

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.<sup>11</sup> 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- $\beta$ -phenethylamine was prepared by the method described by Decker<sup>20</sup> for the formylation of  $\beta$ -phenethylamine. Polyphosphoric acid, 13.5 g., and 1.35 g. of N-acetyl- $\beta$ -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.<sup>21</sup> 188–190°). No attempt was made to recover the neutral parts.

### Summary

The cyclodehydration of three  $\alpha$ -acylamino- $\beta$ -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<sup>1</sup>

BY H. R. SNYDER AND FRANK X. WERBER<sup>2</sup>

In the first paper<sup>1</sup> 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.<sup>3</sup> 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  $\alpha$ -hydrindone by the use of polyphosphoric acid.

In the new procedure the pure cyclic ketone is obtained in 50% yield; about 35% of the car-

boxylic acid is recovered pure enough for re-use, so the ultimate yield of ketone is approximately 75%. The Friedel-Crafts method furnishes  $\alpha$ -hydrindone in yields ranging from 55<sup>4</sup> to 95%,<sup>5</sup> based on the acid chloride, and the hydrogen fluoride cyclization of hydrocinnamic acid is reported<sup>6</sup> 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%,<sup>7</sup> while phosphorus pentoxide reacts with hydrocinnamic acid exothermally to give a reaction mixture from which only truxene, the self-condensation product of  $\alpha$ -hydrindone, could be isolated.<sup>8</sup>

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).

appreciable, and small variations in reaction time are of minor importance in determining the proportion of unchanged hydrocinnamic acid, ketone and self-condensation products. The approach of a characteristic scarlet-red color is a useful criterion for judging the point at which the reaction should be stopped.

Polyphosphoric acid appears to be a good solvent for oxygen-containing organic compounds. At room temperature it is a very viscous liquid, but at 50–60° it is sufficiently mobile that no difficulty is encountered in stirring the reaction mixtures. The substance does not react violently with water, so even warm reaction mixtures may be decomposed without inconvenience by addition to water or ice.

The use of the new reagent has been extended to the cyclization of several other acids. 2-Bromo-5-methoxyhydrocinnamic acid<sup>9</sup> was converted to 4-bromo-7-methoxyhydrindone in good yield.  $\gamma$ -Phenylbutyric acid gave  $\alpha$ -tetralone in 66% yield; none of the carboxylic acid could be recovered. Yields of this ketone by the Friedel-Crafts method,<sup>10</sup> and by the hydrogen fluoride<sup>6</sup> and sulfuric acid<sup>11</sup> cyclizations have been reported as 74–91, 92 and 50%, respectively. The cyclization of *o*-benzoylbenzoic acid proceeded at a higher temperature and over a longer period to give anthraquinone quantitatively. *o*-( $\alpha$ -Naphthoyl)-benzoic acid was converted to 1,2-benzanthraquinone in 44% yield; much decomposition occurred during this reaction.

Preliminary experiments have been carried out to test the value of polyphosphoric acid in other reactions normally requiring the presence of a strong dehydrating agent. 6-Nitroquinoline<sup>12</sup> could not be detected in the mixture resulting from an attempted Skraup reaction of *p*-nitroaniline, glycerol, arsenic pentoxide and polyphosphoric acid. An attempt to obtain perinaphthenone<sup>13,14</sup> by the condensation of  $\beta$ -naphthol with glycerol under the influence of polyphosphoric acid likewise failed. The condensation of acetone to mesitylene did occur, but the hydrocarbon was obtained in only 6–8% yield, along with higher boiling oils in 35–40% yield. Both 2-pentanol<sup>15</sup> and methylisobutylcarbinol<sup>16</sup> were dehydrated by polyphosphoric acid; however, the products were not the simple olefins but low, volatile polymers of them. An attempted Beckmann rearrangement of cyclohexanone oxime to  $\epsilon$ -aminocaprolactam<sup>17</sup> in the presence of polyphosphoric acid failed. Certain aromatic hydrocarbons were found to react with simple carboxylic

acids in the presence of polyphosphoric acid to give hydrocarbons. This reaction is being investigated.

### Experimental<sup>18</sup>

**$\alpha$ -Hydrindone.**—In a 250-ml. three-necked round-bottomed flask fitted with a thermometer and a sturdy Hershberg-type stirrer 250 g. of commercial polyphosphoric acid<sup>19</sup> was heated to 50°. To the vigorously stirred warm material was added in one lot 86.5 g. (0.576 mole) of hydrocinnamic acid, previously warmed to a temperature just above its melting point. The heat of reaction raised the temperature to about 65° within two to three minutes; the mixture was then heated gently so that the temperature rose to 95° within the next one and one-half hours. During this time the color passed through various stages of yellow and orange, and the reaction was allowed to proceed until a bright red color had persisted without appreciable darkening for ten to fifteen minutes. The hot solution was poured into 300 g. of cracked ice in an 800-ml. beaker, and the resulting mixture was stirred and allowed to stand to decompose the red complex. The residual material in the flask was washed out with ice, and the washings were added to the main portion. The yellow organic layer was separated from the aqueous material, the latter was extracted with two 100-ml. portions of benzene, and the two extracts were collected separately. The undiluted organic layer was extracted first with 250 ml. and then with 100 ml. of 10% aqueous sodium hydroxide solution, and the combined alkaline extracts were washed with the first and second benzene extracts. The benzene extracts were combined with the bulk of crude  $\alpha$ -hydrindone, the solution was washed with 100 ml. of water, and the benzene was evaporated on a steam-bath, the last of it being allowed to evaporate at room temperature spontaneously or under a current of air. There was obtained 47.07 g. (62%) of crude  $\alpha$ -hydrindone melting at 35–37°. The crude product was purified by distillation, b. p. 75–76° (0.3 mm.). The colorless distillate weighed 38 g. (50%), m. p. 40–42° (lit.,<sup>20</sup> 39–41°). The oxime, recrystallized from dilute ethanol and from a mixture of chloroform and petroleum ether (30–60°) melted at 142–143.5° (lit.,<sup>4</sup> 143–144°). The semicarbazone was recrystallized from glacial acetic acid, m. p. 234–236° (dec.) (lit.,<sup>21</sup> 239°).

From the alkaline extract hydrocinnamic acid could be recovered by careful neutralization of the cooled solution with about 50 ml. of concentrated hydrochloric acid. The acid was liberated as an almost colorless oil which soon crystallized in yellowish-white needles. After the mixture had been cooled for about one hour to allow complete precipitation the material was collected, washed with cold water and dried. The recovered hydrocinnamic acid, m. p. 44–46° (lit.,<sup>22</sup> 47.5–48°), weighed 29 g. (35%) and could be subjected to cyclization without further purification to give  $\alpha$ -hydrindone in only slightly lower yield.

In preliminary experiments solutions of hydrocinnamic acid in polyphosphoric acid were heated at temperatures between 120 and 160° for one to two hours. In all cases dark, amorphous materials were obtained which gave small amounts of colorless needles, m. p. above 300°, by extraction with hot xylene (truxene, lit.,<sup>23</sup> 365–368°).

**4-Bromo-7-methoxy-1-indanone.**—2-Bromo-5-methoxyhydrocinnamic acid,<sup>9</sup> m. p. 81–83°, 0.38 g., was added to 3.6 g. of polyphosphoric acid, and the mixture was heated with vigorous stirring for five minutes at 90–105°. The hot mixture was decomposed with ice, the crude solid which formed was collected by filtration,

(9) Snyder and Marshall, unpublished observation.

(10) Martin and Fieser, "Org. Syntheses," Coll. Vol. II, 569 (1943).

(11) Krollpfeiffer and Schäfer, *Ber.*, **56**, 620 (1923).

(12) Kneuppel, *ibid.*, **29**, 703 (1896).

(13) Fieser and Hershberg, *THIS JOURNAL*, **60**, 1658 (1938).

(14) Calcott, Tinker and Weinmayr, *ibid.*, **61**, 949 (1939).

(15) Norris, "Org. Syntheses," Coll. Vol. I, 2nd ed., 430 (1941).

(16) Van Risseghem, *Bull. soc. chim. Belg.*, **42**, 219 (1933).

(17) Eck and Marvel, "Org. Syntheses," Coll. Vol. II, 371 (1943).

(18) All melting points are corrected. Boiling points are uncorrected.

(19) The authors are indebted to Prof. L. F. Audrieth and to the Victor Chemical Works, Chicago, for samples of this material.

(20) Pacaud and Allen, "Org. Syntheses," [Coll. Vol. II, 336 (1943)].

(21) Revis and Kipping, *J. Chem. Soc.*, **71**, 241 (1897).

(22) Ingersoll, "Org. Syntheses," Coll. Vol. I, 2nd ed., 312 (1941).

(23) Liebermann, *Ber.*, **27**, 1417 (1894).

washed with 10% aqueous sodium hydroxide and with water, and dried. The color phenomena observed during the reaction were the same as those found to take place in the cyclization of hydrocinnamic acid. The yield of crude ketone was 0.27 g. (76%), m. p. 123–128°. Recrystallization from methanol–water raised the melting point to 128–131°. The melting point was not depressed by admixture with a sample of 4-bromo-7-methoxy-1-indanone, m. p. 131.5–132.5°, prepared by the Friedel-Crafts reaction.<sup>9</sup>

When the reaction was carried out at 160° for one hour, the only substance isolated melted at 228–231° after recrystallization from 95% ethanol.

**$\alpha$ -Tetralone.**—Polyphosphoric acid, 133 g., was warmed to 90°, and 22 g. of molten  $\gamma$ -phenylbutyric acid<sup>24</sup> was added with rapid stirring. The temperature rose to 125° while the solution was heated and stirred for a total of two and one-half minutes. The mixture was allowed to cool for five minutes before it was decomposed with about 100 g. of ice. The aqueous mixture was extracted three times with 25 ml. of ether, and the combined ether extracts were washed twice with 30-ml. portions of 10% aqueous sodium hydroxide and with water. The washed organic extract was dried (Drierite), and the solvent was evaporated on the steam-bath. There remained about 17.5 g. of a brown oil which on vacuum distillation gave 13.0 g. (66%) of colorless liquid, b. p. 96° (2 mm.) (lit.,<sup>17,25</sup> 105–107° (2 mm.)),  $n_D^{20}$  1.5688 (lit.,<sup>26</sup> 1.5691). The semicarbazone was prepared; m. p. 216°, after one recrystallization from 95% ethanol (lit.,<sup>26</sup> 217°).

**Anthraquinone.**—A mixture of 17.14 g. of *o*-benzoylbenzoic acid and 35.8 g. of polyphosphoric acid was heated at 140–150° with vigorous stirring for forty minutes. A dark yellow solid deposited during this time. The warm

reaction mixture was decomposed with ice, and the cream-colored product was collected, washed with water and dried. After one recrystallization from glacial acetic acid there was obtained 16.7 g. of yellow needles, m. p. 281–284° (lit.,<sup>27</sup> 286°).

**1,2-Benzanthraquinone.**—A mixture of 6.4 g. of *o*-( $\alpha$ -naphthoyl)-benzoic acid and 18.7 g. of polyphosphoric acid was heated on a steam-bath with stirring for about twelve hours. The isolation method was similar to that of anthraquinone. The crude product was washed with 10% sodium hydroxide and with water and dried. One recrystallization from glacial acetic acid gave 2.6 g. (44%) of 1,2-benzanthraquinone, m. p. 160–164°. One recrystallization from benzene raised the melting point to 164–166° (lit.,<sup>28</sup> 168°).

### Summary

Polyphosphoric acid has been applied as a condensing agent in the synthesis of cyclic ketones. A procedure for the cyclization of hydrocinnamic acid to  $\alpha$ -hydrindone has been developed. The method has been extended to the cyclization of 2-bromo-5-methoxyhydrocinnamic acid.  $\alpha$ -Tetralone is obtained in 66% yield from  $\gamma$ -phenylbutyric acid. The cyclization of *o*-benzoylbenzoic acid to anthraquinone proceeds quantitatively, while 1,2-benzanthraquinone is obtained in 44% yield from *o*-( $\alpha$ -naphthoyl)-benzoic acid.

(27) Kempf, *J. prakt. Chem.*, [2] **78**, 257 (1908).

(28) Heller and Schuelke, *Ber.*, **41**, 3633 (1908); Elbs, *ibid.*, **19**, 2209 (1886).

URBANA, ILLINOIS

RECEIVED JANUARY 5, 1950

(24) Martin, "Org. Syntheses," Coll. Vol. II, 499 (1943).

(25) Thompson, "Org. Syntheses," **20**, 94 (1940).

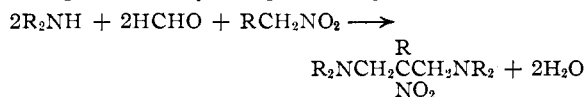
(26) v. Auwers, *Ann.*, **416**, 162 (1918).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, COMMERCIAL SOLVENTS CORPORATION]

## The Preparation and the Hydrogenation of 5-Nitropentoxazolidines

By MURRAY SENKUS

The experimental data presented in the papers on the reaction of amines with formaldehyde and nitroparaffins by Henry,<sup>1</sup> Mousset,<sup>2</sup> Duden<sup>3</sup> and Cerf<sup>4</sup> indicated that the reaction is limited to secondary amines and primary nitroparaffins as represented by the general equation



When it was discovered in this Laboratory that isopropylamine reacts with formaldehyde and 2-nitropropane to yield N-(2-nitroisobutyl)-isopropylamine<sup>5</sup> in good yield, it became apparent that the limitations that were advanced for the reaction of amines with formaldehyde and nitroparaffins by the earlier authors were not supported by sufficient experimental data. The reaction therefore has been reinvestigated and as

a consequence its scope has been greatly extended.

The new nitro amines which have been prepared during investigations in this Laboratory have been derived from primary amines and primary nitroparaffins,<sup>5</sup> primary amines and secondary nitroparaffins,<sup>5</sup> secondary amines and secondary nitroparaffins<sup>6</sup> as well as from ammonia and secondary nitroparaffins.<sup>7</sup> With the aid of a basic catalyst the reaction was also extended to aryl and alkaryl amines and primary and secondary nitroparaffins.<sup>8</sup> Finally it was reported that the reaction of two moles of a primary amine with three moles of formaldehyde and one mole of a primary nitroparaffin yields a 5-nitrohexahydropyrimidine.<sup>9</sup>

Work on the reaction of amines with formaldehyde and nitroparaffins has continued in this Laboratory. It has been found recently that one mole of a primary amine reacts with three moles of formaldehyde and one mole of a primary ni-

(1) Henry, *Bull. acad. roy. Belgique*, [3] **33**, 412 (1897).

(2) Mousset, *ibid.*, [3] **33**, 622 (1901).

(3) Duden, Bock and Reid, *Ber.*, **38**, 2036 (1905).

(4) Cerf, *Bull. soc. chim.*, [5] **4**, 1451 (1937).

(5) Senkus, *This Journal*, **68**, 10 (1946).

(6) Johnson, *ibid.*, **68**, 12 (1946).

(7) Johnson, U. S. Patents 2,408,171 and 2,408,172.

(8) Johnson, *This Journal*, **68**, 14 (1946).

(9) Senkus, *ibid.*, **68**, 1611 (1946).