Phosphoramides; VI. Phenyl *N,N,N',N'*-Tetraethylphosphorodiamidate as a Reagent in Syntheses of 2-Diethylaminoquinolines

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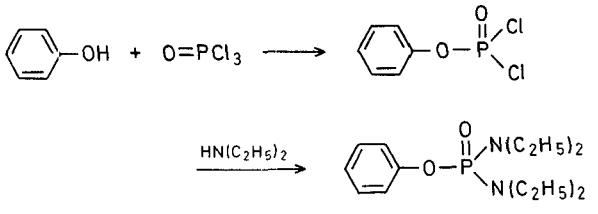
Two 3-step synthesis routes are known for substituted 2-diethylaminoquinolines, starting from either *ortho*-aminocinnamic acids[1,2] or the corresponding quinolines[3]. In both cases the starting materials are not always easily available and a more direct route to the above quinolines would be desirable.

In an earlier investigation[4] it was demonstrated that 2-dimethylaminoquinolines could be obtained in excellent yields by heating acetanilides to reflux temperature in hexamethylphosphoric triamide/dimethylformamide (5:1). It could thus be foreseen that an appropriate phosphoramide should produce the corresponding 2-diethylaminoquinolines under similar conditions. In our hands this preparation succeeded best with phenyl *N,N,N',N'*-tetraethylphosphorodiamidate (**1**). Although hexamethylphosphoric triamide has been extensively investigated as a reagent in organic synthesis[5] the phosphoramide **1** does not seem to have been used as such until now. Compound **1** is easily prepared from phenol by reaction with phosphoryl chloride followed by treatment with diethylamine[6].



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It was found that heating of **1**, an acetanilides **2**, and *N,N*-diethylformamide **3** at 250° leads to the formation of the corresponding 2-diethylaminoquinoline **4** in 17–47% yield.

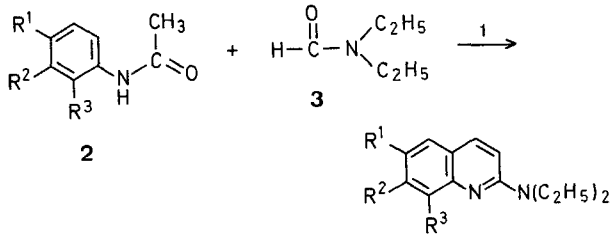
Table. Preparation of 2-Diethylaminoquinolines **4**

R^1	R^2	R^3	Yield [%]	m.p. (solvent) or b.p./torr	n_{25}^D	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS, 60 MHz) δ [ppm]	U.V. (C_2H_5OH) λ [nm] (log ε)	M.S. $m/e(M^+)$[b]
H	H	H	36	118°/0.2 (154–155°/4)[8]	1.6239	$C_{13}H_{16}N_2$[c] (200.3)	1.21 (t, 6H, J=7.2 Hz); 3.63 (q, 4H, J=7.2 Hz); 6.77 (d, 1H, J=9.2 Hz); 6.9–8.3 (m, 5H)	211 (4.65); 252 (4.65); 355 (3.87)	200
CH_3	H	H	33	116–120°/0.35	1.6136	$C_{14}H_{18}N_2$ (214.3)	1.20 (t, 6H, J=7.1 Hz); 2.40 (s, 3H); 3.58 (q, 4H, J=7.1 Hz); 6.70 (d, 1H, J=8.8 Hz); 7.1–7.4 (m, 2H); 7.53 (d, 1H, J=8.7 Hz); 7.65 (d, 1H, J=8.8 Hz)	211 (4.56); 250 (4.56); 358 (3.81)	214
Cl	H	H	38	122–126°/0.3	1.6281	$C_{15}H_{15}ClN_2$ (234.5)	1.18 (t, 6H, J=7.1 Hz); 3.57 (q, 4H, J=7.1 Hz); 6.72 (d, 1H, J=8.8 Hz); 7.1–7.8 (m, 4H)	213 (4.53); 250 (4.56); 363 (3.83)	234
H_3CO	H	H	17	43–46° (PE)	—	$C_{14}H_{18}N_2O$ (230.3)	1.20 (t, 6H, J=7.3 Hz); 3.6 (q, 4H, J=7.3 Hz); 3.82 (s, 3H); 6.6–7.9 (m, 5H)	214 (4.48); 245 (4.51); 370 (3.77)	230
CH_3	CH_3	H	32	128–132°/0.3	1.6169	$C_{15}H_{20}N_2$ (228.3)	1.20 (t, 6H, J=7.1 Hz); 2.30 (s, 3H); 2.34 (s, 3H); 3.60 (q, 4H, J=7.1 Hz); 6.70 (d, 1H, J=9.2 Hz); 7.27 (s, 1H); 7.47 (s, 1H); 7.65 (d, 1H, J=9.2 Hz)	213 (4.61); 252 (4.65); 355 (3.86)	228
H	H	CH_3	47	116–120°/0.3	1.6085	$C_{14}H_{18}N_2$ (214.3)	1.22 (t, 6H, J=7.1 Hz); 2.65 (s, 3H); 3.62 (q, 4H, J=7.1 Hz); 6.74 (d, 1H, J=9.2 Hz); 6.9–7.5 (m, 3H); 7.72 (d, 1H, J=9.2 Hz)	211 (4.62); 254 (4.60); 355 (3.80)	214

[a] All compounds gave satisfactory microanalyses (C ±0.4%, H ±0.2%, N ±0.2%).

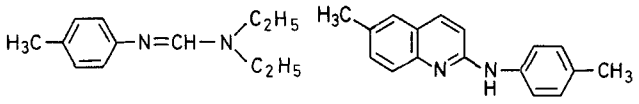
[b] For Cl^{35} species.

[c] m.p. of picrate: 182–184°; Lit.[8] 184–185°.



2 **3** **4**

In the synthesis of the quinoline **4** (R^1=CH_3, R^2, R^3=H) the by-products **5** and **6** were also isolated.



5 **6**

The formamidine **5** was always present as an impurity, when the reation mixture was worked up by distillation. Chromatography was therefore the preferred method for isolating this as well as all other quinolines **4**. Compound **5** was probably formed from *N*-(4-methylphenyl)-formamide, which could be produced by reacylation of *N*-(4-methylphenyl)-acetamide with the *N*,*N*-diethylformamide present in the reaction mixture. The suggested formamide synthesis is very similar to the known synthesis *N*,*N*-dimethylformamidines from formanilides and hexamethylphosphoric triamide[7].

In the reaction of the unsymmetrically acetanilide **2** (R^1, R^2=CH_3; R^3=H), where two different *ortho* positions are conceivable to the phosphoramide-induced ring closure reaction, the quinoline **4** (R^1, R^2=CH_3; R^3=H) was formed. The isomeric 5,6-dimethyl-2-diethylaminoquinoline was probably formed in trace amounts as an impurity, indicated by two small doublets at δ=6.77 and 8.00 ppm which were present in the ^{1}H-N.M.R. spectrum of the above quinoline.

Preparation of 2-Diethylaminoquinolines (4); General Procedure: A mixture of the acetanilide **2** (0.05 mol), *N*,*N*-diethylformamide (**3**; 10.2 g, 0.1 mol), and phenyl *N*,*N*,*N*′,*N*′-tetraethylphosphorodiamidate (**1**; 28.4 g, 0.1 mol) is heated in a distillation flask on a silicone oil bath at 250° for 20 h. During the reaction diethylamine distills off. The hot reaction mixture is poured directly into ice (~200 g) in a separating funnel, and ether (200 ml) is added. The mixture was extracted with 4 normal hydrochloric acid (4×50 ml). The aqueous phase is clarified by filtration through kieselguhr, and is then made alkaline with normal sodium hydroxide. The aqueous phase is extracted with chloroform. The organic extract is dried and evaporated and the residue is subjected to silica gel column chromatography. Elution with ether/petroleum ether (1:9) gives the title compounds.

Isolation of *N*,*N*-Diethyl-*N*′-*p*-tolylformamidine 5 and 6-Methyl-2-*p*-tolylaminoquinoline 6:

N-(4-Methylphenyl)-acetamide (7.5 g) is reacted as described under the general procedure and the products are worked up in a similar way. Instead of column chromatography, distillation gave a fraction of b.p. 80–95/0.05 torr. Preparative T.L.C. of this fraction gives N,N-*diethyl*-N′-*tolylformamidine* **5**; yield: 0.8 g (9%).

^{1}H-N.M.R. ($CDCl_3$): δ=1.17 (t, 6H, J=7.1 Hz); 2.30 (s, 3H); 3.34 (q, 4H, J=7.1 Hz); 6.6–7.3 (m, 4H); 7.51 ppm (s, 1H).

M.S. m/e=190.1440 (M^+); calc. for $C_{12}H_{18}N_2$: 190.1470.

A second fraction of b.p. 103–105/0.05 torr contains mainly *2-diethylamino-6-methylquinoline*; yield: 2.4 g. A third fraction of b.p. 140–180/0.1 torr, which is recrystallized from petroleum ether (100–140°) to give *6-methyl-2-p-toylaminoquinoline* **6**; yield: 0.2; m.p. 115–117°.

^{1}H-N.M.R. ($CDCl_3$): δ=2.30 (s, 3H); 2.43 (s, 3H); 6.6–7.9 ppm (m, 10H).

I.R. (KBr): ν_{max}=3240 cm^{-1}.

M.S.: m/e=248.1252 (M^+); calc. for $C_{17}H_{16}N_2$: 248.1313.

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