphenylpicolinic Acid.—The oxidation of 6.60 g. (0.020 mole) of 2-styryl-3,5-diphenylpyridine in 350 ml. of acetone was effected by the addition of powdered potassium permanganate at 0–5° with good stirring over a 2-hr. period until the permanganate color persisted for 30 minutes. The mixture was filtered and the residue manganese dioxide washed twice with 300-ml. portions of 50% aqueous acetone. Concentration of the combined filtrate to 100 ml., followed by treatment with Norite, filtration and acidification gave 3.20 g. of material melting at 138–142°. Two recrystallizations from ligroin (b.p. 93–130°) raised the melting point to 155–156°, yield 1.58 g. (29%). The acid gave a red color with ferrous sulfate in aqueous ethanol.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76. Found: C, 78.67; H, 4.67.

Decarboxylation of 0.497 g. of the acid was effected by heating it at 175–180° for 8 minutes. Crystallization of the residue from ethanol gave 0.375 g. (90%) of material melting at 135–139°. Recrystallization raised the melting point to 137–139°, undepressed by admixture of authentic 3,5-diphenylpyridine.[1] The picrate melted at 207–208° (lit.[1] 204.5–205.5°) and did not depress the melting point of an authentic sample.

Condensation of Phenylacetaldehyde, Propionaldehyde and Ammonia.—The condensation product from 1 mole of phenylacetaldehyde and 0.5 mole of propionaldehyde with ammonia deposited 14.22 of 3,5-diphenylpyridine after the preliminary distillation (see General Procedure) and another 2.31 g. after concentration of the ether solution of the bases. This material was removed and the remainder distilled and divided into five arbitary fractions. Fraction 1 (0.94 g.) boiled at 80–120° (13 mm.), $n^{20}D$ 1.5205; its picrate melted in the 150–190° range and resisted purification. An equivalent weight determination of the base on the crude picrate gave a value of 139, in fair agreement with a calculated 135 for ethyldimethylpyridines which might be formed by condensation of three moles of propionaldehyde with one of ammonia.

Fraction 2, 16.46 g., b.p. 120–200°, $n^{20}D$ 1.5510–1.5839, gave 19.13 g. of picrate melting at 176–184°. Attempted purification of this picrate by recrystallization was unpromising. The picrate was decomposed by dissolving it in 500 ml. of hot acetone and passing the solution through a column of 200 g. of Alcoa F-20 alumina. The picric acid remained on the column as a red-orange band and the free base was washed through with an additional 300 ml. of acetone. Concentration gave 7.90 g. of oil which was dissolved in ligroin (b.p. 60–71°) and chromatographed on a column of 100 g. of Alcoa F-20 alumina. The progress of the chromatogram was followed by testing the eluate with copper chloride paper[17] with which the various pyridine bases gave yellow, green, blue or purple colors. From the ligroin eluate (700 ml. total, of which the first 300 ml. contained no substance) was isolated 5.59 g. of oil, $n^{20}D$ 1.5930. The material (2-ethyl-3-methyl-5-phenylpyridine, XII) was distilled and a fraction of b.p. 174–175° (14 mm.), $n^{20}D$ 1.5925, was submitted for analysis.

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.22; H, 7.67; equiv. wt., 197. Found: C, 85.30; H, 7.55; equiv. wt., 199.

The ultraviolet spectrum showed maxima at 247 mμ (ε 15,800) and 277 mμ (ε 9,320) with a minimum at 270 mμ (ε 8,690).

The picrate prepared from the undistilled oil in 91% yield melted at 183–185°. Recrystallization raised the melting point to 184–185°.

Anal. Calcd. for $C_{20}H_{18}N_4O_7$: C, 56.33; H, 4.26. Found: C, 56.75; H, 4.43.

Change of the eluent to 40 volume % benzene in ligroin (b.p. 60–71°) eluted 1.42 g. of oil, $n^{20}D$ 1.6074, which upon distillation yielded 1.08 g. of distillate, b.p. 158–160° (14 mm.), $n^{20}D$ 1.6053, and a residue from which 0.28 g. of 3,5-diphenylpyridine, m.p. 135–137°, was isolated by crystallization from ethanol. The distillate (3-methyl-5-phenylpyridine X) gave a picrate, m.p. 191–192°, in 89% yield. The mixture melting point with 2-methyl-5-phenylpyridine picrate was depressed to 160–170°. Recrystallization of the picrate left its melting point unchanged.

Anal. Calcd. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54; equiv. wt. of base, 169. Found: C, 54.46; H, 3.56; equiv. wt. of base, 170.

Fraction 3, b.p. 200–245° (13 mm.), $n^{20}D$ 1.6155, weighed 19.80 g. and on standing deposited 0.63 g. of 3,5-diphenylpyridine, m.p. 137–138°. The liquid part gave 26.08 g. of picrate, m.p. 170–181°, which resisted purification. It was decomposed with alumina as described above to give 15.10 g. of oil which was dissolved in benzene and chromatographed on 200 g. of Alcoa F-20 alumina. The benzene eluate gave 12.67 of 2-ethyl-3,5-diphenylpyridine (VI), $n^{20}D$ 1.6317. An analytical sample, obtained by distillation, boiled at 230–231° (14 mm.) and had $n^{20}D$ 1.6320.

Anal. Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; equiv. wt., 259. Found: C, 87.50; H, 6.38; equiv. wt., 262.

The ultraviolet spectrum showed a maximum at 240 mμ (ε 22,200) and at 278 mμ (ε 9,360) with a minimum at 275 mμ (ε 9,150).

The picrate melted at 190–191° after recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{20}N_4O_7$: C, 61.47; H, 4.13. Found: C, 61.43; H, 3.96.

Further elution of the chromatogram with 1:1 (by volume) benzene–ether gave 1.60 g. of 3,5-diphenylpyridine, m.p. 137–138°, undepressed by admixture of an authentic sample.

Fraction 4, 1.24 g., b.p. 245–255° (13 mm.), $n^{20}D$ 1.6309, upon chromatography gave 0.87 g. of oil from which 1.23 of picrate was prepared. The picrate melted at 188–191°, undepressed by admixture of 2-ethyl-3,5-diphenylpyridine picrate. Further elution of the chromatogram gave 3,5-diphenylpyridine which after recrystallization from ethanol weighed 0.20 g. and melted at 136–137°.

Fraction 5 was collected at 255–280° (13 mm.) and weighed 11.69 g. It was dissolved in ether, extracted with 2 *N* hydrochloric acid, the acid solution made basic with ammonia and re-extracted into ether. From the residual oil, 2.0 g. of picrate, m.p. 160–167° raised to 163–172° by recrystallization from ethanol, was isolated but was not identified. When the original ether solution (after extraction with 2 *N* hydrochloric acid) was treated with 5 ml. of concentrated hydrochloric acid a white solid separated. It was collected, washed with water, dissolved in hot ethanol and the ethanol solution was treated with concentrated ammonia solution.

(16) R. Graf, *J. prakt. Chem.*, **133**, 19 (1932).

(17) Prepared by wetting strips of filter paper with a solution of 5 g. of cupric chloride in 20 ml. of water and 25 g. of glycerol: R. Vignes and P. Chervet, *Compt. rend.*, **232**, 1419 (1951).

On cooling, 0.90 g. of a white solid melting at 72–74° crystallized. Recrystallization from ethanol raised the melting point to 74–75°. The analysis corresponds to a diphenylbenzylpyridine.

Anal. Calcd. for $C_{24}H_{19}N$: C, 89.68; H, 5.96; equiv. wt., 321. Found: C, 89.52; H, 6.17; equiv. wt., 325.

The ultraviolet spectrum showed a maximum at 240 mμ (ε 22,500) and a shoulder at 277 mμ (ε 10,000).

The picrate melted at 164–165° after recrystallization from ethanol.

Anal. Calcd. for $C_{30}H_{22}N_4O_7$: C, 65.45; H, 4.03. Found: C, 65.68; H, 4.08.

From the ethanol distillate of the original condensation, a small amount of toluene was isolated and identified by the 2,4-dinitro derivative.

5-Phenylnicotinic Acid (XI).—To a well-stirred, boiling suspension of 1 g. of distilled 3-methyl-5-phenylpyridine in 100 ml. of water plus 5 ml. of 10% aqueous potassium hydroxide was added powdered potassium permanganate over a 2-hr. period until the purple color persisted for 30 minutes. After addition of a few drops of methanol the hot reaction mixture was filtered and the residual manganese dioxide washed with two 75-ml. portions of boiling water. The combined filtrate was treated with Norite and Celite, filtered again and acidified with hydrochloric acid. 5-Methyl nicotinic acid precipitated and was collected, m.p. 267–269°, wt. 0.49 g. (42%). Two sublimations at 230° (14 mm.) left the melting point unchanged. The acid gave no color with aqueous alcoholic ferrous sulfate.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55. Found: C, 72.12; H, 4.60.

Decarboxylation of 5-Phenylnicotinic Acid (XI).—An intimate mixture of 1 g. of soda lime and 0.50 g. of 5-phenylnicotinic acid (XI) was placed in a 25-ml. distilling flask and heated to 300° in a Wood metal-bath. The acid sublimed onto the cooler parts of the flask. It was scraped back into the soda lime, and the mixture was heated rapidly with the full flame of a bunsen burner. This caused distillation of a yellow liquid which was converted to the picrate, m.p. 159–160°, wt. 0.89 g. (92%). Admixture of 3-phenylpyridine picrate caused no depression in melting point.

Oxidation of 2-Ethyl-3-methyl-5-phenylpyridine (XII).—The oxidation of 5.50 g. of pure XII[18] in 300 ml. of water by means of potassium permanganate took 5 hr. for completion. The mixture was worked up as described for 3-methyl-5-phenylpyridine. Upon acidification a precipitate of 2.65 g. (48%) of 5-phenylnicotinic acid (XI) was obtained, m.p. 265–267°, undepressed by admixture with the sample described above obtained by oxidation of 3-methyl-5-phenylpyridine.

The mother liquor after removal of XI was treated with an excess of copper acetate and the precipitated copper salt was collected with the aid of Celite, slurried with water, treated with hydrogen sulfide and filtered. The filtrate was evaporated to dryness leaving a light brown solid which gave a red color with aqueous ferrous sulfate solution. This material decomposed at 110° with gas evolution when heated slowly or at 170° when heated rapidly but resisted further purification. It was dissolved in aqueous ammonia and the ammonium salt precipitated by the addition of ethanol; wt. 0.60 g., dec. 230°. This salt also gave a red color with aqueous ferrous sulfate.

5-Phenylquinolinimide (XIV).—The above ammonium salt (0.21 g.) was heated slowly to 140° with 1 ml. of acetic anhydride. The excess anhydride was then removed *in vacuo* and the residue crystallized from carbon tetrachloride (Norite) to yield 0.17 g. of white needles, m.p. 75–79°. Two sublimations at 90° (14 mm.) raised the melting point to 78–79°. The material showed absorption bands in the infrared at 5.9 and 7.25 μ.

Anal. Calcd. for $C_{13}H_8N_2O_2$: N, 12.50. Found: N, 12.30.

Oxidation of 2-Ethyl-3,5-diphenylpyridine (VI).—Since direct oxidation of this material was unsuccessful and preparation of a stilbazole derivative appeared unpromising,[19] oxidation was effected *via* the N-oxide and carbinol.[6] A solution of 1.76 g. of 2-ethyl-3,5-diphenylpyridine (VI) in 6 ml. of acetic acid was heated with 1 ml. of 30% hydrogen peroxide at 80–90° for 2 hr. Another milliliter of hydrogen peroxide was added and heating continued for 10 hr. The reaction mixture was concentrated *in vacuo* and 6 ml. of acetic anhydride was added to the residue which was then heated at 100° for 9 hr. and again concentrated *in vacuo*. The residue was boiled with 30 ml. of 10% aqueous sodium hydroxide for 6 hr., cooled to 90° and treated with potassium permanganate in small portions until the purple color persisted for 30 minutes. After the addition of a few drops of methanol the manganese dioxide was removed in the usual way and the filtrate acidified. There was thus obtained 0.18 g. of 3,5-diphenylpicolinic acid, m.p. 152–156°. Recrystallization from ligroin (b.p. 93–130°) returned 0.15 g., m.p. 155–157°, undepressed by admixture of a sample obtained by oxidation of 2-methyl-3,5-diphenylpyridine (V) as described above.

2-Benzoyl-3,5-diphenylpyridine (?).—Oxidation of 3.30 g. of the material which had been assigned the 2-benzyl-3,5-diphenylpyridine structure was effected with potassium permanganate in aqueous pyridine. The precipitated manganese dioxide was filtered and washed with pyridine and the combined filtrate diluted with water. An oil precipitated which crystallized on chilling, wt. 2.05 g., m.p. 65–95°. This was apparently a mixture of starting material and product. Three recrystallizations from ethanol returned 1.56 g. (45%) melting at 133–136°. The analytical sample melted at 136–137°.

Anal. Calcd. for $C_{24}H_{17}NO$: C, 85.94; H, 5.11. Found: C, 86.18; H, 5.12.

The material absorbed at 6.05 μ in the infrared.

Condensation of Phenylacetaldehyde, Isobutyraldehyde and Ammonia.—When the alcoholic solution obtained in the condensation was cooled, 22.05 g. of diphenylpyridine, m.p. 135–137°, precipitated and was collected. After distillation of the ethanol, another 10.00 g. of the same material separated. The residue was worked up in the usual way. At the end of the extractions with 2 *N* hydrochloric acid, a solid material appeared in the separatory funnel. When this was collected, dissolved in ethanol and treated with ammonia it yielded 0.43 g. of benzyldiphenylpyridine, m.p. 72–74°, undepressed by admixture of similar material obtained in the propionaldehyde condensation.

The basic material from the reaction deposited another 4.14 g. of 3,5-diphenylpyridine, m.p. 135–137°, which was removed. The remaining material was distilled into arbitrary fractions.

Fraction 1, b.p. 120–170° (13 mm.), $n^{20}D$ 1.5246, gave no picrate and was discarded. Fractions 2–4, boiling between 170 and 265° at 13 mm., weighed 31.92 g. ($n^{20}D$ 1.5640–1.6160) and yielded a total of 18.03 g. of picrate melting at 190–200°. This was decomposed by means of alumina, and the resulting base was crystallized from ligroin (b.p. 93–130°) to give 8.20 g. of 2-isopropyl-3,5-diphenylpyridine (?), m.p. 101–102°.

Anal. Calcd. for $C_{20}H_{19}N$: C, 87.87; H, 7.01; equiv. wt., 273. Found: C, 88.23; H, 7.10; equiv. wt., 274.

The ultraviolet spectrum showed maxima at 240 mμ (ε 21,100) and 279 mμ (ε 8,780) with a minimum at 275 mμ (ε 8,570).

The picrate melted at 207–209° after crystallization from ethanol.

Anal. Calcd. for $C_{26}H_{22}N_4O_7$: C, 62.15; H, 4.41. Found: C, 62.33; H, 4.47.

Fraction 5, b.p. 265–290° (13 mm.), $n^{20}D$ 1.6285–1.6287, weighed 16.27 g. It yielded a picrate which after crystallization from acetic acid weighed 7.08 g. and melted at 164–165°. It did not depress the melting point of the benzyldiphenylpyridine picrate described previously. The base (3.60 g. from 6.50 g. of picrate) liberated by means of an alumina column melted at 73–74° and did not depress the melting point of the benzyldiphenylpyridine obtained previously.

From the original ethanol distillate in this condensation there was isolated 0.69 g. of toluene, b.p. 110–111°, identified by the dinitro derivative.

Attempts to oxidize the isopropyldiphenylpyridine obtained in this condensation with acidic or basic permanganate, chromic acid or *via* the N-oxide either led to the recovery of starting material or yielded benzoic acid.

(18) This sample gave a picrate melting at 183–185° in 91% yield.

(19) A. P. Phillips, *J. Org. Chem.*, **13**, 622 (1948); THIS JOURNAL, **76**, 3986 (1954).

Condensation of Phenylacetaldehyde, Benzaldehyde and Ammonia.—After concentration of the ethanolic solution of the condensation products, 9.70 g. of solid, m.p. 110–160°, was collected from the residue diluted with an equal volume of ether. The crude basic material during the ether extraction yielded an additional 10.35 g., m.p. 90–145°. The rest of the material was distilled. The first fraction, b.p. 106–107° (14 mm.), $n^{20}D$ 1.5393, weighed 2.13 g. and was identified as benzyl alcohol by its infrared spectrum. (This material was apparently carried through the acid extraction in the third layer which resulted here as in all other cases.) The α-naphthylurethan melted at 133–134° after crystallization from ligroin (literature data for benzyl alcohol: b.p. 93° (10 mm.), $n^{20}D$ 1.5396; α-naphthylurethan, m.p. 134°). Fraction 2, b.p. 107–207° (14 mm.), $n^{20}D$ 1.5943, weighed 3.30 g. and yielded 0.22 g. of 3,5-diphenylpyridine, m.p. 135–137°, and 0.56 g. of 3,5-diphenylpyridine picrate, m.p. 203–205°. The higher boiling material, collected at 207–290° (14 mm.), weighed 59.45 g. and formed a solid or glass. By judicious crystallization of this material as well as the solids mentioned above from ethanol, ether and ligroin (b.p. 60–71°) three crystalline fractions were obtained. The least soluble one melted at 256–257° after final crystallization from ligroin. The total amount of this material was 5.13 g.

Anal. Calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; equiv. wt., 307. Calcd. for $C_{24}H_{19}N$: C, 89.68; H, 5.96; equiv. wt., 321. Found: C, 89.62; H, 5.50; equiv. wt., 320.

The ultraviolet spectrum of this material showed a maximum at 240 mμ (ε 27,000 for a molecular wt. of 321) and a shoulder at 280 mμ (ε 8,800).

The picrate decomposed at 232°.

Anal. Calcd. for $C_{29}H_{20}N_4O_7$: C, 64.92; H, 3.76. Calcd. for $C_{30}H_{22}N_4O_7$: C, 65.45; H, 4.03. Found: C, 65.37; H, 3.82.

The material of intermediate solubility proved to be 3,5-diphenylpyridine, m.p. 135–137°, undepressed by admixture of an authentic sample. The total amount of this material isolated was 17.51 g. (including the material obtained from fraction 2); in addition, 4.92 g. of 3,5-diphenylpyridine picrate, m.p. 205-207°, undepressed by admixture with an authentic sample, was isolated in addition to the picrate isolated from fraction 2.

The most soluble material, after final crystallization from ligroin (b.p. 60–71°), melted at 123–124°. This material is a triphenylpyridine, probably the 2,3,5-isomer.

Anal. Calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; equiv. wt., 307. Found: C, 89.81; H, 5.47; equiv. wt., 314.

The ultraviolet spectrum showed a maximum at 249 mμ (ε 23,900) and a shoulder at 280 mμ (ε 17,000).

The total amount of this material isolated was 25.73 g. In addition there was isolated 5.10 g. of triphenylpyridine picrate, m.p. 230–233°. The analytical sample of this picrate was prepared from the parent base and melted at 232–234° after crystallization from acetone.

Anal. Calcd. for $C_{29}H_{20}N_4O_7$: C, 64.92; H, 3.76. Found: C, 64.95; H, 3.69.

The original ethanol distillate of this condensation was worked up in the usual way. After the pentane had been removed, the temperature of the distillate rose rapidly to 106°. The material collected at 106–109° weighed 0.89 g. and was identified as toluene by its 2,4-dinitro derivative. No benzene was isolated.

NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. V.[1] ω-Fluoronitriles and ω-Fluoro-ω′-nitroalkanes

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Representative members of the series of ω-fluoronitriles, $F(CH_2)_nCN$, and ω-fluoro-ω′-nitroalkanes, $F(CH_2)_nNO_2$, were synthesized and their chemical, physical and toxicological properties determined. Evidence was obtained for the mode of breakdown *in vivo* of aliphatic nitriles and nitroalkanes.

Introduction

In earlier reports on the study of toxic fluorine compounds we have described some ω-fluoroalcohols[2] and ω-fluorohalides,[3] all of which exhibited the alternation in toxicity characteristic of the ω-fluorocarboxylic acids. We next turned our attention to other series of aliphatic compounds containing an ω-fluorine atom, which are, in most cases, accessible from the intermediate ω-fluorohalides. This paper deals with two such series, the ω-fluoronitriles and the ω-fluoro-ω′-nitroalkanes.

No member of the ω-fluoro-ω′-nitroalkane series has been prepared previously. Of the members of the ω-fluoronitrile series, fluoroacetonitrile has been fully described,[4,5] 3-fluoropropionitrile has been prepared[6] since the completion of our work, and 4-fluorobutyronitrile has been listed with its physical constants but with no details of its preparation.[7]

Fluoroacetonitrile has been reported to be non-toxic,[4,8] a fact implying that the nitrile is not hydrolyzed *in vivo* to the toxic fluoroacetic acid. This observation conforms to the reported metabolic breakdown of nitriles to hydrogen cyanide and the next lower acid[9]; the fluoroacetonitrile would thus be expected to form the relatively non-toxic fragments derived from the hypothetical fluoroformic acid. A simple means of confirming this breakdown mechanism was to examine the toxicological properties of the higher ω-fluoronitriles. The results and conclusions are discussed below. In addition to their biological interest, the ω-fluoronitriles proved to be important intermediates in the preparation of other series, such as ω-fluoroalkylamines and ω-fluorocarboxylic acids.

(1) Issued as DRB Report No. SW-21. For part IV, see ref. 3.

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(9) R. T. Williams, "Detoxication Mechanisms: The Metabolism of Drugs and Allied Organic Compounds," Chapman and Hall Ltd., London, 1947, p. 125.