POLYPHOSPHORIC ACID AS A REAGENT IN ORGANIC CHEMISTRY

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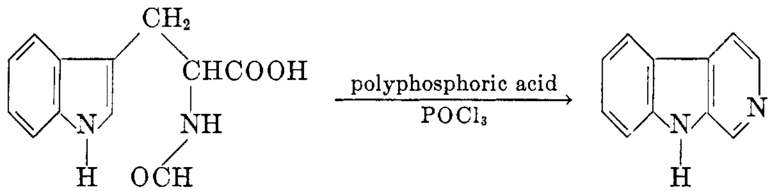
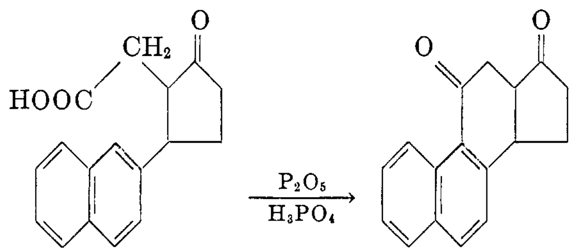
I. INTRODUCTION

Polyphosphoric acid (PPA) has, in recent years, achieved prominence as a reagent in synthetic organic chemistry. Since only one rather abbreviated review of this subject has been published (199) up to the present, it was felt that a reasonably thorough treatment of the topic would be desirable at this time. In this paper an attempt will be made to point out both the advantages and the disadvantages of polyphosphoric acid as a condensing agent and as a general acid catalyst. While no pretense is made that all of the literature on the subject has been included, the recent issues of the major chemical journals have been scanned carefully in order to obtain as complete a coverage of the subject as possible.

The first report in the literature of the application of polyphosphoric acid as a reagent in organic chemistry to achieve widespread attention appeared in 1950 (321). It was found that whereas an aged batch of phosphorus oxychloride was an effective agent for the conversion of *N*-formyltryptophan to norharman, pure phosphorus oxychloride was ineffective. It was thought that one of the active agents present in the aged phosphorus oxychloride might have been polyphosphoric acid, which could have arisen by a process of hydrolysis and polymerization. In order to test this hypothesis, the cyclization-decarboxylation reaction was carried out in commercial polyphosphoric acid containing a small quantity of phosphorus oxychloride. This combination of reagents was found to be capable of reproducing in every respect the results obtained with the aged phosphorus oxychloride.



Although the study cited above represented the first report to gain widespread attention of the use of polyphosphoric acid in organic synthesis, the patent literature contained mention of such uses prior to 1950 (294, 329), and the application of a solution of phosphorus pentoxide in syrupy phosphoric acid to effect the cyclization of 3-β-naphthylcyclopentan-1-one-2-acetic acid to 3′,4-diketo-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene was described in 1938 (204).



Throughout this review the nomenclature of the original authors will be maintained if possible. Since many of the references contain only one or two examples of the use of polyphosphoric acid more or less buried in a relatively large amount of other material, this practice should help the reader to locate readily the specific examples in the original papers.

II. Nature of the Reagent

There are three major sources of polyphosphoric acid: a commercial product named "Polyphosphoric Acid" manufactured by the Victor Chemical Company, another commercial product named "Phospholeum" manufactured by the Monsanto Chemical Company, and a solution of phosphorus pentoxide in orthophosphoric acid which may be prepared as needed. It has been found that the reagent from any of these sources is equally effective in a given reaction (178), and, indeed, there is no essential difference in these products other than that which is solely the consequence of any possible difference in theoretical content of P_2O_5. It is generally thought (19) that the reagent is best characterized by specifying its total phosphorus content in terms of weight per cent P_2O_5, although, as will be shown below, the reagent contains many different compounds.

Earlier attempts to determine the exact composition of commercial polyphosphoric acid (or, as it is sometimes called, the strong or condensed phosphoric acids) by a wet-chemical method (47, 48) proved to be partially inadequate. The use of a recently developed (363) filter paper chromatographic method of analysis of the phosphate components has made it possible to overcome the deficiencies of the methods previously employed (179, 338). As the result of these analyses and also of a theoretical analysis based on statistical methods (267), the conclusion has been reached that only orthophosphoric acid, pyrophosphoric acid, and linear polyphosphoric acids are present in mixtures of the condensed phosphoric acids having a theoretical P_2O_5 content of 81–85 per cent. No cyclic acids could be detected by the paper chromatographic method except when the theoretical content of P_2O_5 exceeded 85 per cent (338). Although the chromatographic method would not have been adequate to detect the presence of branched acids because of the fact that these acids, unlike the linear ones, undergo very rapid hydrolysis to form linear phosphates upon dissolution and neutralization in an aqueous medium in preparation for analysis (338, 351), the theoretical treatment (267) indicated that no branched acids were present in the condensed phosphoric acids of the composition cited above. The analytical results and the theoretical treatment show that a characteristic equilibrium mixture exists for each ratio of phosphorus pentoxide to water. The experimental results obtained by one group of workers (179) are summarized in table 1. It should be emphasized that there is substantial, but not exact, agreement concerning the composition of the various mixtures as determined theoretically (267) and experimentally (179, 338).

Titration experiments carried out in aqueous solution show (351) that all of the phosphoric acids possess one strongly acidic hydrogen atom per phosphorus atom. Neutralization of this hydrogen is achieved at pH 3.8 to 4.2. A variety of ionization constants have been reported for orthosphosphoric acid and pyrophosphoric acid (1, 44, 147, 196, 206, 207, 234, 235, 243, 345, 360). Apparently reliable values for orthophosphoric acid are $K_1 = 7.516 \times 10^{-3}$ (147), $K_2 = 6.226 \times 10^{-8}$ (147), and $K_3 = 2 \times 10^{-13}$ (196), all at 25°C.; for pyrophosphoric acid, $K_1 = 1.4 \times 10^{-1}$, $K_2 = 1.1 \times 10^{-2}$, $K_3 = 2.9 \times 10^{-7}$, and $K_4 = 3.6 \times 10^{-9}$ at 18°C. (1). The ionization constants of tripolyphosphoric acid have not been reported, but the values are thought to be close to those of pyrophosphoric acid, with the most weakly acidic hydrogen being dissociated to a somewhat greater degree (351). A brief summary of the acid dissociation constants of the

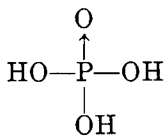
TABLE 1

Composition of the condensed phosphoric acids

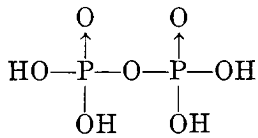
P_2O_5	Total Phosphorus in the Component Phosphoric Acids									
	Ortho	Pyro	Tripoly	Tetrapoly	Pentapoly	Hexapoly	Heptapoly	Octapoly	Nonapoly	"Hypoly"
weight per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
68.80	100	Trace								
69.81	98	2								
70.62	95	5								
72.04	90	10								
72.44	87	13								
73.43	77	23								
74.26	68	29	3							
75.14	56	39	5							
75.97	49	42	8	1						
77.12	40	47	11	2						
78.02	27	49	17	5	2					
78.52	25	48	18	7	2					
79.45	17	43	22	11	4	2	1			
80.51	13	35	25	14	7	3	3			
81.60	8	27	22	17	11	6	4	2	2	1
82.57	5	20	16	16	13	9	6	4	4	7
83.48	5	17	16	16	12	10	7	5	3	9
84.20	4	11	11	13	12	10	8	6	5	20
84.95	2	7	8	11	10	10	9	8	6	29
86.26	2	3	3	5	5	6	4	3	3	66

relatively common phosphoric acids has been given in a previous review article (279).

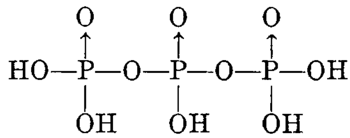
The structures of some of the individual phosphoric acids found in polyphosphoric acid are shown below:



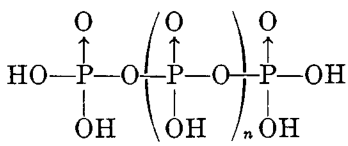
Orthophosphoric acid



Pyrophosphoric acid

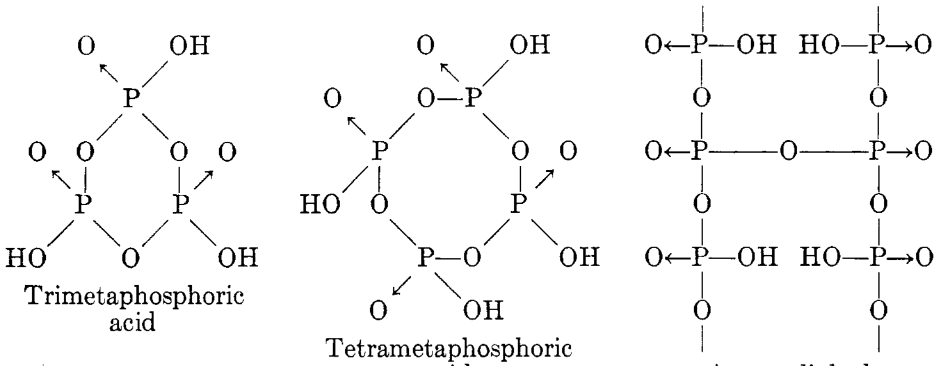


Tripolyphosphoric acid



$n = 2$, tetrapolyphosphoric acid,
$n = 3$, pentapolyphosphoric acid, etc.

Although commercial polyphosphoric acid (82–84 per cent P_2O_5) does not contain any detectable quantity of cyclic phosphoric acids, small amounts of these acids have been found in mixtures having a theoretical P_2O_5 content greater than 85 per cent (338). For example, there is paper chromatographic evidence that polyphosphoric acid having a theoretical P_2O_5 content of 90 per cent contains about 3 per cent of trimetaphosphoric acid and also a trace of tetrametaphosphoric acid. Data have also been provided (338) to show that condensed phosphoric acids having a theoretical P_2O_5 content greater than 85 per cent contain some cross-linked (branched) polyphosphoric acids. Since evidence for the presence of the cyclic acids appears only when cross-linked polyphosphoric acids are also present, there is some possibility that the cyclic acids actually arise only upon hydrolysis of the cross-linked acids in the preparation of the mixture for the paper chromatographic analysis. This problem has not been resolved (338).



Trimetaphosphoric acid   Tetrametaphosphoric acid   A cross-linked polyphosphoric acid

With regard to the polyphosphoric acid mixtures in which only linear acids are found, the component acids (and water) present can be represented by the general formula $H_{n+2}P_nO_{3n+1}$, where $n = 0, 1, 2 \ldots$. When all of the component acids can be determined quantitatively for any given mixture, a "free water" content may also be calculated (179). Actually, this water is strongly solvated and is "free" only in the sense that it is not combined with phosphorus pentoxide in the form of a component acid. It is of interest that condensed phosphoric acids contain "free water" up to a P_2O_5 content of 80.5 per cent, although "100% H_3PO_4" has a theoretical P_2O_5 content of only 72.4 per cent. Although crystalline orthophosphoric acid, m.p. 42.4°C., is a pure compound (338), it should be pointed out that the pure material, when melted, undergoes partial condensation, presumably according to the following equation (308, 309):

$$3H_3PO_4 = H_4P_2O_7 + H_3O^+ + H_2PO_4^-$$

Another point of interest with regard to condensed phosphoric acids is that, for any given content of phosphorus pentoxide, the same ratio of component acids results no matter what the method of preparation of the acid, provided that a homogeneous melt is obtained during the course of the preparative procedure (47, 48, 179, 338). Condensed phosphoric acids may be prepared by thermal dehydration of orthophosphoric acid, by dissolution of phosphorus pentoxide in syrupy phosphoric acid with heating, or by reaction of phosphorus oxychloride with orthophosphoric acid at an elevated temperature, hydrogen chloride being expelled.

Polyphosphoric acid is a clear, colorless, extremely viscous, hygroscopic liquid having a specific gravity of 2.060 at 20°C. when the theoretical P_2O_5 content equals 83 per cent. None of the individual component acids crystallize from the mixture when the temperature is lowered to −60°C. in a moisture-free atmosphere; a rigid glass is formed instead. However, the substance is conveniently fluid at 60°C.

The versatility and general utility of polyphosphoric acid arise from the fact that it is a mild reagent even though a strong dehydrating agent. Generally it does not bring about charring of organic compounds, and it does not undergo a violent reaction with hydroxylic compounds. It does not bring about phosphonation of aromatic compounds. For these reasons its use frequently leads to fewer side reactions and higher yields of desired products than the use of other agents such as sulfuric acid, hydrogen fluoride, phosphoric anhydride, or aluminum chloride (199).

Many different experimental conditions have been reported for the use of polyphosphoric acid. A convenient preliminary test has been devised to determine the approximate temperature range at which a given reaction should be carried out (350). The compound (1 part) is added to polyphosphoric acid (10–30 parts) at room temperature. If the mixture darkens immediately, cooling of the reaction mixture is indicated for the preparative run. If the mixture darkens slowly, the preparative run can probably be carried out at room temperature. If the probe mixture remains colorless, then heating is required for the preparative procedure. In at least one series of experiments, the use of a solution of polyphosphoric acid in acetic acid gave worthwhile results in intramolecular acylation experiments (71). In the isolation of products, polyphosphoric acid is readily disposed of by pouring the reaction mixture into water.

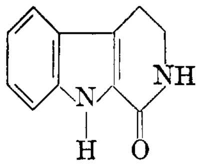
Very little is known about the precise mechanisms of reactions catalyzed by polyphosphoric acid. Indeed, owing to the fact that detailed knowledge of the composition of polyphosphoric acid has only recently been made available (179, 267, 338), there has not been sufficient time for mechanism studies to have been undertaken and completed. Certain mechanisms which have been proposed for reactions catalyzed by polyphosphoric acid are, of necessity, only speculative schemes (100).

III. Cyclization Reactions

A. PREPARATION OF HETEROCYCLIC COMPOUNDS

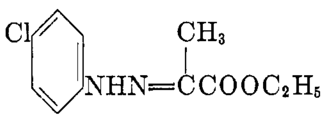
1. Fischer indole synthesis

Polyphosphoric acid has been found to be an effective condensing agent for the Fischer indole synthesis. Aryl- and alkyl-substituted indoles may be obtained in good yields, not only from ketone phenylhydrazones, but also from mixtures of phenylhydrazine and ketone (113, 201). The yields realized by this method are in most cases equal to those obtained by other methods, and the chief advantage lies in the ease with which the reactions may be brought about. In at least one case (201), an *N*-alkylphenylhydrazone, specifically the *N*-methyl-phenylhydrazone of acetophenone, was treated with polyphosphoric acid and gave the desired *N*-alkylindole, 1-methyl-2-phenylindole. The polyphosphoric acid-catalyzed reaction has also been applied successfully to the preparation of the appropriate indolenine from the phenylhydrazone of isobutyrophenone (201, 366). To date, polyphosphoric acid has been found to be of little use in effecting the preparation of indoles unsubstituted in the 2-position from aldehyde arylhydrazones (113, 201). Attempts to convert the phenylhydrazone of 2,3-dioxopiperidine to 1,2,3,4-tetrahydro-1-oxo-β-carboline (I) led to extensive charring unless the reaction was carried out on a very small scale (3). There have been many other reports of tar formation when polyphosphoric acid is used as the condensing agent in the Fischer indole synthesis, but the claim has been made that such charring can be avoided if the reaction mixture is cooled just after the start of the exothermic reaction (201).



I

A variety of α-keto esters have been subjected to the polyphosphoric acid-catalyzed Fischer indole synthesis. Negative results were reported for the attempted cyclization of methyl pyruvate phenylhydrazone (113). However, ethyl pyruvate *p*-chlorophenylhydrazone (II) gave ethyl 5-chloroindole-2-carboxylate (III), and ethyl 7-chloroindole-2-carboxylate (IV) was obtained from ethyl pyruvate *o*-chlorophenylhydrazone (300). Although various workers (298, 310) were unable to confirm earlier reports of the Fischer cyclization of ethyl pyruvate *o*-nitrophenylhydrazone, the use of polyphosphoric acid as the condensing agent gave (310) ethyl 7-nitro-2-indolecarboxylate (V).



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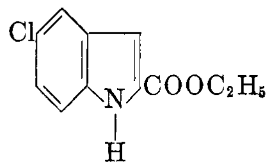

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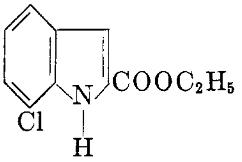

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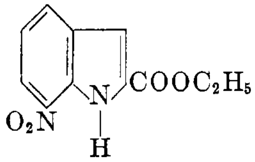


V

Table 2 contains a summary of the available data on the polyphosphoric acid-catalyzed Fischer indole synthesis.

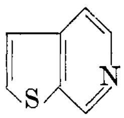
TABLE 2

Fischer indole synthesis

Ketone or Aldehyde	Hydrazine	Indole	Yield	Temperature	References
			per cent	°C.	
Acetaldehyde	Phenyl-				(113)
Acetone	Phenyl-	2-Methyl-	60	203	(201)
			76	175	(113)
Acetophenone	α-Methyl-α-phenyl-	1-Methyl-2-phenyl-	73	100	(201)
	Phenyl-	2-Phenyl-	76	180	(201)
			89	100	(113)
Acetoveratrone	Phenyl-	2-Veratryl-			(368)
2-Acetylpyridine	Phenyl-	2-(2′-Pyridyl)-	88	180	(331)
3-Acetylpyridine	Phenyl-	2-(3′-Pyridyl)-	67		(331)
			55	125	(139)
4-Acetylpyridine	Phenyl-	2-(4′-Pyridyl)-	89		(331)
			65	115	(139)
Butanone	Phenyl-	2,3-Dimethyl-	68	230	(201)
			67	160	(113)
n-Butyraldehyde	Phenyl-				(201, 113)
Cyclohexanone	Phenyl-	1,2,3,4-Tetrahydrocarbazole	76	140	(113)
Desoxybenzoin	Phenyl-	Polymer			(201)
Dibenzyl ketone	Phenyl-	Polymer			(201)
Diethyl ketone	Phenyl-	2-Ethyl-3-methyl-	73	150	(113)
2,3-Dioxopiperidine	Phenyl-	1,2,3,4-Tetrahydro-1-oxo-β-carboline	93		(3)
Ethyl levulinate	Phenyl-				(113)
Ethyl pyruvate	*o*-Chlorophenyl-	2-Carbethoxy-7-chloro-	52	190	(300)
	p-Chlorophenyl-	2-Carbethoxy-5-chloro-	54	180	(300)
	o-Nitrophenyl-	2-Carbethoxy-7-nitro-	13	195	(310)
Isobutyraldehyde	Phenyl-	2,3-Dimethyl-	26	100	(113)
Isobutyrophenone	Phenyl-	3,3-Dimethyl-2-phenylindolenine			(366)
			45	155	(201)
p-Methoxypropiophenone	Phenyl-	2-*p*-Methoxyphenyl-3-methyl-			(366)
Methyl pyruvate	Phenyl-				(113)
Phenylacetaldehyde	Phenyl-				(201)
p-Phenylacetophenone	Phenyl-	2-(*p*-Biphenylyl)-	63	185	(201)
Propionaldehyde	Phenyl-				(113)
Propiophenone	Phenyl-	3-Methyl-2-phenyl-	58	170	(201)
			69	160	(113)

2. Pomeranz–Fritsch reaction

Although the statement has been made (121) that the use of polyphosphoric acid for the cyclization of benzylideneaminoacetals to isoquinolines suffers from the fact that the azomethine linkage is unstable towards the reagent, several examples of polyphosphoric acid-catalyzed Pomeranz–Fritsch reactions have been reported. It was found that better yields of thieno[2,3-*c*]pyridine (VI) and thieno[3,2-*c*]pyridine (VII) resulted when the Schiff bases obtained from the appropriate thiophenecarboxaldehydes and aminoacetal were cyclized by the use of polyphosphoric acid containing a small amount of phosphorus oxychloride than by the use of sulfuric acid (160). Thianaphtheno[2,3-*c*]pyridine (VIII) and thianaphtheno[3,2-*c*]pyridine (IX) could not be obtained by the action of sulfuric acid on the appropriate Schiff bases, but the use of polyphosphoric acid–phosphorus oxychloride gave the compounds in 18 and 12 per cent yields, respectively.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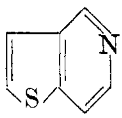
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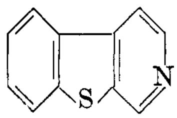
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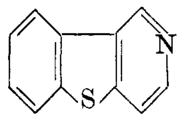
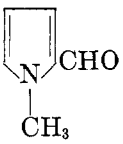

IX

Whereas cyclization of the Schiff base derived from pyrrole-2-carboxaldehyde and aminoacetal with the aid of polyphosphoric acid–phosphorus oxychloride gave a mixture of pyrrolo[1,2-*a*]pyrazine and pyrrolo[2,3-*c*]pyridine (159), action of the condensing agent on the aminoacetal derivative of 1-methylpyrrole-2-carboxaldehyde (X) gave a single product, 1-methylpyrrolo[2,3-*c*]pyridine (XI). Application of this procedure to the aminoacetal derivative (XII) of 2-acetylpyrrole gave a mixture of apoharmine (XIII) and 1-methylpyrrolo[1,2-*a*]pyrazine (XIV).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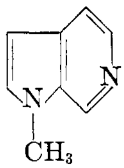
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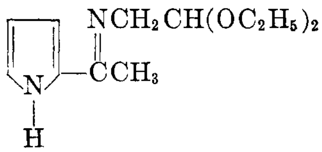
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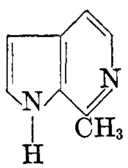
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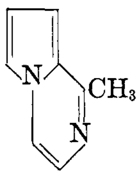

XIV

Both 6,7-dimethoxyisoquinoline (275) and 7,8-dimethoxyisoquinoline (103) have been prepared by polyphosphoric acid-catalyzed Pomeranz–Fritsch reactions, whereas the use of sulfuric acid gave negative results. However, the aminoacetal derivative of furfural could not be cyclized by the use of polyphosphoric acid as the condensing agent (157).

In table 3 there is presented a summary of all the known Pomeranz–Fritsch reactions catalyzed by polyphosphoric acid.

3. Synthesis of other nitrogen heterocycles

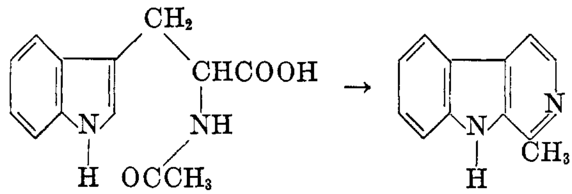
The conversion of *N*-formyltryptophan to norharman by the action of polyphosphoric acid–phosphorus oxychloride has already been mentioned. Analogous reactions were also found to occur with *N*-acetyltryptophan (XV) and *N*-acetyl-

TABLE 3

Pomeranz–Fritsch reaction

Aminoacetal Derivative of	Product	Yield	Reference
		per cent	
2-Acetylpyrrole	1-Methylpyrrolo[1, 2-*a*]pyrazine	23	(159)
	Apoharmine	5	(159)
2, 3-Dimethoxybenzaldehyde	7, 8-Dimethoxyisoquinoline	17	(103)
1-Methylpyrrole-2-carboxaldehyde	1-Methylpyrrolo[2, 3-*c*]pyridine	27	(159)
Pyrrole-2-carboxaldehyde	Pyrrolo[1, 2-*a*]pyrazine	21	(159)
	Pyrrolo[3, 2-*c*]pyridine	2	(159)
2-Thianaphthenealdehyde	Thianaphtheno[3, 2-*c*]pyridine	18	(160)
3-Thianaphthenealdehyde	Thianaphtheno[2, 3-*c*]pyridine	12	(160)
Thiophene-2-carboxaldehyde	Thieno[2, 3-*c*]pyridine	1	(160)
Thiophene-3-carboxaldehyde	Thieno[3, 2-*c*]pyridine	11	(160)
Veratraldehyde	6, 7-Dimethoxyisoquinoline	53	(275)

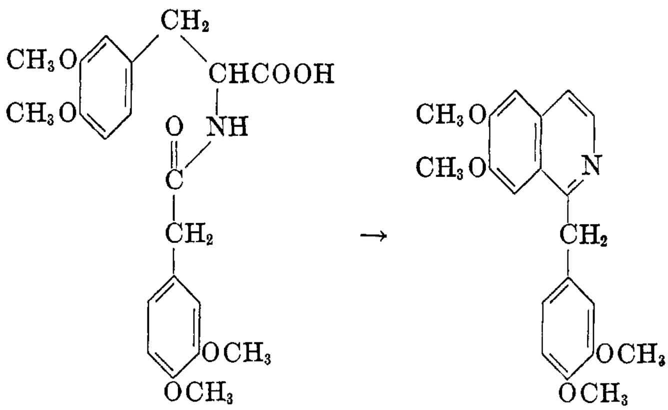
phenylalanine, harman (XVI) and 1-methylisoquinoline, respectively, being produced (321, 362).



XV
N-Acetyltryptophan

XVI
Harman

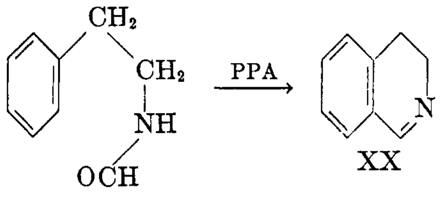
The suggestion has been made (126) that the type of reaction cited above could be used for the conversion of *N*-(3′,4′-dimethoxyphenylacetyl)-3,4-dimethoxyphenylalanine (XVII) to papaverine (XVIII), but this synthesis has not actually been carried out.



XVII

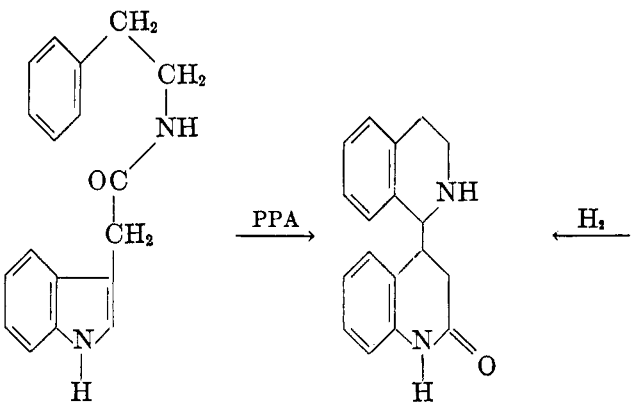
XVIII
Papaverine

That polyphosphoric acid might be a useful agent for effecting the Bischler–Napieralski synthesis is indicated by the fact that the reagent brings about the conversion of *N*-formylphenethylamine (XIX) to 3,4-dihydroisoquinoline (XX) in as high as 79 per cent yield (277, 321), whereas the use of phosphorus pentoxide in a conventional Bischler–Napieralski procedure affords the product in only 18 per cent yield (324). Also, *N*-acetylphenethylamine has been converted to 1-methyl-3,4-dihydroisoquinoline in as high as 55 per cent yield by the use of polyphosphoric acid as the cyclodehydration agent (76, 321). It is of interest that the same product, 1-methyl-3,4-dihydroisoquinoline, can be obtained in 20 per cent yield by the action of polyphosphoric acid on *N*-(β-phenylethyl)cyanoacetamide (220). Attempts to cyclize *N*-homoveratroyl-2-(2-pyrrolo)ethylamine by the use of polyphosphoric acid gave only an intractable material (158).

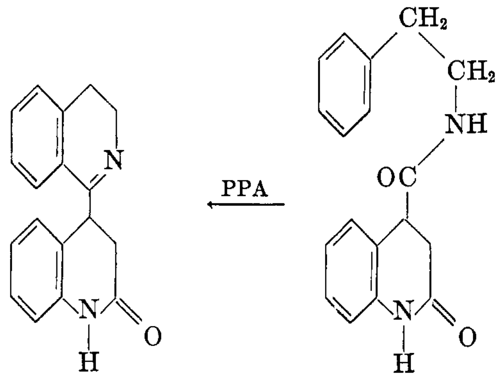


XIX XX

A rearrangement reaction occurred on cyclization of heteroauxin(β-phenethylamide) (XXI) by the action of polyphosphoric acid, 4-(1,2,3,4-tetrahydro-1-isoquinolyl)hydrocarbostryril (XXII) being formed (337). Treatment of the β-phenethylamide (XXIV) of carbostyril-4-carboxylic acid with polyphosphoric acid gave 4-(3,4-dihydro-1-isoquinolyl)carbostyril (XXIII) in quantitative yield; catalytic hydrogenation of the latter compound furnished XXII, thus confirming its structure.

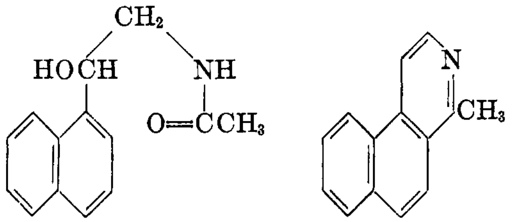


XXI XXII



XXIII XXIV

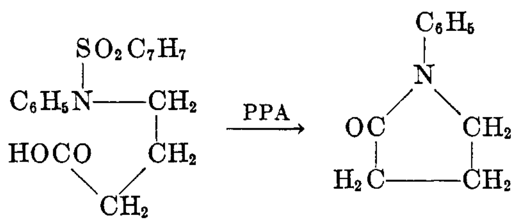
Although a successful application of the Pictet–Gams modification of the Bischler–Napieralski reaction was reported (273) in 1913 for the synthesis of 4-methylbenz[*f*]isoquinoline (XXVI) from the amido-alcohol XXV, attempts (101, 205) to repeat this work have given negative results. It has been suggested (205) that studies analogous to those reported (321) for the conversion of *N*-formyltryptophan to norharman might help to clear up this and similar discrepancies in the literature.



XXV XXVI

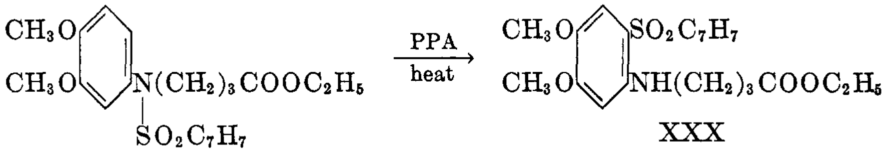
An attempted Skraup reaction of *p*-nitroaniline, glycerol, arsenic pentoxide, and polyphosphoric acid failed to give any detectable quantity of 6-nitroquinoline (322).

Treatment of *N*-tosyl-γ-anilinobutyric acid (XXVII) with polyphosphoric acid yielded *N*-phenyl-α-pyrrolidone (XXVIII) in 94 per cent yield (18). The action of aluminum chloride on the acid chloride of XXVII also gave XXVIII but in only 71 per cent yield. By the action of hot polyphosphoric acid on ethyl



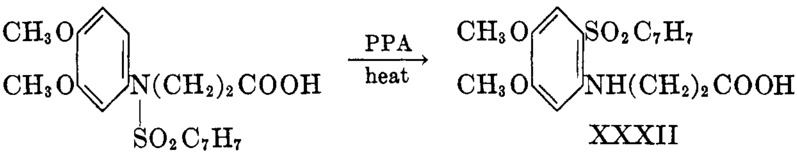
XXVII XXVIII

γ-*N*-(3,4-dimethoxyphenyl)toluene-*p*-sulfonamidobutyrate (XXIX) an apparent aromatic electrophilic rearrangement was brought about, the ester XXX being produced in 48 per cent yield (278). However, treatment of γ-*N*-(3,4-



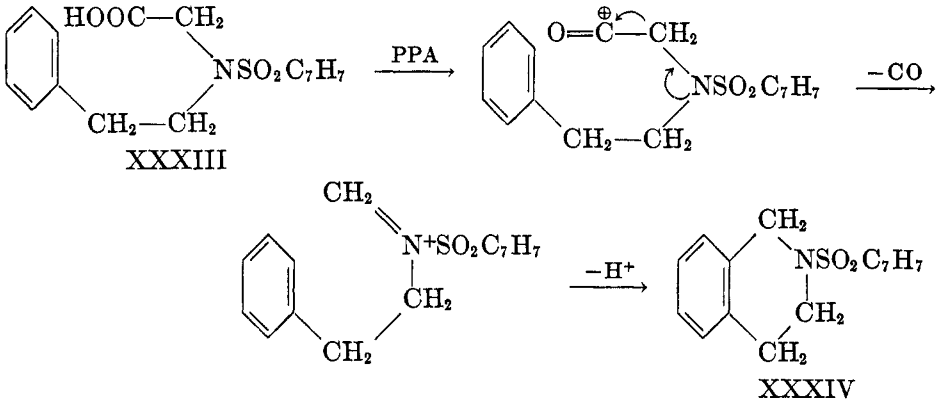
XXIX XXX

dimethoxyphenyl)toluene-*p*-sulfonamidobutyric acid with polyphosphoric acid at an elevated temperature gave a 2-pyrrolidone, again with migration of the tosyl group to either the 2- or the 6-position of the *N*-(3,4-dimethoxyphenyl) group. It is of interest that the reaction of anisole with toluene-*p*-sulfonic acid in hot polyphosphoric acid gave 4-methoxy-4′-methyldiphenyl sulfone (278). Whereas β-*N*-(3,4-dimethoxyphenyl)toluene-*p*-sulfonamidopropionyl chloride gave the anticipated quinoline when treated with stannic chloride, the corresponding acid (XXXI), when treated with hot polyphosphoric acid, afforded the rearrangement product (XXXII).



XXXI XXXII

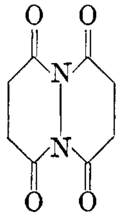
Attempts to bring about cyclization of the acid XXXIII with the aid of polyphosphoric acid gave, instead of the expected product, 2-tosyl-1,2,3,4-tetrahydroisoquinoline (XXXIV), possibly by the following mechanism (278):



XXXIII XXXIV

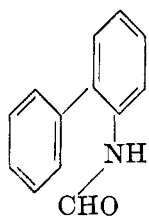
Only an intractable gum was formed on treatment of *N*-(3,4-dimethoxyphenethyl)-*N*-tosylglycine with polyphosphoric acid (278). An elimination reaction giving veratrylamine occurred when β-(3,4-dimethoxybenzylamino)propionic acid was mixed with polyphosphoric acid, even at room temperature. Polyphosphoric acid brought about the cleavage of *N*-(3,4-dimethoxybenzyl)-β-toluene-*p*-sulfonamidopropionic acid, *N*-(3,4-dimethoxybenzyl)-*p*-toluenesulfonamide being formed (278).

A new synthesis of bicyclic disuccinhydrazides has been developed with polyphosphoric acid as the condensation agent (120). Perhydro-1,4,6,9-tetraketopyridazo[1,2-*a*]pyridazine (XXXV) was prepared in 80 per cent yield when succinic acid and hydrazine hydrate in a 2:1 molar ratio were subjected to the dehydrating action of polyphosphoric acid. Analogous reactions have been carried out with methylsuccinic acid, phenylsuccinic acid, and *meso*-dimethylsuccinic acid, respectively, taking the place of the parent acid.

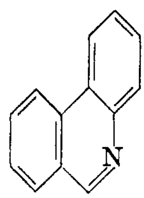


XXXV

Several reports of the synthesis of the phenanthridine nucleus by means of polyphosphoric acid-catalyzed reactions have appeared in the literature. The cyclization of 2-formamidobiphenyl (XXXVI) to phenanthridine (XXXVII) itself has received a fair amount of attention. The use of zinc chloride as the cyclization agent has been reported (265) to give a 42 per cent yield of XXXVII, while use of a mixture of phosphorus oxychloride, nitrobenzene, and anhydrous stannic chloride gave the heterocyclic base in 90 per cent yield. Two groups of workers have independently reported the application of polyphosphoric acid for this cyclization reaction (140, 336). Phenanthridine (XXXVII) may be obtained in greater than 90 per cent yield if a mixture of 2-formamidobiphenyl (XXXVI) and polyphosphoric acid is stirred for 1 hr. at 140–160°C. When the mixture is not continuously stirred, the only compound isolated is one having a molecular formula of $C_{25}H_{20}N_2$, probably *N*,*N'*-bis(*o*-biphenylyl)formamidine.



XXXVI

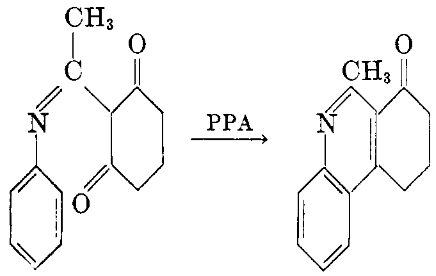


XXXVII

Substituted phenanthridines have been prepared in the same manner as that cited above for the parent heterocyclic compound (28). Treatment of 5-bromo-2-formamidobiphenyl with polyphosphoric acid gave 3-bromophenanthridine in

85 per cent yield. It was of interest that the use of polyphosphoric acid having a theoretical P_2O_5 content of less than 84 per cent led to the formation of 2-amino-5-bromobiphenyl rather than the desired heterocyclic compound. 2-Bromophenanthridine was prepared in 85 per cent yield and 7-bromophenanthridine in 80 per cent yield from 4-bromo-2-formamidobiphenyl and 4′-bromo-2-formamidobiphenyl, respectively.

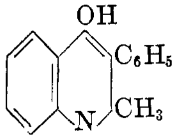
Although 2,6-diketocyclohexylmethyleneaniline did not undergo cyclodehydration on treatment with polyphosphoric acid or anhydrous hydrogen fluoride (293), 1-(2,6-diketocyclohexyl)ethylideneaniline (XXXVIII) was converted to 5,6,7,8-tetrahydro-8-keto-9-methylphenanthridine (XXXIX) in 92 per cent yield by the action of polyphosphoric acid (314), and 1-(2,6-diketocyclohexyl)propylideneaniline, heated in polyphosphoric acid at 180°C. for 1 hr., gave a 65 per cent yield of 5,6,7,8-tetrahydro-8-keto-9-ethylphenanthridine (293). Similarly, 1′-(2,6-diketocyclohexyl)ethylidene-1-naphthylamine gave, in 67 per cent yield, 3,4,5,6-tetrahydro-3-keto-2-methyl-1-azachrysene, which could be converted in several additional steps to 1-azachrysene, the parent heterocycle of a number of alkaloids (293).



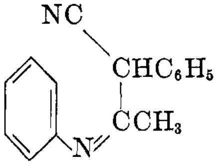
XXXVIII XXXIX

Cyclization of *o*-biphenylyl isocyanate may be carried out conveniently with the aid of polyphosphoric acid, an 87 per cent yield of phenanthridone being produced (336). This is claimed to be the most convenient method of synthesis of this compound.

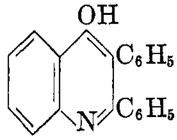
By use of the Conrad–Limpach synthesis, it is possible to prepare 2-methyl-3-phenyl-4-quinolinol (XL) from aniline and ethyl α-phenylacetoacetate in only 4 per cent yield (4). However, XL may be prepared in 79 per cent yield by polyphosphoric acid-catalyzed cyclization of the anil (XLI) of α-acetyl-α-tolunitrile (152). 2,3-Diphenyl-4-quinolinol (XLII) may be prepared in a similar manner from the anil of α-benzoyl-α-tolunitrile. Perhaps the amide (XLIII) is an intermediate in the conversion of XLI to XL. In any event, polyphosphoric acid is known to catalyze the conversion of nitriles to amides (317), and, in a separate experiment, it was demonstrated (152) that XLIII could be converted to XL under the same conditions used for the conversion of XLI to XL. Also, ammonia must be eliminated in the cyclization step, because 2-methyl-3-phenyl-4-aminoquinoline (XLIV) is stable towards polyphosphoric acid under the conditions of the reactions cited above.



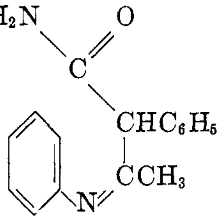
XL



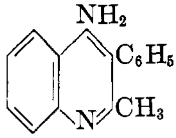
XLI



XLII

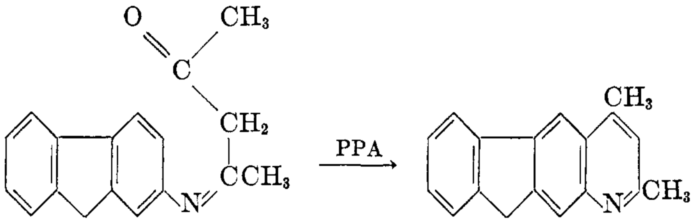


XLIII



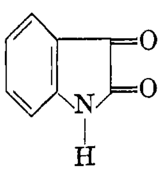
XLIV

In a very similar reaction to those described above, the condensation product (XLV) derived from 2-aminofluorene and acetylacetone was converted in 79 per cent yield to 2,4-dimethylindeno(3′,2′:6,7)quinoline (XLVI) by the action of polyphosphoric acid (74).

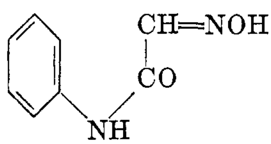


XLV XLVI

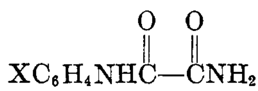
Isatin (XLVII) and a number of its derivatives have been prepared by treatment of isonitrosoacetanilide (XLVIII) and its derivatives with polyphosphoric acid (113, 274). In some of the reactions, a substituted oxamide (XLIX) was isolated in addition to the isatin derivative. The conversion of XLVIII to XLVII may also be catalyzed by sulfuric acid (228). The data (274) on the polyphosphoric acid-catalyzed preparation of isatin derivatives are summarized in table 4.



XLVII



XLVIII



XLIX

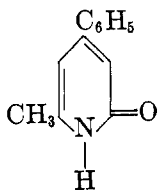
A new synthesis of 2-pyridones has been developed since the advent of polyphosphoric acid as a commonly used catalyst in organic reactions. The 2-pyri-

TABLE 4

Preparation of isatins from isonitrosoacetanilides

Isonitrosoacetanilide	Isatin	Yield	N-Phenyloxamide	Yield
		per cent		*per cent*
2-Bromo-	7-Bromo-	Trace	2-Bromo-	45
3-Bromo-	4-Bromo- 6-Bromo-	Mixture	3-Bromo-	5
4-Bromo-	5-Bromo-	Trace	4-Bromo-	25
2-Chloro-	7-Chloro-	Trace	2-Chloro-	50
4-Chloro-	5-Chloro-	Trace	4-Chloro-	50
2,4-Dimethyl-	5,7-Dimethyl-	45		
2-Methoxy-	7-Methoxy-	11	2-Methoxy-	5
4-Methoxy-	5-Methoxy-	24	4-Methoxy-	12
2-Methyl-	7-Methyl-	40		
4-Methyl-	5-Methyl-	60	4-Methyl-	6
Unsubstituted	Unsubstituted	50		

dones are formed as a result of the action of polyphosphoric acid on mixtures of β-keto amides and ketones or β-keto nitriles and ketones (149). For example, treatment of a mixture of benzoylacetamide and acetone with polyphosphoric acid gave 4-phenyl-6-methyl-2-pyridone (L) in 60 per cent yield. In an analogous manner, 3-phenyl-4,6-dimethyl-2-pyridone and 3,6-dimethyl-4-phenyl-2-pyridone were prepared in yields of 18 and 30 per cent, respectively, from α-acetyl-α-toluamide and α-benzoylpropionamide.



L

Owing to the fact that polyphosphoric acid catalyzes the conversion of β-keto nitriles to β-keto amides (148), it is not surprising that the reaction of the nitriles with ketones in the presence of polyphosphoric acid also produces 2-pyridones. However, for a reason which is not apparent, the use of β-keto nitriles seems to give somewhat better yields of 2-pyridones than the use of β-keto amides. The results of a number of polyphosphoric acid-catalyzed condensation reactions of β-keto nitriles with ketones are summarized in table 5.

There are insufficient data available to make an adequate comparison of the method of preparation of 2-pyridones described above with other methods. Whereas 4-phenyl-6-methyl-2-pyridone (L) was prepared in 60 per cent yield by the use of polyphosphoric acid, it was synthesized in only 10 per cent yield by one of the older methods (43). However, 4,6-diphenyl-2-pyridone, obtained in only 5 per cent yield by the use of polyphosphoric acid, was prepared in much better yield by an older procedure (42).

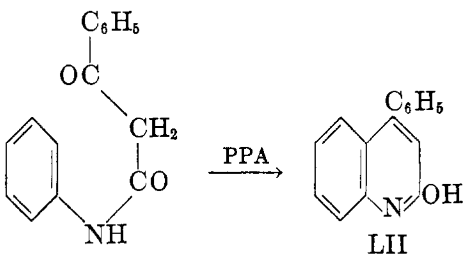
A polyphosphoric acid-catalyzed conversion of *N*-(benzoylacetyl)aniline (LI) to 4-phenylcarbostyril (LII) was effected in 70 per cent yield (325), and

TABLE 5

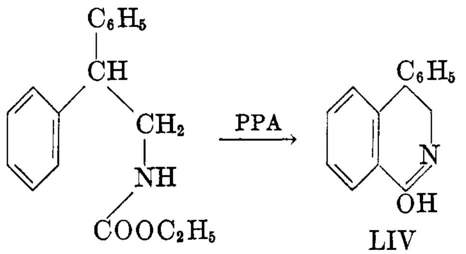
Condensation of β-keto nitriles with ketones

Nitrile	Ketone	2-Pyridone	Yield
			per cent
α-Acetyl-α-tolunitrile	Acetone	3-Phenyl-4,6-dimethyl-	29
	Phenylacetone	3,5-Diphenyl-4,6-dimethyl-	58
Benzoylacetonitrile	Acetone	4-Phenyl-6-methyl-	68
	Acetophenone	4,6-Diphenyl-	5
	Cyclohexanone	2-Hydroxy-4-phenyl-5,6,7,8-tetrahydro-quinoline	53
	Phenylacetone	4,5-Diphenyl-6-methyl-	63
α-Benzoylpropionitrile	Acetone	3,6-Dimethyl-4-phenyl-	43
	Phenylacetone	4,5-Diphenyl-3,6-dimethyl-	60
α-Nicotinylpropionitrile	Phenylacetone	3,6-Dimethyl-4-nicotinyl-5-phenyl-	34

cyclization of the urethan (LIII) with the aid of polyphosphoric acid afforded 3,4-dihydro-4-phenylisocarbostyril (LIV) in fair yield (325).



LI LII



LIII LIV

Polyphosphoric acid has been found to be an effective and convenient catalyst for the Phillips benzimidazole synthesis and related condensation reactions (156). It serves as a suitable solvent for the reactions, and carboxylic acids, amides, esters, or nitriles may be used in the condensation reaction with the aromatic diamine. For example, 2-phenylbenzimidazole may be prepared from *o*-phenylenediamine and any one of the reagents benzoic acid, benzamide, methyl benzoate, or benzonitrile. The available data (156) are summarized in table 6.

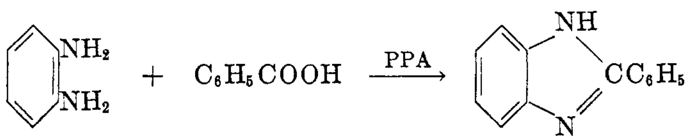
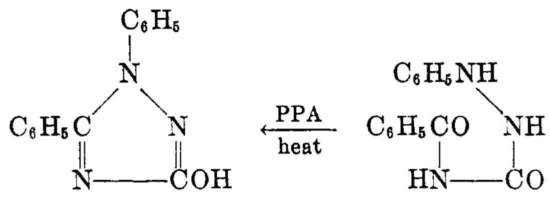


TABLE 6

Synthesis of benzimidazoles

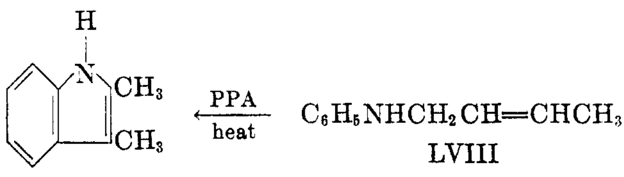
Reagent Used with *o*-Phenylenediamine	Temperature	Time	Yield of 2-Substituted Benzimidazole
	°C.	*hours*	*per cent*
Acetic acid	125	3.5	69
Anthranilic acid	250	3.5	60
Benzamide	250	4	72
Benzoic acid	175	2	81
Benzonitrile	250	4	69
o-Chlorobenzoic acid	250	4	51
3,4-Dichlorobenzoic acid	250	4	62
3-Hydroxy-2-naphthoic acid	250	4.5	13
Methyl benzoate	175	2	67
Nicotinic acid	250	4	11
Phthalic acid	250	4	58
Salicylic acid	250	4	29
m-Toluic acid	250	3.5	85

Although 3-hydroxy-1,5-diphenyl-1,2,4-triazole (LV) could be prepared in 41 per cent yield by treatment of 4-benzoyl-1-phenylsemicarbazide (LVI) with aqueous sodium hydroxide, followed by acidification of the reaction mixture with acetic acid, the same procedure did not effect ring closure of 4-benzoyl-1-*p*-nitrophenylsemicarbazide (14). However, treatment of the latter compound with hot polyphosphoric acid provided 3-hydroxy-1-*p*-nitrophenyl-5-phenyl-1,2,4-triazole in quantitative yield. The triazole LV could also be obtained in 75 per cent yield by heating LVI with polyphosphoric acid (14).



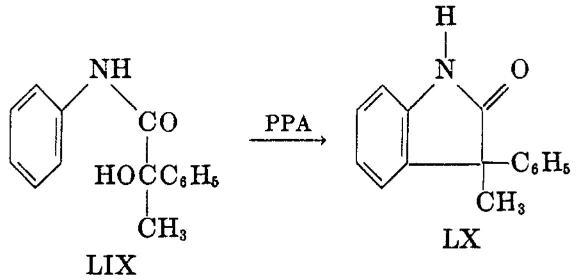
LV LVI

2,3-Dimethylindole (LVII) has been prepared in good yield by heating *N*-butenylaniline (LVIII) with polyphosphoric acid (25).

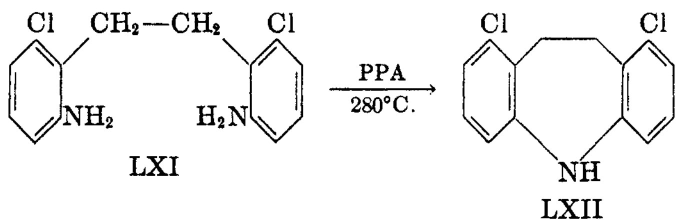


LVII LVIII

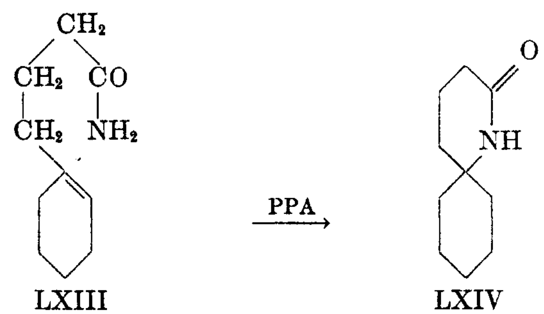
The conversion of (±)-atrolactanilide (LIX) to 3-methyl-3-phenyloxindole (LX) has been brought about in 78 per cent yield with the aid of polyphosphoric acid. Attempts to effect the cyclization by the action of sulfuric acid proved fruitless. Polyphosphoric acid was also found to be effective in the conversion of (±)-mandelanilide to 3-phenyloxindole (326).



When the diphosphate of 2,2′-diamino-6,6′-dichlorobibenzyl (LXI) was heated with polyphosphoric acid at 280°C., 1,9-dichloroiminobibenzyl (LXII) was obtained in 70 per cent yield (133). 2,2′-Diamino-4,4′-dichlorobibenzyl diphosphate was converted to 3,7-dichloroiminobibenzyl in 85 per cent yield by the same method.

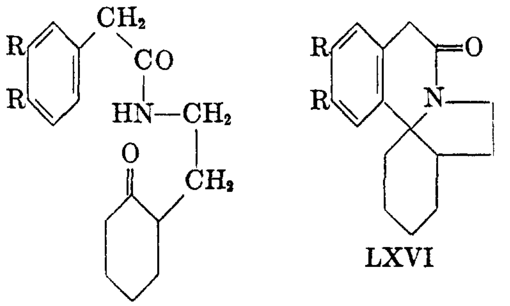


The conversion of γ-(1-cyclohexenyl)butyramide (LXIII) to 1-azaspiro[5.5]-undecanone-2 (LXIV) was achieved in quantitative yield by the use of polyphosphoric acid as the catalyst (164).



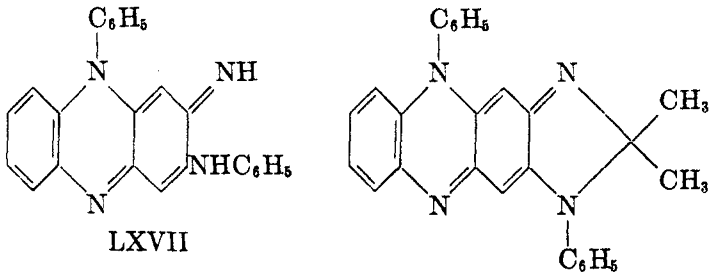
2-(β-Phenylacetamidoethyl)cyclohexanone (LXV: R = H), when heated in an excess of polyphosphoric acid, was converted to 8-oxoerythrinane (LXVI: R = H) in 60 per cent yield (49). The dimethoxy analog of LXVI (R = OCH_3) was obtained (50) in 71 per cent yield by application of the same procedure to LXV (R = OCH_3).

Diketopiperazines have been obtained in good yields by the treatment of glycine, alanine, leucine, isoleucine, and phenylalanine with polyphosphoric acid (313). 2,3-Dihydro-1-phenyl-4(1*H*)quinolone was obtained in 52 per cent yield by the polyphosphoric acid-catalyzed ring-closure reaction of *N*,*N*-diphenyl-β-alanine (180).



LXV LXVI

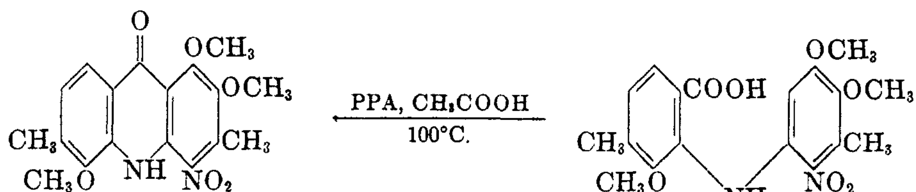
Treatment of a mixture of anilinoaposafranine (LXVII), acetone, and ethanol with polyphosphoric acid gave (41) 5,2′-dihydro-2′,2′-dimethyl-5,1′-diphenylglyoxalino(5′,4′,2,3)phenazine (LXVIII).



LXVII LXVIII

An attempt to prepare 5-phenylacridine by the condensation of diphenylamine with benzoic acid in the presence of polyphosphoric acid met with failure. A dibenzoyldiphenylamine was obtained instead of the desired product (113).

4-Nitro-1,2,5-trimethoxy-3,6-dimethylacridone (LXIX) was prepared in 82 per cent yield by treatment of 6′-nitro-6,3′,4′-trimethoxy-5,5′-dimethyldiphenylamine-2-carboxylic acid (LXX) with a 15 per cent solution of polyphosphoric acid in glacial acetic acid for 10 min. at 100°C. (71). This procedure is of interest because it represents the first reported use of a solution of polyphosphoric acid in another solvent as the condensing agent.



LXIX LXX

Although treatment of 3-amino-*N*-benzyl-5,6-diphenylpyrazinamide, 3-(3-phenylureido)-*N*-benzyl-5,6-diphenylpyrazinamide, or 3-(3-phenylureido)-5,6-diphenylpyrazinamide (LXXI) with hot polyphosphoric acid afforded mainly 3-

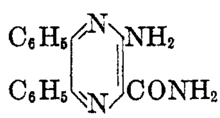
TABLE 7

Preparation of furans from 1,4-diketones

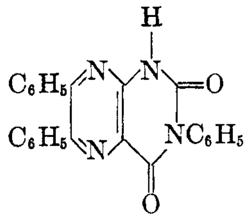
1,4-Diketone	Furan	Temperature	Time	Yield
		°C.	*min.*	*per cent*
Acetonylacetone	None (tar formation)	140–150	30	
1,2-Bis(*p*-bromobenzoyl)ethane	2,5-Bis(*p*-bromophenyl)-	145–150	90	91
1,2-Bis(*p*-bromobenzoyl)-1,2-dibromoethane	2,5-Bis(*p*-bromophenyl)-3,4-dibromo-	150–155	90	43
1,2-Bis(*p*-chlorobenzoyl)ethane	2,5-Bis(*p*-chlorophenyl)-	130–140	90	97
1,2-Bis(*p*-toluyl)ethane	2,5-Bis(*p*-tolyl)-	145–150	20	61
1,2-Dibenzoylcyclohexane	1,3-Diphenyl-4,5,6,7-tetrahydroisobenzofuran	140–150	30	62
1,2-Dibenzoyl-4,5-dibromocyclohexane	5,6-Dibromo-1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran	140–150	30	26
1,2-Dibenzoylethane	2,5-Diphenyl-	130–140	90	95

amino-5,6-diphenylpyrazinamide (LXXII), a low yield of 3,6,7-triphenyl-2,4-(1*H*,3*H*)pteridinedione (LXXIII) was obtained by the reaction of LXXI with polyphosphoric acid at 150°C. for 2 hr. (335).

LXXI



LXXII



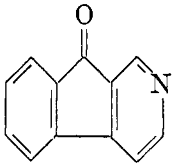
LXXIII

4. Synthesis of sulfur and oxygen heterocycles

The claim has been made (264) that 2,5-diarylfurans (LXXIV) can be prepared from 1,2-diaroylethanes (1,4-diaryl-1,4-butanediones) in better yields by the use of polyphosphoric acid as the dehydration agent than by the use of other agents, such as sulfuric acid, acetic anhydride, hydrochloric acid, zinc chloride, or phosphorus pentoxide. The available data (264) on the polyphosphoric acid-catalyzed reactions are summarized in table 7.

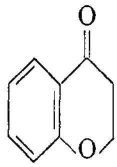
LXXIV

A sterically hindered 1,2-diaroylethane is not converted to a furan by the action of polyphosphoric acid but is, in most instances, cleaved to an aromatic hydrocarbon plus an acid (264). This result was not unexpected, inasmuch as it is known (226) that 1,2-dimesitoylethane is cleaved by the action of 85 per cent phosphoric acid at an elevated temperature, mesitylene and succinic acid being formed. 1,2-Dimesitoylethane, 1,2-dimesitoylcyclohexane, and benzoyl-mesitylene all gave mesitylene when heated with polyphosphoric acid at about 180°C. for 30–45 min. (264). However, 1,2-bis(2,4,6-triisopropylbenzoyl)ethane, in which steric hindrance is more pronounced than for the compounds cited above, underwent neither cleavage nor furanization in contact with polyphosphoric acid at temperatures up to 210°C. (264). Additional examples of the cleavage of hindered ketones came to light when it was found (124) that 2-azafluorenone (LXXV) is produced by the action of hot polyphosphoric acid on either 3-mesitoyl-4-phenylpyridine or 3-duroyl-4-phenylpyridine. It was assumed (124) that 4-phenylnicotinic acid was formed as an intermediate and then underwent intramolecular acylation to give LXXV. In an analogous reaction, 3,4-benzo-2-azafluorenone was produced by the treatment of 3-mesitoyl-4-phenylquinoline with hot polyphosphoric acid.



LXXV

A number of 4-chromanones have been prepared by polyphosphoric acid-catalyzed reactions. Chromanone (LXXVI) itself may be prepared in 87 per cent yield by the action of polyphosphoric acid on β-phenoxypropionic acid (225). By analogous reactions, 6-phenylchromanone (225), 7-methoxychromanone (225), and 6-nitrochromanone (180) have been prepared from the appropriate



LXXVI

β-aryloxypropionic acids. Furthermore, 3-phenylmercaptopropionic acid was cyclized to 4-thiochromanone by treatment with polyphosphoric acid (180). Phosphorus oxychloride also promoted the cyclization of 3-(*p*-nitrophenoxy)-propionic acid and 3-phenylmercaptopropionic acid, but the products contained chlorine.

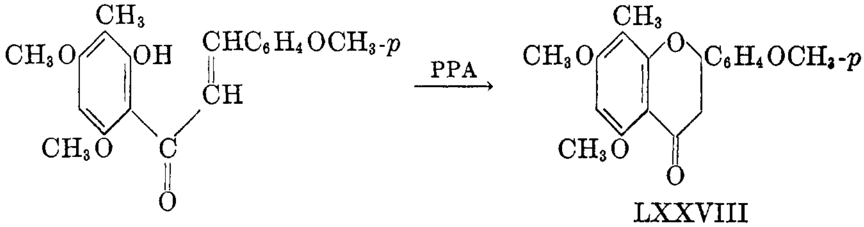
Several examples of the use of polyphosphoric acid as the condensing agent in the Pechmann synthesis of coumarins have appeared in the literature. 4,7-Dimethylcoumarin was prepared in 76 per cent yield from *m*-cresol and ethyl acetoacetate (113). Actually, sulfuric acid is about as effective a catalyst for this reaction as polyphosphoric acid (123). Resorcinol has been condensed with each of the β-keto esters, ethyl acetoacetate, ethyl α-methylacetoacetate, and ethyl benzoylacetate, in the presence of polyphosphoric acid, to give, respectively, 4-methyl-7-hydroxycoumarin, 3,4-dimethyl-7-hydroxycoumarin, and 4-phenyl-7-hydroxycoumarin in 80–95 per cent yields (213).

TABLE 8

Conversion of 2-phenoxycyclohexanones to 1,2,3,4-tetrahydrodibenzofurans

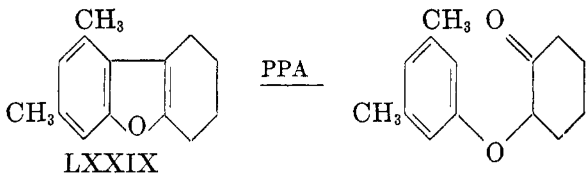
2-Phenoxycyclohexanone	1,2,3,4-Tetrahydro-dibenzofuran	2-Phenoxycyclohexanone	1,2,3,4-Tetrahydro-dibenzofuran
4-Methyl-	3-Methyl-	2′,4′-Dimethyl-	6,8-Dimethyl-
2′-Methyl-	6-Methyl-	2′,5′-Dimethyl-	6,9-Dimethyl-
4′-Methyl-	8-Methyl-	3′,4′-Dimethyl-	7,8-Dimethyl-
2′,3′-Dimethyl-	6,7-Dimethyl-	3′,5′-Dimethyl-	7,9-Dimethyl-

The chalcone LXXVII has been converted to the flavanone LXXVIII in 80 per cent yield by the action of polyphosphoric acid (251).



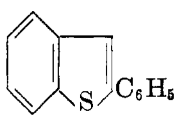
LXXVII LXXVIII

A number of substituted 1,2,3,4-tetrahydrodibenzofurans have been prepared by the treatment of substituted 2-phenoxycyclohexanones with polyphosphoric acid (346). For example, 1,2,3,4-tetrahydro-7,9-dimethyldibenzofuran (LXXIX) was prepared in 93 per cent yield from 2-(3,5-dimethylphenoxy)-cyclohexanone (LXXX) by this method. Other examples (346) of this reaction are listed in table 8.



LXXIX LXXX

The conversion of α-(arylthio)ketones to thianaphthenes is usually brought about by the action of phosphorus pentoxide or fused zinc chloride; however, these procedures failed when applied to phenacyl phenyl sulfide (33). The use of polyphosphoric acid brought about cyclization of the compound, but 2-phenylthianaphthene (LXXXI) was produced rather than 3-phenylthianaphthene, the



LXXXI

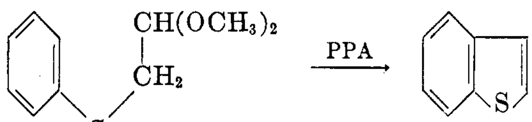
TABLE 9

Conversion of aryl phenacyl sulfides to thianaphthenes

Sulfide	Thianaphthene	Temperature	Time	Yield
		°C.	*hours*	*per cent*
4-Methoxyphenacyl phenyl	2-*p*-Methoxyphenyl-	190	1	44
m-Methoxyphenyl phenacyl	6-Methoxy-2-phenyl-	190	3	
Phenacyl phenyl	2-Phenyl-	180–190	3	32
Phenacyl *m*-tolyl	6-Methyl-2-phenyl-			28
Phenacyl *p*-tolyl	5-Methyl-2-phenyl-			26

anticipated product (33). The use of either sulfuric acid or polyphosphoric acid as the cyclization agent led to the production of 6-methoxy-2-phenylthianaphthene from *m*-methoxyphenyl phenacyl sulfide (33). This same type of ring closure accompanied by rearrangement has been observed (88) upon treatment of phenoxyacetophenone with polyphosphoric acid, 2-phenylbenzofuran being produced. It is of interest that ring closure occurs without rearrangement when the sulfur or oxygen of the compounds cited above is replaced by a methylene group. For example, β-(3,4-dimethoxyphenyl)propiophenone, on treatment with polyphosphoric acid, gave 5,6-dimethoxy-3-phenylindene (88, 211). The results (33) of a number of rearrangement-cyclization reactions of aryl phenacyl sulfides, catalyzed by polyphosphoric acid, are summarized in table 9.

Numerous thianaphthenes have been prepared by the treatment of arylthioacetaldehyde acetals with polyphosphoric acid. For example, phenylthioacetaldehyde dimethyl acetal (LXXXII) was converted to thianaphthene (LXXXIII) in as high as 72 per cent yield by this method (281). The most satisfactory pro-



LXXXII LXXXIII

cedure for carrying out these reactions is to utilize a sufficiently low pressure and high temperature so that the product distills as it is formed (339). Attempts to bring about ring closure by the use of acetic anhydride, zinc chloride, or pyridine hydrochloride failed (281). Table 10 contains a summary of the polyphosphoric acid-catalyzed reactions giving thianaphthenes from arylthioacetaldehyde acetals.

5. Additional applications

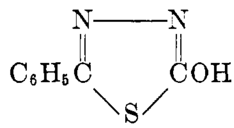
2-Phenylthiazoline has been prepared by the cyclization of 2-thiobenzamidoethanol under the influence of polyphosphoric acid (219). In a similar reaction, thiobenzamidoacetaldehyde diethyl acetal, when treated with polyphosphoric acid at 100°C., gave 5-ethoxy-2-phenylthiazoline. However, when the temperature was raised to 180°C., 2-phenylthiazole was produced. 1-Thiobenzoylsemi-

TABLE 10

Preparation of thianaphthenes from arylthioacetaldehyde acetals

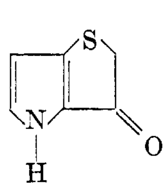
Acetal or Related Starting Material	Product	Yield	References
		per cent	
p-Bromophenylthioacetaldehyde diethyl acetal	5-Bromothianaphthene	49	(32)
o-Bromophenylthioacetaldehyde dimethyl acetal	7-Bromothianaphthene	39	(280)
		72	(281)
p-Bromophenylthioacetaldehyde dimethyl acetal	5-Bromothianaphthene	13	(280)
2-Chloro-1-naphthylthioacetaldehyde dimethyl acetal	9-Chloronaphtho[1′,8′-*bc*]thiapyran	11	(102)
8-Chloro-1-naphthylthioacetaldehyde dimethyl acetal	3′-Chlorobenzo[1′,2′,6,7]thianaphthene	82	(102)
o-Chlorophenylthioacetaldehyde dimethyl acetal	7-Chlorothianaphthene	41	(332)
m-Chlorophenylthioacetaldehyde dimethyl acetal	6-Chlorothianaphthene	32	(332)
p-Chlorophenylthioacetaldehyde dimethyl acetal	5-Chlorothianaphthene	43	(332)
2,5-Dimethylphenylthioacetaldehyde diethyl acetal	4,7-Dimethylthianaphthene	86	(323)
p-Ethoxyphenylthioacetaldehyde dimethyl acetal	5-Ethoxythianaphthene	15	(333)
3-Methoxy-4-methylphenylthioacetaldehyde dimethyl acetal	6-Methoxy-5-methylthianaphthene	64	(333)
o-Methoxyphenylthioacetaldehyde dimethyl acetal	7-Methoxythianaphthene	18	(333)
m-Methoxyphenylthioacetaldehyde dimethyl acetal	6-Methoxythianaphthene	62	(333)
p-Methoxyphenylthioacetaldehyde dimethyl acetal	5-Methoxythianaphthene	Poor	(333)
Naphthalenebis(1,5-thioacetaldehyde dimethyl acetal)	1,6-Dithiapyrene	33	(340)
Naphthalenebis(2,6-thioacetaldehyde dimethyl acetal)	Thianaphtheno[4,5,5′,4′]thianaphthene	15	(340)
Naphthalenebis(2,7-thioacetaldehyde dimethyl acetal)	Thianaphtheno[4,5,4′,5′]thianaphthene		(134)
α-Naphthylthioacetaldehyde dimethyl acetal	Benzo[6,7]thianaphthene	48	(32, 91, 340)
	Naptho[1′,9′,8′,2,3,4]thiapyran	4	(32, 91, 340)
α-Naphthylthioacetaldehyde diethyl acetal	Benzo[6,7]thianaphthene	20	(32)
β-Naphthylthioacetaldehyde dimethyl acetal	Benzo[4,5]thianaphthene	59	(340)
2-(2-Naphthylmercapto)-3,α-dihydro-1(2*H*)-naphthalenone	1,2-Dihydro-9-thiabenzo[3,4]thiafluorene		(282)
o-Nitrophenylthioacetaldehyde dimethyl acetal			(280)
p-Nitrophenylthioacetaldehyde dimethyl acetal	5-Nitrothianaphthene	14	(280)
3-Phenanthrylthioacetaldehyde dimethyl acetal	Benzo[7,8]thiophenanthrene	69	(341)
2′-Phenylmercapto-3,4-dihydro-1(2*H*)-naphthalenone	1,2-Dihydro-9-thiabenzo[3,4]fluorene		(282)
Phenylthioacetaldehyde diethyl acetal	Thianaphthene	32	(339)
Phenylthioacetaldehyde dimethyl acetal	Thianaphthene	37	(339)
		72	(281)
6-Tetralylthioacetaldehyde diethyl acetal	Mixture of tetrahydrobenzothianaphthenes	58	(89)
2-Thienylthioacetaldehyde dimethyl acetal	Thieno[2,3-*b*]thiophene	46	(135)
o-Tolylthioacetaldehyde dimethyl acetal	7-Methylthianaphthene	53	(332)
m-Tolylthioacetaldehyde dimethyl acetal	6-Methylthianaphthene	42	(332)
		78	(281)
p-Tolylthioacetaldehyde dimethyl acetal	5-Methylthianaphthene	49	(332)

carbazide when heated alone, with hot concentrated hydrochloric acid, or with polyphosphoric acid gave 2-hydroxy-5-phenyl-1,3,4-thiadiazole (LXXXIV) in 83, 64, and 88 per cent yields, respectively (219).



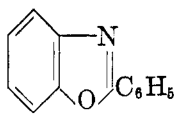
LXXXIV

A convenient synthesis of thieno[3,2-*b*]pyrrole has recently been described (229). One of the steps consisted in the cyclization of (3-pyrrolylthio)acetic acid to 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (LXXXV) by the action of polyphosphoric acid.



LXXXV

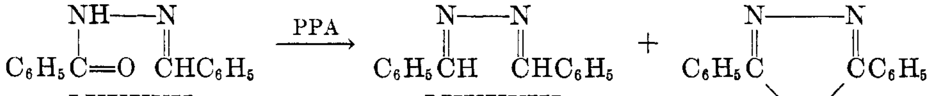
The condensation of *o*-aminophenols or *o*-aminothiophenols with carboxylic acids to form benzoxazoles or benzothiazoles, respectively, has been effected by the use of polyphosphoric acid as the condensing agent. The reaction of benzoic acid with *o*-aminophenol, carried out for 4 hr. at 250°C., produced 2-phenylbenzoxazole (LXXXVI) in 75 per cent yield. In like manner, 2-phenyl-5-chlorobenzoxazole, 2-phenylbenzothiazole, and 2-*o*-aminophenylbenzothiazole were obtained in 30, 90, and 52 per cent yields, respectively, from the appropriate reagents (156).



LXXXVI

3,4-Dihydrothieno[3,2-*c*]pyridine was prepared in 8 per cent yield by treatment of *N*-formyl-2-(2-thienyl)ethylamine with polyphosphoric acid (161). However, an attempt to cyclize *N*-benzoyl-1-furyl-2-aminoethanol to 1-phenylfurano[3,2-*c*]pyridine by the action of polyphosphoric acid failed (157).

By the action of polyphosphoric acid on 1-benzoyl-2-benzalhydrazine (LXXXVII), a mixture of benzaldazine (LXXXVIII) and 2,5-diphenyloxadiazole (LXXXIX) resulted. The results (181) of similar reactions are summarized in table 11. Previous workers had thought that treatment of compounds related

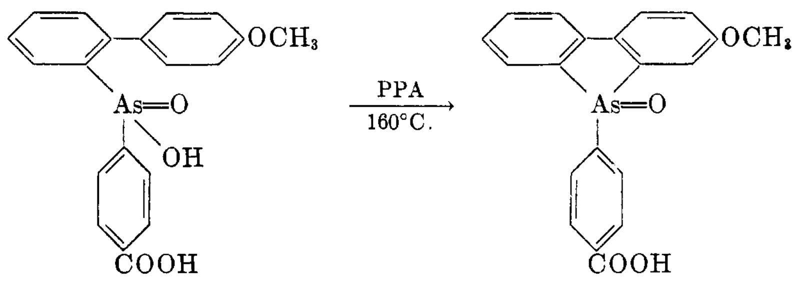


LXXXVII LXXXVIII LXXXIX

to LXXXVII by acidic reagents gave substituted phthalazines (5, 6). However, when attempts were made to cyclize 1-benzoyl-2-*o*-nitrobenzalhydrazine or 1-benzoyl-2-*m*-nitrobenzalhydrazine with a variety of acidic reagents, including polyphosphoric acid, only the corresponding benzaldazines were isolated (291). Further investigations (181, 291) revealed that all of the alleged phthalazine preparations reported (5, 6) by the earlier workers were in error.

7-Acetonylxanthopterine was converted to 4-hydroxy-2-amino-5′-methyl-(furano-2′,3′:6,7-pteridine) in 78 per cent yield by the action of polyphosphoric acid at 125°C. for 30 min. (348). By treatment with polyphosphoric acid at 150°C. for 1 hr., 7-(β-hydroxypropyl)xanthopterine was cyclized to 4-hydroxy-2-amino-5′-methyl(dihydrofurano-2′,3′:6,7-pteridine) (347).

Several diarylarsinic acids have been converted to 9-arsafluorene oxides by treatment with sulfuric acid. However, the arsinic acid XC underwent sulfonation when handled in this manner. The desired 9-arsafluorene oxide (XCI) was obtained in 94 per cent yield when XC was subjected to the action of polyphosphoric acid at 160°C. for 3 min. (73).



XC XCI

TABLE 11

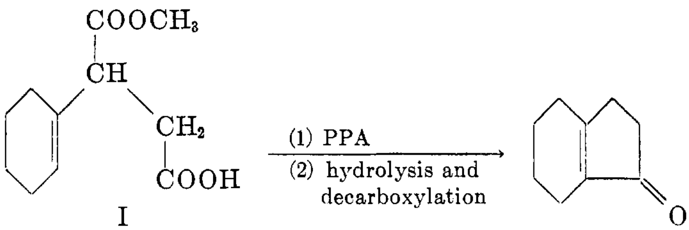
Conversion of substituted hydrazines into aldazines and oxadiazoles

Hydrazine	Product(s)	Temperature	Time	Yield
		°C.	*hours*	*per cent*
1-Benzoyl-2-benzalhydrazine	Benzaldazine	100	5	44
	2,5-Diphenyloxadiazole			33
1-Benzoyl-2,2-dibenzylhydrazine	2,5-Diphenyloxadiazole	120	4	48
1-Benzoyl-2-benzylhydrazine	2,5-Diphenyloxadiazole	120	4	68
1,2-Dibenzoylhydrazine	2,5-Diphenyloxadiazole	100	4	65
1,2-Di-*m*-methoxybenzoylhydrazine	2,5-Di-*m*-methoxyphenyloxadiazole	100	3	53
1-*m*-Methoxybenzoyl-2-benzalhydrazine	Benzaldazine	120	2	61
	2,5-Di-*m*-methoxyphenyloxadiazole			23

B. INTRAMOLECULAR ACYLATION

A variety of methods has been developed for the preparation of cyclic ketones by intramolecular acylation reactions (193). These methods include the cyclization of carboxylic acids of appropriate structure by the action of hydrogen fluoride or sulfuric acid and the application of the Friedel–Crafts reaction to acid chlorides of suitable structure. Recently, polyphosphoric acid has achieved importance as a catalyst for intramolecular acylation reactions.

For each cyclization reaction, an optimum yield of product can be obtained only after a number of experiments have been carried out to determine the proper temperature and time of reaction. The data (95) given below illustrate the effects of these variables on the conversion of the monomethyl ester of cyclohexenylsuccinic acid (I) to 4,5,6,7-tetrahydroindane-1-one (II). The times and temperatures refer to the initial polyphosphoric acid-catalyzed reaction.



I II

Time	Temperature	Yield of II	Time	Temperature	Yield of II
hours	°C.	*per cent*	*hours*	°C.	*per cent*
1	97	25	6	85–90	44
2	97	38	12	85–90	54
3	97	51	15	85–90	55
3.5	97	65	6	70–75	19
4	97	51	12	70–75	22
6	97	44	20 days	25	10

Much data of the type cited above appear in the literature, but conditions vary considerably from one reaction to another. Therefore no attempt will be made to include all such information in this review paper. In subsequent tables, the conditions for optimum yields of products will be given, provided, of course, that these conditions have actually been determined by experimentation.

In most cyclization reactions polyphosphoric acid is used in large excess. In at least one case, however, it has been demonstrated that the yield of product is affected by variation of the amount of polyphosphoric acid used (131). The yield of 2,3,4-trimethoxybenzosuberone from γ-(3,4,5-trimethoxyphenyl)propylmalonic acid was found to vary between 50 and 79 per cent, depending on the amount of polyphosphoric acid employed in the reaction.

Although the data are limited, it appears that esters can be cyclized about as readily as the acids from which they are derived. For example, both β-phenylpropionic acid and its methyl ester were converted to α-hydrindone in better

TABLE 12

Comparison of methods for effecting intramolecular acylation

Acid Cyclized	Yield of Cyclanone by PPA	Reference	Other Methods	Yield	Reference
	per cent			*per cent*	
trans-2-Benzylcycloheptylacetic	100	(8)	$AlCl_3$ on acid chloride	81	(8)
trans-2-Benzylcyclohexylacetic	100	(9)	$AlCl_3$ on acid chloride	83	(9)
trans-2-Benzylcyclopentylacetic	96	(8)	$AlCl_3$ on acid chloride	65	(8)
Benzylsuccinic anhydride	69	(174)	Sulfuric acid	64	(174)
2-Carboxy-β-(1-naphthyl)cinnamic	36	(263)	$SnCl_4$ on acid chloride	18	(263)
Cycloheptylidenesuccinic	42	(95)	Acetic anhydride and $ZnCl_2$	5	(95)
β-Cyclohexyl-β-phenylpropionic	81	(37)	$AlCl_3$ on acid chloride	11	(37)
β-(3,4-Dimethoxyphenyl)propionic	90	(211)	Hydrogen fluoride	88	(194)
β-(3,4-Dimethoxyphenyl)valeric	84	(211)	$SnCl_4$ on acid chloride	79	(77)
γ-(2,4-Dimethylphenyl)butyric	92	(115)	Sulfuric acid	60	(29)
			$AlCl_3$ on acid chloride	92	(155)
Hydrocinnamic	94	(211)	$AlCl_3$ on acid chloride	99	(194)
δ-(5-Hydrindyl)-*n*-valeric	85	(92)	$AlCl_3$ on acid chloride	72	(92)
β-(3-Indolyl)propionic	0	(190)	Phosphorus pentoxide	Low	(190)
γ-(2-Methoxy-4-methylphenyl)butyric	64	(87)	Phosphorus oxychloride	50	(87)
5-Methoxy-1-naphthylacetic	55	(141)	$AlCl_3$ on acid chloride	31	(141)
7-Methoxy-1-naphthylacetic	27	(141)	Sulfuric acid	0	(141)
γ-(5-Methoxy-1-naphthyl)butyric	50	(141)	$SnCl_4$ on acid chloride	46	(141)
γ-(7-Methoxy-1-naphthyl)butyric	86	(21)	$SnCl_4$ on acid chloride	80	(21)
3-(β-6′-Methoxynaphthyl)cyclopentan-1-one-2-acetic	25	(61)	Hydrogen fluoride	0	(61)
α-2-(6-Methoxy-1-naphthyl)ethylglutaric	83	(141)	Sulfuric acid	96	(141)
β-(5-Methoxy-1-naphthyl)propionic	65	(141)	Sulfuric acid	85	(141)
β-(6-Methoxy-1-naphthyl)propionic	44	(141)	$SnCl_4$ on acid chloride	48	(141)
4,5-Methylenedioxy-2-(3′,4′,5′-trimethoxybenzoyl)benzoic	93	(211)	Sulfuric and phosphoric acids	54	(211)
α-Naphthylacetic	40	(141)	$AlCl_3$ on acid chloride	3	(141)
γ-Phenylbutyric	93	(211)	$AlCl_3$ on acid chloride	90	(194)
3-Phenylcyclohexanecarboxylic	77	(34)	$AlCl_3$ on acid chloride	61	(34)
β-Phenylvaleric	91	(37)	$AlCl_3$ on acid chloride	11	(37)
1,2,3,4-Tetrahydro-8-methyl-1-*o*-tolyl-2-naphthaleneacetic	63	(261)	$AlCl_3$ on acid chloride	39	(261)
γ-(1,2,3,4-Tetrahydro-1-naphthyl)butyric	93	(137)	$AlCl_3$ on acid chloride	29	(137)
δ-(2,3,4-Trimethoxyphenyl)valeric	91	(211)	Phosphorus pentoxide	60	(154)

than 90 per cent yield by the action of polyphosphoric acid (136). Similar results were observed in the conversion of δ-phenylvaleric acid and its methyl ester to benzosuberone and in the preparation of α-tetralone from γ-phenylbutyric acid and its methyl ester (136).

It is instructive to compare the results of polyphosphoric acid-catalyzed intramolecular acylation reactions with those of other well-known methods. Many such comparisons are given in table 12, and it is obvious that the polyphosphoric acid method is frequently superior and seldom markedly inferior to the other methods.

A great number of polyphosphoric acid-catalyzed intramolecular acylation reactions have been described in the literature. An attempt will be made to discuss only a few representative reactions in this section. The remaining examples are given in table 13.

Suitably constituted lactones have, in the past, been converted to cyclopentenones by a variety of methods (122), but the reaction mixtures were generally

TABLE 13

Intramolecular acylation reactions

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		per cent	
β-(5-Acenaphthyl)propionic acid	3,4-Aceperinaphthenone-7 and 1'-keto-4,5-cyclopentenoacenaphthene	150	2 min.		(85)
β-Acetamido-γ-phenylvaleric acid	7-Acetamidobenzosuberone	125	20 min.	76	(177)
α-Amino-β-phenylpropionic acid	Intractable gum	150	2 hr.		(113)
γ-(p-Anisyl)butyric acid	7-Methoxy-1-tetralone	80	30 min.	88	(285)
Benzhydrylmalonic acid	3,4,7,8-Tetrahydro-3,4-diketo-1,2,5,6-dibenzopantalene	120	1 hr.	27	(31a)
Benzocycloheptyl-5-acetic acid	3,4-Tetramethyleneindan-1-one	97	3 hr.	92	(93, 97)
β-(5-Benzosuberyl)propionic acid	3-Keto-1,2,3,7,8,9,10,10a-octahydrocyclohepta[*de*]naphthalene			93	(137)
o-Benzoylbenzoic acid	Anthraquinone	150	40 min.	100	(322)
1-Benzoyl-3-(β-carboxyethyl)-2,3-dihydroindole	1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole			Low	(215)
trans-2-Benzylcycloheptylacetic acid	*trans*-4-Keto-1,4,5,6,7,8,9,10,11,12-decahydro-2,3-benzheptalene	100	2 hr.	100	(8)
trans-2-Benzylcyclohexylacetic acid	*trans*-2,3-Benzo-5,6-cyclohexanocycloheptanone	100	2 hr.	100	(9)
trans-2-Benzylcyclopentylacetic acid	*trans*-7-Keto-1,2,3,4,7,8,9,10-octahydro-5,6-benzazulene	100	2 hr.	96	(8)
2-Benzylidene-3-phenylindan-1-one epoxide	1,3-Dihydroxy-2,4-diphenylnaphthalene	192	2 min.		(31a)
Benzylsuccinic anhydride	1-Tetralone-3-carboxylic acid	100	2 hr.	69	(174)
Bis(3-carboxypropyl)ferrocene	Bis[1,2-(α-ketotetramethylene)]-ferrocene		4 hr.		(260)
2,7-Bis(3-carboxypropyl)phenanthrene	1,12-Diketo-1,2,3,4,9,10,11,12-octahydropicene	60	48 hr.	60	(269)
2-Bromo-5-methoxyhydrocinnamic acid	4-Bromo-7-methoxy-1-indanone	105	5 min.	76	(322)
β-Bromo-β-phenylpropionic acid	Material decomposed	90	1 hr.	0	(113)
β-Carbethoxy-β-cyclododecylidenepropionic acid	Ethyl bicyclo[10.3.0]-1(12)-pentadecene-13-one-15-carboxylate	98	3 hr.		(58a)
2-(1-Carboxy-3-butyl)-7-(3-carboxypropyl)phenanthrene	1,12-Diketo-4-methyl-1,2,3,4,9,10,11,12-octahydropicene	60	48 hr.	83	(272)
α-(2-Carboxyethyl)-α-(*m*-methoxyphenyl)glutarimide	1,2,3,4-Tetrahydro-7-methoxy-4-ketonaphthalene-1-spiro-α-glutarimide	100	45 min.	80	(63, 163)
α-(2-Carboxyethyl)-α-(*p*-methoxyphenyl)glutarimide	1,2,3,4-Tetrahydro-6-methoxy-4-ketonaphthalene-1-spiro-α-glutarimide	100	1 hr.	67	(63, 163)
α-(2-Carboxyethyl)-α-phenylglutarimide	1,2,3,4-Tetrahydro-4-ketonaphthalene-1-spiro-α-glutarimide	100	2 hr.	70	(63, 163)
2-Carboxy-3-methyl-4-(3',4'-dimethoxyphenyl)butyric acid	3-Methyl-6,7-dimethoxy-1-tetralone			Low	(307)
o-Carboxymethylphenylpropionic acid	(1-Keto-4-indanyl)acetic acid	95	2 hr.	78	(286)
2-Carboxy-β-1-naphthylcinnamic acid	3,4-Benzopyrene-1,5-quinone	170	20 min.	36	(263)
γ-Carboxy-γ-phenylpimelic acid	β-(1-Carboxy-1,2,3,4-tetrahydro-4-keto-1-naphthyl)propionic acid	100	1 hr.	34	(163)
γ-Cyano-β,γ-diphenylbutyric acid	α,β-Diphenylglutarimide and 1,2,3,4-tetrahydro-4-keto-2-phenyl-1-naphthamide	100	2 hr.		(188)
Cycloheptylidenesuccinic acid	Δ^9-Octahydro-1-ketoazulene	100	1.5 hr.	42	(95)
γ,δ-Cyclohexano-δ-valerolactone	4,5,6,7-Tetrahydroindan-1-one	80	3 hr.	68	(100)
β-Cyclohexyl-β-phenylpropionic acid	3-Cyclohexylindan-1-one	100	2 hr.	81	(37)
γ,δ-Cyclopentano-δ-valerolactone	Bicyclo[0.3.3]-7-octen-1-one	60	4.5 hr.	92	(100)

TABLE 13—*Continued*

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		*per cent*	
Dibenzyl-*o*-carboxylic acid	2,3,6,7-Dibenzocyclohept-2,6-dien-1-one	170	2 hr.	91	(75)
α,β-Dibromo-β-phenylpropionic acid	Only starting material recovered	150	1 hr.	0	(113)
β,β-Dicarboxy-ε-(3,4,5-trimethoxyphenyl)caproic acid	Enol lactone of 2,3,4-trimethoxybenzosuberone-6-acetic acid	185	10 min.	98	(131)
(3,4-Dimethoxybenzyl)succinic acid	3-Carboxy-6,7-dimethoxy-1-tetralone	90	15 min.	61	(174)
γ-(2,4-Dimethoxyphenyl)butyric acid	5,7-Dimethoxy-1-tetralone	165	3 min.	5	(86, 96)
γ-(2,5-Dimethoxyphenyl)butyric acid	1,4-Dimethoxy-5-keto-5,6,7,8-tetrahydronaphthalene	165	3 min.	93	(117)
γ-(2,4-Dimethoxyphenyl)-α-methylbutyric acid	3,4-Dihydro-2-methyl-5,7-dimethoxy-1-(2*H*)-naphthalenone	165	3 min.	66	(304)
γ-(2,4-Dimethoxyphenyl)-β-methylbutyric acid	3,4-Dihydro-3-methyl-5,7-dimethoxy-1-(2*H*)-naphthalenone	160	8 min.	63	(304)
2-(3,4-Dimethoxyphenyl)-3-methylglutaric acid	3,4-Dihydro-6,7-dimethoxy-3-methyl-1(2)-naphthalenone-4-carboxylic acid	90	1 min.	63	(111)
β-(2,3-Dimethoxyphenyl)propionic-acid	4,5-Dimethoxy-1-indanone	60	20 min.	99	(211)
β-(3,4-Dimethoxyphenyl)propionic acid	5,6-Dimethoxy-1-indanone	65 95	25 min. 90 min.	90 95	(211) (350)
δ-(2,3-Dimethoxyphenyl)valeric acid	1,2-Dimethoxybenzosuberone			64	(132)
δ-(2,5-Dimethoxyphenyl)valeric acid	1,4-Dimethoxybenzosuberone	60	1 hr.	55	(10)
δ-(3,4-Dimethoxyphenyl)valeric acid	2,3-Dimethoxybenzosuber-5-one	75	1 hr.	84	(211)
β-(2,2′-Dimethylbenzhydryl)-glutaric acid	5,6,6a,7,8,12b-Hexahydro-1,12-dimethylbenzo[*c*]phenanthrene-5,8-dione	130	45 min.	82	(261)
γ-(2,4-Dimethylphenyl)butyric acid	5,7-Dimethyl-1-keto-1,2,3,4-tetrahydronaphthalene	160 130	3 min. 5 min.	92	(115, 116) (237)
γ-(2,5-Dimethylphenyl)butyric acid	5,8-Dimethyl-1-keto-1,2,3,4-tetrahydronaphthalene	100 165	30 min. 3 min.	93 93	(327) (116)
4-(2,4-Dimethylphenyl)pentanoic acid	4,6,8-Trimethyl-1-tetralone	140 155	 3 min.	77 85	(236) (195)
4-(2,5-Dimethylphenyl)pentanoic acid	4,5,8-Trimethyl-1-tetralone	140		66	(236)
4-(3,4-Dimethylphenyl)pentanoic acid	4,6,7-Trimethyl-1-tetralone			70	(236)
5-(2,5-Dimethylphenyl)pentanoic acid	1,4-Dimethylbenzosuberone	95	35 min.	67	(10)
5-(3,4-Dimethylphenyl)pentanoic acid	2,3-Dimethylbenzosuberone	95	2 hr.	56	(10)
γ,δ-Dimethyl-δ-valerolactone	2,3-Dimethyl-2-cyclopenten-1-one	97	4.5 hr.	80	(100)
γ-(5,8-Dimethyltetralyl)-(6)-butyric acid	1,2,3,4,5,6,7,8-Octahydro-9,10-dimethyl-1-ketoanthracene	110	40 min.	75	(327)
δ-(5,8-Dimethyltetralyl)-(6)-valeric acid	1,2,3,4,5,7,8,9,10-Nonahydro-6,11-dimethyl-1-ketocycloheptanaphthalene	130		80	(327)
α,β-Diphenylglutaric acid	α-(3-Ketoindan-1-yl)-α-phenylacetic acid	100	2 hr.	Low	(188)
α,β-Diphenylpropionic acid	2-Phenylindan-1-one	170		60	(191)
β,β-Diphenylpropionic acid	3-Phenylindan-1-one	110	30 min.	77	(325)
Ethyl α,α-bis(3,4-dimethoxyphenyl)hydrogensuccinate	*trans*-3-Carbethoxy-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-tetralone	100	30 min.	53	(352)

TABLE 13—*Continued*

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		per cent	
Ethyl 2-bromo-4,5-dimethoxybenzylhydrogensuccinate	3-Carbethoxy-5-bromo-7,8-dimethoxy-1-tetralone	100	30 min.	39	(353)
Ethyl 2-carbethoxy-3-methyl-4-(3,4-dimethoxyphenyl)butyrate	3-Methyl-6,7-dimethoxy-1-tetralone			Low	(307)
Ethyl 2-carbomethoxy-6-carboxymethyl-2-methyl-5-phenylcyclohexylideneacetate	Anhydride of 2-carboxy-9-keto-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrylideneacetic acid	100	2 hr.	44	(349)
Ethyl 3,4-dimethoxybenzylhydrogensuccinate	6,7-Dimethoxy-3-carbethoxy-1-tetralone	100	7 min.	68	(174)
Ethyl α-(3,4-dimethoxybenzyl)-β-methylhydrogensuccinate	2-Methyl-3-carbethoxy-6,7-dimethoxy-1-tetralone	100	15 min.	38	(353)
	2-Methyl-3-carboxy-6,7-dimethoxy-1-tetralone			19	
Ethyl 1-keto-3-phenylindane-1-carboxylate	3,4,7,8-Tetrahydro-3,4-diketo-1,2,5,6-dibenzopentalene	160	3 min.	45	(31a)
Ethyl 3-(p-methoxyphenyl)-butyrate	3-Methyl-6-methoxy-1-indanone			21	(167)
Ethyl 3-(p-methoxyphenyl)-3-methylbutyrate	3,3-Dimethyl-6-methoxy-1-indanone			31	(167)
Ethyl β-(p-methoxyphenyl)-propionate	6-Methoxy-1-indanone			18	(167)
Ethyl α-methyl-β-hydroxy-β,β-bis(3,4-dimethoxyphenyl)propionate	2-Methyl-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindenone	75	30 min.	70	(169, 352)
β-(7-Ethyl-1-naphthyl)propionic acid	9-Ethylperinaphthanone	110	10 min.	44	(361)
Ethyl 2-phenyl-3,4,5,6-tetrahydrobenzoate	1,2,3,4-Tetrahydrofluorenone	130	10 min.	69	(55)
γ-Ferrocenylbutyric acid	1,2-(α-Ketotetramethylene)ferrocene				(287, 288)
β-Ferrocenylpropionic acid	1,1′-(α-Ketotrimethylene)ferrocene				(287, 288)
δ-Ferrocenylvaleric acid	1,2-(α-Ketopentamethylene)ferrocene				(287, 288)
β-(1-Fluorenyl)acrylic acid	3′-Keto-1,2-cyclopentenofluorene	125	2 hr.	88	(53)
γ-(5-Hydrindenyl)butyric acid	6,7-cyclopenteno-1-tetralone	110	5 min.	45	(16)
δ-(5-Hydrindyl)-n-valeric acid	2,3,6,7,8,9-Hexahydrocyclohept[f]-indene-5-(1H)-one	100	135 min.	85	(92)
Hydrocinnamic acid	α-Hydrindone	70	80 min.	95	(211)
		95	90 min.	75	(322)
β-(2-Hydroxycycloheptyl)-γ-butyrolactone	3-Methyl-1-keto-Δ^9-octahydroazulene	80	1 hr.		(187)
β-(2-Hydroxy-3-methyl-6-isopropylcycloheptyl)-γ-butyrolactone	3,8-Dimethyl-5-isopropyl-1-keto-Δ^9-octahydroazulene				(187)
3-(4-Indanyl)propionic acid	Cyclopent[e]-1-indanone	100	1 hr.	84	(286)
1-Indolinepropionic acid	Cyclopent[ij]-2,3-dihydro-4-quinolone	100	24 hr.	62	(286)
β-(3-Indolyl)propionic acid	2,3-Dihydro-1-ketocyclopentindole			0	(190)
β-(7-Isopropyl-1-naphthyl)propionic acid	9-Isopropylperinaphthanone	118	20 min.	33	(361)
trans-3-Keto-2-(α-naphthyl)-cyclohexylacetic acid	7,8,8a,9,10,11,12,12a-Octahydro-7,12-diketobenzo[4.5]cyclohepta-[1.2.3-de]naphthalene	100	4 hr.	76	(202)
trans-3-Keto-2-phenylcycloheptylpropionic acid	*trans*-3,10-Diketo-3,4,5,6,7,8,9,10,11,12-decahydro-1,2-benzheptalene	100	2 hr.		(8)
1-Keto-3-phenyl-2-indanylglyoxylic acid	3,4,7,8-Tetrahydro-3,4-diketo-1,2,5,6-dibenzopentalene	85	30 min.		(31a)
β-(2-Methoxy-5-methylphenyl)-adipic acid	Lactone of 4-keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid			62	(108)
γ-(2-Methoxy-4-methylphenyl)-butyric acid	5-Methoxy-7-methyl-1-tetralone	165	3 min.	64	(87)
4-Methoxy-1-naphthylacetic acid	No cyclic ketone obtained	100	30 min.	0	(141)

TABLE 13—*Continued*

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		*per cent*	
5-Methoxy-1-naphthylacetic acid	6-Methoxyacenaphthenone	100	30 min.	55	(141)
6-Methoxy-1-naphthylacetic acid	Intractable gum	100	30 min.	0	(141)
7-Methoxy-1-naphthylacetic acid	8-Methoxyacenaphthenone	100	30 min.	27	(141)
γ-(5-Methoxy-1-naphthyl)butyric acid	8-Methoxyhomoperinaphthanone	100	30 min.	50	(141)
γ-(7-Methoxy-1-naphthyl)butyric acid	6-Methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene	85	2 hr.	86	(21)
3-β-6′-Methoxynaphthylcyclopentan-1-one-2-acetic acid	3′,4-Diketo-7-methoxy-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene	100	1 hr.	19	(204)
		125	3 min.	25	(61)
α-2-(5-Methoxy-1-naphthyl)-ethylglutaric acid	Intractable gum	100	30 min.	0	(141)
α-2-(6-Methoxy-1-naphthyl)-ethylglutaric acid	β-(1,2,3,4-Tetrahydro-7-methoxy-1-keto-2-phenanthryl)propionic acid	100	30 min.	83	(141)
β-(5-Methoxy-1-naphthyl)propionic acid	7-Methoxyperinaphthanone	100	30 min.	65	(141)
β-(6-Methoxy-1-naphthyl)propionic acid	3′-Methoxy-4,5-benzindan-1-one	100	30 min.	44	(141)
		130	20 min.	57	(59)
β-(7-Methoxy-1-naphthyl)propionic acid	9-Methoxyperinaphthanone	100	30 min.	18	(141)
3-(*p*-Methoxyphenyl)butyric acid	3-Methyl-6-methoxy-1-indanone			22	(167)
α-(*o*-Methoxyphenyl)glutaric acid	No reaction	100		0	(162)
α-(*m*-Methoxyphenyl)glutaric acid	1,2,3,4-Tetrahydro-4-keto-7-methoxy-1-naphthoic acid	100	15 min.	60	(162)
α-(*p*-Methoxyphenyl)glutaric acid	No reaction	100		0	(162)
3-(*p*-Methoxyphenyl)-3-methylbutyric acid	3,3-Dimethyl-6-methoxy-1-indanone			33	(167)
4-(*m*-Methoxyphenyl)-5-methylhexanoic acid	1,2,3,4-Tetrahydro-6-methoxy-1-keto-4-isopropylnaphthalene	160	30 min.	90	(35)
β-(*m*-Methoxyphenyl)-β-phenylpropionic acid	5-Methoxy-3-phenyl-1-indanone	100	2 hr.	66	(37)
β-(*p*-Methoxyphenyl)-β-phenylpropionic acid	3-(*p*-Methoxyphenyl)-1-indanone	100	2 hr.	20	(37)
β-(*m*-Methoxyphenyl)propionic acid	5-Methoxy-α-hydrindone	145	3 min.	61	(61)
		60	30 min.	85	(350)
β-(*p*-Methoxyphenyl)propionic acid	6-Methoxy-1-indanone			43	(167)
		60	50 min.	87	(350)
δ-(2-Methoxyphenyl)valeric acid	Unidentified neutral product				(132)
δ-(4-Methoxyphenyl)valeric acid	Unidentified neutral material				(132)
β-(6-Methyl-4-coumarin)propionic acid	Starting material recovered			0	(108)
Methyl cycloheptenylhydrogensuccinate	Δ^9-Octahydro-1-keto-3-carbomethoxyazulene	100	1 hr.	61	(94, 95)
Methyl cyclohexenylhydrogensuccinate	4,5,6,7-Tetrahydro-1-indanone	97	3.5 hr.	65	(95)
				55	(94)
γ-Methyl-γ-decanolactone	3-Methyl-2-*n*-amyl-2-cyclopentenone	100	2.5 hr.	92	(283)
Methyl α,γ-di(*p*-anisyl)butyrate	7-Methoxy-2-(*p*-anisyl)-1-tetralone			70	(125)
		100	2 hr.	70	(242)
β-(6-Methyl-3,4-dihydro-4-coumarin)propionic acid	4-Keto-5-methyl-8-hydroxy-1,2,3,4-tetrahydro-1-naphthylacetic acid lactone	100	3 hr.	80	(108)
3-Methyl-4-(3,4-dimethoxyphenyl)butyric acid	3-Methyl-6,7-dimethoxy-1-tetralone	100	40 min.	87	(307)
α-Methyl-β,β-di(3,4-dimethoxyphenyl)propionic acid	*trans*-2-Methyl-3-(3,4-dimethoxyphenyl)-5,6-dimethoxy-1-indanone	100	75 min.	25	(352)

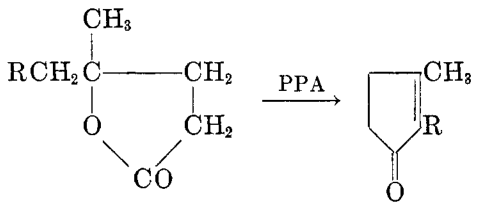
TABLE 13—*Continued*

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		*per cent*	
δ-(3,4-Methylenedioxyphenyl)-valeric acid	A polymeric material resulted				(132)
4,5-Methylenedioxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid	1,2,3-Trimethoxy-6,7-methylenedioxyanthraquinone	85	6 hr.	93	(211)
γ-Methyl-γ-heptanolactone	3-Methyl-2-ethyl-2-cyclopentenone	100	2.5 hr.	91	(283)
γ-(2-Methyl-4-methoxyphenyl)-butyric acid	5-Methyl-7-methoxy-1-tetralone	100	90 min.	78	(107)
Methyl 3-methyl-3-phenylbutyrate	3,3-Dimethyl-1-indanone	100	3 hr.	97	(167)
β-(7-Methyl-1-naphthyl)propionic acid	9-Methylperinaphthenone	140	45 min.	39	(361)
	9-Methylperinaphthanone	118	10 min.	48	(361)
γ-Methyl-γ-nonanolactone	3-Methyl-2-*n*-butyl-2-cyclopentenone	100	2.5 hr.	94	(283)
γ-Methyl-γ-octanolactone	3-Methyl-2-*n*-propyl-2-cyclopentenone	100	2.5 hr.	95	(283)
Methyl γ-phenylbutyrate	α-Tetralone			70	(136)
3-Methyl-3-phenylbutyric acid	3,3-Dimethyl-1-indanone	100	2 hr.	78	(167)
Methyl β-phenylpropionate	α-Hydrindone	100	2 hr.	93	(136)
Methyl 2-phenyl-3,4,5,6-tetrahydrobenzoate	1,2,3,4-Tetrahydrofluorenone	130	10 min.	68	(55)
α-Methyl-γ-(2,4,5-trimethoxyphenyl)butyric acid	5,7,8-Trimethoxy-2-methyl-1-tetralone	60	30 min.	95	(118)
β-Methyl-γ-(2,4,5-trimethoxyphenyl)butyric acid	5,7,8-Trimethoxy-3-methyl-1-tetralone				(118)
Methyl γ-phenylvalerate	4-Methyl-1-tetralone				(369)
Methyl δ-phenylvalerate	Benzosuberone			90	(136)
β-Methyl-γ-phenylvaleric acid	3,4-Dimethyl-1-tetralone				(369)
δ-(2-Methylphenyl)valeric acid	1-Methylbenzosuberone	140	4 hr.	89	(10)
γ-Methyl-γ-undecanolactone	3-Methyl-2-*n*-hexyl-2-cyclopentenone	100	2.5 hr.	93	(283)
o-(α-Naphthoyl)benzoic acid	1,2-Benzanthraquinone	100	12 hr.	44	(322)
10-(1-Naphthoyl)-9-phenanthrenecarboxylic acid	1,2,3,4,5,6-Tribenzanthraquinone	225	1 hr.	98	(217)
1-Naphthylacetic acid	Acenaphthenone	100	30 min.	40	(141)
3-(β-Naphthyl)cyclohexan-1-one-2-acetic acid	1,11-Diketo-1,2,3,4,4a,11,12,12a-octahydrochrysene			90	(258)
3-(β-Naphthyl)cyclopentan-1-one-2-acetic acid	3′,4-Diketo-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene	100	1 hr.	62	(204)
2-Nonenoic acid	2-*n*-Butylcyclopenten-2-one			63	(105)
1,2,3,7,8,9,10,10a-Octahydro-7-cyclohepta[*de*]naphthylacetic acid	2-Keto-1,2,5,6,7,7a,8,8a,10,10a-decahydrocyclohepta[*klm*]benz[*e*]-indene	100	2 hr.	99	(130)
Paraconic acid	Δ^9-Octahydro-1-ketoazulene	100	1.5 hr.	29	(95)
4-Phenanthrenecarboxylic acid	4,5-Phenanthrylene ketone	105	60 hr.	76	(297)
β-(2-Phenanthryl)butyric acid	1′-Keto-3′-methyl-1,2-cyclopentenophenanthrene	70	6 hr.	76	(271)
γ-Phenylbutyric acid	1-Tetralone	70	40 min.	93	(211)
		125	2.5 min.	66	(322)
				70	(136)
		145	3 min.	86	(61)
		155	2 min.	90	(116)
ε-Phenylcaproic acid	1,2-Benzcycloöct-1-ene-3-one			Low	(315)
trans-2-Phenylcycloheptylpropionic acid	*trans*-3-Keto-3,4,5,6,7,8,9,10,11,12-decahydro-1,2-benzheptalene	100	2 hr.	100	(8)
3-Phenylcyclohexanecarboxylic acid	4,8-Endomethylenebenzocycloöcten-3-one	100	1.5 hr.	77	(34)
2-Phenylcyclopentane-1-carboxylic acid	4-Keto-1,2,3,4,10,11-hexahydrocyclopentindene	100	3 hr.	73	(31)
3-Phenylcyclopentane-1-carboxylic acid	4-Keto-1,3-endomethylene-1,2,3,4-tetrahydronaphthalene	100	3 hr.	85	(31)
α-Phenyl-β-(3,4-dimethoxyphenyl)propionic acid	5,6-Dimethoxy-2-phenyl-1-indanone	160		30	(191)
o-(β-Phenethyl)phenylacetic acid	1,2,5,6-Dibenz-1,5-cycloöctadien-3-one	100	2 hr.	93	(84)
α-Phenylglutaric anhydride	4-Carboxy-1-tetralone	110	15 min.	80	(223)

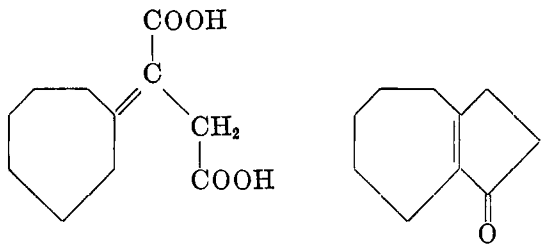
TABLE 13—*Concluded*

Acid or Acid Derivative	Cyclic Ketone	Temperature	Time	Yield	References
		°C.		*per cent*	
α-Phenyl-β-(*m*-methoxyphenyl)-propionic acid	5-Methoxy-2-phenyl-1-indanone	160		40	(191)
α-Phenyl-β-(*p*-methoxyphenyl)-propionic acid	6-Methoxy-2-phenyl-1-indanone	187		20	(191)
trans-8-Phenyl-5-octenoic acid	7-Keto-1,2,3,10a-tetrahydropleiadane				(13)
β-Phenylpropionic acid	α-Hydrindone	100	2 hr.	93	(136)
2-Phenyl-3,4,5,6-tetrahydro-benzoic acid	1,2,3,4-Tetrahydrofluorenone	130	10 min.	52	(55)
β-Phenylvaleric acid	3-Ethyl-1-indanone	100	2 hr.	91	(37)
δ-Phenylvaleric acid	Benzosuberone	95	2 hr.	84	(137, 178)
				89	(97)
	Benzosuberone			61	(129)
	δ-[4-(δ-Phenylvaleroyl)]phenyl-valeric acid			5	
2a,3,4,5-Tetrahydro-5-acenaph-theneacetic acid	2a,3,4,4a-Tetrahydro-1-pyracenone	80	40 min.	61	(9a)
7,8,9,10-Tetrahydro-7-cyclo-hepta[*de*]naphthylacetic acid	2-Keto-1,2,8,9,10,10a-hexahydro-cyclohepta[*klm*]benz[*e*]indene	100	7 min.	94	(130)
1,2,3,4-Tetrahydro-4-keto-2-phenyl-1-naphthoic acid	3,4,10,11-Tetrahydro-3-keto-1,2-benzofluorenone	100	40 min.		(188)
1,2,3,4-Tetrahydro-8-methyl-1-(*o*-tolyl)-2-naphthaleneacetic acid	5,6,6a,7,8,12b-Hexahydro-5-keto-1,12-dimethylbenzo[*c*]phenanthrene	130	3 hr.	63	(261)
1,2,3,4-Tetrahydro-1,4-naph-thalenediacetic acid	1-Keto-2a,3,4,5-tetrahydro-5-ace-naphthenacetic acid	80	40 min.	72	(9a)
γ-1,2,3,4-Tetrahydro-1-naph-thylbutyric acid	7-Keto-1,3,4,7,8,9,10,10a-octahydro-cyclohepta[*de*]naphthalene	95	2 hr.	93	(137)
γ-(5,6,7,8-Tetrahydro-2-naph-thyl)valeric acid	1-Keto-4-methyl-1,2,3,4,5,6,7,8-octahydroanthracene	140		71	(238)
γ-(1,2,3,4-Tetrahydrophenan-thryl)butyric acid	7-Keto-1,2,3,3a,4,5,6,7-octahydro-cyclohepta[*jk*]phenanthrene			76	(178)
trans-1,2,3,4-Tetrahydro-2-phenyl-1-naphthylacetic acid	*trans*-1,2,7,8,15,16-Hexahydro-2-ketochrysene	130	4 hr.		(188)
4-(2,3,5,6-Tetramethylphenyl)-pentanoic acid	4,5,6,7,8-Pentamethyl-1-tetralone	180		30	(236)
γ-Thianaphthylbutyric acid	4-Keto-1,2,3,4-tetrahydrodibenzo-thiophene	80		90	(83)
γ-(*p*-Tolyl)butyric acid	7-Methyl-1,2,3,4-tetrahydro-1-keto-naphthalene	155	3 min.	90	(116)
β-(*o*-Tolyl)propionic acid	4-Methyl-1-indanone	97	2 hr.	71	(96)
γ-(*p*-Tolyl)valeric acid	4,7-Dimethyl-1-tetralone	100	2 hr.	91	(270)
		161	2.5 min.	88	(116)
β-[2-(2,3,4-Trimethoxyphenyl)-cycloheptane]propionic acid	5,6,7,7a,8,9,10,11,12,12a-Deca-hydro-1,2,3-trimethoxy-5-keto-benzo[*a*]heptalene	70	25 min.	77	(142)
β-[2-(2,3,4-Trimethoxyphenyl)-cyclohexane]propionic acid	6,7,7a,8,9,10,11,11a-Octahydro-1,2,3-trimethoxy-5-keto-5*H*-di-benzo[*a,c*]cycloheptatriene	70	25 min.	77	(142)
β-(3,4,5-Trimethoxyphenyl)pro-pionic acid	5,6,7-Trimethoxy-1-indanone	70	1 hr.	91	(211)
γ-(3,4,5-Trimethoxyphenyl)-propylmalonic acid	2,3,4-Trimethoxybenzosuberone-6-acetic acid	100	20 min.	79	(131)
γ-(3,4,5-Trimethoxyphenyl)-propylsuccinic acid	Enol lactone of 2,3,4-trimethoxy-benzosuberone-6-acetic acid	100	11 min.	60	(131)
δ-(2,3,4-Trimethoxyphenyl)-valeric acid	1,2,3-Trimethoxybenzosuber-5-one	75	50 min.	91	(211)
δ-(3,4,5-Trimethoxyphenyl)-valeric acid	2,3,4-Trimethoxybenzosuber-5-one	80	50 min.	94	(208)
		100	40 min.	91	(131)
				100	(132)
Undecylenic acid	2-*n*-Hexyl-2-cyclopentenone	60		60	(105)
2,5-*p*-Xylenebis(γ-methyl-butyric acid)	1,5-Diketo-4,8,9,10-tetramethyl-1,2,3,4,5,6,7,8-octahydroanthra-cene	145	15 min.	63	(240)

heterogeneous and the yields only moderate (20–50 per cent). The use of polyphosphoric acid has now been found to give homogeneous reaction mixtures, and the yields are frequently greater than 90 per cent (283, 284).

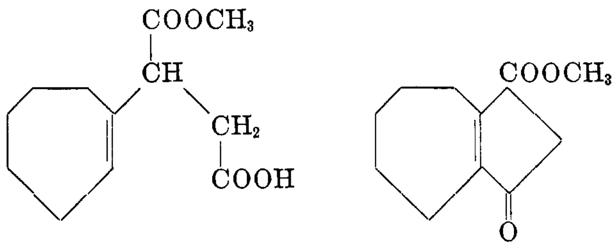


Certain β,γ- or γ,δ-unsaturated acids have been converted to cyclenones with the aid of polyphosphoric acid. For example, cycloheptylidenesuccinic acid (III) was cyclized to cycloheptenocyclopentanone (IV) by treatment with polyphosphoric acid, followed by decarboxylation of the intermediate cyclic acid



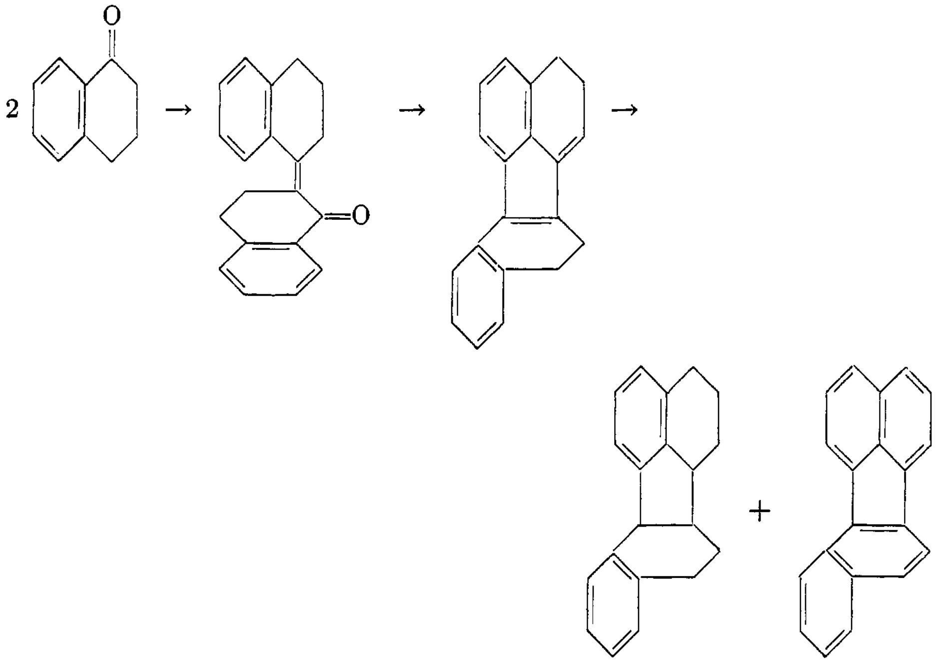
III IV

(95). In a similar manner, the γ,δ-unsaturated acid V was converted to methyl Δ^9-octahydro-1-ketoazulene-3-carboxylate (VI) by the action of polyphosphoric acid (94, 95).



V VI

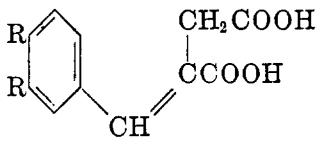
Indanones have been prepared by polyphosphoric acid-catalyzed intramolecular acylation reactions of β-arylpropionic acids, and tetralones have been synthesized in a similar manner from γ-aryl-n-butyric acids. Many examples of such reactions are given in table 13. Whereas tetralones were obtained in 80–93 per cent yields by treatment of γ-arylvaleric or γ-aryl-γ-methylvaleric acids with polyphosphoric acid for 2–3 min. at 150–170°C., the employment of higher temperatures or longer reaction periods caused the yields of tetralones to drop, and various by-products were isolated (115, 116). Similar compounds were obtained when α-tetralone itself was heated at 170°C. with polyphosphoric acid; from the mixture of products, a colorless hydrocarbon believed to be 1,2,3,4,9,12,13,14-octahydro-10,11-benzofluoranthene (VII) and a yellow hydrocarbon shown to be 10,11-benzofluoranthene (VIII) were obtained. The course of the reaction of tetralone with polyphosphoric acid was thought (116) to be as follows:



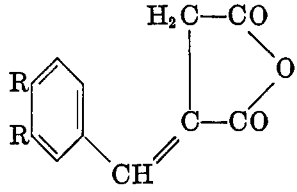
VII VIII

On the basis of the reaction scheme cited above, any tetralone unsubstituted in the 8-position might be expected to form a benzofluoranthene on treatment with polyphosphoric acid at an elevated temperature. In accord with this idea, substances thought to be methylbenzofluoranthenes were isolated as by-products from the cyclization reactions of γ-(2,4-dimethylphenyl)-*n*-butyric acid and γ-*p*-tolylvaleric acid, whereas only a colorless α,β-unsaturated ketone, $C_{24}H_{26}O$, was obtained as a by-product of the cyclization of γ-(2,5-dimethylphenyl)-*n*-butyric acid (116).

A rather detailed study has been made of the use of polyphosphoric acid in the cyclization of dibasic acids and some of their derivatives (174). It was found that either polyphosphoric acid or sulfuric acid could be used with about equal effectiveness for the cyclization of benzylsuccinic acids to tetralone-3-carboxylic acids provided that no strongly electron-donating substituent was present on the aromatic ring. However, the presence of a substituent such as the methoxyl group caused the yield of the tetralone to drop markedly when sulfuric acid was used as the catalyst but not when polyphosphoric acid was employed. Apparently sulfonation occurred in the presence of the former acid. Attempts to cyclize cinnamic acids of type IX to hydroxynaphthalene derivatives met with failure; only itaconic anhydrides of type X were obtained (174).

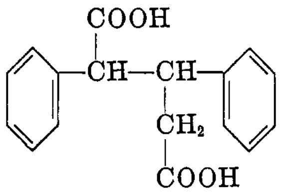


IX

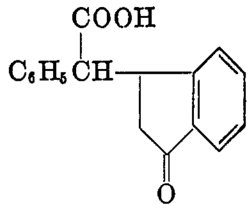


X

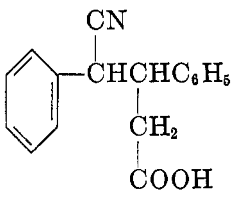
Owing to the fact that cyclization of α,β-diphenylglutaric acid (XI) gave the indanone derivative XII, the behavior of γ-cyano-β,γ-diphenylbutyric acid (XIII) towards the usual cyclization agents was investigated in order to determine whether formation of a tetralone derivative could be brought about in this instance. No cyclization reaction occurred in the presence of hydrogen fluoride, but a mixture of 3-phenyl-1-tetralone-4-carboxamide (XIV) and α,β-diphenylglutarimide was obtained by the action of polyphosphoric acid on XIII (188). As mentioned previously, a nitrile is readily converted to an amide under the influence of polyphosphoric acid (317), and therefore the isolation of an amide rather than a nitrile was not unexpected.



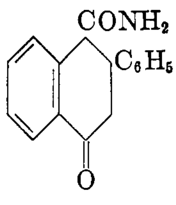
XI



XII

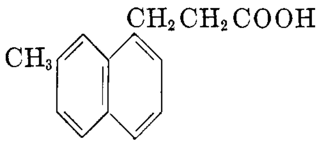


XIII

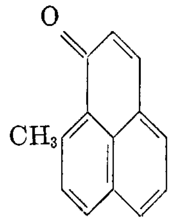


XIV

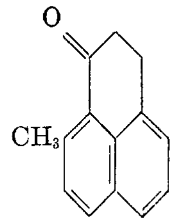
Whereas treatment of β-(7-methyl-1-naphthyl)propionic acid (XV) with polyphosphoric acid for 45 min. at 140°C. gave 9-methylperinaphthenone (XVI) as the sole product, the action of polyphosphoric acid on XV for 15 min. at 110–120°C. produced mainly the perinaphthanone XVII (361). The explanation for this behavior became apparent when it was shown that polyphosphoric acid could bring about dehydrogenation of XVII to XVI at a sufficiently high temperature (361).



XV

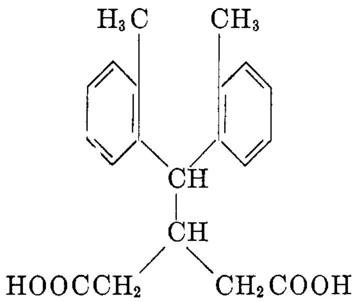


XVI

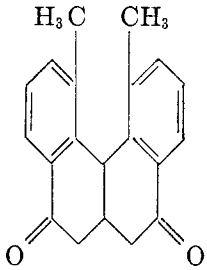


XVII

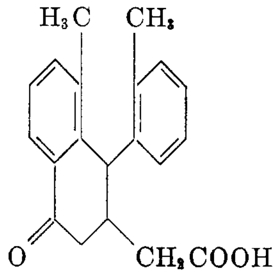
A double cyclization reaction took place when β-(2,2′-dimethylbenzhydryl)-glutaric acid (XVIII) was subjected to the action of hot polyphosphoric acid, 5,6,6a,7,8,12b-hexahydro-1,12-dimethylbenzo[*c*]phenanthrene-5,8-dione (XIX) being produced in 82 per cent yield (261). Treatment of the bis acid chloride of XVIII with stannic chloride afforded only the singly cyclized product, 1,2,3,4-tetrahydro-8-methyl-4-keto-1-*o*-tolyl-2-naphthaleneacetic acid (XX) (261).



XVIII

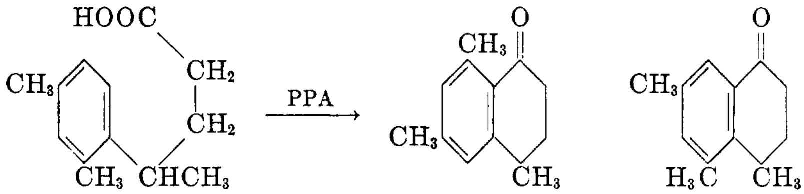


XIX

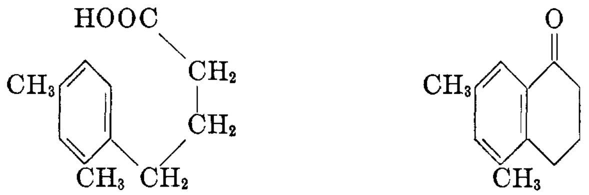


XX

When 4-(2,4-dimethylphenyl)pentanoic acid (XXI) was treated with polyphosphoric acid, a rearranged product, 4,6,8-trimethyl-1-tetralone (XXII), was produced (236) instead of the expected product, 4,5,7-trimethyl-1-tetralone (XXIII). The latter compound was obtained, however, by cyclization of the acid chloride of XXI under the influence of stannic chloride. In contrast to the behavior of XXI, no rearrangement accompanied the cyclization of γ-(2,4-dimethylphenyl)butyric acid (XXIV) in polyphosphoric acid solution or of the acid chloride of XXIV in the presence of stannic chloride; 5,7-dimethyl-1-tetralone (XXV) was produced in each of these reactions (237). It was suggested (236) that the rearrangement leading to the formation of XXII actually occurred with the acid XXI, the valeric acid moiety initially migrating to a position of symmetry on the ring before the ring-closure step. In support of this contention, it was demonstrated (236) that the tetralone XXIII was stable towards hot polyphosphoric acid and therefore could not have been the precursor of XXII. However, it should not be inferred from this result that migration of a methyl group from one position to another of an aromatic ring never occurs under the influence of polyphosphoric acid. As a matter of fact, the polyphosphoric acid-catalyzed cyclization of 4-(2,3,5,6-tetramethylphenyl)pentanoic acid (XXVI)

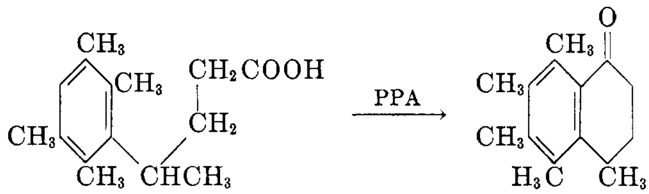


XXI XXII XXIII



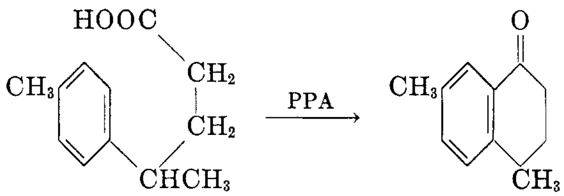
XXIV XXV

was found (236) to produce a mixture of products, of which 4,5,6,7,8-pentamethyl-1-tetralone (XXVII) was one component.



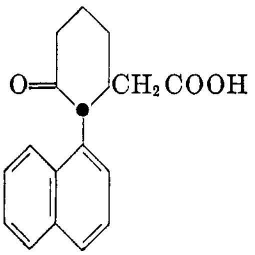
XXVI XXVII

It seems likely that the rearrangement of XXI involves, at one stage of the reaction, the separation of the side chain essentially as a carbonium ion. In the case of XXI, this process would be favored by the fact that the carbonium ion is a secondary one and also by the fact that some relief of steric strain caused by the presence of adjacent methyl groups would accompany the extrusion of the side chain. The importance of the latter point becomes apparent when the fact (270) that γ-*p*-tolylvaleric acid (XXVIII) undergoes polyphosphoric acid-catalyzed cyclization, without rearrangement, to form 4,7-dimethyl-1-tetralone (XXIX) is considered.

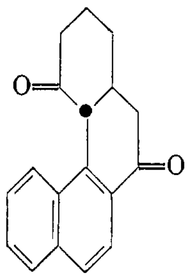


XXVIII XXIX

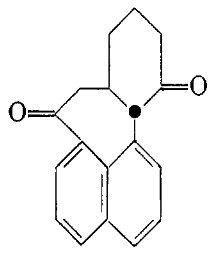
An unexpected orientation effect came to light when *trans*-3-keto-2-(α-naphthyl)cyclohexylacetic acid (XXX) was cyclized by the action of two different agents. The use of hydrogen fluoride afforded the octahydrodiketobenzophenanthrene XXXI, while polyphosphoric acid brought about conversion of XXX to the isomeric diketone XXXII, each cyclization reaction taking place in good yield (202).



XXX

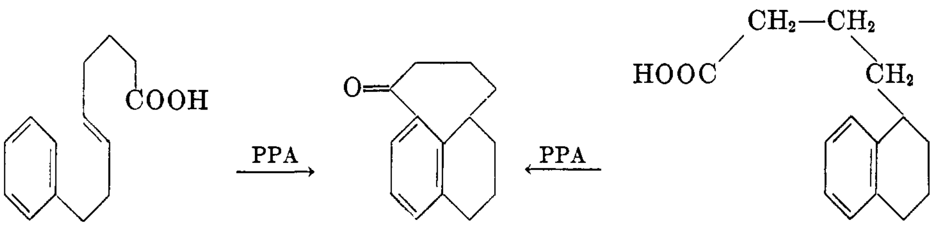


XXXI



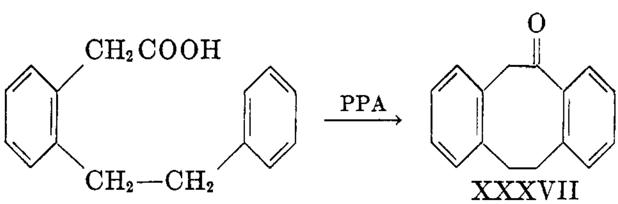
XXXII

An unusual double cyclization took place on treatment of *trans*-8-phenyl-5-octenoic acid (XXXIII) with hot polyphosphoric acid. 7-Keto-1,2,3,10a-tetrahydropleiadane (XXXIV) was produced (13), the tetrahydronaphthalenebutyric acid XXXV presumably being formed as an intermediate. In any event, the latter compound has been found (137) to give XXXIV on treatment with polyphosphoric acid. There appears to be no precedent for an intramolecular reaction of this type, but the condensation of phthalideneacetic acid with naphthalene to yield 3,4-benzpyrene-1,5-quinone has been formulated as involving intermolecular alkylation followed by intramolecular acylation (305).



XXXIII XXXIV XXXV

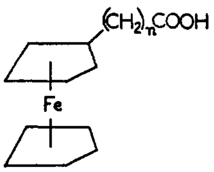
Cyclization of *o*-(β-phenethyl)phenylacetic acid (XXXVI) to 1,2,5,6-dibenz-1,5-cyclooöctadiene-3-one (XXXVII) has been effected in 93 per cent yield by the use of polyphosphoric acid (84). This represents the only reported case of the formation of a cyclooöctanone derivative in high yield by a polyphos-



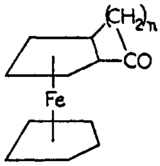
XXXVI XXXVII

phoric acid-catalyzed reaction, but treatment of ϵ-phenylcaproic acid with polyphosphoric acid was reported (315) to give a low yield of 1,2-benzcycloöct-1-ene-3-one.

Both polyphosphoric acid and trifluoroacetic anhydride are useful agents for effecting the cyclization of β-ferrocenylpropionic acid (XXXVIII: $n = 2$), γ-ferrocenylbutyric acid (XXXVIII: $n = 3$), and δ-ferrocenylvaleric acid (XXXVIII: $n = 4$). The ferrocenylbutyric and ferrocenylvaleric acids gave homoannular cyclized products (XXXIX: $n \geq 3$ and 4, respectively), but β-ferrocenylpropionic acid, when treated with polyphosphoric acid, gave a compound thought to be the heteroannular cyclized product XL (287, 288). Neither ferrocenylacetic acid (XXXVIII: $n = 1$) nor ϵ-ferrocenylcaproic acid (XXXVIII: $n = 5$) gave cyclic ketones on treatment with polyphosphoric acid (287). Attempts to effect the cyclization of bis(3-carboxypropanoyl)ferrocene or bis(3-carbomethoxypropanoyl)ferrocene in polyphosphoric acid medium failed, but bis(3-carboxypropyl)ferrocene afforded a compound, $C_{18}H_{18}O_2Fe$, thought (260) to be XLI. In any event, Clemmensen reduction of the product gave bis(tetrahydroindenyl)iron.



XXXVIII



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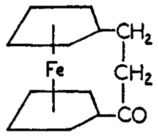

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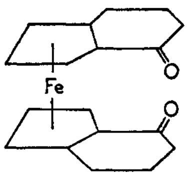


XLI

C. CYCLODEHYDRATION REACTIONS OF ALDEHYDES, KETONES, AND ALCOHOLS

1. Use of aldehydes and ketones

Cyclic olefins are readily produced by polyphosphoric acid-catalyzed intramolecular dehydration reactions of aldehydes or ketones having a suitable aryl substituent two, three, or four carbon atoms removed from the carbonyl group. A summary of such reactions is given in table 14, while some of the more unusual or important individual examples are discussed in the following paragraphs.

When ethyl α-keto-β-carbethoxy-γ-(2,3-dimethoxyphenyl)butyrate (I) was

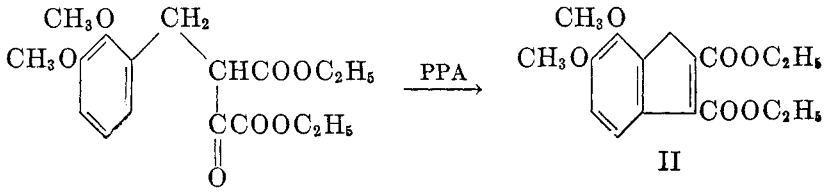
TABLE 14

Cyclodehydration reactions of aldehydes and ketones

Aldehyde or Ketone	Cyclic Olefin	Temperature	Time	Yield	Reference
		°C.		*per cent*	
Acyloin of methyl β-(m-methoxyphenyl)propionate	1,2,7,8-Tetrahydro-4,10-dimethoxychrysene	70	20 min.	98	(62)
α-(2-Biphenylyl)-α-isobutyroacetonitrile	9-Isopropyl-10-phenanthronitrile	85	28 hr.	48	(64)
Cyclohexanone	Dodecahydrotriphenylene	160	12 hr.	36	(46)
1-[2-(1,3-Diketocyclohexyl)ethyl]-6-methoxynaphthalene	1,2,3,4,5,6-Hexahydro-3-keto-10-methoxychrysene	100	15 min.	74	(62)
3,4-Dimethoxybenzylacetone	5,6-Dimethoxy-3-methylindene	40	25 min.	58	(211)
3,4-Dimethoxybenzylacetophenone	5,6-Dimethoxy-3-phenylindene	60	50 min.	93	(211)
α-(4,4′-Dimethoxy-4-biphenylyl)-4-methoxybutyrophenone	2,7-Dimethoxy-9-(p-methoxyphenyl)-10-ethylphenanthrene	150	30 min.	66	(65)
α-(3,4-Dimethoxyphenyl)-β-(2-hydroxy-4-ketocyclohex-2-ene)propionic acid	1,2,3,9,10,10a-Hexahydro-3-keto-7-methoxy-9-carboxyphenanthrene	100	1 hr.	95	(356)
3-[γ-(3,4-Dimethoxyphenyl)propyl]-4-hydroxy-6-methyl-5,6-dihydro-2-pyrone	2,3-Dimethoxy-5-(β-hydroxypropyl)-6-carboxybenzosuber-5-ene lactone	85	1.9 hr.	14	(355)
Ethyl 3,4-dimethoxybenzylacetoacetate	Ethyl 5,6-dimethoxy-3-methylindene-2-carboxylate	25	30 min.	85	(211)
Ethyl α-(ethoxyalyl)-β-(3,4,5-trimethoxyphenyl)propionate	Diethyl 4,5,6-trimethoxyindene-2,3-dicarboxylate	5	10 min.	92	(210)
Ethyl α-(ethoxalyl)-δ-(3,4,5-trimethoxyphenyl)valerate	Diethyl 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylate	5	3 min.	97	(214)
Ethyl α-formyl-δ-benzoylamino-δ-(3,4-dimethoxyphenyl)valerate	Ethyl 2,3-dimethoxy-9-benzoylaminobenzosuber-5-ene-6-carboxylate	5	10 min.	45	(209)
Ethyl α-formyl-δ-(3,4-dimethoxyphenyl)valerate	2,3-Dimethoxybenzosuber-5-ene-6-carboxylate	10	30 min.	66	(209)
Ethyl α-formyl-β-(3,4,5-trimethoxyphenyl)propionate	Ethyl 4,5,6-trimethoxyindene-2-carboxylate	10	10 min.	91	(210)
Ethyl α-formyl-δ-(3,4,5-trimethoxyphenyl)valerate	Ethyl 2,3,4-trimethoxybenzosuber-5-ene-6-carboxylate	25	30 min.	90	(214)
Ethyl α-keto-β-carbethoxy-γ-(2,3-dimethoxyphenyl)butyrate	Diethyl 6,7-dimethoxyindene-2,3-dicarboxylate	85	25 min.	90	(168)
Ethyl α-keto-β-carbethoxy-δ-(3,4-dimethoxyphenyl)valerate	Diethyl 6,7-dimethoxy-3,4-dihydronaphthalene-1,2-dicarboxylate		10 min.	92	(175)
α-(3-Methoxyphenyl-β-(2-hydroxy-4-ketocyclohex-2-ene)propionic acid	1,2,3,9,10,10a-Hexahydro-3-keto-7-methoxy-9-carboxyphenanthrene	100	1 hr.	95	(356)
Ethyl (3,4-methylenedioxybenzyl)acetoacetate	Ethyl 5,6-methylenedioxy-3-methylindene-2-carboxylate	25	30 min.	80	(211)
Ethyl (3-phenyl-2-quinolyl)pyruvate	Benz[a]acridine-5-carboxylic acid	195	15 min.	65	(153)
5-Methoxy-1-m-methoxyphenethyl-2-tetralone	1,2,7,8-Tetrahydro-3,10-dimethoxychrysene	80	20 min.	64	(82)
5-Methoxy-1-phenethyl-2-tetralone	1,2,7,8-Tetrahydro-3-methoxychrysene	180	45 min.	51	(214)
γ-(2-Naphthyl)butyraldehyde	Phenanthrene*	100	3 hr.		(104)
		165	4 hr.		(104)
2-(β-2-Naphthylethyl)cyclohexanone	Benz[a]anthracene*	100	3 hr.	84	(104)
		165	4 hr.		(104)
6-(2-Naphthyl)-3-hexanone	1-Ethylanthracene*	100	1.5 hr.	63	(51)
2-(α-Naphthylmethyl)-1-tetralone	A compound, $C_{21}H_{16}O$			Trace	(334)
2-(β-Naphthylmethyl)-1-tetralone	3,4(or 7,8)-Dihydrodibenzo-1,2,5,6-fluorene	100	8 hr.	43	(54)
5-(2-Naphthyl)-2-pentanone	1-Methylanthracene*	100	3 hr.		(104)
	4-Methylanthracene*	165	4 hr.		(104)
5-(2-Naphthyl)-3-pentanone	1-Ethyl-3H-benz[e]indene*	100	1.5 hr.	72	(104)
2-Phenacyl-3-phenylquinoline	5-Phenylbenz[a]acridine	195	1.5 hr.	87	(153)
2-Phenacyl-3-phenyl-4-phenoxyquinoline	5-Phenyl-12-phenoxybenz[a]acridine	195	2.5 hr.	62	(153)
2-(2-Phenethyl)cyclohexane-1,3-dione	1,2,3,4,9,10-Hexahydro-1-keto phenanthrene	160	45 min.	95	(62)
2-(γ-Phenylpropyl)cycloheptanone	Mixture including 1-cyclohexyltetralin, 2-cyclohexyltetralin, 1-cyclohexylnaphthalene, and 2-cyclohexylnaphthalene	100–200			(145)
1-(2,3,6-Trimethoxyphenanthryl-9-methyl)-2-(carboxaldehyde)pyridinium bromide	A 2,3,6-trimethoxydibenzo[h,j]acridizinium salt	80	5 hr.	60	(66)

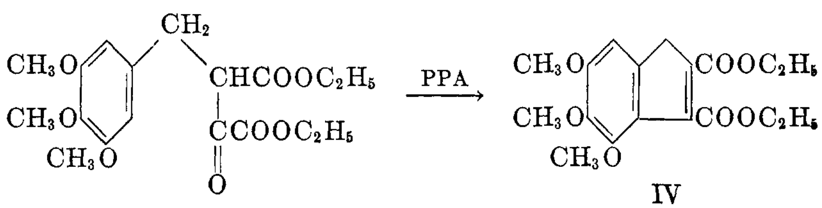
* Product obtained after dehydrogenation of the initially formed cyclic olefin.

subjected to the usual conditions of the Bougault glyoxylate cyclization reaction, the diester II could not be obtained (168). However, the use of polyphosphoric acid afforded diethyl 6,7-dimethoxyindene-2,3-dicarboxylate (II) in 90 per cent yield (168). Also, whereas ethyl α-ethoxalyl-β-(3,4,5-trimethoxyphenyl)-propionate (III) was cyclized to diethyl 4,5,6-trimethoxyindene-2,3-dicarboxylate (IV) in 77 per cent yield by the use of a sulfuric acid–phosphoric acid mix-



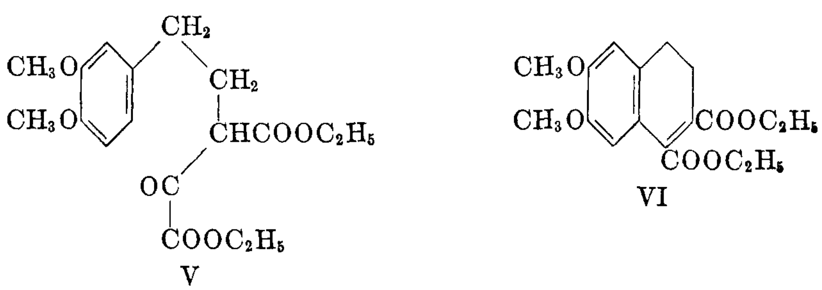
I　　II

ture as the dehydration medium, the action of polyphosphoric acid provided IV in 92 per cent yield (210).



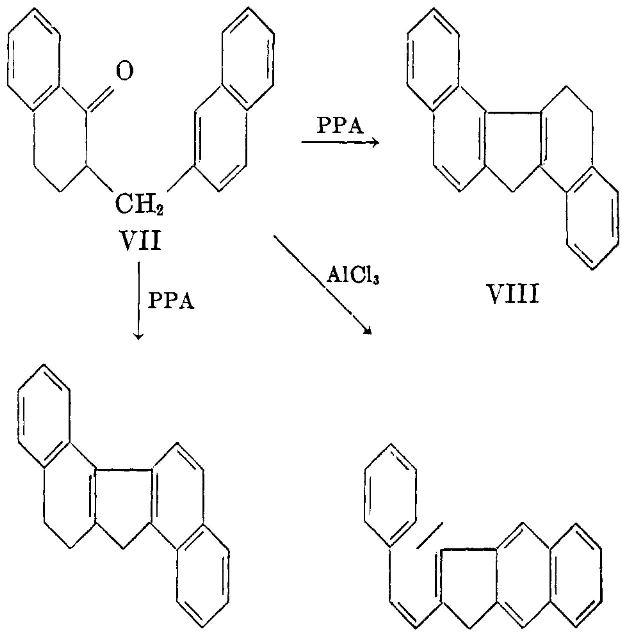
III　　IV

A number of additional examples have come to light in which polyphohoric acid proved to be a selective agent for effecting certain cyclodehydration reactions. The glyoxylate V was converted to diethyl 6,7-dimethoxy-3,4-dihydronaphthalene-1,2-dicarboxylate (VI) in 92 per cent yield by the action of polyphosphoric acid, but the use of sulfuric acid led to formation of an anhydride



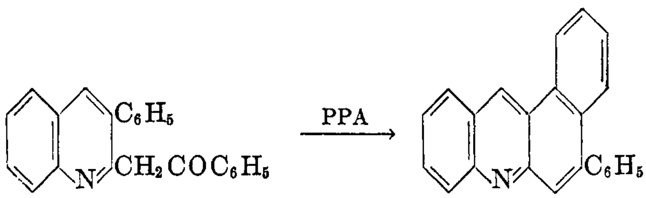
V　　VI

(175). Cyclization of 2-(2-naphthylmethyl)-1-tetralone (VII) under the influence of polyphosphoric acid gave either 3,4-dihydrodibenzo-1,2,5,6-fluorene (VIII) or 7,8-dihydrodibenzo-1,2,5,6-fluorene (IX), whereas the use of sulfuric acid provided no isolable product. The action of phosphorus pentoxide on VII gave an intractable oil, and the use of aluminum chloride afforded X (54).



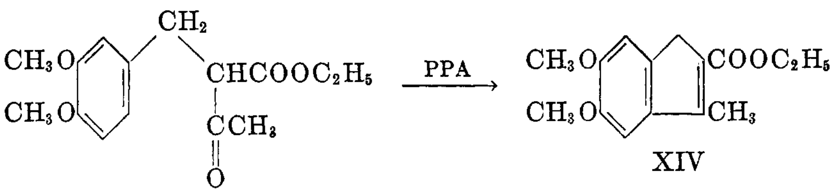
VII VIII IX X

A novel method for the synthesis of certain benz[*a*]acridines has been developed. For example, treatment of 2-phenacyl-3-phenylquinoline (XI) with polyphosphoric acid gave 5-phenylbenz[*a*]acridine (XII) in 87 per cent yield (153).



XI XII

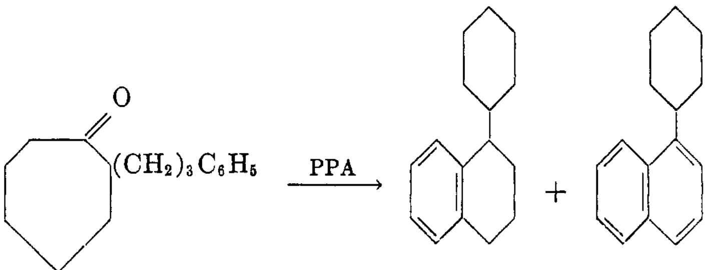
Ethyl 3,4-dimethoxybenzylacetoacetate (XIII) and ethyl 3,4-methylenedioxybenzylacetoacetate were converted in high yields to ethyl 5,6-dimethoxy-3-methylindene-2-carboxylate (XIV) and ethyl 5,6-methylenedioxy-3-methylin-



XIII XIV

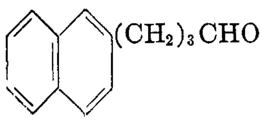
dene-2-carboxylate, respectively (211). The yields of the indene derivatives were much lower when a mixture of sulfuric acid and phosphoric acid was used as the dehydration agent (212).

A complex rearrangement-cyclodehydration reaction, presumably involving carbonium-ion intermediates, occurred on treatment of 2-(γ-phenylpropyl)cycloheptanone (XV) with polyphosphoric acid. The products included 1-cyclohexyltetralin (XVI), 2-cyclohexyltetralin, 1-cyclohexylnaphthalene (XVII), and 2-cyclohexylnaphthalene (144, 145). The results cited above represented a correction of previously reported (143) data.

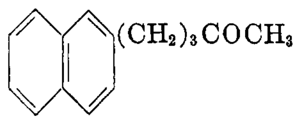


XV XVI XVII

Phenanthrene was prepared by catalytic dehydrogenation of the compound obtained by polyphosphoric acid-catalyzed ring closure of γ-(2-naphthyl)butyraldehyde (XVIII). However, dehydrogenation of the product obtained by the action of polyphosphoric acid on 5-(2-naphthyl)pentan-2-one (XIX) afforded a mixture of 1-methylanthracene and 4-methylanthracene. The change in orientation in the ring-closure step of the latter reaction was attributed to the increased steric requirements of the aceto group over the aldehyde group (51, 104).



XVIII



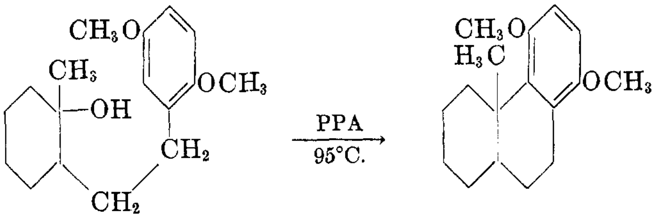
XIX

The pyridinium bromide obtained by the reaction of 2,3,6-trimethoxy-9-bromomethylphenanthrene with pyridine-2-carboxaldehyde could be cyclized in polyphosphoric acid medium under a nitrogen atmosphere. The product, a 2,3,6-trimethoxydibenzo[*h*,*j*]acridizinium salt, was converted to (±)-cryptopleurine by catalytic hydrogenation (66, 67).

2. Use of alcohols

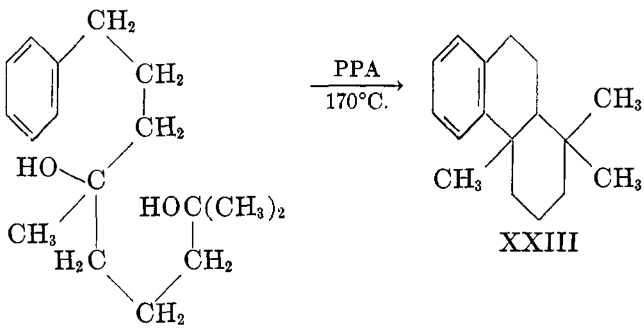
There are very few examples in the literature of uncomplicated cyclodehydration reactions involving alkylcarbinols having a suitably situated aryl substituent. In most cases, the action of polyphosphoric acid on an alcohol leads to the formation of a rearranged product, and such reactions will be discussed in a later section of this review paper.

Treatment of 1-methyl-2-[β-(2,5-dimethoxyphenyl)ethyl]cyclohexanol (XX) with polyphosphoric acid at 95°C. for 1 hr. gave 5,8-dimethoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XXI) in 81 per cent yield (39).



XX XXI

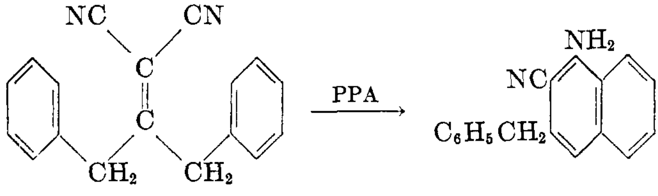
In like manner, 5,8-dimethoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene was obtained from 2-[β-(2,5-dimethoxyphenyl)ethyl]cyclohexanol. A rearranged product was also isolated from the latter reaction mixture (39). A remarkable double cyclization took place when 1-phenyl-4,8-dimethyl-4,8-dihydroxynonane (XXII) was dehydrated by the action of polyphosphoric acid at 170°C., 1,2,3,4,4a,9,10,10a-octahydro-1,1,4a-trimethylphenanthrene (XXIII) being produced in 75 per cent yield (257). In a very similar reaction, 2,6-dimethyl-9-phenyl-6-hydroxy-2-nonene was converted to XXIII in 80 per cent yield (257). The latter result suggests that the alkene is an intermediate in the formation of XXIII from XXII.



XXII XXIII

D. MISCELLANEOUS EXAMPLES OF CYCLIZATION REACTIONS

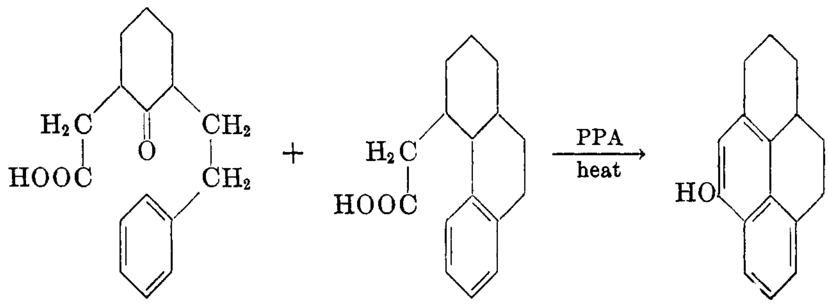
Some of the reactions given in this part of the review paper could, perhaps, be classified under other headings. However, each of the examples provided here has at least one unusual feature that makes it partially unsuitable for classification in any of the previous sections.



I II

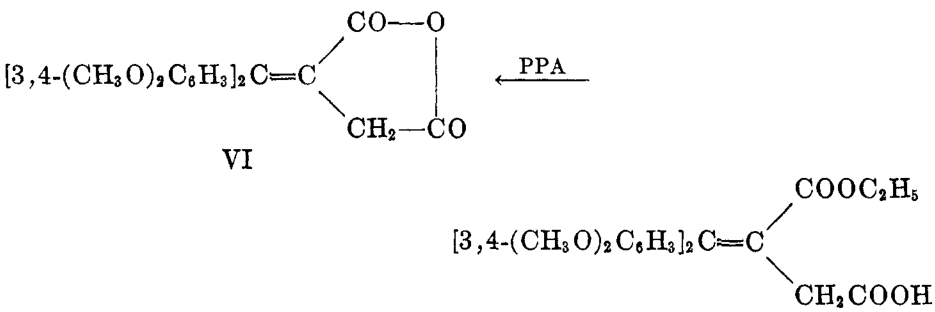
Treatment of *sym*-diphenylisopropylidenemalononitrile (I) with polyphosphoric acid gave 3-benzyl-2-cyano-1-naphthylamine (II) (109).

When a mixture of the keto acid III and the octahydrophenanthrylacetic acid IV was heated in polyphosphoric acid, the hexahydropyrenol V was produced in moderate yield (301).



III IV V

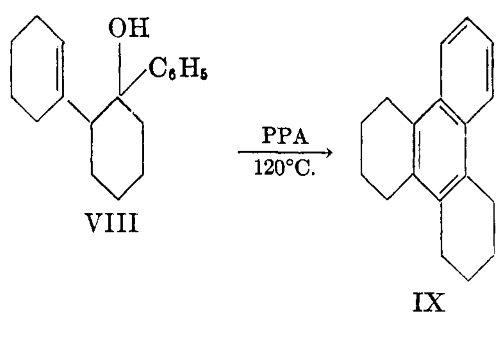
α,α-Bis(3,4-dimethoxyphenyl)itaconic anhydride (VI) was obtained when VII, the product of the Stobbe condensation of 3,4,3′,4′-tetramethoxybenzophenone with ethyl succinate, was subjected to the action of polyphosphoric acid (352).



VI

VII

Treatment of 2-cyclohex-1′-enyl-1-phenylcyclohexanol (VIII) with polyphosphoric acid at 120°C. for 1 hr. afforded 1,2,3,4,5,6,7,8-octahydrotriphenylene (IX) in low yield (46).



VIII

IX

3′,4′-Dihydro-7,8,6′,7′-tetramethoxynaphtho[1′,2′,3,4]isocoumarin was synthesized in 94 per cent yield from α-(2-carboxy-3,4-dimethoxyphenyl)-γ-(3,4-dimethoxyphenyl)butyric anhydride by the action of polyphosphoric acid at 100°C. for 20 min. (30). Only an intractable amorphous solid was obtained when 7,8 - dimethoxy - 4 - (3,4 - methylenedioxyphenylethyl)homophthalimide was treated similarly (30).

IV. Rearrangements

A. BECKMANN REARRANGEMENT

The first workers to attempt a polyphosphoric acid-catalyzed Beckmann rearrangement reported that the results were unsatisfactory (322). More recently, however, numerous reports that polyphosphoric acid is an excellent catalyst for this rearrangement reaction have appeared in the literature.

Simple ketoximes undergo rearrangement in polyphosphoric acid medium in essentially quantitative yield within 5–15 min. at 90–130°C. The reactions are particularly satisfactory when applied to the oximes of diaryl ketones, aryl alkyl ketones, and cyclic ketones (170, 171). Aldoximes also undergo the Beckmann rearrangement in polyphosphoric acid medium (172). For example, the polyphosphoric acid-catalyzed rearrangement of *n*-heptaldoxime gave *n*-heptamide in 92 per cent yield (172). The suggestion has been made (166) that nitriles are intermediates in the conversion of aldoximes to simple amides ($RCONH_2$). It is known that the action of polyphosphoric acid transforms nitriles to amides (317). It is of interest that *anti*-benzaldoxime gave only benzamide when treated with polyphosphoric acid at 130°C., whereas *syn*-benzaldoxime gave a mixture of benzamide and formanilide (172). It was concluded that the *syn*-isomer undergoes partial isomerization to the *anti*-oxime in contact with polyphosphoric acid. It is also noteworthy that the polyphosphoric acid-catalyzed rearrangement of *anti*-benzaldoxime hydrochloride gave a higher yield of benzamide than did the reaction of the oxime itself (172). The results of numerous polyphosphoric acid-catalyzed Beckmann rearrangements are summarized in table 15.

Oximes of cyclohexenones tend to undergo acid-catalyzed dehydration-aromatization reactions to yield the conjugate acids of aromatic amines; this type of reaction is sometimes referred to as the Wolff aromatization (367). By the action of polyphosphoric acid on 3,5-dimethyl-2-cyclohexen-1-one oxime (I), the lactam II was produced in 30 per cent yield (173). The use of the more common acid catalysts would, presumably, have produced the conjugate acid of 3,5-dimethylaniline. One reaction somewhat related to the Wolff aromatization has been shown to occur in polyphosphoric acid: 1,4-cyclohexanedione dioxime hydrochloride monohydrate gave the conjugate acid of 1,4-diamino-2-chlorobenzene in 18 per cent yield (227).

Although all previous attempts to convert 1-tetralone oxime to homodihydrocarbostyril by means of a Beckmann rearrangement had failed, the use of polyphosphoric acid effected this reaction readily, a 91 per cent yield of the desired product being obtained (173).

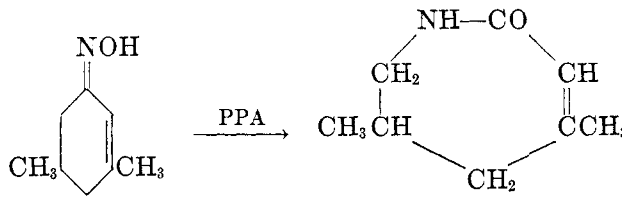
TABLE 15

Beckmann rearrangement

Oxime	Product	Temperature	Time	Yield	Reference
		°C.	min.	per cent	
Acetophenone oxime	Acetanilide	95	10	97	(171)
Anthraquinone dioxime	Dianthranilide	140	80	85	(299)
anti-Benzaldoxime	Benzamide	90		5	(172)
	Recovered oxime			30	
	Benzamide	130		41	(172)
syn-Benzaldoxime	Formanilide	90		8	(172)
	Benzamide			10	
	Recovered oxime			13	
	Formanilide	130		9	(172)
	Benzamide			25	
anti-Benzaldoxime hydrochloride	Benzamide	130	5	80	(172)
α-Benzil monoxime	Benzoic acid	100	30	100	(173)
	Benzamide			40	
Benzophenone oxime	Benzanilide	130	10	99	(171)
Benzophenone + nitromethane or hydroxylamine hydrochloride	Benzanilide	190		91	(12)
3-Carbethoxytetralone-1 oxime	2-Keto-4-carbethoxy-2,3,4,5-tetrahydrobenzazepine	110	5	86	(224)
3-Carbomethoxytetralone-1 oxime	2-Keto-4-carbomethoxy-2,3,4,5-tetrahydrobenzazepine	110	5	50	(224)
4-Carbomethoxytetralone-1 oxime	2-Keto-5-carbomethoxy-2,3,4,5-tetrahydrobenzazepine	110	5	92	(223)
4-Carboxytetralone-1 oxime	Oxindole-3-propionic acid	110	5	20	(223)
Cyclohexanone oxime	ε-Caprolactam	115	10	89	(171)
syn-2-Cyclohexenone oxime	6-Amino-2-hexenoic acid lactam	135	10	25	(106)
Cyclopentanone oxime	δ-Valerolactam	130	10	74	(171)
1,5-Dichloroanthraquinone *cis-trans*-dioxime	1,6(or 4,9)-Dichloro-11-ketoisoindolo-[2,1-*a*]benziminazole	90	120	58	(299)
1,5-Dichloroanthraquinone *trans-trans*-dioxime	4,10-Dichlorodianthranilide	90	120	72	(299)
1,5-Dichlorodianthranilide mixed dioximes	4,10-Dichlorodianthranilide	150		52	(299)
	1,6(or4,9)-Dichloro-11-ketoisoindolo-[2,1-*a*]benziminazole			15	
1,1-Dihydroxytetrahydro-1,4-thiapyrone oxime	No isolable product	115	15		(36)
p,p'-Dimethoxybenzophenone oxime	Anisoylanisidine	130	10	91	(171)
3,5-Dimethyl-2-cyclohexen-1-one oxime	3,5-Dimethyl-7-amino-7-heptenoic acid lactam	130	5	30	(173)
2,6-Dimethyltetrahydro-1,4-pyrone oxime	1-Oxa-2,7-dimethyl-5-keto-4-azacycloheptane	115	15	70	(36)
2,2-Diphenylcycloheptanone oxime	7,7-Diphenylheptamide and an unidentified compound, $C_{19}H_{19}NO$				(165)
2,6-Diphenyltetrahydro-1,4-thiapyrone oxime	1-Thia-2,7-diphenyl-5-keto-4-azacycloheptane	115	15	75	(36)
Fluorenone oxime	Phenanthridone	180		93	(173)
Fluorenone + nitromethane or hydroxylamine hydrochloride	Phenanthridone	250		67	(12)
n-Heptaldoxime	*n*-Heptamide	130		92	(172)
p-Methoxyacetophenone oxime	*p*-Methoxyacetanilide	120	10	99	(171)
4a-Methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene *cis*-oxime	Cis isomer of 2-keto-5-methyl-4,5-cyclohexano-2,3,4,5-tetrahydro-6,7-benzazepine-1	130	10	60	(40)
4a-Methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene *trans*-oxime	Trans isomer of 2-keto-5-methyl-4,5-cyclohexano-2,3,4,5-tetrahydro-6,7-benzazepine-1	130	10	92	(40)

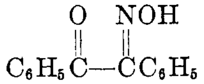
TABLE 15—*Concluded*

Oxime	Product	Temperature	Time	Yield	Reference
		°C.	min.	per cent	
1-Methyl-4-piperidone oxime	Intractable oil	115	15		(36)
Methyl 2-quinoxaline ketone oxime	Quinoxaline-2-carboxylic acid				(290)
Methyl 5,6,7,8-tetrahydro-2-naphthyl ketoxime	6-Acetamido-1,2,3,4-tetrahydronaphthalene	105	10	96	(358)
Phenylacetone oxime	*N*-Benzylacetamide	100	5	29	(173)
Spiro[4.5]decanone-1 oxime	$\Delta^{9,10}$-Octalone-1				(165)
Spiro[4.5]decanone-6 oxime	2-Cyclopentylidene cyclopentanone δ-Cyclopentylvaleramide				(165)
Spiro[4.4]nonanone-1 oxime	$\Delta^{8,9}$-Hydrindenone-4	125	10		(165)
Spiro[5.5]undecanone-1 oxime	Bicyclo[5.4.0]undecen-10-one-4 δ-Cyclohexylvaleramide				(165)
Tetrahydro-1,4-thiapyrone oxime	1-Thia-5-keto-4-azacycloheptane	115	15	85	(36)
Tetralone-1 oxime	Homodihydrocarbostyril	120	10	91	(173)

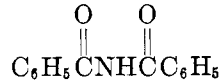


I II

Owing to the fact that the polyphosphoric acid-catalyzed rearrangement of α-benzil monoxime (III) gave a mixture of benzoic acid and benzamide, but no benzonitrile, it was originally believed (173) that dibenzamide (IV) was initially formed from III and subsequently underwent hydrolysis. However, later studies of the behavior of amides and imides in polyphosphoric acid solution indicated that complete hydrolysis of dibenzamide would probably not have occurred under the conditions of the Beckmann reaction (113). Also, inasmuch as benzonitrile has been converted to benzamide in 96 per cent yield by polyphosphoric acid-catalyzed hydrolysis (317), any benzonitrile formed from III in an abnormal Beckmann reaction would subsequently have been converted to the amide, one of the products actually isolated. Finally, the demonstration that desoxybenzoin could undergo reaction with sodium nitrite and polyphosphoric acid at room temperature to form benzoic acid and benzonitrile completed the argument in favor of the contention that III actually underwent cleavage rather than rearrangement in the initial reaction in polyphosphoric acid solution (113).



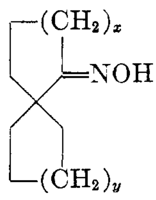
III



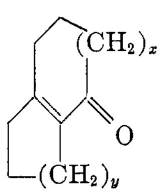
IV

Although all other oximes studied were found to undergo rearrangement in polyphosphoric acid at temperatures not exceeding 150°C., a temperature of 175–180°C. was required to effect the conversion of fluorenone oxime to phenanthridone (173). The yield was 93 per cent. Strangely enough, there has also been a report that fluorenone oxime could be obtained in excellent yield by heating a mixture of fluorenone and nitromethane with polyphosphoric acid at 190°C. (12). The apparent discrepancy is probably a result of the difference in the composition of the polyphosphoric acid used in the respective reactions. Commercial polyphosphoric acid was used in the former case and a solution of phosphorus pentoxide in syrupy phosphoric acid in the latter case. As pointed out in the discussion of the nature of the reagent (Section II), the ratio of component acids in polyphosphoric acid depends on the theoretical P_2O_5 content. It is conceivable that certain of the individual polyphosphoric acids might be more efficient catalysts than others in any given reaction. It also is of interest that nitromethane could be hydrolyzed to formic acid and a salt of hydroxylamine by the action of polyphosphoric acid, and that oximation of fluorenone occurred readily when hydroxylamine hydrochloride replaced nitromethane in the reaction cited above (12). When the temperature was raised to 250°C. in the reaction of fluorenone with nitromethane in polyphosphoric acid, phenanthridone was formed in high yield (12).

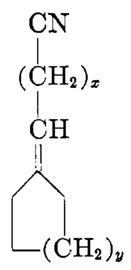
Unexpected results have been observed when certain α,α-disubstituted cyclic ketones were treated with polyphosphoric acid (165): spiro[4.4]nonanone-1 oxime (V) gave $\Delta^{8,9}$-hydrindenone-4 (VI); spiro[4.5]decanone-1 oxime (VII) afforded $\Delta^{9,10}$-octalone-1 (VIII); spiro[4.5]decanone-6 oxime (IX) yielded a mixture of 2-cyclopentylidene cyclopentanone and δ-cyclopentylvaleramide; spiro[5.5]undecanone-1 oxime (X) gave a mixture of bicyclo[5.4.0]undecen-10-one-4 (XI) and δ-cyclohexylvaleramide. This unusual behavior is not limited to spiro ketones; 2,2-diphenylcycloheptanone oxime gave a mixture of 7,7-diphenylheptamide plus an unidentified amide, $C_{19}H_{19}NO$, on treatment with polyphosphoric acid. Although detailed mechanisms have not been proposed for these reactions, it appears that unsaturated nitriles are formed as intermediates. In any event, the unsaturated nitriles XII, XIII, and XIV were prepared, together with the expected lactams, by treatment of the spiro ketoximes V, VII, and IX, respectively, with thionyl chloride. These unsaturated nitriles were then transformed by the action of polyphosphoric acid into the same products obtained from the parent oximes as cited above.



V: $x = y = 1$
VII: $x = 1, y = 2$
IX: $x = 2, y = 1$
X: $x = y = 2$



VI: $x = y = 1$
VIII: $x = 1, y = 2$
XI: $x = y = 2$



XII: $x = 2, y = 1$
XIII: $x = y = 2$
XIV: $x = 3, y = 1$

The oxime of acetylferrocene failed to undergo the Beckmann rearrangement when treated with polyphosphoric acid (151). In like manner, the use (151) of boron trifluoride under the usual conditions for effecting the Beckmann reaction (15) failed to bring about the rearrangement of the oxime.

B. LOSSEN REARRANGEMENT

Hydroxamic acids undergo the Lossen rearrangement when treated with polyphosphoric acid (113). For example, the action of polyphosphoric acid on potassium benzohydroxamate gives aniline in 67 per cent yield, and α-naphthylamine is obtained in 73 per cent yield from potassium α-naphthohydroxamate in a similar reaction (319). However, a more convenient procedure for the conversion of aromatic carboxylic acids to arylamines consists in the reaction of the acid with either hydroxylamine hydrochloride or hydroxylamine sulfate in polyphosphoric acid. The mixture is usually heated at 150–170°C. for 5 or 10 min., carbon dioxide being evolved (319). Certain acid derivatives, such as esters and amides, also undergo the reaction, but usually lower yields of amines are obtained from the derivatives than from the parent acids. Some ketones are also converted to amines by this method. Apparently a Beckmann rearrangement first occurs, and the resulting amide is then converted to the appropriate amine by the action of hydroxylamine and polyphosphoric acid. The available data (319) for these reactions are summarized in table 16.

TABLE 16

Modified Lossen rearrangement reactions

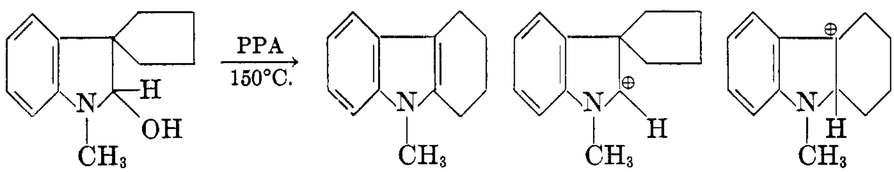
Reactant	Expected Product	Yield
		per cent
Benzanilide	Aniline	76
Benzamide	Aniline	43
Benzoic acid	Aniline	66
Benzonitrile	Aniline	20
Benzophenone	Aniline	66
Benzoyl chloride	Aniline	51
o-Bromobenzoic acid	*o*-Bromoaniline	53
m-Bromobenzoic acid	*m*-Bromoaniline	46
p-Bromobenzoic acid	*p*-Bromoaniline	43
Caprylic acid	*n*-Heptylamine	0
p-Chlorobenzamide	*p*-Chloroaniline	0
p-Chlorobenzoic acid	*p*-Chloroaniline	32
p,p'-Dichlorobenzanilide	*p*-Chloroaniline	48
p,p'-Dichlorobenzophenone	*p*-Chloroaniline	15
p,p'-Dichlorobenzophenone oxime	*p*-Chloroaniline	40
Ethyl benzoate	Aniline	68
N-Methylbenzamide	Aniline, methylamine	0
N-Methyl-*p*-chlorobenzamide	*p*-Chloroaniline, methylamine	0
α-Naphthoic acid	α-Naphthylamine	80
β-Naphthoic acid	β-Naphthylamine	82
o-Nitrobenzoic acid	*o*-Nitroaniline	0
m-Nitrobenzoic acid	*m*-Nitroaniline	53
p-Nitrobenzoic acid	*p*-Nitroaniline	0
o-Phenylbenzoic acid	Phenanthridone	40
Salicylic acid	Benzoxazolone	33
m-Toluic acid	*m*-Toluidine	76
p-Toluic acid	*p*-Toluidine	72
Valeric acid	*n*-Butylamine	0

Although caprylic acid and valeric acid gave no *n*-heptylamine and *n*-butylamine, respectively, when subjected to the reaction conditions cited above, cyclohexanecarboxylic acid was converted to cyclohexylamine in 36 per cent yield by treatment with polyphosphoric acid and hydroxylamine at a temperature of 135°C. In like manner, *n*-amylamine was prepared from caproic acid in 25 per cent yield (317). Only a relatively low yield (25 per cent) of 1-aminofluorene was obtained by the reaction of 1-fluorenecarboxylic acid with hydroxylamine in polyphosphoric acid (359). Although *O*-methylhydroxylamine could not be used to convert carboxylic acids to amines in polyphosphoric acid, this compound did undergo reaction with benzophenone to produce benzanilide (113).

C. WAGNER–MEERWEIN REARRANGEMENT

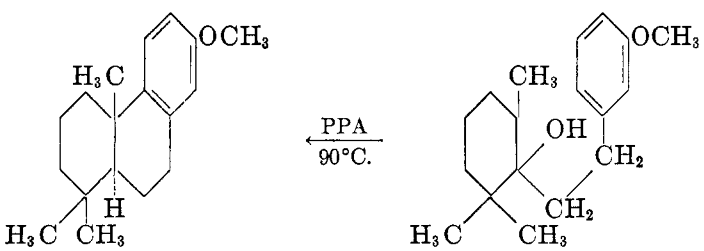
Certain Wagner–Meerwein rearrangement reactions were discussed in previous sections of this review. In particular, some examples were given in which rearrangements preceded cyclodehydration reactions. No attempt will be made to review these cases here, but several additional examples of polyphosphoric acid-catalyzed Wagner–Meerwein rearrangements, not previously discussed, will be considered.

Spiro(cyclopentane-1,3′-*N*-methyl-2′-hydroxyindole) (I), on treatment with polyphosphoric acid at 150°C., gave the rearranged product, 9-methyltetrahydrocarbazole (II). Probably the carbonium ions III and IV were formed as transition ions (365).



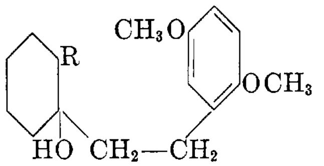
I II III IV

1,1,4a-Trimethyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (V), an intermediate product in one synthesis of certain diterpenes, was obtained by the action of polyphosphoric acid at 90°C. on 1-(*m*-methoxyphenethyl)-2,2,6-trimethylcyclohexanol (VI) (38).

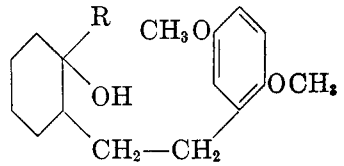


V VI

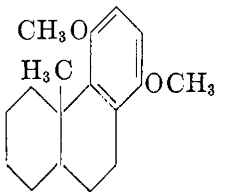
The polyphosphoric acid-catalyzed rearrangement-cyclization of four β-arylethylcyclohexanols (VII to X) has been studied (39). Both of the alcohols VIII and X gave the same product, 5,8-dimethoxy-4a-methyl-1,2,3,4,4a,9,10,10aoctahydrophenanthrene (XI), in 57 and 81 per cent yields, respectively. The configurations of the alcohols and the phenanthrene derivatives were not established, but both alcohols gave the same racemate of XI. The alcohol VII gave the spirane XII in 56 per cent yield, and the alcohol IX gave a mixture of XII and XIII. Mechanisms have been proposed (39) for these reactions.



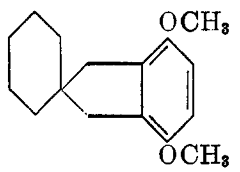
VII: R = H
VIII: R = CH_3



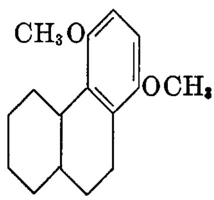
IX: R = H
X: R = CH_3



XI

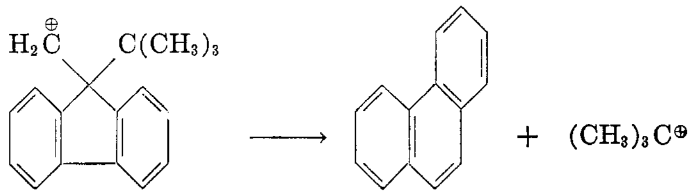


XII



XIII

The action of polyphosphoric acid on 9-fluorenylmethanol gave phenanthrene in high yield (45). 2-Nitro-9-fluorenylmethyl acetate afforded 2-nitrophenanthrene in 89 per cent yield in a polyphosphoric acid-catalyzed rearrangement reaction (45). 9-Alkyl-9-fluorenylmethanols have been converted to 9-alkylphenanthrenes by treatment with polyphosphoric acid at 160°C. (11). 9-Methyl-, 9-ethyl-, and 9-*tert*-butylphenanthrene were prepared in this way. The reaction of 9-*tert*-butyl-9-fluorenylmethanol with hot polyphosphoric acid also gave phenanthrene and a trace of a third compound in addition to 9-*tert*-butylphenanthrene. It was shown by experimentation that the latter compound was stable towards polyphosphoric acid even at 200°C. and that phenanthrene was not alkylated by *tert*-butyl alcohol under similar conditions. Therefore it was concluded (11) that the carbonium ion XIV, initially formed from 9-*tert*-butyl-9-fluorenylmethanol, underwent, in part, a reaction involving elimination of a *tert*-butyl cation.



XIV

Treatment of benzilic acid with polyphosphoric acid at 180°C. gave fluorene-9-carboxylic acid in low yield (11).

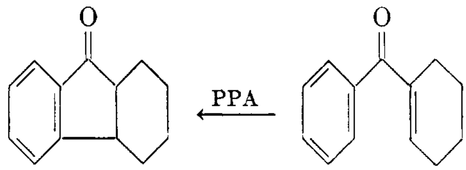
D. SCHMIDT REARRANGEMENT

Only a few examples of polyphosphoric acid-catalyzed Schmidt reactions have been reported in the literature. Benzanilide was obtained in 80 per cent yield after treatment of benzophenone with sodium azide in polyphosphoric acid for 3 hr. at 50°C. (113). A similar reaction with benzoic acid provided aniline in 48 per cent yield, together with a relatively small amount of *N*,*N'*-diphenylurea. *p*-Nitrobenzoic acid failed to undergo the Schmidt reaction under these conditions (113), whereas the use of sulfuric acid in the usual Schmidt procedure gave *p*-nitroaniline in 41 per cent yield (69).

V. Intermolecular Acylation and Alkylation

Several incomplete reviews of polyphosphoric acid-catalyzed intermolecular acylation reactions have been published (20, 216, 259). Although a variety of cycloalkenes and aromatic compounds have been acylated by reaction with carboxylic acids or some of their derivatives in the presence of polyphosphoric acid, the major applications of intermolecular acylation reactions have been with phenols and phenolic ethers or esters. Some polyphosphoric acid-catalyzed alkylation reactions have also been studied, and these reactions will be discussed at the end of this section of the review paper.

One of the first and most interesting intermolecular acylation reactions in polyphosphoric acid to be investigated was that between benzoic anhydride and cyclohexene. In the first experiments, hexahydrofluorenone (I) was obtained in 20 per cent yield (94). In later work, it was shown that I could be prepared in 40 per cent yield by this method and that the ketone II, a probable intermediate in the formation of I, could be converted to I in 65 per cent yield by treatment with polyphosphoric acid (99).



I II

Additional examples of polyphosphoric acid-catalyzed intermolecular acylation reactions followed by intramolecular alkylation reactions came to light when cyclohexene and cyclopentene were caused to react with unsaturated acids (99). For example, the reaction of cyclohexene with crotonic acid in polyphosphoric acid solution at 57°C. for 30 min. gave 3-methyl-4,5,6,7-tetrahydroindan-1-one (III) in 60 per cent yield. In like manner, the polyphosphoric acid-catalyzed condensation of cyclopentene with crotonic acid at 40°C. for 1 hr. afforded 1-methylbicyclo[3.3.0]-$\Delta^{7,8}$-octen-3-one (IV) in 22 per cent yield. Additional examples of similar reactions are given in table 17.

The action of polyphosphoric acid at 55°C. for 45 min. on a mixture of cyclohexene and acetic acid gave 1-acetylcyclohexene in 60 per cent yield (98). It is

TABLE 17

*Intermolecular acylation reactions**

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		*per cent*	
Acetomesitylene	Acetomesitylene	1,1-Dimesitylethylene	150	2 hr.	17	(320)
2-Acetyl-α-naphthol	Acetic acid	2,4-Diacetyl-α-naphthol			60	(255)
	Propionic acid	2-Acetyl-4-propionyl-α-naphthol			41	(255)
4-Acetyl-α-naphthol	Acetic acid	2,4-Diacetyl-α-naphthol			52	(255)
	Propionic acid	4-Acetyl-2-propionyl-α-naphthol			16	(255)
Aniline	Benzoic acid	Benzanilide	150	10 min.	0	(317)
Anisole	Acetic anhydride	4-Methoxyacetophenone	50	3.7 hr.	83	(127)
	Acetic acid	4-Methoxyacetophenone	100	35 min.	64	(254)
	Benzoic acid	*p*-Methoxybenzophenone	100	30 min.	62	(253)
			75	2 hr.	91	(127)
	n-Butyric acid	*p*-Methoxybutyrophenone	80	1.5 hr.	91	(98)
			100	32 min.	60	(254)
	Caproic acid	*p*-Methoxycaprophenone			80	(98)
			100	20 min.	61	(254)
	β-Carbomethoxypropionic acid	Methyl β-(4-methoxybenzoyl)-propionate	30	4.5 hr.	75	(127)
	8-Carboxymethyl-5-hydroxy-7,4′-dimethoxyflavone	8-(*p*-Methoxyphenacyl)-5-hydroxy-7,4′-dimethoxyflavone				(249)
	6-Carboxymethyl-5,7,4′-trimethoxyflavone	6-(*p*-Methoxyphenacyl)acacetin-5,7-dimethyl ether				(256)
	8-Carboxymethyl-5,7,4′-trimethoxyflavone	8-(*p*-Methoxyphenacyl)-5,7,4′-trimethoxyflavone				(249)
	Cinnamic acid	4-Methoxyphenyl cinnamyl ketone	100	15 min.	45	(254)
			125	25 min.	50	(318)
	Crotonic acid	*p*-Methoxycrotonophenone	55	40 min.	80	(98)
	Cyclohexanol	2-Cyclohexylanisole 4-Cyclohexylanisole	85	35 min.	72	(127)
	p-Hydroxybenzoic acid	4-Methoxy-4′-hydroxybenzophenone	100	20 min.	26	(253)
	p-Methoxybenzoic acid	4,4′-Dimethoxybenzophenone	100	30 min.	21	(253)
	p-Methoxyphenylacetic acid	4-Methoxyphenyl 4-methoxybenzyl ketone	100	5 min.	74	(254)
	Phenylacetic acid	4-Methoxyphenyl benzyl ketone				(248)
			100	5 min.	73	(254)
			100	45 min.	77	(129)
	Phenylpropionic acid	4-Methoxyphenyl phenethyl ketone	100	10 min.	50	(254)
	2-Propanol	2-Isopropylanisole	85	1 hr.	34	(127)
		4-Isopropylanisole			13	
	Propionic acid	4-Methoxypropiophenone	100	23 min.	64	(254)
	Sorbic acid	*p*-Methoxysorbophenone	55	30 min.	60	(98)
	Toluene-*p*-sulfonic acid	4-Methoxy-4′-methyldiphenyl sulfone	95	3.5 hr.	65	(278)
	Valeric acid	4-Methoxyvalerophenone	100	20 min.	72	(254)
Benzyl alcohol	L-Alanine	L-Alanine benzyl ester				(114)
	L-Cysteine	L-Cysteine benzyl ester	105	4 hr.	45	(114)
	L-Cystine	L-Cystine benzyl ester				(114)
	L-Leucine	L-Leucine benzyl ester				(114)
	DL-Phenylalanine	DL-Phenylalanine benzyl ester	95	4 hr.	65	(114)
	L-Phenylalanine	L-Phenylalanine benzyl ester				(114)
	L-Tyrosine	L-Tyrosine benzyl ester				(114)
Catechol	Acetic acid	Acetocatechol		15 min.	59	(245)
	Benzoic acid	Pyrocatechol monobenzoate	100	30 min.	61	(253)
	p-Methoxybenzoic acid	Pyrocatechol monoanisate	25	48 hr.	44	(253)
	Propionic acid	Propiocatechol			12	(245)
o-Chloroaniline	Benzoic acid	Benz-*o*-chloroanilide	150	10 min.	39	(317)
m-Cresol	*n*-Caproic acid	*o*-Caproyl-*m*-cresol	80	1 hr.	22	(318)

* A few alkylation reactions are also included.

TABLE 17—*Continued*

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		*per cent*	
Cyclohexene	Acetic acid	1-Acetylcyclohexene	55	45 min.	60	(98)
	Acrylic acid	4,5,6,7-Tetrahydroindan-1-one	57	30 min.	16	(99)
	Benzoic anhydride	Hexahydrofluorenone	57	30 min.	42	(99)
	Cinnamic acid	3-Phenyl-4,5,6,7-tetrahydroindan-1-one	57	30 min.	26	(99)
	Crotonic acid	3-Methyl-4,5,6,7-tetrahydroindan-1-one	57	30 min.	60	(99)
Cyclopentene	Acetic acid	1-Acetylcyclopentene	40	45 min.	27	(98)
	Crotonic acid	1-Methylbicyclo[3.3.0]-$\Delta^{7,8}$-octen-3-one	40	1 hr.	22	(99)
o-Dimethoxybenzene	Acetic acid	3,4-Dimethoxyacetophenone	60	2.5 hr.	83	(176)
	Phenylacetic acid	3,4-Dimethoxyphenyl benzyl ketone				(248)
	2,4,6-Trimethoxyphenylacetic acid	3,4-Dimethoxyphenyl 2,4,6-trimethoxybenzyl ketone	100	5 min.	55	(254)
m-Dimethoxybenzene	Acetic acid	2,4-Dimethoxyacetophenone	60	2.5 hr.	98	(176)
					65	(245)
	Benzoic acid	Resbenzophenone dimethyl ether			76	(245)
	Propionic acid	Respropiophenone dimethyl ether			80	(245)
p-Dimethoxybenzene	Acetic acid	2,5-Dimethoxyacetophenone	85	45 min.	45	(176)
	γ-Carbethoxybutyryl chloride	γ-(2,5-Dimethoxybenzoyl)-butyric acid	70	2.5 hr.	28	(10)
3,5-Dimethoxyphenol	Acetic acid	2,4-Diacetyl-3,5-dimethoxyphenol	100	15 min.	50	(252)
	Propionic acid	2,4-Dipropionyl-3,5-dimethoxyphenol	100	15 min.	30	(252)
2,4-Dinitroaniline	Acetic acid	2,4-Dinitroacetanilide	150	10 min.	92	(317)
	Benzoic acid	Benz-2,4-dinitroanilide	150	10 min.	98	(317)
	o-Nitrobenzoic acid				0	(317)
	p-Nitrobenzoic acid				0	(317)
2,2-Diphenolisatin	Acetic acid	Ester			50	(250)
	Benzoic acid	Ester			59	(250)
Diphenylamine	Benzoic acid	*p,p'*-Dibenzoyldiphenylamine	160		40	(318)
Durene	*n*-Butyric acid	$C_{24}H_{32}$	140	2.5 hr.		(320)
	Propionic acid	$C_{23}H_{30}$	145	5 hr.	10	(320)
Guaiacol	Acetic acid	Acetovanillone			36	(245)
	Propionic acid	Propiovanillone			61	(245)
Hydroquinone	Acetic acid	Hydroquinone diacetate			51	(250)
	Benzoic acid	Hydroquinone dibenzoate			58	(250)
	Anisic acid	Hydroquinone dianisate	100	20 min.	47	(253)
	Phenylacetic acid	Hydroquinone diphenylacetate			29	(250)
	Propionic acid	Hydroquinone dipropionate			54	(250)
	Salicylic acid	Hydroquinone disalicylate	100	20 min.	51	(253)
5-Hydroxy-7,4'-dimethoxyflavone	Acetic acid	6-Acetylacacetine-7-methyl ether				(256)
2-Hydroxy-4-methoxyacetophenone	Acetic acid	2,4-Diacetyl-5-methoxyphenol			36	(245)
	Propionic acid	2-Acetyl-4-propionyl-5-methoxyphenol			26	(245)
Mesitylene	Acetic acid	1,1-Dimesitylethylene			9	(320)
	n-Butyric acid	1,1-Dimesitylbutene	140	2.5 hr.	48	(320)
	Chloroacetic acid	ω-Chloroacetomesitylene		5 hr.	16	(320)
		Bis(ω-chloroaceto)mesitylene			3	
	Propionic acid	1,1-Dimesitylpropene	145	5 hr.	39	(320)
Methoxyamine	Benzoic acid				0	(317)
4-Methoxy-4'-hydroxybenzophenone	*p*-Methoxybenzoic acid	4-Methoxy-4'-anisoyloxybenzophenone				(253)
p-Methylphenol	Phenylacetic acid	*p*-Tolyl phenylacetate		20 min.	44	(250)
2-Methylthiophene	Acetic anhydride	2-Methyl-5-acetylthiophene	110	3 hr.		(138)
α-Naphthol	Acetic acid	2-Acetyl-α-naphthol			37	(255)
		4-Acetyl-α-naphthol			32	

TABLE 17—*Continued*

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		per cent	
	Acetic acid (different conditions)	2,4-Diacetyl-α-naphthol			29	(255)
		2-Acetyl-α-naphthol			14	
		4-Acetyl-α-naphthol			10	
	n-Butyric acid	2-Butyl-α-naphthol			72	(255)
		4-Butyl-α-naphthol			3	
	Caproic acid	2-Caproyl-α-naphthol			46	(255)
	Propionic acid	2-Propionyl-α-naphthol			42	(255)
		4-Propionyl-α-naphthol			1	
	Valeric acid	2-Valeryl-α-naphthol			53	(255)
		4-Valeryl-α-naphthol			Trace	
α-Naphthyl acetate		2-Acetyl-α-naphthol			56	(255)
		4-Acetyl-α-naphthol			21	
α-Naphthyl *n*-butyrate		2-Butyryl-α-naphthol			69	(255)
α-Naphthyl caproate					0	(255)
α-Naphthyl propionate		2-Propionyl-α-naphthol			80	(255)
		4-Propionyl-α-naphthol			1	
α-Naphthyl valerate		2-Valeryl-α-naphthol			44	(255)
o-Nitroaniline	Benzoic acid	Benz-*o*-nitroanilide	150	10 min.	71	(317)
p-Nitroaniline	Acetic acid	*p*-Nitroacetanilide	150	10 min.	67	(317)
	Benzoic acid	Benz-*p*-nitroanilide	150	10 min.	54	(317)
	Chloroacetic acid	α-Chloro-*p*-nitroacetanilide	150	10 min.	7	(317)
	o-Chlorobenzoic acid	*o*-Chlorobenz-*p*-nitroanilide	150	10 min.	64	(317)
	o-Nitrobenzoic acid				0	(317)
	m-Nitrobenzoic acid	*m*-Nitrobenz-*p*-nitroanilide	150	10 min.	8	(317)
	p-Nitrobenzoic acid				0	(317)
	p-Toluic acid	*p*-Tolu-*p*-nitroanilide	150	10 min.	60	(317)
Phenol	Acetic acid	*o*-Hydroxyacetophenone	100	10 min.	20	(247)
		p-Hydroxyacetophenone			65	
		Phenyl acetate			3	
	Acetic acid	*p*-Hydroxyacetophenone	75	1.5 hr.	67	(318)
	Acetic acid	Phenyl acetate	Cold	24 hr.	45	(250)
	Acetic acid	Phenyl acetate	100	15 min.	29	(250)
		p-Hydroxyacetophenone			33	
	Acetic acid	*p*-Hydroxyacetophenone	100		33	(254)
	Acetic anhydride	4-Acetylphenyl acetate	75	1.5 hr.	51	(128)
	Benzoic acid	*p*-Hydroxybenzophenone	100	20 min.	16	(246)
		Phenyl benzoate			68	
	Benzoic acid	Phenyl benzoate				(26)
	Benzoic acid	*o*-Hydroxybenzophenone	100	10 min.	1	(247)
		p-Hydroxybenzophenone			9	
		Phenyl benzoate			90	
	Benzoic acid	Phenyl benzoate	100	10 min.	97	(250)
	n-Butyric acid	*p*-Hydroxybutyrophenone	100	5 min.	54	(254)
	n-Butyric acid	*o*-Hydroxybutyrophenone	100	10 min.	5	(247)
		p-Hydroxybutyrophenone			76	
		Phenyl *n*-butyrate			15	
	Caproic acid	*p*-Hydroxycaprophenone	100	20 min.	41	(254)
	Caproic acid	*p*-Hydroxycaprophenone	100	10 min.	40	(247)
		Phenyl caproate			57	
	o-Chlorobenzoic acid	2-Chloro-4′-hydroxybenzophenone	100	20 min.	13	(246)
		Phenyl *o*-chlorobenzoate			78	
	m-Chlorobenzoic acid	3-Chloro-4′-hydroxybenzophenone	100	20 min.	5	(246)
		Phenyl *m*-chlorobenzoate			42	
	p-Chlorobenzoic acid	4-Chloro-4′-hydroxybenzophenone	100	20 min.	2	(246)
		Phenyl *p*-chlorobenzoate			26	
	Cinnamic acid	*p*-Hydroxyphenyl cinnamyl ketone	100	13 min.	20	(254)
	Cyclohexanol	*o*-Cyclohexylphenol	85	40 min.	22	(127)
		p-Cyclohexylphenol			17	
	Diglycolic acid	Phenyl diglycolate				(26)
	o-Hydroxybenzoic acid	2,4′-Dihydroxybenzophenone	100	20 min.	2	(246)
		Phenyl *o*-hydroxybenzoate			78	
	m-Hydroxybenzoic acid	3,4′-Dihydroxybenzophenone	100	20 min.	7	(246)
		Phenyl *m*-hydroxybenzoate			41	

TABLE 17—*Continued*

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		per cent	
Phenol (*continued*).....	*p*-Hydroxybenzoic acid	Phenyl *p*-hydroxybenzoate	25	48 hr.	29	(253)
	p-Hydroxybenzoic acid	4,4'-Dihydroxybenzophenone	100	30 min.	21	(253)
	p-Hydroxybenzoic acid	4,4'-Dihydroxybenzophenone	100	20 min.	47	(246)
		Phenyl *p*-hydroxybenzoate			12	
	Levulinic acid	Phenyl levulinate			35	(26)
	Maleic anhydride	Phenyl maleate				(26)
	Methacrylic acid	Phenyl methacrylate			55	(26)
	o-Methoxybenzoic acid	2-Methoxy-4'-hydroxybenzophenone	100	20 min.	61	(246)
		Phenyl *o*-methoxybenzoate			5	
	m-Methoxybenzoic acid	3-Methoxy-4'-hydroxybenzophenone	100	20 min.	15	(246)
		Phenyl *m*-methoxybenzoate			65	
	p-Methoxybenzoic acid	Phenyl anisate	25	24 hr.	48	(253)
	p-Methoxybenzoic acid	4-Methoxy-4'-hydroxybenzophenone	100	5 min.	29	(253)
	p-Methoxybenzoic acid	4-Methoxy-4'-hydroxybenzophenone	100	20 min.	75	(246)
	o-Toluic acid	2-Methyl-4'-hydroxybenzophenone	100	20 min.	47	(246)
		Phenyl *o*-toluate			38	
	m-Toluic acid	3-Methyl-4'-hydroxybenzophenone	100	20 min.	19	(246)
		Phenyl *m*-toluate			67	
	p-Toluic acid	4-Methyl-4'-hydroxybenzophenone	100	20 min.	24	(246)
		Phenyl *p*-toluate			59	
	o-Nitrobenzoic acid	2-Nitro-4'-hydroxybenzophenone	100	20 min.	Trace	(246)
		Phenyl *o*-nitrobenzoate			11	
	m-Nitrobenzoic acid	3-Nitro-4'-hydroxybenzophenone	100	20 min.	1	(246)
		Phenyl *p*-nitrobenzoate			11	
	p-Nitrobenzoic acid	4-Nitro-4'-hydroxybenzophenone	100	20 min.	Trace	(246)
		Phenyl *p*-nitrobenzoate			2	
	Phenylacetic acid	*p*-Hydroxyphenyl benzyl ketone				(248)
	Phenylacetic acid	*o*-Hydroxyphenyl benzyl ketone	100	10 min.	4	(247)
		p-Hydroxyphenyl benzyl ketone			19	
		Phenyl phenylacetate			74	
	Phenylacetic acid	*p*-Hydroxyphenyl benzyl ketone	100	15 min.	28	(254)
	Phenylpropionic acid	*o*-Hydroxyphenyl phenethyl ketone	100	10 min.	13	(247)
		p-Hydroxyphenyl phenethyl ketone			18	
		Phenyl phenylpropionate			67	
	Phenylpropionic acid	*p*-Hydroxyphenyl phenethyl ketone	100	15 min.	27	(254)
	Phthalic anhydride	Phenyl phthalate				(26)
	Propionic acid	*p*-Hydroxypropiophenone	100	5 min.	58	(254)
	Propionic acid	*o*-Hydroxypropiophenone	100	10 min.	5	(247)
		p-Hydroxypropiophenone			81	
		Phenyl propionate			3	
	Salicylic acid	Phenyl salicylate	100	15 min.	59	(253)
			100	24 hr.	95	(26)
	Stearic acid	Phenyl stearate				(26)
	Valeric acid	*p*-Hydroxyvalerophenone	100	15 min.	47	(254)
	Valeric acid	*o*-Hydroxyvalerophenone	100	10 min.	2	(247)
		p-Hydroxyvalerophenone			58	
		Phenyl valerate			35	
Phenolphthalein........	Acetic acid	Ester			56	(250)
	Benzoic acid	Ester			70	(250)

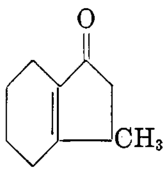
TABLE 17—*Continued*

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		per cent	
Phenyl acetate		*o*-Hydroxyacetophenone			53	(247)
		p-Hydroxyacetophenone			20	
		p-Hydroxyacetophenone	75	1.5 hr.	69	(318)
		p-Hydroxyacetophenone	70	1.5 hr.	50	(128)
			90	1.5 hr.	35	
	Acetic acid	*p*-Acetylphenyl acetate	75	1.5 hr.	50	(128)
	Benzoic acid	*p*-Acetylphenyl benzoate	90	1 hr.	21	(128)
		p-Benzoylphenyl acetate			3	
Phenyl anisate		4-Methoxy-4′-hydroxybenzophenone	100	30 min.	43	(253)
		4-Methoxy-4′-anisoyloxybenzophenone			16	
Phenyl benzoate		4-Hydroxybenzophenone	80	2.5 hr.	25	(128)
		p-Benzoylphenyl benzoate			13	
		4-Hydroxybenzophenone	100	30 min.	8	(253)
		o-Hydroxybenzophenone			6	(247)
		p-Hydroxybenzophenone			1	
	Acetic acid	*p*-Acetylphenyl benzoate	90	1 hr.	21	(128)
Phenyl *n*-butyrate		*o*-Hydroxybutyrophenone			45	(247)
		p-Hydroxybutyrophenone			13	
Phenyl caproate		*o*-Hydroxycaprophenone			36	(247)
		p-Hydroxycaprophenone			2	
Phenyl phenylacetate		*o*-Hydroxyphenyl benzyl ketone			8	(247)
		p-Hydroxyphenyl benzyl ketone			1	
Phenyl phenylpropionate		*o*-Hydroxyphenyl phenethyl ketone			10	(247)
		p-Hydroxyphenyl phenethyl ketone			1	
Phenyl propionate		*o*-Hydroxypropiophenone			61	(247)
		p-Hydroxypropiophenone			13	
Phenyl valerate		*o*-Hydroxyvalerophenone			40	(247)
		p-Hydroxyvalerophenone			6	
Phloroglucinol	Acetic acid	2,4,6-Triacetylphloroglucinol	100	10 min.	12	(252)
	Benzoic acid	Phloroglucinol tribenzoate	100	30 min.	42	(253)
	Propionic acid	2,4,6-Tripropionylphloroglucinol	100	10 min.	20	(252)
Phloroglucinol monomethyl ether	Acetic acid	2,4,6-Triacetylphloroglucinol monomethyl ether	100	10 min.	34	(252)
	Propionic acid	2,4,6-Tripropionylphloroglucinol monomethyl ether			32	(252)
Resacetophenone	Acetic acid	4,6-Diacetylresorcinol			13	(245)
	Propionic acid	4-Acetyl-6-propionylresorcinol			32	(245)
Resorcinol	Acetic acid	Resacetophenone		20 min.	71	(245)
	Acetic acid	Resorcinol diacetate	25	24 hr.	36	(250)
	Acetic acid	4,6-Diacetylresorcinol	100	20 min.	9	(250)
		2-Acetylresorcinol			4	
		Resacetophenone			9	
	Anisic acid	Resorcinol dianisate	25	48 hr.	32	(253)
	Benzoic acid	Resorcinol dibenzoate	100	20 min.	71	(250)
	n-Butyric acid	Resbutyrophenone			44	(245)
	Propionic acid	Respropiophenone			65	(245)
Resorcinol monomethyl ether	Acetic acid	2-Methoxy-4-hydroxyacetophenone			27	(245)
		2-Hydroxy-4-methoxyacetophenone			25	
		4,6-Diacetylresorcinol monomethyl ether			5	
	Propionic acid	2-Hydroxy-4-methoxypropiophenone			30	(245)
		4-Methoxy-2-hydroxypropiophenone			28	
		4,6-Dipropionylresorcinol monomethyl ether			1	

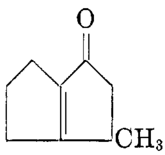
TABLE 17—*Concluded*

Compound Acylated	Acylating Agent	Product	Temperature	Time	Yield	Reference
			°C.		*per cent*	
Resorcinol diacetate....		4,6-Diacetylresorcinol	70	2 hr.	19	(128)
Respropiophenone......	Propionic acid	4,6-Dipropionylresorcinol			33	(245)
Respropiophenone monomethyl ether....	Acetic acid	4-Acetyl-6-propionyl-3-methoxyphenol			37	(245)
	Propionic acid	4,6-Dipropionyl-3-methoxyphenol			30	(245)
Thiophene..............	Acetic acid	2-Acetylthiophene	75	3 hr.	70	(318)
Toluene................	Acetic acid	Methyl *p*-tolyl ketone	85	2.2 hr.	75	(98)
	Benzoic acid	4-Methylbenzophenone	165	3 hr.	70	(318)
1,2,3-Trimethoxybenzene..............	Acetic acid	2,3,4-Trimethoxyacetophenone	60	2.5 hr.	96	(176)
			45	3 hr.	92	(127)
1,2,4-Trimethoxybenzene..............	γ-Carbethoxybutyric acid	Ethyl γ-(2,4,5-trimethoxybenzoyl)butyrate	45	2 hr.	63	(10)
1,3,4-Trimethoxybenzene..............	Acetic acid	2,4,5-Trimethoxyacetophenone	45	2.5 hr.	84	(176)
1,3,5-Trimethoxybenzene..............	Acetic acid	2,4,6-Trimethoxyacetophenone	60	2.5 hr.	57	(176)
					76	(252)
	Propionic acid	2,4,6-Trimethoxypropiophenone			53	(252)
Trimethylpyrogallol....	Acetic anhydride	2,3,4-Trimethoxyacetophenone	45	3 hr.	93	(127)
	Benzoic acid	2,3,4-Trimethoxybenzophenone	80	2 hr.	92	(127)
	β-Carbomethoxypropionic acid	Methyl β-(2,3,4-trimethoxybenzoyl)propionate	45	2.5 hr.	79	(127)
Veratrole..............	Acetic acid	Acetoveratrone			61	(245)
	Benzoic acid	Benzoveratrone			62	(245)
	Propionic acid	Propioveratrone			51	(245)

of interest that ethylbenzene was formed as a by-product of this reaction, and that the yield of the latter compound rose to 38 per cent when forcing conditions were employed (98). Cyclopentene has been acetylated in low yield by treatment with acetic acid in polyphosphoric acid at 40°C. (98), and successful acylation reactions have been reported (312) for the polyphosphoric acid-catalyzed reactions of cyclohexene and 1-methylcyclohexene with acetic, propionic, and *n*-butyric acids.



III



IV

Many examples of the acylation of phenolic ethers in polyphosphoric acid medium are given in table 17. Some of the most useful applications of this reaction have been with unsaturated acids. For example, the reaction of anisole with crotonic acid provided *p*-methoxycrotonophenone in 80 per cent yield, and the acylation of the ether with sorbic acid gave *p*-methoxysorbophenone in 60 per cent yield (98).

Aliphatic carboxylic acids are generally readily esterified by reaction with phenols in polyphosphoric acid at a relatively low temperature (25°C.). When the same reactions are carried out for 10–30 min. at 100°C., however, alkyl hydroxyaryl ketones are usually formed (250, 254). Many aromatic carboxylic acids behave differently in that they are esterified by phenols even at 100°C. (250). The assertion has been made that the classical aluminum chloride-catalyzed Fries rearrangements generally give results superior to those obtained by the use of polyphosphoric acid (127, 128).

Aromatic compounds, such as phenol and thiophene, known to be highly reactive in aromatic electrophilic substitution reactions, undergo acetylation at a temperature of 75°C., and the resulting ketones are stable in polyphosphoric acid at this temperature. However, less reactive compounds, such as benzene and toluene, do not undergo acetylation at temperatures sufficiently low to permit isolation of the respective acetophenones. When the temperatures are raised to the level required for the acetylation reactions to occur, the resulting ketones undergo self-condensation reactions. Of course, this difficulty does not arise when aromatic carboxylic acids are employed, and diaryl ketones may be prepared at relatively high temperatures subject to the usual restriction of a Friedel–Crafts reaction: namely, that the presence of a strongly electron-withdrawing substituent on the aromatic compound being acylated inhibits the reaction (318). Furthermore, the presence of an electron-withdrawing substituent in the aromatic acid, particularly in the ortho or para position, has an adverse effect on the acylating ability of the acid (20, 246, 318). This seems logical in that the actual acylating agent must be either the conjugate acid of the carboxylic acid or its oxocarbonium ion, and the formation of either cation would be inhibited by the presence of an electron-withdrawing substituent.

Some noteworthy differences have been observed between acylation reactions carried out in polyphosphoric acid and those brought about in other acidic media. Whereas the use of sulfuric acid to effect condensation of cinnamic acid with anisole led to the formation of a β,β-diarylpropionic acid, the use of polyphosphoric acid gave benzal-*p*-methoxyacetophenone (V). The reaction of cinnamoyl chloride with anisole, catalyzed by aluminum chloride, gave the former product (318). The action of polyphosphoric acid on a mixture of phenol and levulinic acid afforded phenyl levulinate in 35 per cent yield. However, when the reaction was catalyzed by sulfuric, hydrochloric, or syrupy phosphoric acid, the product was γ,γ-bis(*p*-hydroxyphenyl)valeric acid (VI) (27).

$$p\text{-}CH_3OC_6H_4COCH{=}CHC_6H_5$$

V

$$CH_3\overset{\displaystyle C_6H_4OH\text{-}p}{\underset{\displaystyle C_6H_4OH\text{-}p}{C}}CH_2CH_2COOH$$

VI

Benzyl esters of amino acids, useful intermediates for the synthesis of peptides, have been prepared in high yields in polyphosphoric acid solution (114). The procedure consisted in treatment of the mixture of amino acid and benzyl alcohol with polyphosphoric acid at 90–105°C. for 4 hr. The results of several such reactions are given in table 17.

Polyalkylbenzenes, such as mesitylene and durene, have been found (320, 322) to undergo reaction with carboxylic acids in the presence of polyphosphoric acid at 140–150°C. to form hydrocarbons. At lower temperatures the normal acyl derivatives may be prepared in low yields. For example, treatment of mesitylene with acetic acid in polyphosphoric acid under mild conditions afforded a low yield of acetomesitylene. When the latter compound was heated in polyphosphoric acid solution at 140°C., or when mesitylene and acetic acid were caused to react at that temperature, 1,1-dimesitylethylene was produced (320). Only a mixture of ω-chloroacetomesitylene and bis(ω-chloroaceto)mesitylene was formed, even at 140°C., when mesitylene and chloroacetic acid underwent reaction in polyphosphoric acid. Other aromatic compounds having a carbonyl group have been found to undergo reaction with benzene or benzene derivatives to form hydrocarbons (70, 192, 292). Some of these reactions proved to be quite complex. For example, in the polyphosphoric acid-catalyzed reaction of acetophenone with benzene, the major product was a yellow hydrocarbon, $C_{32}H_{24}$ (292). Small amounts of benzoic acid, dypnone, and 1,3,5-triphenylbenzene were also isolated from the reaction mixture (70, 192). Furthermore, it was found (70) that dypnone was an intermediate in the formation of the yellow compound. It was assumed but not proved that the yellow compound was 1,3,9-triphenyl-9-methylfluorene (192).

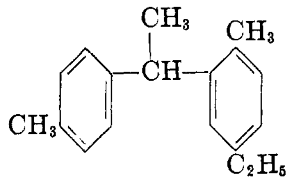
Carboxylic acids undergo polyphosphoric acid-catalyzed condensation with weakly basic amines to form *N*-substituted amides (317). For example, acetic acid reacts with 2,4-dinitroaniline at about 150°C. in polyphosphoric acid medium to give 2,4-dinitroacetanilide in 92 per cent yield. Many additional examples of such reactions are given in table 17.

The patent literature contains a tremendous amount of data on alkylation reactions. For the most part these reactions are not specifically catalyzed by polyphosphoric acid but rather by a variety of acid catalysts including polyphosphoric acid. Some patents (72, 218) do not specifically mention the use of polyphosphoric acid but instead refer to "acids of phosphorus." A molecular compound formed from boron trifluoride and various acids of phosphorus has also been reported to be a useful catalyst in alkylation reactions (342). It is not clear whether polyphosphoric acid is included in this group or not.

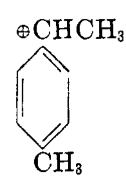
Alkylation of aromatic hydrocarbons or those aliphatic hydrocarbons having at least one tertiary carbon atom can be accomplished by the action of olefins in the presence of polyphosphoric acid (294). Hydrocarbons suitable for use in gasoline have been obtained by the treatment of isobutane or isopentane with ethylene or propylene in this manner.

Olefins have been used to alkylate phenols in polyphosphoric acid medium. For example, the reaction of *p*-cresol with isobutylene afforded 2,6-di-*tert*-butyl-4-methylphenol (328). By alkylation of phenol with isobutylene and diisobutylene, *tert*-butylphenols and octylphenols, respectively, have been prepared (17). Dealkylation of substituted phenols has also been observed to occur in the presence of polyphosphoric acid (329, 330).

Several procedures have been developed for the preparation of diarylalkanes (184, 185). One, which makes use of polyphosphoric acid as the catalyst, consists in the reaction of a suitable *p*-dialkylbenzene with either a cyclic (or branched) alkene or a *p-tert*-alkylphenol. For example, treatment of *p*-ethyltoluene with 4-methylcyclohexene in the presence of polyphosphoric acid gives 1-*p*-tolyl-1-(2-methyl-5-ethylphenyl)ethane (VII) plus methylcyclohexane. If a *p-tert*-alkylphenol is used in place of 4-methylcyclohexene in this reaction, the products include VII, phenol, and the alkane corresponding to the *tert*-alkyl substituent of the substituted phenol. Clearly, the *p-tert*-alkylphenol or 4-methylcyclohexene functions, in the presence of polyphosphoric acid, as the source of a carbonium ion which can enter into an electrophilic displacement reaction with *p*-ethyltoluene to produce the new carbonium ion VIII. This then attacks a second molecule of *p*-ethyltoluene in an electrophilic substitution reaction to produce VII.

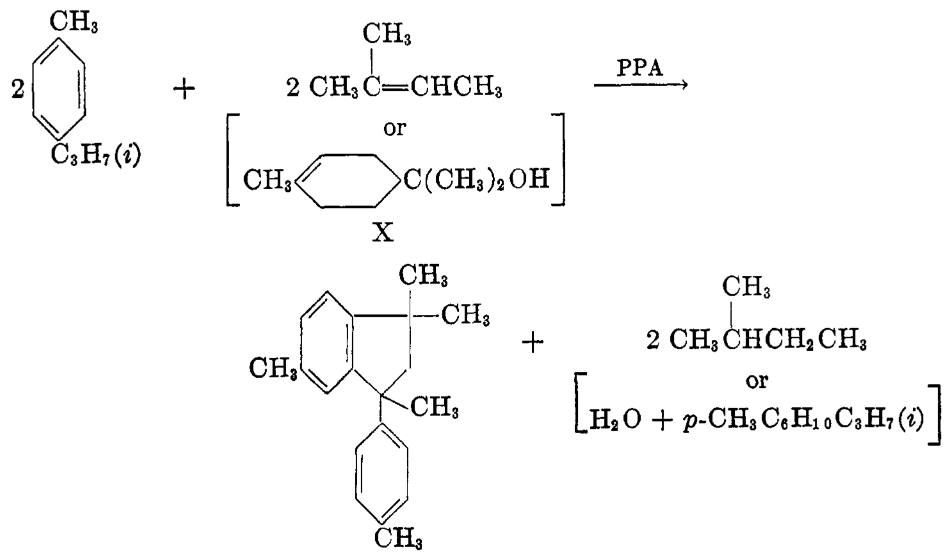


VII



VIII

An arylpolyalkylindane may be prepared by the acid-catalyzed reaction of a suitable *p*-dialkylbenzene with a branched olefin (183). Polyphosphoric acid is an acceptable but not unique catalyst for such a reaction. As an example of such a reaction, 1,3,3,6-tetramethyl-1-*p*-tolylindane (IX) may be prepared from *p*-cymene and 2-methyl-2-butene as shown below.

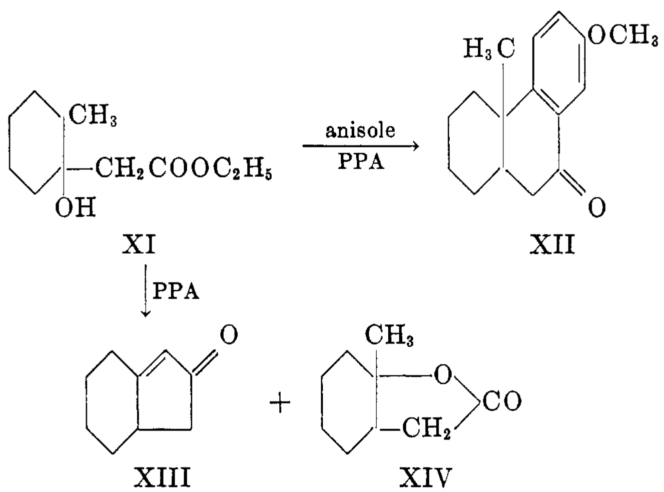


IX

It is possible to employ a suitable unsaturated alcohol in place of the branched alkene in the type of reaction cited above. For example, the reaction of cymene with the alcohol X gives IX plus water and 1-methyl-4-isopropylcyclohexane (186).

An aromatic hydrocarbon having a bicycloalkyl substituent may be prepared by treatment of an aromatic compound with a bicycloalkene in the presence of an acid catalyst (182). Polyphosphoric acid can serve as the catalyst for such a reaction. The preparation of 2-phenyl-2,6-dimethylbicyclo[3.2.1]-2-octene from benzene and 2,6-dimethylbicyclo[3.2.1]-2-octene may be cited as an example of this type of reaction.

What appears to be a succession of dehydration, intermolecular alkylation, and intramolecular acylation reactions occurred when anisole was caused to react with ethyl 2-methyl-1-hydroxycyclohexane-1-acetate (XI) in the presence of polyphosphoric acid (90). There was obtained in 43 per cent yield 1,2,3,4,9,10,11,12-octahydro-12-methyl-9-keto-7-methoxyphenanthrene (XII) together with an unidentified isomer. The action of polyphosphoric acid on XI alone gave the cyclenone XIII and the lactone XIV.



VI. Other Uses of Polyphosphoric Acid

A. NITRATION

It has been found (200) that nitration of diethyl alkylmalonates may be carried out in polyphosphoric acid solution. In general, high yields of diethyl alkylnitromalonates are obtained by this procedure, and the hazards of the older pro-

Compound	Yield	Compound	Yield
	per cent		*per cent*
Diethyl *n*-butylnitromalonate	75	Diethyl isobutylnitromalonate	78
Diethyl cyclohexylnitromalonate	15	Diethyl isopropylnitromalonate	60
Diethyl *n*-decylnitromalonate	97		

cedures are reduced by the use of a solution of 100 per cent nitric acid in polyphosphoric acid as the nitrating medium. The nitro derivatives which have been prepared by this procedure are listed in the table at the bottom of page 387.

B. BROMINATION

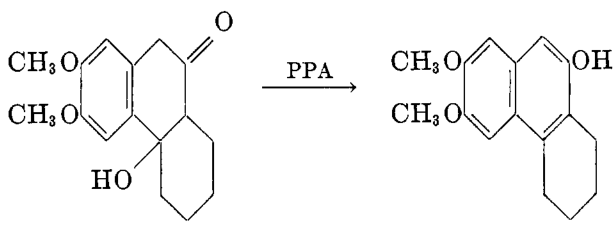
α-Bromocarboxylic acids are readily prepared by bromination of the acids in polyphosphoric acid solution. The acids are first dissolved in polyphosphoric acid at an elevated temperature; then bromine is slowly added at a temperature close to 100°C., and the reaction mixture is stirred until the evolution of hydrogen bromide ceases (311). The yields of α-bromo acids are, in general, as high as those obtained by the use of bromine and red phosphorus. The available results are tabulated below:

α-Bromo Acid	Yield	α-Bromo Acid	Yield
	per cent		*per cent*
Acetic	68	Isovaleric	61
n-Butyric	75	Propionic	76
Cyclohexanecarboxylic	77	Valeric	86
Isobutyric	87		

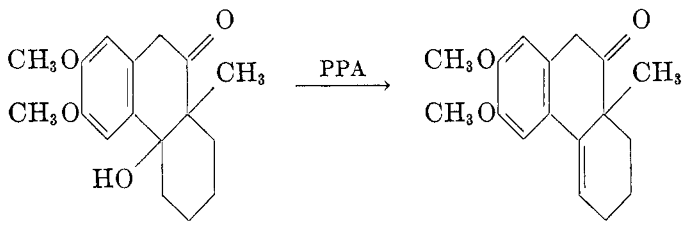
C. DEHYDRATION

In common with other mineral acids, polyphosphoric acid is a useful catalyst for the preparation of olefins by the dehydration of alcohols. In some cases, its use has been reported to give better results than the use of other acids. For example, the conversion of the alcohol I to the β-naphthol derivative II seemed to proceed most satisfactorily when polyphosphoric acid was the catalyst employed in the dehydration (354, 357). Owing to the presence of the angular methyl group, the alcohol III gave the unsaturated ketone IV rather than a β-naphthol derivative, when subjected to polyphosphoric acid-catalyzed dehydration (357). Ethyl 2-hydroxy-2-phenyl-4-ketocyclohexanecarboxylate (V) afforded 3-phenyl-4-carbethoxycyclohex-2-en-1-one (VI) in an analogous dehydration reaction (357).

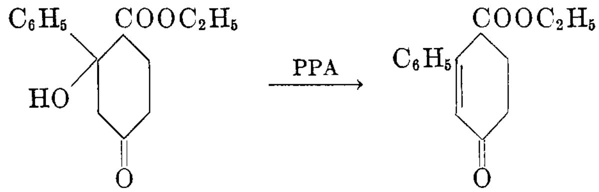
Both dehydration and intramolecular acylation occurred in the polyphosphoric acid-catalyzed conversion of ethyl α-methyl-β-hydroxy-β,β-bis(3,4-dimethoxyphenyl)propionate (VII) to 2-methyl-3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone (VIII) (352). Several other examples of complex reac-



I II

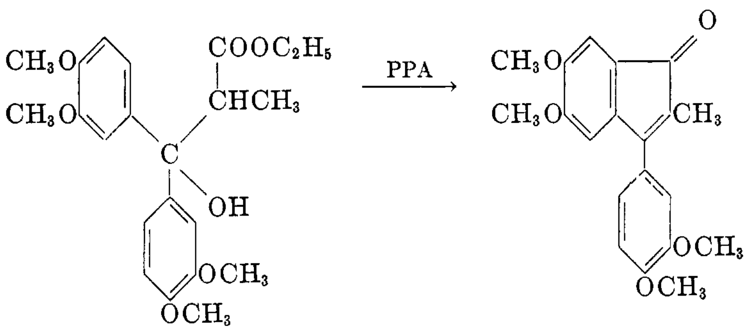


III IV



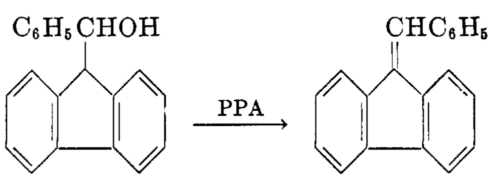
V VI

tions which include a dehydration step have been given in previous sections of this article.



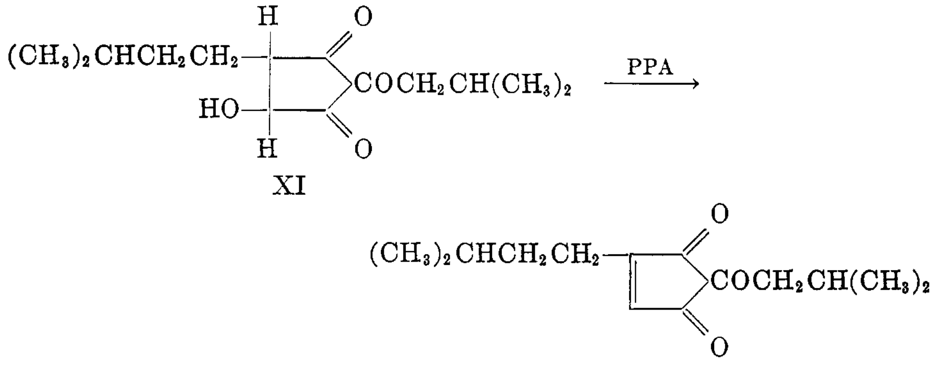
VII VIII

The action of polyphosphoric acid on 9-(α-hydroxybenzyl)fluorene (IX) produced 9-benzalfluorene (X) (11). Similarly, the polyphosphoric acid-catalyzed



IX X

dehydration of dihydrohumulinic acid (XI) gave the unsaturated compound XII (60).



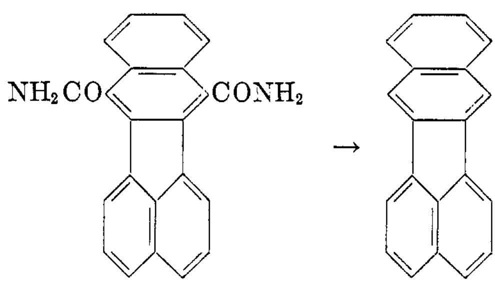
XI

XII

Potentially significant sequences of dehydration and polymerization reactions have been observed when relatively simple alcohols or mixtures of alcohols were treated with polyphosphoric acid under pressure and at an elevated temperature. For example, a liquid motor fuel of high quality was produced by the treatment of ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *n*-amyl, isoamyl, any one of several hexyl alcohols or suitable mixtures of these alcohols with polyphosphoric acid at 200–350°F. under a pressure of 250–350 pounds per square inch (189). Also, both 2-pentanol and methylisobutylcarbinol, when heated in the presence of polyphosphoric acid, gave mainly liquid polymers of low molecular weight (322). From 2-pentanol there was obtained in 17 per cent yield a mixture of 1-pentene and 2-pentene, together with a relatively large amount of polymeric material (362).

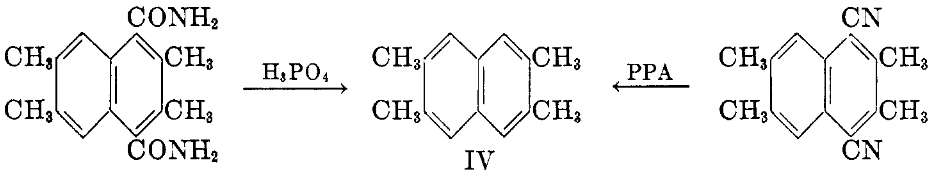
D. HYDROLYSIS

The use of orthophosphoric acid for the hydrolysis of nitriles to carboxylic acids has been known for many years (52). Furthermore, the complete removal of two carboxamide groups was observed (241, 266) when benz[*k*]fluoranthene-7,12-dicarboxamide (I) was treated with "100% phosphoric acid." Benz[*k*]-



I II

fluoranthene (II) was produced. An analogous conversion of 2,3,6,7-tetramethylnaphthalene-1,4-dicarboxamide (III) to 2,3,6,7-tetramethylnaphthalene (IV) was found to occur in the presence of orthophosphoric acid (239). Treatment of 2,3,6,7-tetramethylnaphthalene-1,4-dinitrile (V) with polyphosphoric acid also gave IV in good yield (239). That this method might prove to be a fairly general one for the removal of sterically hindered nitrile groups is indicated by the fact that cyanomesitylene is converted to mesitylene by treatment with polyphosphoric acid at 160°C. (317). However, 2,4,6-triisopropylbenzonitrile and 1-hydroxy-2-cyano-3-methylnaphthalene were found (317) to be inert towards polyphosphoric acid at this temperature.



III IV V

Despite the examples cited above, the utility of polyphosphoric acid as a catalyst for the Beckmann rearrangement suggests that most amides are quite stable in this medium. In fact, it has been mentioned several times in preceding sections of this paper that nitriles may be hydrolyzed to amides in polyphosphoric acid solution (317). Many examples of such reactions are given in table 18. It should also be noted that β-keto nitriles are readily converted to β-keto amides in the presence of either polyphosphoric acid or boron trifluoride (148). The polyphosphoric acid-catalyzed reactions of this type are also summarized in table 18.

TABLE 18

Hydrolysis reactions

Substance Hydrolyzed	Product	Temperature	Time	Yield	Reference
		°C.	*hours*	*per cent*	
α-Acetyl-α-tolunitrile	α-Acetyl-α-toluamide	100	0.5	58	(148)
		100	0.3	56	(152)
Benzonitrile	Benzamide	110	1	96	(317)
Benzoylacetonitrile	Benzoylacetamide	100	0.5	87	(148)
α-Benzoylpropionitrile	α-Benzoylpropionamide	100	0.5	71	(148)
α-Benzoyl-α-tolunitrile	α-Benzoyl-α-toluamide	100	0.5	69	(148)
α-Benzoyl-*n*-valeronitrile	α-Benzoyl-*n*-valeramide	100	0.5	82	(148)
6,7-Dimethoxyisoquinaldonitrile	6,7-Dimethoxyisoquinaldamide	100	1	95	(276)
2,4-Dimethylbenzoylacetonitrile	2,4-Dimethylbenzoylacetamide	80	2.5	78	(317)
Ethyl cyanoacetate	Ethyl malonamate	100	2	65	(317)
α-Hydroxyisobutyronitrile	α-Hydroxyisobutyramide	25	18	31	(317)
α-Hydroxyisobutyronitrile	2,2,5,5-Tetramethyl-4-oxazolidone	85	0.5	47	(317)
N-Isobutyrylbenzamide	Benzamide and isobutyric acid	100	0.5	60	(110)
α-Naphthonitrile	α-Naphthamide	110	2	95	(317)
Phenylacetonitrile	Phenylacetamide	115	1	96	(317)
α-Propionylpropionitrile	α-Propionylpropionamide	100	0.5	34	(148)
α-Propionyl-α-tolunitrile	α-Propionyl-α-toluamide	100	0.5	79	(148)
o-Tolunitrile	*o*-Toluamide	115	1.5	95	(317)
p-Tolunitrile	*p*-Toluamide	120	1	94	(317)

E. POLYMERIZATION

As might have been anticipated, most of the data on polyphosphoric acid-catalyzed polymerization reactions are to be found in the patent literature. Procedures have been developed for effecting the polymerization of hydroxypivalic acid (7), rosin and rosin esters (296), phenols and related compounds (221), *o*-(*p*-toluyl)benzoic acid (295), olefins (222), and alcohols (189) in the presence of polyphosphoric acid or some other acid. Coumarone-indene resins having low softening points may be upgraded by treatment with a source of formaldehyde and polyphosphoric acid (68). The molecular weights of olefins can be increased by subjecting them to the action of alkyl chlorides and a solid catalyst which might contain polyphosphoric acid as an ingredient (303). Polyphosphoric acid has been used in the preparation of several types of solid catalysts which are useful in accelerating olefin polymerization reactions (56, 57, 58, 230, 231, 232, 233). Molecular compounds derived from boron trifluoride and acids of phosphorus appear to be active polymerization catalysts (343, 344). It is not certain whether these contain polyphosphoric acid or not.

F. PHOSPHORYLATION

Polyphosphoric acid may be used for the phosphorylation of alcohols (80, 81, 197, 198). For example, methyl phosphate, benzyl phosphate, and cetyl phosphate have been prepared by reaction of the respective alcohols with polyphosphoric acid (80). Lactic acid, β-aminoethanol, and choline were also converted to phosphates in a similar manner (80). A large number of aminoalcohols have been converted to aminoalkylphosphoric acids by treatment with polyphosphoric acid at 110°C. for 2 or 3 hr. (78). The presence of a carboxyl group in the molecule inhibits the phosphorylation of carbinol groups, but the phosphorylation of hydroxy esters, amides, or nitriles is readily accomplished (79). The corresponding phosphorylated hydroxy acids may be obtained by selective hydrolysis of the compounds cited above. A convenient procedure for the preparation of glucose-6-phosphate by the action of polyphosphoric acid on glucose has been developed (306). As a matter of fact, phosphorylation also occurs at the other hydroxyl groups, but only the 6-phosphate survives acid-catalyzed hydrolysis.

Polyphosphoric acid of varying theoretical P_2O_5 content has also been used for the phosphorylation of proteins (119), isopropylidenepyridoxine (22), 2′,3′-isopropylidene-uridine (146), uridine (146), cytidine (146), and pyridoxamine dihydrochloride (268, 364).

G. ADDITIONAL APPLICATIONS

Certain condensation reactions of the aldol type are catalyzed by polyphosphoric acid. For example, dypnone may be prepared in good yield by treatment of acetophenone with polyphosphoric acid at an elevated temperature (23, 24). Mesitylene may be obtained from acetone in about 8 per cent yield, but the major products are compounds of higher molecular weight (322). The latter products appear to contain from nine to eighteen carbon atoms per molecule

(362). Ethyl benzalmalonate may be obtained in 70 per cent yield by the polyphosphoric acid-catalyzed condensation of benzaldehyde with ethyl malonate, but condensation reactions did not occur when acetophenone was treated with ethyl malonate, β-picoline with benzaldehyde, or paraldehyde with ethyl malonate (113).

The Ritter reaction, which consists of the addition of an olefin to a nitrile to form an *N*-alkylamide in the presence of concentrated sulfuric acid (289), has been found to take place in polyphosphoric acid (113). However, the yields were much lower than those obtained when sulfuric acid was employed. For example, the polyphosphoric acid-catalyzed reaction of acetonitrile with styrene gave *N*-(α-phenethyl)acetamide in only 37 per cent yield, and the analogous reaction between acetonitrile and isobutylene (from *tert*-butyl alcohol as the actual reagent) afforded *N*-*tert*-butylacetamide in but 16 per cent yield.

Alkyl azides may be prepared by the acid-catalyzed addition of hydrogen azide to alkenes. Polyphosphoric acid is a suitable catalyst for this reaction (302).

Azelaonitrile has been prepared by the reaction of azelaic acid with ammonia at 300°C. in the presence of a catalytic amount of polyphosphoric acid (112).

Polyphosphoric acid has been found to be of use in the catalytic reforming of petroleum stocks containing significant amounts of nitrogen compounds (244). It effects removal of ammonia formed during the cracking operation.

Attempts to prepare Schiff bases of ketones by the use of polyphosphoric acid as a dehydrating agent proved to be fruitless (113).

The polyphosphoric acid-catalyzed condensation of benzoic acid with *N*-methyl-*o*-nitroaniline gave 4-methylamino-3-nitrobenzophenone (2). Perhaps *N*-methylbenz-*o*-nitroanilide was formed initially and subsequently underwent rearrangement to the benzophenone derivative (317). The reaction of 2-naphthoic acid with *N*-methyl-*o*-nitroaniline gave 2-naphthyl 4-methylamino-3-nitrophenyl ketone (2).

Treatment of benzhydrazide with hot polyphosphoric acid gave 2,5-diphenyl-1,3,4-oxadiazole in 87 per cent yield (113).

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