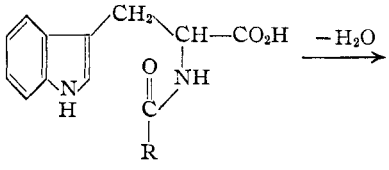
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

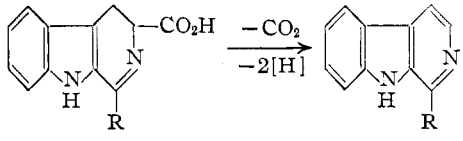
Polyphosphoric Acid as a Dehydrating Agent. I. The Cyclodehydration of Some α-Acylamino-β-arylpropionic Acids

BY H. R. SNYDER AND FRANK X. WERBER[1]

Norharman (formula V), the parent compound of the β-carboline series, is not available in good over-all yield[2] from *dl*-tryptophan by the method employed for the synthesis of harman.[3] It seemed desirable, therefore, to investigate the cyclodehydration of N-formyl-*dl*-tryptophan (formula I) as an alternative route. The expected 3,4-dihydro-β-carboline-3-carboxylic acid (formula III) might then be degraded to V by a suitable method of oxidative decarboxylation in one step, or by decarboxylation followed by dehydrogenation.

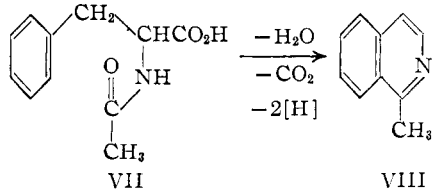


I, R = H
II, R = CH_3



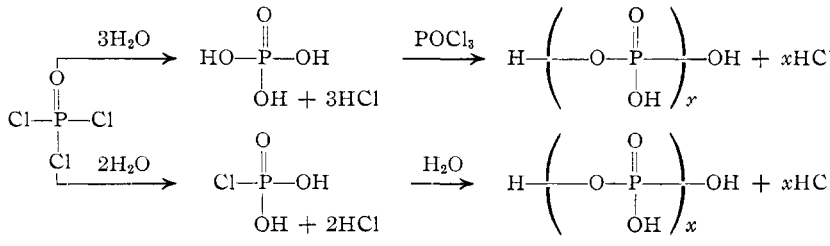
III, R = H
IV, R = CH_3

V, R = H
VI, R = CH_3



VII VIII

The cyclization was first attempted with phosphorus oxychloride as a dehydrating agent. The sample used had been standing in the laboratory for some years. To our surprise the reaction proceeded with the loss of carbon dioxide to give V directly as the only isolable product, in a yield of 35%. The base was identified by mixed melting point and comparison of the infrared absorption with that of authentic norharman.[2] A detailed investigation of this reaction revealed that neither fresh, pure phosphorus oxychloride nor any of the three other standard dehydrating agents commonly employed in analogous cyclodehydrations[4] was capable of furnishing any but resinous products under a variety of conditions. These other agents were phosphorus pentoxide, thionyl chloride and zinc chloride. It appeared, therefore, that cyclization was effected by a product of the slow hydrolysis of phosphorus oxychloride, or by a mixture of such products, and that this mixture was specifically required for the cyclodehydration to occur. Accordingly, phosphorus oxychloride was treated with various deficient amounts of water and the mixtures so formed were tested on I as cyclizing media; similarly mixtures of phosphoric acid and phosphorus oxychloride and of phosphorus pentoxide and phosphorus oxychloride, respectively, were prepared and their actions were examined. An experiment with phosphoric acid alone was also carried out. In all cases only tars were formed. It was then suggested that the active agent present in the aged phosphorus oxychloride might be a polymer[5] of phosphoric acid which could have arisen by a process of slow hydrolysis, followed by polymerization either *via* reaction of the phosphoric acid so formed with phosphorus oxychloride or *via* self-condensation of a chlorophosphoric acid. In order to test this hypothesis the reaction was carried out in polyphosphoric acid, a commercially available mixture of the "strong phosphoric acids."[6] This mixture is defined in terms of its phosphorus concentration as 82–84% phosphorus pentoxide. The presence of a small amount of phosphorus oxychloride was required. This combination of reagents was capable of reproducing in every respect the results obtained with the aged phosphorus oxychloride. With phosphorus pentachloride and polyphosphoric acid a smaller yield of V was obtainable. When polyphosphoric acid alone was used, however, no product could be isolated.



(1) Wm. S. Merrell Research Fellow, 1947–1949. Present address: B. F. Goodrich Research Center, Brecksville, Ohio.

(2) Snyder, Walker and Werber, THIS JOURNAL, **71**, 527 (1949).

(3) Snyder, Parmerter and Katz, *ibid.*, **70**, 222 (1948).

(4) Whaley and Govindachari, "The Bischler-Napieralski Reaction," in Adams, "Organic Reactions," forthcoming volume.

(5) The authors are indebted to Professor L. F. Audrieth for this suggestion.

(6) Bell, *Ind. Eng. Chem.*, **40**, 1464 (1948); **39**, 136 (1947).

A survey of the literature revealed no report of a successful cyclodehydration involving a derivative of alanine bearing an acyl group on the α-amino nitrogen atom and an aromatic nucleus on the β-carbon atom. Several esters of such acids have been cyclized[7] and in each case the expected 3-carbalkoxy-3,4-dihydroisoquinolines were obtained. The cyclization of N-acetyltryptophan has been attempted under a variety of conditions[8] employing standard acidic condensing agents, but no product could be isolated. When subjected to treatment with a mixture of polyphosphoric acid and phosphorus oxychloride, however, N-acetyl-*dl*-tryptophan reacted with evolution of carbon dioxide to give harman (formula VI) in a yield of 5–15%. This base was identified by mixed melting points and by comparison of the infrared absorption with that of an authentic sample.[3]

In order to determine whether substitution of the phenyl for the indole nucleus in the β-position would affect the course of the reaction, two N-acylphenylalanines were similarly treated with a mixture of polyphosphoric acid and phosphorus oxychloride. From N-acetyl-*dl*-phenylalanine a base was isolated as a picrate in a yield below 5% and was identified as the salt of 1-methylisoquinoline (formula VIII) by mixed melting points and by comparison of the infrared absorption with that of authentic 1-methylisoquinoline picrate. No product was obtained when VII was treated with polyphosphoric acid alone. N-Formyl-*l*-phenylalanine reacted with loss of carbon dioxide, but only a minute amount of a base was obtained and it was not possible to purify it.

Theoretically the possibility exists that dehydrogenation of the acylamino acid in the α,β-position is the first step, and is followed by cyclodehydration to yield the fully aromatized β-carboline- or isoquinoline-3-carboxylic acid intermediate. A number of such acids of the β-carboline series have been reported,[7,9] however, and have exhibited no remarkable tendency toward decarboxylation. That the corresponding 3,4-dihydro-3-carboxylic acids are the probable intermediates is suggested by the work of Harwood and Johnson,[7b] who prepared 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-3-carboxylic acid from the corresponding methyl ester. This acid was shown to have certain unexpected properties. When treated with phosphorus pentachloride it gave the expected 3,4-dihydroacid chloride; treatment with thionyl chloride, however, transformed the compound with loss of two hydrogen atoms into the corresponding *fully aromatized* acid chloride. The acid in question was decarboxylated, without dehydrogenation, *in boiling benzene* to 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline. A more detailed study of the behavior of a similar 3,4-dihydrocarboxylic acid under the conditions of the over-all cyclodehydration of the corresponding uncyclized α-acylamino-β-arylpropionic acid might be expected to furnish information on the course of the cyclization. However, attempts to prepare such an intermediate (III) by cyclization of the methyl ester of N-formyl-*dl*-tryptophan under the influence of a mixture of phosphorus oxychloride and polyphosphoric acid or of phosphorus pentachloride in chloroform were unsuccessful.

Some insight into the manner in which decarboxylation and dehydrogenation took place was gained by elucidation of the following points in the case of the cyclization of I: (1) the reaction proceeded at the same rate and gave the same yield of V in the presence or absence of air; (2) carbon dioxide, and not carbon monoxide, was the liberated gas; (3) molecular hydrogen probably was not produced; and (4) the reaction was inhibited, rather than promoted, by some of the common oxidizing agents such as nitrobenzene, choranil and ferric chloride, a fact which indicates that the dehydrogenation cannot be regarded as a true oxidation. A mechanism involving decarbonylation and subsequent dehydration of III is untenable, inasmuch as carbon monoxide is not formed.

The specificity of action exhibited by polyphosphoric acid in at least two of the cyclodehydrations discussed in this communication brought to mind the possibility of its more general usefulness as a condensing agent. Preliminary experiments indicate that polyphosphoric acid may be of use in the Bischler–Napieralski synthesis[4] of 3,4-dihydroisoquinolines from N-acyl-β-arylethylamines. Thus N-formylphenethylamine was cyclodehydrated to 3,4-dihydroisoquinoline, isolated as the picrate, in an over-all yield of 31%. No resinification took place. Previous workers, using phosphorus pentoxide have obtained yields of 0[10] and 18%[11]; considerable tar formation was reported.[12] In one experiment N-acetylphenethylamine was cyclized to 1-methyl-3,4-dihydroisoquinoline in a 23% yield. Reported yields[11,12] for the same reaction vary from 11 to 83% when phosphorus pentoxide, phosphorus oxychloride and mixtures of the two reagents were used. Other applications of polyphosphoric acid in intramolecular dehydrations will be reported in a later communication.

(7) (a) Swiss Patents 92,004, 92,610, 92,611, 92,612 [*Chem. Zentr.*, **94**, II, 574 (1923)]; German Patent 399,805 (*Frdl.*, **14**, 1313); U. S. Patent 1,437,802 [*C. A.*, **17**, 854 (1923)]; British Patent 191,233 [*C. A.*, **17**, 3073 (1923)]; (b) Harwood and Johnson, THIS JOURNAL, **56**, 468 (1934).

(8) (a) Harvey, Miller and Robson, *J. Chem. Soc.*, 153 (1941); (b) Snyder, Hansch, Katz, Parmerter and Spaeth, THIS JOURNAL, **70**, 219 (1948).

(9) King and Stiller, *J. Chem. Soc.*, 472 (1937).

(10) Decker and Becker, *Ann.*, **395**, 328 (1913).

(11) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(12) Whaley and Hartung, *J. Org. Chem.*, **14**, 650 (1949); Dey and Ramanathan, *Proc. Natl. Inst. Sci. India*, **9**, 193 (1943); Pictet and Kay, *Ber.*, **42**, 1973 (1909).

Experimental[13,14]

N-Formyl-*dl*-tryptophan (I).—To a solution of 24 ml. of acetic anhydride in 80 ml. of formic acid was added 20 g. of *dl*-tryptophan. The mixture was refluxed for twenty-five minutes, and was then concentrated under reduced pressure on the steam-bath to a thick sirup. About 180 ml. of water was added slowly and with agitation. The mixture was allowed to stand in the ice-box overnight before the product was collected and washed with 2% aqueous hydrochloric acid and with water. It weighed 18.1 g.; m. p. 158.5–161°. From the mother liquor 1.1 g. of additional material was obtained, to give an over-all yield of 84%. A small sample, recrystallized repeatedly from absolute ethanol–benzene, melted at 161–162.5°.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.04; H, 5.21; N, 12.07. Found. C, 62.33; H, 5.45; N, 11.86.

Cyclization of N-Formyl-*dl*-tryptophan.—In a typical experiment 1.0 g. of N-formyl-*dl*-tryptophan, 11.9 g. of polyphosphoric acid[15] and 1 ml. of phosphorus oxychloride were mixed in a 50-ml. flask fitted with a Hershberg-type stirrer. The purple mixture was heated with vigorous stirring in an oil-bath at 125° for eighty minutes. Carbon dioxide and hydrogen chloride were rapidly evolved during most of this period. At the end of this time the hot, almost black mixture was decomposed with ice and the granular resin which deposited was removed by filtration. The filtrate was carefully neutralized with concentrated aqueous ammonia, and 0.5 g. of a crude, brown base was collected. On recrystallization from benzene 0.26 g. (36%) of colorless needles, m. p. 197–198°, was obtained. Admixture with a sample of authentic norharman (V) (m. p. 199–201°) did not depress the melting point, and the infrared spectra were the same.

Yields of V as stated were obtained under the following conditions:

Reagent mixture	Temp., °C.	Reaction time, hours	Yield of V, %
Aged $POCl_3$	110–130	1.5–4	35[a,b,c]
Aged $POCl_3$	95–100	1	27
Polyphosphoric acid and $POCl_3$	125–130	1.3	35[a,c]
Polyphosphoric acid and PCl_5	120	1.5	14

[a] The off-gases were collected in a saturated solution of barium hydroxide in 5% aqueous sodium hydroxide. A precipitate formed which was identified as barium carbonate. Hydrogen chloride was identified by odor and by precipitation of silver chloride. [b] The off-gases were tested with filter paper impregnated with palladium chloride and sodium acetate. No carbon monoxide or hydrogen could be detected by this method, but the test is not conclusive for the latter gas. [c] Nitrogen was run through the reaction vessel containing the inorganic reagents for twelve hours prior to the start of the experiment and while the reaction was in progress.

None of the cyclization product was isolated from experiments (carried out at temperatures between 100 and 150° with reaction times of one to four hours) in which the following substances or mixtures were tested as condensing agents: phosphorus pentoxide in toluene, fresh phosphorus oxychloride, aged phosphorus oxychloride in benzene, thionyl chloride in toluene, zinc chloride in acetic anhydride, polyphosphoric acid, phosphorus oxychloride and phosphoric acid, phosphorus oxychloride and water (various proportions), phosphoric acid, phosphorus oxychloride and phosphorus pentoxide, polyphosphoric acid and phosphorus oxychloride in the presence of nitrobenzene, polyphosphoric acid and phosphorus oxychloride in the presence of chloranil, aged phosphorus oxychloride and ferric chloride.

Cyclization of N-Acetyl-*dl*-tryptophan (II).—The acetyl derivative, II[16] 1.41 g., was mixed with 14.0 g. of polyphosphoric acid and 3.0 ml. of phosphorus oxychloride, and the mixture was treated as in the cyclization of I. Carbon dioxide and hydrogen chloride were evolved. About 0.050 g. of a base, m. p. 228–232° (dec.), was isolated in the manner described for the isolation of V. Sublimation *in vacuo* gave a sample, m. p. 234–235° (dec.), whose melting point was not depressed by admixture with authentic harman (VI)[3] [m. p. 233° (dec.)], and comparison of infrared spectra confirmed its identity. In a preliminary experiment 60 mg. of II was treated with 1 ml. of aged phosphorus oxychloride. About 10 mg. of VI, m. p. 229–231° (dec.) after recrystallization from benzene, was obtained.

Cyclization of N-Acetyl-*dl*-phenylalanine (VII).—The reaction was carried out with 0.76 g. of VII,[16] 8.9 g. of polyphosphoric acid and 1.5 ml. of phosphorus oxychloride. Heating at 125° was continued for two hours, while carbon dioxide and hydrogen chloride were evolved. By the isolation procedure previously described a brown oil was liberated and was collected by extraction with four 15-ml. portions of ether. The combined extracts were dried (sodium sulfate) and the solvent was replaced with 20 ml. of benzene on the steam-bath. On addition of a saturated solution of picric acid in benzene 30 mg. of a picrate, m. p. 221–224°, was obtained. One recrystallization from absolute ethanol raised the melting point to 226° (1-methylisoquinoline picrate, 225–226°,[11] 209–210°,[17] 206–208°[18]). A sample mixed with the picrate of authentic 1-methylisoquinoline (Reilly) (m. p. 227°) melted at the same temperature, and comparison of the infrared spectra demonstrated the identity of the samples.

From an experiment in which polyphosphoric acid alone and no phosphorus oxychloride was used no pure picrate could be isolated; an odor reminiscent of that of isoquinoline bases was noted, however.

Methyl α-Formylamino-β-(3-indolyl-)-propionate.—A solution of diazomethane in 70 ml. of ether was prepared according to a standard method[19] from 5 g. of nitrosomethylurea. The ethereal solution was added to a suspension of 4 g. of I in 65 ml. of absolute ether at room temperature over a forty-five-minute period. Before all the acid had gone into solution the ester appeared as a colorless solid. The mixture was allowed to stand overnight, and the product was collected, m. p. 92–94°. It was insoluble in alkali and weighed 3.6 g. (86%). Repeated recrystallization from methanol–water raised the melting point to 97–99°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73. Found: C, 63.79; H, 5.64.

Several attempts were made to cyclize this material. Two runs were made with aged phosphorus oxychloride, one at a temperature of 85–90°, the other at 135°. In a third experiment the ester was allowed to react with phosphorus pentachloride in chloroform for five days. In all cases only resinous material was obtained.

3,4-Dihydroisoquinoline.—In a 50-ml. flask were placed 15.9 g. of polyphosphoric acid and 2.70 g. of N-formyl-β-phenethylamine.[20] The solution was heated at 145° with efficient stirring for one and one-half hours. The still hot reaction mixture was decomposed with ice, 2 ml. of concentrated hydrochloric acid was added, and the neutral components were extracted with four 20-ml. portions of ether. The aqueous acidic solution was cautiously neutralized with concentrated aqueous ammonia, and the liberated oil was extracted with four 15-ml. portions of

(13) All melting points are corrected.

(14) The authors are indebted to Mrs. Agatha R. Johnson and Miss Elizabeth Petersen for the infrared absorption data, and to Miss Emily Davis and Mrs. Jane Wood for the analyses.

(15) The authors are indebted to the Victor Chemical Works for a sample of this material.

(16) The authors are indebted to Dr. E. E. Howe, Merck and Company, Inc., for a sample of this compound.

(17) Kraus, *Monatsh.*, **11**, 262 (1890).

(18) Pictet and Gams, *Ber.*, **43**, 2384 (1910).

(19) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 378.

(20) Decker, *Ann.*, **395**, 286 (1913).

benzene. The extract was washed with water and evaporated on the steam-bath to one-half of its original volume. A saturated solution of picric acid in benzene was added with agitation till there was no further precipitation of the bright yellow picrate. The crystalline material was collected by filtration, washed with water and dried; it weighed 1.79 g., m. p. 157–164°. One recrystallization from 95% ethanol gave 1.42 g. of 3,4-dihydroisoquinoline picrate, m. p. 176–177° (lit.[11] 175–176°). The ether solution of neutral materials was dried (sodium sulfate) and the solvent was removed. To the residual material was added 8 g. of polyphosphoric acid and the mixture was heated with stirring for two and one-half hours at 150°. An isolation procedure similar to that described for the main portion of product was used to obtain 0.59 g. more of 3,4-dihydroisoquinoline picrate after one recrystallization from 95% ethanol, m. p. 172–174°. The over-all yield of 3,4-dihydroisoquinoline picrate was 31%.

1-Methyl-3,4-dihydroisoquinoline.—N-Acetyl-β-phenethylamine was prepared by the method described by Decker[20] for the formylation of β-phenethylamine. Polyphosphoric acid, 13.5 g., and 1.35 g. of N-acetyl-β-phenethylamine were heated at 160° for one and one-half hours with efficient stirring. 1-Methyl-3,4-dihydroisoquinoline picrate, 0.70 g. (23%), was isolated as described above, m. p. 186.5–188.5° (lit.[21] 188–190°). No attempt was made to recover the neutral parts.

Summary

The cyclodehydration of three α-acylamino-β-arylpropionic acids, N-formyl-*dl*-tryptophan, N-acetyl-*dl*-tryptophan and N-acetyl-*dl*-phenylalanine, has been found to proceed with decarboxylation and with the loss of two hydrogen atoms to give norharman, harman and 1-methylisoquinoline, respectively. In at least two of these cases a mixture of polyphosphoric acid and phosphorus oxychloride was the only catalyst which would effect cyclization.

Preliminary experiments indicate that polyphosphoric acid, a reagent not heretofore used in organic synthesis, may be of value in the Bischler–Napieralski synthesis of 3,4-dihydroisoquinolines.

(21) Pictet and Kay, *Ber.*, **42**, 1977 (1909).

URBANA, ILLINOIS RECEIVED NOVEMBER 21, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyphosphoric Acid as a Dehydrating Agent. II. Intramolecular Acylation[1]

BY H. R. SNYDER AND FRANK X. WERBER[2]

In the first paper[1] the application of polyphosphoric acid to a novel variant of the Bischler–Napieralski reaction was reported. The present communication deals with some further practical extensions of the use of this new condensing agent.

A number of methods for the preparation of cyclic ketones by intramolecular acylation of aryl–aliphatic acids are in general use.[3] The methods which, in general, appear to give the highest yields are the Friedel–Crafts reaction through the acid chloride and the direct ring-closure of the acid in the presence of hydrogen fluoride. The Friedel–Crafts method is cumbersome, not only because it involves the preparation of the acid chloride as a separate step, but also because the chloride must be obtained in a state of high purity for the cyclization to occur in good yields. Disadvantages of hydrogen fluoride are the obvious hazards in its use and the difficulty of extension to large-scale procedures. Vigorous condensing agents such as sulfuric acid and phosphorus pentoxide have found application, but frequently these materials cause self-condensation of the ketonic products. A procedure has now been developed for the cyclodehydration of hydrocinnamic acid to α-hydrindone by the use of polyphosphoric acid.

In the new procedure the pure cyclic ketone is obtained in 50% yield; about 35% of the carboxylic acid is recovered pure enough for re-use, so the ultimate yield of ketone is approximately 75%. The Friedel–Crafts method furnishes α-hydrindone in yields ranging from 55[4] to 95%,[5] based on the acid chloride, and the hydrogen fluoride cyclization of hydrocinnamic acid is reported[6] to give the ketone in 73% yield. Polyphosphoric acid offers no advantage over these reagents from the standpoint of yield, but the convenience of its use may outweigh this factor. The optimum yield reported with sulfuric acid as the medium is 27%,[7] while phosphorus pentoxide reacts with hydrocinnamic acid exothermally to give a reaction mixture from which only truxene, the self-condensation product of α-hydrindone, could be isolated.[8]

In the cyclization with polyphosphoric acid the reaction time and temperature are critical factors. At temperatures above 120° after heating periods of one hour or more only truxene could be isolated; the primary cyclization at such temperatures is complete within one to two minutes. Even at 110° at least three-quarters of the hydrocinnamic acid undergoes cyclodehydration within two to five minutes; therefore, it is advisable to operate between 60 and 90°. In this range a period of one to one and one-half hours is required to reach the point of optimum conversion, *i.e.*, the maximum yield of ketone which can be obtained before self-condensation becomes

(1) For the preceding paper, see Snyder and Werber, THIS JOURNAL, **72**, 2962 (1950).

(2) Wm. S. Merrell Research Fellow 1947–1949. Present address: B. F. Goodrich Research Center, Brecksville, Ohio.

(3) Johnson, in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 114.

(4) Kipping, *J. Chem. Soc.*, **65**, 480 (1894).

(5) Thiele and Wanscheidt, *Ann.*, **376**, 269 (1910).

(6) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939).

(7) Price and Lewis, *ibid.*, **61**, 2553 (1939).

(8) Kipping, *J. Chem. Soc.*, **65**, 269 (1894).