[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CANISIUS COLLEGE]

Schmidt Reactions in Polyphosphoric Acid. I. Rearrangement of Ketones

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A method for effecting the Schmidt transformation of ketones employing polyphosphoric acid as both the solvent and catalyst is described. Rearrangement products have been obtained in a relatively pure state and in high yield from diaryl, aryl-alkyl, and symmetrical and unsymmetrical alicyclic ketones, indicating that polyphosphoric acid may be superior to other reagents as a catalyst in the Schmidt reaction.

Since the original observation by Schmidt[1] that certain ketones were converted to the corresponding amides on treatment with hydrazoic acid in the presence of acidic dehydrating agents, extensive studies of the scope, limitations, and mechanism of this transformation have appeared. Applications of the Schmidt reaction have been important in both preparative and theoretical chemistry and many different conditions have been developed for effecting the reaction between ketones and hydrazoic acid. These matters have been adequately discussed in an excellent review by Wolfe[2] and more recently by Smith[3] in a rather detailed series of papers.

In the course of an investigation of the abnormal Beckmann rearrangement of certain disubstituted ketoximes in polyphosphoric acid,[4,5] it became of interest, as a correlative study, to investigate the similarity between the Beckmann and Schmidt reactions in this medium. As a portion of this study, it was found necessary to investigate the polyphosphoric acid catalysis on the reaction. Only two examples of Schmidt reactions of ketones in this medium have been reported. Elston[6] rearranged benzophenone to benzanilide in 80% yield at 50° in polyphosphoric acid. Recently, Arcus, Marks, and Coombs[7] reported an unsuccessful attempt to rearrange fluorenone by a method similar to the procedure reported here. The latter report, has prompted the author to report the initial results of this investigation.

It has now been found that a variety of ketones on treatment with hydrazoic acid using polyphosphoric acid as the solvent and catalyst results in the isolation of the normal amide or lactam rearrangement products in high yield. It is felt that this method has certain advantages over previously reported methods.[2] Since polyphosphoric acid is a reasonably good solvent for organic materials, the use of an organic solvent was eliminated. The amide or lactam products of the rearrangement are not subject to further reactions due to the medium[5] or the catalyst, therefore many of the tarry by-products which are often obtained using other methods are reduced.

The method employs a 15 to 20 fold excess of polyphosphoric acid to ketone. To this mixture, while agitated, small portions of sodium azide are added. The mixture is then maintained at a temperature between 25 and 75° until the evolution of nitrogen ceases. Generally, the products are isolated by standard methods. However, when the reaction products are soluble in the hydrolysis mixture, extraction methods had to be employed and the yields were slightly reduced. The ketones rearranged in this study are summarized in Table I. The yields and the experimental conditions for the rearrangements are those which were found to be the optimum in this study. Examples of typical rearrangement procedures are given in the experimental section. The rearrangement products were identified in all cases with authentic samples prepared by reported procedures. The criteria of identity were two; no depression in mixed melting point and identical infrared spectra.

The unsymmetrical alkyl substituted cyclopentanones and cyclohexanones all yielded a single rearrangement product. It was observed that the yields obtained from the rearrangement of the substituted cyclohexanones were higher than those obtained from the rearrangement of the corresponding cyclopentanones. These results agree favorably with the studies made by Shechter and Kirk[8] on these compounds using other methods and also the analogous increase in yield observed in the Beckmann rearrangement of the oximes of these ketones.[9] 2-Cyanocyclohexanone (I) on rearrangement yielded two products, 7-Cyano-2-keto-hexamethyl-

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(3) (a) P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 320 (1948); (b) P. A. S. Smith and J. P. Horwitz, *J. Am. Chem. Soc.*, **72**, 3718 (1950); (c) P. A. S. Smith and B. Ashby, *J. Am. Chem. Soc.*, **72**, 2503 (1950).

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(9) (a) J. L. Hildebrand and M. T. Bogert, *J. Am. Chem. Soc.*, **58**, 650 (1936); (b) H. E. Ungnade and A. D. McLaren, *J. Org. Chem.*, **10**, 29 (1945); (c) A. D. McLaren and G. Pitzl, *J. Am. Chem. Soc.*, **67**, 1625 (1945).

TABLE I
SUMMARY OF SCHMIDT REACTIONS IN POLYPHOSPHORIC ACID

Ketone	Product	Yield, %	M.P., °C.	Time, Hr.	Temp., °C.
Cyclopentanone	Piperidone	83	38.5–39.5[a]	9.5	55
2-Methylcyclopentanone	6-Methylpiperidone	87	87–88[b]	12.5	50
2-Propylcyclopentanone	6-Propylpiperidone	82	91–93[c]	14.0	50
Cyclohexanone	2-Keto-hexamethylenimine	89	64–67[d]	8.5	50
2-Methylcyclohexanone	2-Keto-7-methyl-hexamethylenimine	96	90–91[e]	9.0	50
2-Propylcyclohexanone	2-Keto-7-propyl-hexamethylenimine	95	97–98[f]	8.5	50
2-Cyanocyclohexanone	7-Cyano-2-keto-hexamethylenimine	76	126–127[g]	10.0	25
	7-Carboxamido-2-keto-hexamethylenimine	8	239–241[h]		
2-Carbethoxycyclohexanone	7-Carbethoxy-2-keto-hexamethylenimine	75	96.5–98[i]	12.0	25
Cycloheptanone	2-Keto-heptamethylenimine	83	96.5–97[j]	9.0	50
1-Hydrindone	Dihydrocarbostyril	90	162–163[k]	10.0	50
1-Tetralone	Homodihydrocarbostyril	95	141–142[l]	10.0	50
Acetophenone	Acetanilide	98	113–114[m]	7.0	50
p-Methoxyacetophenone	*p*-Methoxyacetanilide	98	125–126[n]	7.5	50
Benzophenone	Benzanilide	99	160–162[o]	8.5	50
p,p'-Dimethoxybenzophenone	Anisoylanisidine	91	200–203[p]	8.5	50
Fluorenone	Phenanthridone	92	286–288[q]	22.0	70
1-Acetonaphthone	1-Acetanaphthalide	72	158–159[r]	12.0	55
2-Acetonaphthone	2-Acetanaphthalide	81	132–134[s]	12.0	55
1-Benzoylnaphthalene	1-Naphthanilide	72	161–163[t]	10.0	50
o-Benzoylbenzoic acid	*N*-Benzoylanthranilic acid	87	178–179[u]	10.0	50
Benzalacetone	*N*-Methylcinnamamide	58	110–111[v]	8.0	25
Benzylacetone	*N*-(2-phenylethyl)-acetamide	95	114–115[w]	7.5	25
Phenylacetone	*N*-Benzylacetamide	50	53–54[x]	7.5	25

[a] Ref. 12, m.p. 39–40°. [b] Ref. 8, m.p. 87.5–88.0°, Ref. 3a, m.p. 87.2–88.0°. [c] Ref. 8, m.p. 91.4–92.6°, Ref. 3a, m.p. 91.5–92.5°. [d] Ref. 12, m.p. 65–68°, Ref. 23, m.p. 68–70°. [e] Ref. 8, m.p. 90.5–91.5°, O. Wallach, *Ann.*, **346**, 252 (1906) reports m.p. 90.5–91.5°. [f] Ref. 8, m.p. 98.6–99.2°, Ref. 9c, m.p. 100.5–101.5°. [g] Ref. 8, m.p. 126.6–127.4°. [h] New compound. [i] Ref. 8, m.p. 97.2–98.0°. [j] O. Wallach, *Ann.*, **312**, 205 (1900) reports m.p. 95–96.5°. [k] Friedlander and Weinberg, *Ber.*, **15**, 1423 (1882) report m.p. 163°. [l] L. H. Briggs and G. E. De Ath, *J. Chem. Soc.*, 456 (1937) report m.p. 141°. [m] Ref. 12, m.p. 114°. [n] Ref. 12, m.p. 127°. [o] Ref. 12, m.p. 162–163°. [p] Ref. 12, m.p. 202°. [q] Ref. 25, m.p. 293°. [r] Ref. 3a, m.p. 160°. [s] C. Libermann and F. Scheiding, *Ann.*, **183**, 267 (1876) report m.p. 132°. [t] Ref. 3a, m.p. 162–163°. [u] Ref. 3a, m.p. 179°. [v] L. H. Briggs, G. C. Ath, and G. E. De Ath, *J. Chem. Soc.*, 61 (1942) report m.p. 111°. [w] Ref. 3a, m.p. 114–115°. [x] Ref. 11, m.p. 51–55°.

enimine (II) and 7-Carboxamido-2-keto-hexamethylenimine (III). These products were separated by elution chromatography over alumina. The amido-lactam III product was found to be formed by the hydration of the cyano group by the polyphosphoric acid.[10] The variation of the products of the rearrangement of 2-cyanocyclohexanone with temperature is tabulated in Table II. It was found

TABLE II
THE VARIATION OF THE PRODUCTS OF THE REARRANGEMENT OF 2-CYANOCYCLOHEXANONE WITH TEMPERATURE

Temp., °C.	Yield, %	Product (-hexamethylenimine)
25	76	7-Cyano-2-keto-
	8	7-Carboxamido-2-keto-
35	54	7-Cyano-2-keto-
	30	7-Carboxamido-2-keto-
45	37	7-Cyano-2-keto-
	45	7-Carboxamido-2-keto-
65	0	7-Cyano-2-keto-
	83	7-Carboxamido-2-keto-

that the cyano-lactam II could be quantitatively converted to the amido-lactam III by treatment with polyphosphoric acid at 60°. These transformations are shown in Figure 1. The structure of the amido-lactam was established by combustion analysis, Rast determination of the molecular weight, and by hydrolysis with 30% sulfuric acid to 2-amino-1,7-heptandioic acid.

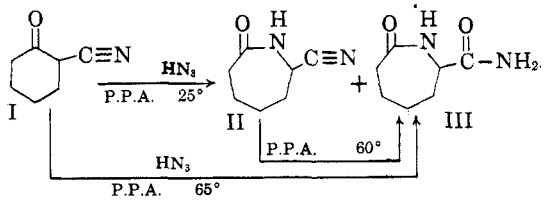

Figure 1.

Fluorenone, which has been observed to give no rearranged product under conditions similar to those used in this study,[7] has been found to rearrange in good yield using more strenuous conditions. A qualitative study of the temperature dependence of this reaction has indicated that the rearrangement proceeds extremely slowly below 50°. These results can be correlated to those obtained in the Beckmann rearrangement of fluorenone oxime in polyphosphoric acid,[11] in which it was observed

(10) See H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954) for discussion of nitrile hydration in polyphosphoric acid.

(11) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

that the oxime could be recovered unchanged at 120°; however at 180° an almost quantitative yield of phenanthridone was obtained. The rearrangement of benzalacetone and phenylacetone proceeded smoothly, however, in low yield. In both cases, an appreciable quantity of an intractable black tar was formed. Further work was not attempted in an effort to obtain an increased yield.

The general reaction conditions employed in this study were found to differ from those previously reported.[2] In this medium, in all the rearrangements studied, the reaction proceeds at a very slow rate. This appears to indicate that the polyphosphoric acid does not have as vigorous a catalytic effect on the reaction as the other reagents usually employed. This observation is in general agreement with the role of polyphosphoric acid in the Beckmann rearrangement.[12] While no detailed description of the mechanism can be advanced as yet, since it is possible that the catalytic role of the reagent may be through the formation of a phosphate ester type intermediate, similar to the intermediate proposed for the Beckmann rearrangement,[12] the general mechanism appears to follow the mechanism proposed for the general acid catalysis of the Schmidt reaction, involving the formation of a hydroxycarbonium ion[13] (in this case, a phosphate ester carbonium ion), followed by the addition of hydrogen azide and subsequent elimination of water (phosphate elimination), followed by electrophilic attack on the nitrogen through a Beckmann type intermediate,[3] which is the major factor governing the course of the rearrangement. This mechanism has been supported in this study as in those previously carried out by the rearrangement of diaryl, alkyl-aryl, and unsymmetrical cycloalkanones.[8] It has been shown that the amide and lactam products are stable in polyphosphoric acid;[14] therefore, the absence of hydrolysis and dehydrated species in the reaction products was not unexpected. While exceptions may possibly be found to the generality of the method reported here, our results indicate that polyphosphoric acid may be the reagent of choice for effecting this transformation.

Other special cases of the Schmidt reaction of ketones are currently under investigation and while these studies are not complete, it has been observed that certain 2,2 disubstituted ketones undergo abnormal rearrangements similar to those observed in the Beckmann rearrangements of their respective oximes in this medium. It is hoped to report the results of these and the Schmidt reactions of acids in this medium in the near future.

(12) E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, **74**, 2680 (1952).

(13) M. S. Newman and H. Gildenhorn, *J. Am. Chem. Soc.*, **70**, 317 (1948).

(14) See R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957) for possible exceptions to this observation.

EXPERIMENTAL

All melting points are corrected. The infrared spectra used for comparison were determined using a Baird, model 2-B, double beam, recording spectrophotometer. *Reactants:* 2-Methylcyclopentanone,[15] 2-propylcyclopentanone,[16] 2-methylcyclohexanone,[17] 2-propylcyclohexanone,[8,18] 2-cyanocyclohexanone,[19] 2-carbethoxycyclohexanone,[20] 1-hydrindone,[21] and 1-tetralone[21] were prepared by reported procedures. Benzylacetone was prepared from benzalacetone by reduction with Raney nickel according to the procedure outlined by Cornubert.[22] All other reactants were obtained from commercial sources and purified by distillation or recrystallization where necessary.

2-Keto-hexamethylenimine from cyclohexanone. To a mixture of 9.81 g. (0.1 mole) of cyclohexanone in 190 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The temperature was slowly increased to 50° on a water bath. The reaction temperature was maintained at the specified temperature for 8.5 hr. and then poured into 1000 g. of crushed ice and water. The solution was alkalized with cold 50% sodium hydroxide and the resulting solution extracted 5 times with 200-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a mass of crystals, 2-keto-hexamethylenimine; wt. 10.1 g. (89%). Recrystallization from benzene–petroleum ether produced a colorless product, m.p. 64–67° (lit., 65–68°,[12] 68–70°[23]).

7-Cyano-2-keto-hexamethylenimine from 2-cyanocyclohexanone. To a mixture of 12.30 g. (0.1 mole) of 2-cyanocyclohexanone in 196 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. After stirring for 10 hr. at room temperature, the mixture was hydrolyzed in 1000 g. of crushed ice and water. The aqueous solution was neutralized in the cold with dilute sodium hydroxide and extracted 3 times with 300-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated. The light yellow residue was dissolved in a minimum amount of chloroform and chromatographed over an ether packed alumina column. The first cut, 7-cyano-2-keto-hexamethylenimine was obtained by elution with ether; wt. 10.4 g. (76%) m.p. 126–127° (lit., 126.6–127.4°[8]). A second product was obtained from the elution of the column with a 1:1 mixture of chloroform and ether and identified as 7-carboxamido-2-keto-hexamethylenimine; wt. 1.24 g. (8%) m.p. 239–241°.

Anal. Calcd. for $C_7H_{11}N_2O_2$: C, 54.18; H, 7.15; N, 18.06; mol. wt., 155. Found: C, 54.10; H, 7.14; N, 18.11; mol. wt. (Rast), 151.

2-Amino-1,7-heptanedioic acid from 7-carboxamido-2-keto-hexamethylenimine. The structure of 7-carboxamido-2-keto-hexamethylenimine was established by hydrolysis to 2-amino-1,7-heptanedioic acid. 7-Carboxamido-2-keto-hexamethylenimine (1.5 g.) was refluxed with 30% sulfuric acid

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(21) H. R. Snyder and F. X. Weber, *J. Am. Chem. Soc.*, **72**, 2965 (1950).

(22) R. Cornubert, *Bull. chim. soc. France*, 522 (1954).

(23) O. Wallach, *Ann.*, **312**, 187 (1900).

(25 ml.) for 8 hr. The solution was diluted with water and almost neutralized with hot, saturated barium hydroxide solution. The mixture was centrifuged and the decantate evaporated to dryness under vacuum to yield white crystals of 2-amino-1,7-heptanedioic acid; wt. 0.72 g., (41%) m.p. 221–223° (lit., 225°[24]).

7-Carboxamido-2-ketohexamethylenimine from 7-cyano-2-ketohexamethylenimine. Two grams of 7-cyano-2-ketohexamethylenimine was added to 25 g. of polyphosphoric acid at 65°. After 8 hr., the mixture was hydrolyzed and extracted as described above to yield 7-carboxamido-2-ketohexamethylenimine; wt. 2.05 g. (91%) m.p. 239–241°. On mixing with the product obtained from the Schmidt reaction, no depression of the melting point was observed; m.p. 239–241°.

7-Carboxamido-2-ketohexamethylenimine from 2-cyanocyclohexanone. To a mixture of 12.30 g. (0.1 mole) of 2-cyanocyclohexanone in 192 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The mixture was slowly heated at 65° and the temperature maintained at the specified temperature for 8 hr. The reaction mixture was hydrolyzed and the products isolated in the usual manner to yield 12.87 g. (83%) of 7-carboxamido-2-keto-hexamethylenimine; m.p. 238–241°. No trace of the nitrile was detected in the infrared spectrum of the crude product.

Acetanilide from acetophenone. To a mixture of 12.10 g. (0.1 mole) of acetophenone in 225 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. After stirring at 50° for 7 hr. the mixture was poured over 500 ml. of crushed ice and water. The product was filtered from the solution to yield 13.35 g. (98%) of acetanilide after air drying. The acetanilide was once recrystallized from water; m.p. 113–114° (lit., m.p. 114°[12]).

Phenanthridone from fluorenone. To a mixture of 18.10 g. (0.1 mole) of fluorenone in 350 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The temperature was cautiously raised to 70° and maintained at that temperature for 22 hr. with constant stirring. The product was collected on hydrolysis by filtration to yield 17.94 g. (92%) of phenanthridone; m.p. 286–288° (lit., m.p. 293°[25]).

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BUFFALO 8, N. Y.

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[CONTRIBUTION FROM THE ORGANIC DIVISION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXX. Reactions of 1-Arylpiperazines with Epoxides

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The search for new pharmaceuticals led to the synthesis of 25 new compounds resulting from the reactions of various 1-arylpiperazines with substituted 1,2-epoxides.

Seven of the 1-arylpiperazines used in these syntheses were prepared by the method of Pollard, *et al.*[1,2] The method of Prelog, *et al.*[3–5] proved more satisfactory for the preparation of the alkoxypiperazines. The hydrobromide of 1-(2-methoxyphenyl)-piperazine was reported by Prelog, Driza, and Hanousek.[3] The free amines, 1-(2-methoxyphenyl)-piperazine and 1-(2-ethoxyphenyl)piperazine were prepared in this laboratory by the Prelog method. The acetic acid salts of these amines were prepared for analyses and subsequent identification.

The reactions of ammonia and amines with 1,2-epoxides to form amino alcohols have been thoroughly investigated by Goldfarb,[6] Horne and Shriner,[7] and Wurtz.[8] Krassousky[9] investigated these reactions with unsymmetrical epoxides and obtained secondary amino alcohols. Castro and Noller[10] established that arylamines reacted with epoxides to produce secondary amino alcohols. The experimental work of Boyd and Knowlton,[11] Boyd,[12] and Stephens[13] also confirmed the secondary alcohol formation from these reactions. Kitchen and Pollard[14] showed that piperazine reacts with epoxides to produce mono as well as disubstituted piperazines, both being secondary amino alcohols. In view of the previous work establishing the for-

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