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# POLYPHOSPHATE ESTER AS A SYNTHETIC AGENT—XI[1]

## A NOVEL SYNTHESIS OF ETHYLINDOLENINES BY ETHYLATION OF 2,3-DISUBSTITUTED INDOLES WITH POLYPHOSPHATE ESTER[2]

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**Abstract**—Tetrahydrocarbazole **3** and 2,3-dimethylindole **10** were ethylated at the β-position by heating with polyphosphate ester (PPE) at 160° to form in about 60% yields ethylindolenines **2** and **11**, respectively. This procedure may provide a simple and convenient method to prepare ethylindolenines from 2,3-disubstituted indoles.

IN THE course of exploring experimental conditions of the Fischer indole synthesis by means of polyphosphate ester (PPE)[3] with cyclohexanone phenylhydrazone **1** as a substrate, an unexpected ethylation of indole nucleus at elevated reaction temperature was observed, which led to the isolation of an indolenine carrying an ethyl group at β-position of indole **2**. The present paper is concerned with this novel synthesis of some ethylindolenines from 2,3-disubstituted indoles with PPE as a special ethylating agent.

When **1** was heated in the presence of excess of PPE at about 160° (bath-temp) for 30 min, an oily basic fraction was isolated from the reaction mixture in a fairly good yield, instead of the non-basic tetrahydrocarbazole **3**, a normal product of the Fischer synthesis of **1**. From this fraction a base was purified as a picrate ($C_{14}H_{17}N.C_6H_3N_3O_7$) and a hydrochloride ($C_{14}H_{17}N.HCl$), whose compositions both indicated incorporation of a $C_2$ fragment into the substrate. The UV spectrum of the perchlorate of **2** in ethanol had an indolenine-like chromophore ($\lambda_{max}$ 279 mμ; log ε 3·79), while the IR spectrum had a strong absorption at 1643 $cm^{-1}$ to be assigned for a conjugated $C{=}N^+$ linkage. The NMR spectrum of the free base had peaks apparently due to the presence of a Me part (0·33 δ, triplet, *J* 7·7 c/s, 3 protons) of an Et group, although the peaks of the methylene were intermixed with other multiplet signals. This compound was eventually proved to be 3-ethyl-2,3-tetramethyleneindolenine **2** by direct comparison of the picrate with the authentic specimen prepared from ethylcyclohexanone-2 by a conventional indolization method as shown in Chart 1.

As reported in our earlier paper,[3] PPE could effect the Fischer indole synthesis under mild conditions. Therefore, it was postulated from the above finding that the indolenine **2** was produced as a result of ethylation of tetrahydrocarbazole **3**, initially formed from **1** in the presence of PPE. In order to confirm this inference, **3** was heated with 10 parts of PPE at 160° (bath temp) for 30 min. Indeed, **2** was obtained in a similar manner. These results indicate that **3** was ethylated at the β-carbon of indole nucleus, and suggest the possibility that PPE is a specific ethylating agent of certain indoles to give corresponding ethylindolenines.

Since the basic fraction obtained from the reaction mixture of **3** with PPE gave

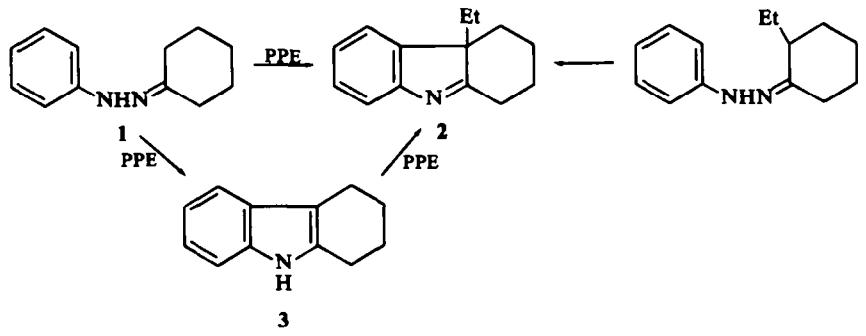



CHART 1

several spots in TLC even after distillation, further study of product analysis was undertaken. Silicagel column chromatography of the distilled basic product yielded two major fractions. From the first fraction eluted with a mixture of methylene chloride and ethyl acetate (10:1, v/v), **2** was obtained by purification through picrate in 57% yield. The second fraction eluted with ethyl acetate gave another base in 7% yield, which formed a crystalline perchlorate. The salt was shown to be identical with 1,3-diethyl-2,3-tetramethyleneindoleninium perchlorate **4**, prepared from **2** by ethylation with ethyl iodide followed by anion exchange.

A neutral fraction from the reaction mixture was also subjected to chromatography to yield an indole **5** in 1% yield together with a trace of the starting material **3**. The IR spectrum of this compound was superimposable with that of N-ethyltetrahydrocarbazole **5**, synthesized from **3** by ethylation with ethyl bromide and sodium in liquid ammonia. The relationship is summarized in Chart 2.

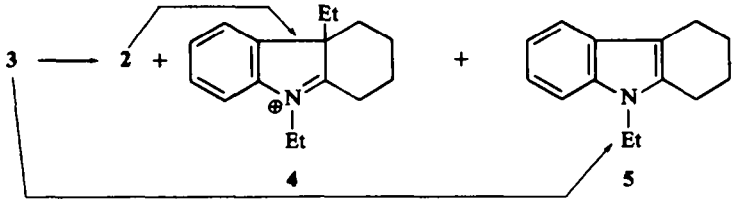
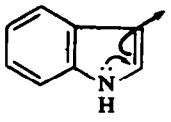



CHART 2

Indole can be regarded as enamines[4] and electrophilic substitution reaction in the series can be generally interpreted as proceeding via **6**. The distribution of the products described above implies that β-position **6** is of primary importance as a nucleophilic site at which the ethylation takes place, in agreement with the behavior as enamines.[4]

There are two alternative routes for the occurrence of **4**; namely, **4** could be formed either by N-ethylation of **2**, or C-ethylation of **5**, or both as outlined in Chart 3.

To account for this special ethylation process, a cyclic mechanism such as **7** might be considered. N-Methyltetrahydrocarbazole **8** was reacted to test whether the mechanism of this kind operates or not. On treatment of **8** with PPE, C-alkylated product **9** was similarly obtained in 62% yield. It is therefore likely that a cyclic mechanism, if any, does not play an important role in the reaction. This formation of



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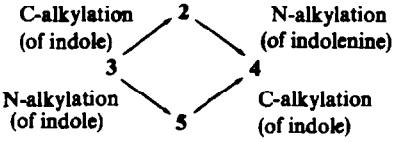
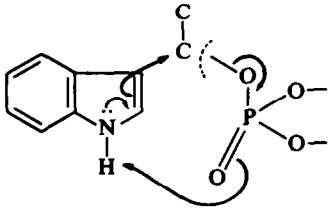
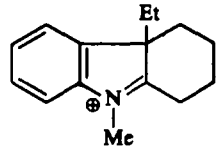



CHART 3

9 from 8 suggests also that the C-alkylation of N-alkylated indole, such a process as 5 → 4 in Chart 3, proceeds in rather comparable rate with that of the C-alkylation of N-unsubstituted indole (3 → 2).

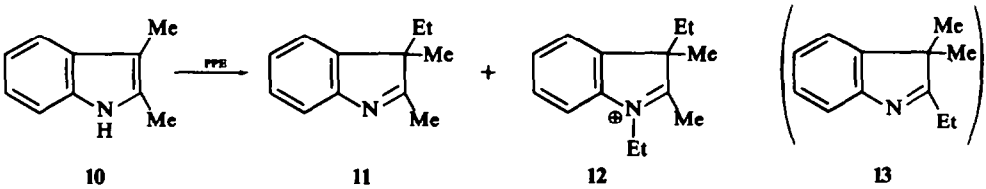


7



9

In order to see general applicability of this method, 2,3-dimethylindole **10** was subjected to the reaction. As in the case of **3**, 2,3-dimethyl-3-ethylindolenine **11** was obtained in 63% yield accompanied by 17% of the N-Et derivative **12**. The IR and UV spectrum of **11** and its perchlorate had definite indolenine characters. The NMR spectrum of **11** had signals of an Et group and two Me groups with different environment in agreement with the assigned structure **11**, which consequently rules out an isomeric rearranged structure **13** for this compound. These results demonstrate that this method provides a novel convenient synthetic route to ethylindolenines from 2,3-disubstituted indoles.




10 11 12 13

CHART 4

The alkylation process of indoles previously known in literatures consists in reaction of alkyl halides either with indoles[5–8] or Grignard derivatives of indoles.[5, 9] The direct action of alkyl halides on indole yields a mixture of polyalkylated derivatives, whereas in the alkylation of indole sodium salts the reaction sites were dependent on alkyl groups and reaction conditions.[8] The alkylation of indolylmagnesium halides attacks largely the β-position. This PPE method will be useful in synthesizing ethylindolenines because the procedure is very simple and, in spite of the ambident character of indole nucleus, major products are so far invariably expected indolenines though accompanied by some N-alkylated and other minor products.

Ethyl phosphate **14** and tetraethyl pyrophosphate (TEP; **15**) were selected as

reference compounds in comparing the alkylating capability of a variety of phosphoric acid esters. None of these phosphates gave basic product when reacted with **3** unlike the case of PPE. Even heated at 200° for 2 hr with **14**, **3** was recovered almost quantitatively. Eventually, 48% of **4** was isolated after heating **3** in the presence of **15** at 200° for 2 hr.

It has been observed that heating causes thermal decomposition of PPE.[2] When temperature rises above 110–120°, gradual decomposition of PPE occurs, which takes place vigorously at 150–160° (bath temp) accompanied by evolution of gas. The gas was shown to be ethylene by conversion to 1,2-dibromoethane and comparison of its IR spectrum with that of an authentic specimen. In an experiment, more than 44% of the Et group in PPE was converted to ethylene by heating at 160° for 30 min.

Since this pyrolysis of PPE is apparently owing to the β-elimination of the ester Et group in PPE, the latter should have the properties of a good leaving group in the elimination process. In contrast, both **14** and **15** are stable to heat indicating that neither of them is a good leaving group in the elimination reaction involving ester groups. In view of the fact that the ethylation by means of PPE is effected at around 160°, and that under these conditions the decomposition takes place vigorously, the alkylation (substitution) and the elimination must be closely associated. This relation is further supported by the observation that a simple phosphate **14** or a pyrophosphate **15** other than PPE is neither thermally unstable nor a good leaving group.

In summary, the yield of the indolenine or the alkylated product will depend upon how effectively the desired substitution reaction at β-carbon of indole competes with the elimination reaction that generally accompanies it. Chart 5 gives this figure, where the substitution(s) by the β-carbon of indole as a nucleophile at the $C_1$ carbon of the ester Et group to produce indolenine competes with the elimination(e) by the Et group to liberate ethylene possibly assisted by some participation of a cyclic mechanism(c).[10] As a whole, then, PPE[P] plays a role as a good leaving group (L) in ether direction (s or e).

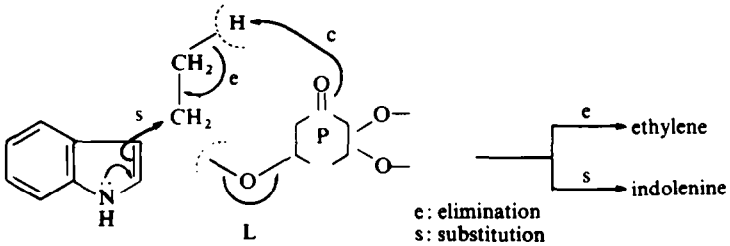



CHART 5

It is of interest that PPE, whose efficacy as a reagent of Lewis acid-type in both condensation[1,11a] and rearrangement reactions[11b] has been amply shown, now has a further application as an alkylating agent. Studies on the scope and limitation of this method are in progress. Elucidation of some minor products in the reaction mixture of **3** or **10** remains for future study.

## EXPERIMENTAL

All m.ps were uncorrected. UV spectra were taken on a Hitachi EPS-3T spectrophotometer. IR spectra

were taken on a JASCO DS-301 spectrophotometer. NMR spectra were determined using a NMR Hitachi H-60 spectrophotometer. Chemical shifts are in ppm ($\delta$) from TMS as internal standard.

*General procedure of the ethylation of indoles.* A mixture of an indole (1 part) and PPE[12] (5 parts) was heated at 160° (bath temp) for 15 min with occasional stirring followed by addition of a 2nd portion of PPE (5 parts) and heating for an additional 15 min. After cooling, crushed ice was added and the reaction mixture was stirred for 30 min to decompose excess of the reagent. The whole was extracted with benzene, the extract washed with NaCl aq, dil $Na_2CO_3$ aq, and dried with $Na_2SO_4$. Removal of a solvent *in vacuo* gave the neutral fraction. The aqueous layer was made alkaline with excess $Na_2CO_3$ under cooling, and extracted with benzene. The aqueous layer was saturated with NaCl and dried with $K_2CO_3$. Removal of the solvent *in vacuo* gave the basic fraction. The reaction conditions of the above procedure were obtained by comparison of following preliminary experimental results: yields of the distilled basic product from 2·0 g of **3**: 0·63 g (100°, 60 min); 1·40 g (130°, 60 min); 1·60 g (160°, 30 min).

*N-Ethyltetrahydrocarbazole* **5**; *3-ethyl-2,3-tetramethyleneindolenine* **2** *and 1,3-diethyl-2,3-tetramethyleneindoleninium salt* **4** *from 1,2,3,4-tetrahydrocarbazole* **3**. Compound **3** (4·00 g) was reacted following the general procedure. TLC (silicagel, benzene: hexane 1:5 v/v) of a neutral fraction (486 mg) showed a main spot, the $R_f$ value of which was identical with that of **5**, prepared from **3** by a conventional N-ethylation.[13] The neutral fraction was dissolved in MeOH containing KOH and stirred at room temp overnight to hydrolyse any possible phosphorylated product, and the soln was evaporated *in vacuo*. The residue was extracted with benzene, washed with water, dried with $Na_2SO_4$ and evaporated *in vacuo* to leave an oil (124 mg), which was applied to a silicagel column (5 g) and eluted with hexane to give **5** as a colorless oil, 56 mg or 1%. The IR of this sample was identical with that of an authentic specimen.[13]

Crude basic fraction (4·7 g) was distilled to give a basic mixture (b.p.$_8$ 146–149°; 3·66 g). The mixture (1·04 g) was applied to a silicagel column (40 g) and eluted with ca 1L of $CH_2Cl_2$: EtOAc (10:1 v/v) and the eluate (870 mg), obtained on evaporation of the solvent, was converted to a picrate which was recrystallized from EtOH as yellow prisms, m.p. 147–148° (lit.,[14] m.p. 147°). Compound **2** (756 mg; 57% based on **3**) was recovered as almost colorless oil, from the MeOH soln of the picrate by treatment with DOWEX 1-X8, NMR ($CCl_4$): 0·33 $\delta$ (3H, triplet, $J$ = 7·7 c/s) (3-$CH_2\underline{CH}_3$). The perchlorate was obtained as colorless needles, m.p. 177–178° from EtOH; UV (EtOH): $\lambda_{max}$ 233 mμ (log $\varepsilon$ 3·87), 239 (3·85), 279 (3·79). (EtOH, containing trace of NaOH): $\lambda_{max}$ 259 mμ (log $\varepsilon$ 3·80); IR (Nujol): 1643 cm$^{-1}$ (C=N$^+$). (Found: C, 56·35; H, 6·25; N, 4·49. Calc. for $C_{14}H_{17}N.HClO_4$: C, 56·11; H, 6·01; N, 4·67%).

Secondly, the above column was eluted with EtOAc (ca 120 ml) followed by evaporation of the solvent *in vacuo* to give **4** as reddish oil (107 mg or 7%), which formed a perchlorate as colorless needles, m.p. 171–173° from EtOH. Perchlorate, UV (EtOH): $\lambda_{max}$ 233 mμ (log $\varepsilon$ 3·80), 240 (3·80), 279 (3·85); (EtOH, containing trace of NaOH): $\lambda_{max}$ 275 mμ (log $\varepsilon$ 3·89), 281 (4·02); IR (Nujol): 1621 cm$^{-1}$ (C=N$^+$). (Found: C, 58·84; H, 6·87; N, 4·22. Calc. for $C_{16}H_{21}N.HClO_4$: C, 58·62; H, 6·71; N, 4·27%). A mixed m.p. with the specimen (m.p. 171–173°), prepared from **2** by reacting EtI and subsequent conversion to perchlorate, showed no depression.

*1-Methyl-3-ethyl-2,3-tetramethyleneindoleninium salt* **9**. Compound **8** (1·00 g) was reacted following the general procedure. The water layer, after separation of neutral fraction, was concentrated *in vacuo* below 30°, and to the residue was added 70% $HClO_4$ (700 mg). On storage in a refrigerator crystals deposited which were recrystallized from EtOH as colorless needles, m.p. 143–145°, 1·05 g or 62%. Perchlorate, UV (EtOH): $\lambda_{max}$ 232 mμ (log $\varepsilon$ 3·80), 239 (3·78), 276 (3·85); (EtOH, containing trace of NaOH): $\lambda_{max}$ 259 mμ (log $\varepsilon$ 3·92). 277 (4·02); IR (Nujol): 1634 cm$^{-1}$ (C=N$^+$). (Found: C, 57·29; H, 6·56; N, 4·36: Calc. for $C_{15}H_{19}N.HClO_4$: C, 57·41; H, 6·37; N, 4·46%). A mixed m.p. with the specimen (m.p. 143–145°), prepared from **2** by reacting MeI and subsequent conversion to perchlorate, showed no depression.

*3-Ethyl-2,3-dimethylindolenine* **11** *and 1,3-diethyl-2,3-dimethylindoleninium salt* **12** *from 2,3-dimethylindole* **10**. Compound **10** (2·00 g) was reacted as in the case of **3**. A crude neutral fraction (107 mg) was not examined further though its TLC suggested that N-ethyl-2,3-dimethylindole could be a major component. A distilled basic fraction (b.p.$_5$ 94–95°) was obtained in a yield of 2·30 g. A portion (1,233 mg) was applied to a silicagel column (40 g) and eluted with $CH_2Cl_2$. The initial fraction, collected from 140 ml of eluate, contained a small amount of unknown components which remained for further study. The second fraction collected from the next 520 ml eluate was evaporated *in vacuo* to leave **11** as an oil (812 mg or 63%); UV (EtOH): $\lambda_{max}$ 257 mμ (log $\varepsilon$ 3·93). (EtOH, containing trace of HCl): $\lambda_{max}$ 231 mμ (log $\varepsilon$ 4·00), 237 (3·98), 280 (3·90). IR (liq): 1610 cm$^{-1}$ (C=N); NMR ($CCl_4$): 7·75 $\delta$ (4 aromatic H); 2·17 (3H, singlet) (2-Me); 1·81 (2H, quartet, $J$ = 7·8 c/s), 0·38 (3H, triplet, $J$ = 7·8 c/s) (3-$CH_2CH_3$). Perchlorate, colorless needles of m.p. 107–109 from EtOH; IR (Nujol): 1638 cm$^{-1}$ (C=N$^+$). (Found: C, 51·93; H, 5·74; N, 5·04. Calc. for

$C_{12}H_{15}N.HClO_4$: C, 51·98; H, 5·77; N, 5·06%). Picrate, yellow long needles, m.p. 149–151° from EtOH (lit.,[15] m.p. 152–153°). (Found: C, 53·63; H, 4·68; N, 14·24. Calc. for $C_{12}H_{15}N.C_6H_3N_3O_7$: C, 53·73; H, 4·47; N, 13·93%). The above column was subsequently eluted with AcOEt to give the third fraction which left on evaporation *in vacuo* a reddish oil (253 mg or 17%). Treatment of the oil with an equimolar amount of 35% $HClO_4$ gave the perchlorate **12**, which formed colorless needles, m.p. 170–171·5° from EtOH; UV (EtOH): $\lambda_{max}$ 239 mμ (log ε 3·74), 280 (3·97); (EtOH, containing trace of NaOH): $\lambda_{max}$ 280 mμ (log ε 4·41); IR (Nujol): 1626 $cm^{-1}$ (C=$N^+$). (Found: C, 55·71; H, 6·67; N, 4·64. Calc. for $C_{14}H_{19}N.HClO_4$: C, 55·53; H, 6·94; N, 4·88%). A mixed m.p. with the specimen (m.p. 170–172°), prepared from **11** by ethylation with EtI and subsequent conversion to perchlorate, showed no depression.

*Thermal decomposition of PPE.* PPE (10·0 g) was heated at 160° (bath temp) for 15 min (a), and 30 min (b), respectively. The gas which evolved during the course of heating was trapped in a soln of $Br_2$ (23·0 g) in water (20 ml). Evolution of gas was vigorous for about 15 min and almost subsided after 25 min. After the reaction the mixture was treated with 10% $Na_2S_2O_3$ aq and extracted with ether. The extract was washed with sat NaCl aq, 10% $Na_2CO_3$ aq and sat NaCl aq, dried with $Na_2SO_4$, and evaporated. The oily residue was distilled to give 1,2-dibromoethane as a colorless oil, b.p. 128–129°, yield, calculated assuming the composition of PPE to be $EtO_3P$[12]: (a) 5·5 g (33%); (b) 7·4 g (44%). The IR of these samples were superimposable with that of an authentic specimen.

*Alkylation with TEP and methyl or ethyl phosphate.* Compound **3** (500 mg) was heated with methyl or ethyl phosphate (10 parts). Even after heating at 200° for 2 hr, **3** was recovered almost quantitatively. TEP[16] could not effect the ethylation of **3** under the conditions for PPE. When **3** was reacted with TEP (5 g) at 200° for 2 hr, 48% of **4** was obtained as perchlorate (m.p. 171–173° from EtOH).

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