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126. Yuichi Kanaoka, Yoshio Ban, Koichi Miyashita, Kimiko Irie, and Osamu Yonemitsu : Polyphosphate Ester as a Synthetic Agent. V.*1 The Fischer Indole Synthesis with Polyphosphate Ester.*2

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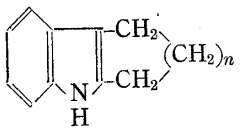
The Fischer synthesis is the most widely applicable method for the preparation of indoles.[1,2] A variety of catalysts, including many Brønsted and Lewis acids, have been employed to effect this indolization of arylhydrazones. It is generally said that acids and many compounds capable of complex formation with organic ligands may act as catalyst.[3] Even a simple thermal indolization without any catalyst was reported recently.[4]

The successful application of polyphosphate ester (PPE) as a reagent of Lewis acid type in several dehydrating condensation reactions[5] prompted us to try this reagent in the Fischer synthesis.

It was found that the use of PPE in chloroform solution gave 1,2,3,4-tetrahydrocarbazole (I) from cyclohexanone phenylhydrazone in a good yield under mild conditions. Simple mixing initiated an exothermic reaction and successive gentle refluxing for five minutes was enough to complete the rearrangement. The indole (I) could be isolated in fairly pure precipitate by adding ice-water to decompose excess of the reagent after evaporation of the solvent. Likewise, phenylhydrazones of cyclic ketones with five and seven-membered rings were converted to the corresponding cyclic derivatives of indol (II and III). The reaction of cyclopentanone and cycloheptanone required a little more prolonged heating than that of cyclohexanone; namely fifteen to twenty minutes. This comparison may be interesting with respect to the relation between the ring-size of cyclic compounds and their reactivity.



I : $n=2$
II : $n=1$
III : $n=3$

The reaction involving N-methylphenylhydrazone of cyclohexanone was carried out in order to see whether PPE could be used for the synthesis of N-substituted indole. As expected, N-methyltetrahydrocarbazole (IV) was obtained in a good yield. *o*-Methoxyphenylhydrazone of cyclohexanone also gave 8-methoxy-1,2,3,4-tetrahydrocarbazole (V) in a similar manner. There was no indication of the formation of 4*b*-methoxy-1,2,3,4-tetrahydro-4*bH*-carbazole, which was reported to form by the cyclization of *o*-methoxyphenylhydrazone of cyclohexanone by means of dilute sulfuric acid.[6]

It is well known that the phenylhydrazone of 2-substituted cyclohexanone may be cyclized to form both a neutral tetrahydrocarbazole (VI) and a basic indolenine (VII). Pausacker examined ratios of products of this reaction under a variety of experimental

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*1 Part IV: Y. Kanaoka, O. Yonemitsu, K. Tanizawa, K. Matsuzaki, Y. Ban: Chem. & Ind. (London), **1964**, 2102.

*2 Preliminary communication : *Ibid.*, **1965**, 473.

*3 Kita-12, Nishi-5, Sapporo (金岡祐一, 伴 義雄, 宮下幸一, 入江喜美子, 米光 宰).

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2) W. C. Sumpter, F. M. Miller : "Heterocyclic compounds with indole and carbazole systems (Ed., A. Weissberger)", 4, Interscience Publ., N. Y. (1954).
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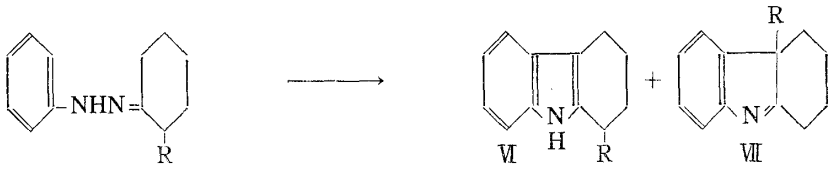
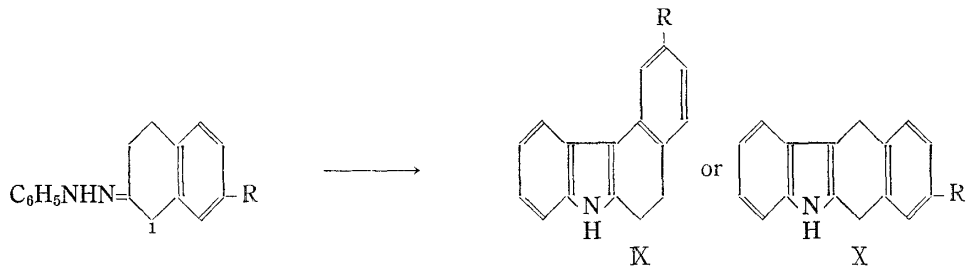
conditions, though any definite conclusion was not reached. The results depended upon both the nature of reagent and the medium.[7,8] In the thermal cyclization technique in diethyleneglycol, the high proportion of indole component was noted.[4]



Since the elucidation of the aspects of the concomitant formation of indole and indolenine appeared important with regard to our synthetic studies of polycyclic indolenine systems related to natural products such as aspidospermine[9] and others,[10] cyclization of 2-ethylcyclohexanone phenylhydrazone by means of PPE was examined. Yields of purified (Ⅵ; $R=C_2H_5$) and (Ⅶ; $R=C_2H_5$) were 21 and 48%, respectively, the ratio being 0.44, which is more then twice as much as the value with glacial acetic acid, 0.17.[7] Therefore, PPE is not a favorable agent when any single product is desired.

For further examples of cyclic ketone, phenylhydrazones of indanone and 7-methoxy-β-tetralone were indolized. 5,10-Dihydroindeno[1,2-*b*]indole (Ⅷ) was obtained from the former. Among two compounds (Ⅸ and Ⅹ; $R=OCH_3$), anticipated to be formed by indolization of the latter, the structure (Ⅸ; $R=OCH_3$) was assigned to the isolated product based on its ultraviolet spectrum, which indicated the presence of an extended conjugation system involving indole ring, with the longest maximum wave length at 314 mμ ($\log \varepsilon$ 4.13), thus ruling out an alternative structure of linear type (Ⅹ; $R=OCH_3$), which is not consistent with the above spectrum. This result is in good conformity with the fact that β-tetralone afforded (Ⅸ; R=H) by indolization,[11] as well as the known reactivity of the benzyl carbon at 1.



Acyclic ketone phenylhydrazones undergo indolization slightly less rapidly than that of cyclohexanone. The experimental data in the Table I show that acyclic α-methylene or methine group can participate in the reaction by boiling for twenty to thirty minutes in chloroform solution in the presence of PPE. Methyl ethyl ketone and methyl isopropyl ketone were thus converted to 2,3-dimethylindole (Ⅺ) and 2,3,3-trimethylindolenine (Ⅻ), respectively. There was no indication of the participation of the methyl group in the reaction. Acetophenone failed to form an indole derivative by this procedure. In the case of propiophenone, the reaction readily proceeded to form 2-phenyl-3-methylindole (ⅩⅢ). The results of indolization of ketone phenylhydrazones are summarized in the Table I.

7) K. H. Pausacker : J. Chem. Soc., **1950**, 621.
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Table I. Indolization of Ketones

Ketone[a]	Reaction time (min.)	Product	Yield (%)
Cyclohexanone	5	1,2,3,4-Tetrahydrocarbazole (I)	86
Cyclopentanone	20	1,2,3,8-Tetrahydrocyclopentindole (II)	49
Cycloheptanone	15	5,6,7,8,9,10-Hexahydrocyclohept[*b*]indole (III)	82
Cyclohexanone[b]	5	9-Methyl-1,2,3,4-tetrahydrocarbazole (IV)	84
Cyclohexanone[c]	3	8-Methoxy-1,2,3,4-tetrahydrocarbazole (V)	50
2-Ethylcyclohexanone	5	1-Ethyl-1,2,3,4-tetrahydrocarbazole (VI; R=C_2H_5)	21
		4*a*-Ethyl-1,2,3,4-tetrahydro-4*aH*-carbazole (VII; R=C_2H_5)	48
Indanone	5	5,10-Dihydroindeno[1,2-*b*]indole (VIII)	73
7-Methoxy-β-tetralone	3	2-Methoxy-5,6-dihydro-7*H*-benzo[*c*]carbazole (IX)	49
Methyl ethyl ketone	30	2,3-Dimethylindole (XI)	64
Methyl isopropyl ketone	20	2,3,3-Trimethylindolenine (XII)	50
Propiophenone	5	2-Phenyl-3-methylindole (XIII)	64

a) phenylhydrazone was used unless otherwise stated.
b) N-Methylphenylhydrazone.
c) *o*-Methoxyphenylhydrazone.

Although many examples were recorded in literatures,[12] it has been known that aldehydes generally give rather poor results in customary Fischer synthesis.[13] One of experimental difficulties encountered in the Fischer synthesis is local overheating caused by accumulation of heat generated in the course of this exothermic reaction. The good solubility of PPE permits the use of chloroform as a reaction medium, which offers particular advantage in regulating temperature in a reaction mixture. This technique was proved useful also for the adaptation of this method to the cyclization of aldehyde phenylhydrazones.

In this way, propionaldehyde and *n*-butyraldehyde were converted to skatol (XIV) and 3-ethylindole (XV), respectively, in moderate yields. As an illustration of aldehyde carrying an active α-methylene group at benzyl position, phenylacetaldehyde phenylhydrazone gave 3-phenylindole (XVI) under very mild conditions. 3,4-Dimethoxyphenylacetaldehyde was similarly converted to the corresponding indole (XVII), which had not been synthesized by the Fischer process. The cyclization of isobutyraldehyde phenylhydrazone (XVIII) was reported earlier by Brunner[14] by means of zinc chloride, to give 3,3-dimethylindolenine (XIX), the trimeric structure of which[15] was reconfirmed recently based on nuclear magnetic resonance data.[16] The treatment of XVIII with PPE gave the same product, XIX, but in a low yield. Our effort to obtain indole with PPE

Table II. Indolization of Aldehydes

Aldehyde	Reaction time (min.)	Product	Yield (%)
Propionaldehyde	5	Skatol (XIV)	22
n-Butyraldehyde	5	3-Ethylindole (XV)	53
Phenylacetaldehyde	5	3-Phenylindole (XVI)	42
3,4-Dimethoxyphenylacetaldehyde	3	3-(3,4-Dimethoxyphenyl)indole (XVII)	54
Isobutyraldehyde	5	3,3-Dimethylindolenine (XIX)	12

12) Ref. 1), p. 12.
13) H. M. Kissman, D. W. Farnsworth, B. Witkop: J. Am. Chem. Soc., **74**, 3948 (1952).
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16) H. Fritz, P. Pfaender: Chem. Ber., **98**, 989 (1965).

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from acetaldehyde phenylhydrazone, which has resisted all attempts of this kind for many years,[4,17] was unsuccessful. The results of indolization of aldehyde phenylhydrazones are listed in the Table II.

In conclusion, PPE serves as a fairly good agent in the Fischer indole synthesis involving phenylhydrazones of various ketones and aldehydes, except ones having methyl group attached to carbonyl. The method thus provides a convenient preparative route to 2-unsubstituted and 2,3-disubstituted indole and indolenine derivatives.

In an experiment at elevated temperature, an occasional formation of ethylindolenine derivative from cyclohexanone phenylhydrazone was observed. This finding led us to establish a novel ethylation process of indole to give ethylindolenine associated with the thermal decomposition of PPE.*2 The detail of this reaction will be the subject of another report.[18]

Experimental*4

General Procedure——To a solution of phenylhydrazone (1 part) in chloroform (5~10 parts) was added PPE[19] (5 parts) by pipetting. Usually a rise of temperature and dark coloring were observed. The mixture was refluxed gently on a water-bath for 5 min. or as specified in the Table, and the solvent was removed *in vacuo*. Ice-water was added to the residue and the mixture was stirred to decompose excess of the reagent (0.5~1 hr.). In some cases where product is oily, 3 to 4 hr. were required to effect complete decomposition of phosphorylated substance. Alkali may be used if necessary. Indole derivative separated as solid precipitate or oil, which was collected by suction or extracted with a solvent as usual, then submitted to an appropriate process of purification. Indolenine derivative was obtained by basifying an aq. layer and woked up as usual.

1,2,3,4-Tetrahydrocarbazole (I)——Cyclohexanone phenylhydrazone (m.p. 74~75°; 3.0 g.) was converted to I, which formed colorless fine prisms of m.p. 116~118° from hexane, and was shown to be identical with the authentic specimen[20] by mixing melting point and IR comparison. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.53), 284 (3.87), 292 (3.81).

1,2,3,8-Tetrahydrocyclopentindole (II)——Cyclopentanone phenylhydrazone was obtained as colorless fine needles from EtOH, m.p. 49~50° (lit[21]., m.p. 50°), which was air-sensitive and decomposed on storage. From this freshly prepared phenylhydrazone (669 mg.), II was obtained as pale orange-yellow oil of $b.p_{2.5}$ 110~116°, which was recrystallized from petroleum ether to form colorless plates of m.p. 107~108° (lit.,[21] m.p. 108°). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.47), 281 (3.84).

5,6,7,8,9,10-Hexahydrocyclohept[*b*]indole (III)——Cycloheptanone phenylhydrazone (m.p. 70~71°; 1.61g.) was converted to III, which formed colorless needles of m.p. 144~145° from EtOH or benzene-hexane (lit.,[22] m.p. 144°). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.57), 285 (3.86), 292 (3.83).

9-Methyl-1,2,3,4-tetrahydrocarbazole(IV)——Cyclohexanone N-methylphenylhydrazone ($b.p_{12}$ 155° (lit.,[23] $b.p_{1.7}$ 126~127°); 4.41 g.) was treated with PPE as in the general procedure. After adding water, the whole was made strongly alkaline with NaOH and stirred for 3 hr., extracted with benzene and worked up as usual. IV was obtained as colorless blades of m.p. 51° from MeOH (lit.,[24] m.p. 50°). UV λ_{max}^{EtOH} mμ (log ε): 231 (4.55), 287 (3.84), 294 (3.82).

8-Methoxy-1,2,3,4-tetrahydrocarbazole (V)——*o*-Methoxyphenylhydrazine was prepared from *o*-anisidine.[25] Cyclohexanone *o*-methoxyphenylhydrazone (m.p. 68~69° (lit.[26], m.p. 67~68°); 4.0 g.) was warmed for 3 min. with PPE (20 g.) in $CHCl_3$ (20 ml.). After removal of the solvent *in vacuo*, ice-water was added and the whole was made alkaline with NaOH and stirred for 4 hr. The mixture was then extracted with ether, the extract was washed with aq. NaCl and dried (Na_2SO_4). On removal of the solvent there was obtained oily product, which was distilled in N_2 stream to give V as yellow oil (1.83 g.) of $b.p_3$ 153° (lit.,[26] $b.p_{15}$ 205~210°). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.61), 274 (3.88), 280 (shoulder) (3.84), 290 (3.65). There was not obtained any product insoluble in ether[26]. The aq. layer showed no significant UV absorption.

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*4 Melting points are uncorrected.

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18) Y. Kanaoka, K. Miyashita: In preparation.
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25) G. Charrier, L. Casale: Gaz. chim. ital., **44**, I 617 (1914).
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1-Ethyl-1,2,3,4-tetrahydrocarbazole(VI; R=C_2H_5) and 4*a*-Ethyl-1,2,3,4-tetrahydro-4*a*H-carbazole(VII; R=C_2H_5)——2-Ethylcyclohexanone was prepared by the ethylation of cyclohexanone with diethyl sulfate (b.p_{13} 60~64°, (lit.,[27] b.p_{15} 65~66°); semicarbazone, m.p. 162~163° (lit.,[27] m.p. 163~164°)). The benzene solution of the ketone and phenylhydrazine (eq. mol. each) was refluxed for 30 min. and evaporated *in vacuo*. This crude phenylhydrazone (3.35 g.) was dissolved in $CHCl_3$ (16 ml.), PPE (16 g.) was added (exothermic), and the mixture was refluxed for 5 min. After removal of the solvent *in vacuo*, ice-water was added and the mixture was stirred for 30 min., then extracted with benzene. The organic layer was washed with 2.5% HCl (20 ml., twice), water and dried (Na_2SO_4). (A). The acid washings were combined with the above water layer, and the whole was made alkaline by adding excess of Na_2CO_3 under ice-cooling and extracted with benzene. This extract was washed with water and dried (Na_2SO_4). (B). On removal of the solvent of the extract (A) *in vacuo*, (VI; R=C_2H_5) was obtained as oily residue, which was distilled to give pale yellow oil of b.$p_{1.5}$ 130~135°; 633 mg. (lit.,[28] b.p_{16} 200~205°). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.48), 285 (3.86), 292 (3.83). The extract (B) was evaporated *in vacuo* to leave oily residue, which was distilled to give (VII; R=C_2H_5) as colorless oil of b.$p_{1.5}$ 106~108°; 1.49 g. (lit.,[28] b.p_{16} 160~161°). Picrate, yellow needles from EtOH of m.p. 146~147° (lit.,[28] m.p. 147°).

5,10-Dihydroindeno[1,2-*b*]indole (VIII)——Indanone phenylhydrazone (m.p. 132~133°, 1.5 g.; lit.,[29] m.p. 131°) was converted to VIII, which formed colorless needles of m.p. 227~228° from MeOH (lit.,[30] m.p. 228°). UV λ_{max}^{EtOH} mμ (logε): 247 (4.35), 326 (4.38), 340 (4.20).

2-Methoxy-5,6-dihydro-7*H*-benzo[*C*]carbazole (IX)——Equimolecular solution of 7-methoxytetralone-2*[5] (b.p_2 142~144°; lit.,[31] b.$p_{0.4}$ 123~125°) in benzene was warmed for 5 min. and the solvent was removed *in vacuo* to leave oily phenylhydrazone. The crude phenylhydrazone (5.26 g.) was treated with PPE (25 g.) as in the general procedure. After adding water, the whole was made alkaline with NaOH and stirred for 4 hr. under ice-cooling, then extracted with benzene. The extract was washed with aq. NaCl, dried (Na_2SO_4), and evaporated *in vacuo* to leave oily residue, which gave only single spot in thin-layer chromatography of silica gel with several solvent systems (benzene, EtOAc, or $CHCl_3$, or mixtures (1:1) of two of them). The oily substance was purified through an alumina column, and eluates with mixtures of hexane and benzene of various ratios were combined, and evaporated *in vacuo* to give a residue, from which IX was obtained as colorless needles of m.p. 121° from ether-petroleum ether; 2.39 g. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.53), 284 (4.18), 314 (4.13). *Anal.* Calcd. for $C_{17}H_{15}ON$ (IX): C, 81.92; H, 6.02; N, 5.62. Found: C, 81.96; H, 6.30; N, 5.67.

2,3-Dimethylindole (X)——Crude phenylhydrazone (2.80 g.) was treated with PPE. Precipitate was collected, dried and eluted through alumina column with hexane to remove phosphate-containing fraction and recrystallized from hexane to give X as colorless feathers of m.p. 105~106° (lit.,[32] m.p. 106°). UV λ_{max}^{EtOH} mμ (log ε): 228 (4.46), 285 (3.76), 292 (3.69).

2,3,3-Trimethylindolenine (XI)——Methyl isopropyl ketone phenylhydrazone (b.p_9 139° (lit.,[33] b.p_{41} 175~176°); 2.02 g.) was treated with PPE. The aq. layer was washed with benzene, and the combined organic layer was extracted with 2.5% HCl. The washing and the aq. layer were combined, cooled, basified with $NaHCO_3$ and extracted with ether and the extract was washed with water and dried (Na_2SO_4). The residual oil, obtained on removal of the solvent, was distilled to give XI as yellow oil of b.p_{12} 111°; 0.9 g. (lit.,[33] b.p. 227~229°). UV λ_{max}^{EtOH} mμ (log ε): 258 (3.80). Picrate, yellow needles from EtOH, 156~158° (lit.,[33] m.p. 158°). Methiodide, slightly colored blades from EtOH, m.p. 253~255° (lit.,[33] m.p. 253°).

2-Phenyl-3-methylindole (XIII)——Propiophenone phenylhydrazone (2.31 g.; crude) was treated with PPE. After evaporation of the solvent *in vacuo*, cold water (10 ml.) was added to the reaction mixture followed by the dropwise addition of MeOH (ca. 20 ml.) to precipitate colorless solid, which was collected, washed with water, dried and recrystallized from hexane to form colorless feathers of m.p. 91~93.5° (lit.,[34] m.p. 92~94°). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.37), 310 (4.29).

Skatol (XIV)——Propionaldehyde phenylhydrazone (5.61 g.; crude) was treated with PPE. The oily product was purified by distillation; 1.67 g. or 38%, b.p_4 107~110°. Recrystallization from hexane gave XIV as colorless blades of m.p. 94~95°; 0.95 g. or 22% (lit.,[32] m.p. 95°). UV λ_{max}^{EtOH} mμ (log ε): 224 (4.52), 283 (3.76), 292 (3.69).

3-Ethylindole (XV)——*n*-Butyraldehyde phenylhydrazone (b.p_{12} 144~146°; 3.0 g.) was treated as in the case of XIV. XV was obtained as colorless oil of b.$p_{13\sim14}$ 145~155° (lit.,[35] b.p_{14} 150°). UV λ_{max}^{EtOH} mμ (logε): 224 (4.52), 284 (3.85), 292 (3.79). Picrate, yellow needles from benzene, m.p. 118~121° (lit.,[36] m.p. 121°).

*5 We are indebted to Mr. K. Hirao for the preparation of this ketone.

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3-Phenylindole (XVI)——Phenylacetaldehyde phenylhydrazone (m.p. 59～60.5°; 1.3 g.) (lit.,[37] m.p. 58°) was treated with PPE as in the case of XIV The distillate (b.$p_{1.5}$ 165～170°) was recrystallized from hexane to give colorless feather of m.p. 86～87° (lit.,[37] m.p. 88～89°). UV λ_{max}^{EtOH} mμ (log ε): 224 (4.51), 271 (4.21).

3-(3,4-Dimethoxyphenyl)indole (XVII)——3,4-Dimethoxyphenylacetaldehyde was prepared from sodium 3,4-dimethoxyphenylglycidate[38]; b.p_2 125°, semicarbazone, m.p. 158～160°. This aldehyde (10 mmol.) and phenylhydrazine (10 mmol.) were mixed and warmed on a water-bath for few min. to give nearly quantitative amount of the phenylhydrazone of m.p. 97～98° (decomp.) from benzene-hexane. To the solution of the phenylhydrazone (1.15 g.) in $CHCl_3$ (9 ml.) was added PPE (5.5 g.) while shaking. An exothermic reaction took place. After refluxing for 3 min., the solvent was removed *in vacuo*, and cold water (8 ml.) was added under ice-cooling followed by EtOH (12 ml.) to precipitate crude XVII, which was collected, washed, dried and recrystallized from MeOH to form colorless pillars of m.p. 144.5～145.5° (lit.,[39] m.p. 148°). UV λ_{max}^{EtOH} mμ (log ε): 268 (4.29).

3,3-Dimethylindolenine(XIX)——To a solution of isobutyraldehyde phenylhydrazone (b.p_{15} 140～141°; 5,539 mg.) in $CHCl_3$ (20 ml.) was added PPE (25 g.) and the mixture was refluxed for 5 min. After cooling, water (30 ml.) was added and the whole was stirred for 1 hr. under cooling. The organic layer was separated and extracted with 2.5% HCl (20 ml.) and the combined aq. layer was basified with excess of $NaHCO_3$ under cooling, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave oil, which was solidified by treatment with EtOH; 722 mg. Recrystallization from benzene-EtOH gave colorless fine needles of m.p. 214～215°; 589 mg. or 12% (lit.,[15] m.p. 215～216°; lit.,[16] m.p. 214～215°). Picrate, yellow needles of m.p. 134～135° (lit.,[15] m.p. 135°).

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Summary

Polyphosphate ester (PPE) was demonstrated to be a good agent in the Fischer indole synthesis involving various ketones and aldehydes except ones having methyl group attached to carbonyl, thus providing a convenient preparative route to 2-unsubstituted and 2,3-disubstituted indole and indolenine derivatives.

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[Chem. Pharm. Bull. 14(9) 939～947 (1966)]

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127. Hidetoshi Yoshimura, Hiroshi Tsuji, and Hisao Tsukamoto: Metabolism of Drugs. LI.*1 The Metabolic Fate of Alkylaryl Ethers in Rabbits.*2

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It has been generally accepted that the alkylaryl ethers are cleaved oxidatively into phenols and aldehydes through their hemiacetal intermediates by the enzyme systems which are localized in liver microsomes and require both reduced nicotinamide-adenine dinucleotide phosphate ($NADPH_2$) and oxygen.[1]

*1 Part L: This Bulletin, **12**, 1151 (1964).
*2 A part of this work was shortly communicated in ref. 3).
*3 Katakasu, Fukuoka (吉村英敏, 辻　宏, 塚元久雄).
1) R. T. Williams: "Detoxication Mechanisms," 2 nd ed., p. 324. Chapman & Hall, London (1959).

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