Studies on Organophosphorus Compounds. IX.*
Hexamethylphosphorhic Triamide (HMPA) as Reagent
in a New Quinoline Synthesis
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Acetanilides, refluxed in DMF and HMPA, produce 2-dimethylamino-quinolines in 40—76%. For other anilides the yields decreased when the size of the acyl-group increased. A mechanism is suggested in which the anilide first produces the corresponding N,N-dimethyl-amidine, which by further reaction with DMF gives the quinoline. The kinetics of the formation of the amidines showed that the reactions were autocatalyzed by $(\text{Me}_3\text{N})_2\text{P(O)}\text{OH}$. Also it was found that acetanilide, when refluxed in HMPA and acetic acid derivatives such as phenylacetate and N,N-dimethyl-acetamide, gave the corresponding 2-dimethylamino-4-methyl-quinoline. Furthermore 23—54% yield of 2-dimethylamino-4-methyl-quinolines were formed when anilines were refluxed in acetic acid and HMPA.

In an earlier investigation it was demonstrated that gentle reflux of secondary carboxamides (RCONHR'), where R or/and R' is aromatic in hexamethylphosphorhic triamide (HMPA) produced the corresponding N,N-dimethyl-amidines in fair yields. However, if R or R' were able to form sufficiently stable carbonium ions fragmentation reactions were found. It was also found that gentle reflux of aliphatic secondary carboxamides produced pyridines, eqn. 1, and it was suggested that the pyridine was formed by the reaction of two different carboxamide molecules. This was confirmed by the observation that a mixture of acetanilide and N-isopropylpivaloamide heated in HMPA formed 2-t-butyl-6-methylpyridine. In a similar experiment it was attempted to prepare 5,6,7,8-tetrahydroquinoline from acetanilide and N-cyclohexyl-formamide by heating in HMPA. Quite unexpectedly the formamide reacted in a different way with acetanilide and instead 2-dimethylamino-quinoline was obtained in 51% yield. As this new quinoline synthesis was very promising—easy available starting materials, simple reaction conditions, fair yield etc. — a thorough investigation was made on this reaction and this paper describes the results of that.

RESULTS AND DISCUSSION

In the reaction of acetanilide and N-cyclohexylformamide with HMPA at reflux temperature cyclohexylamine is split off and 2-dimethylamino-quinoline is produced. It was therefore expected that dimethylformamide (DMF) should undergo a similar reaction and that was indeed found, (Table 1).

Furthermore DMF is a very convenient reagent as side reactions, shown in eqn. 1, are excluded in this quinoline synthesis. The substituents R on the aromatic ring of the acetanilide give no systematic variations of the yields of the quinolines, which are in the order of

\[ \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \rightarrow \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \]

\[ \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \rightarrow \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \]

\[ \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \rightarrow \text{R}_2 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R}^3 + \text{R}^1 \text{CH}_2 \text{N}^+ \text{CH}_2 \text{R} \]

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methylaminoquinoline was obtained in 60% yield. The amidine II is then assumed to be in a tautomeric equilibrium with the highly reactive enamine IV, which undergoes a reaction with DMF to form V. The intermediate V then tautomerizes to its enol-form VI, which subsequently undergoes a ring closure reaction followed by elimination of water to form the quinoline VII. It might be possible that the hydroxyl group of the enol VI is replaced by a dimethylamino group as ketones are known to produce the corresponding N,N-dimethyl-enamines by heating in HMPA. If this is the case, a ring closure reaction followed by elimination of dimethylamine also can give the quinoline VII. Octamethylpyrophosphoramide, OMPA, was isolated in the reaction of p-methyl- and p-methoxy-acetanilide with DMF and HMPA. Its presence in the reaction mixture is best explained by the reaction of primarily formed phosphoric acid derivative III with HMPA, (Scheme 1).

Furthermore, support of the suggested mechanism was also provided by the generation of dimethylamine, which easily could be followed during the reaction by the colour change of silica gel (light blue→dark blue) placed in a drying tube on top of the reflux-condenser. In the synthesis of 6- and 8-methoxy-2-dimethylamino-quinolines the yields were slightly reduced because of further reaction of the methoxy-group with HMPA, (eqn. 2).

### Table 1.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Quinoline (%)</th>
<th>Amidine (%)</th>
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<tbody>
<tr>
<td>o-CH₃</td>
<td>H</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>p-CH₃</td>
<td>H</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>o-CH₃</td>
<td>H</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>p-CH₃</td>
<td>H</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>b-benzo</td>
<td>H</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>72</td>
<td>&lt;1</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>H</td>
<td>Et</td>
<td>26</td>
<td>~10</td>
</tr>
<tr>
<td>H</td>
<td>i-Pr</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

40–76%. However, the substituents R' had a marked influence on the yields, which decreased from 72% to 0%, when hydrogen was replaced by the isopropyl group, (Table 1).

Concerning the mechanism (Scheme 1) it is suggested that the first step is the formation of the corresponding N,N-dimethyl-amidine II, which is a known reaction when acetanilide is heated in HMPA. In fact, when N,N-dimethyl-N'-phenyl-acetanilide is refluxed (as the corresponding anilide) in DMF and HMPA, 2-di-
In the reaction of isovaleranilide no quinoline VII was isolated, but instead II \((R' = \text{i-Pr})\), VIII and \(N,N\)-dimethylvaleramide were found besides some starting material. As III is likely to be present in the reaction mixture (Scheme 2) the suggested equilibrium is quite appropriate. This equilibrium is shifted from VIII towards II as the amidine II is used up in the quinoline syntheses. This was further substantiated in the reaction of acetonilide with HMPA and DMF where only 1% of VIII was isolated and the yield of the quinoline VII was as high as 72% whereas the yields of VIII and VII in the reaction of valeramide were 22% and 0%, respectively, (Table 1). Equilibria as suggested in Scheme 2 can also produce a very complex reaction mixture in other cases. Thus the quinolines, IX–XII are found in the reaction of acetonilide with \(N,N\)-dimethyl-propionamide and HMPA, (Scheme 3). If the above equilibria were of minor importance, only the quinoline X should be formed by analogy to the formation of the quinoline VII (Scheme 1). It is quite obvious that, if \(p\)-methyl-acetonilide is refluxed in \(N,N\)-dimethyl-acetamide and HMPA, transacylation reactions cannot interfere with the quinoline synthesis and a high yield is obtained of the corresponding quinoline, (Table 2). Also phenyl acetate can be used in the reaction with acetonilide and HMPA and

**Scheme 2.**

the corresponding 2-dimethylamino-4-methylquinoline was obtained. In this reaction phenol should be produced in a similar way as dimethylamine did in the reaction of DMF with IV, (Scheme 1). In fact phenol was produced, but it reacted with HMPA as it has been shown recently, and \( C_6H_5OPO(NMe_2)_2 \) and \( (C_6H_5O)PO(NMe_2) \) were found in the reaction mixture. Furthermore in the synthesis of \( N \)-aryl-\( N',N' \)-dimethylacetamidines from acetalanilides in some cases the corresponding 2-dimethylamino-4-methyl-quinolines were obtained as by-products (Table 2). These by-products are produced by the reaction of the formed amidine with the starting material and clearly demonstrate that 2-dimethylamino-quinolines may be formed whenever an acetic acid derivative is heated together with an acetalanilide in HMPA.

2-Dimethylamino-4-methyl-quinolines are formed when anilines are refluxed in acetic acid and HMPA (Table 3). The mechanism of this reaction is easily understood as it is known that acetic acid by heating in HMPA produces \( N,N \)-dimethyl-acetamide.\(^a\) The so formed aceta-

\[ R-\overline{\text{O}}-\text{NH}-\text{CH_3} \text{CH_3CN} \xrightarrow{\text{HMPA}} \]

\[ \begin{array}{c}
\text{CH}_3 \\
\text{NMe_2}
\end{array} \]

\[ R-\overline{\text{O}}-\text{N=\text{C-CH_3}} \text{NMe_2} \]

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Quinoline Amidine (%)</th>
<th>(%)</th>
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<tbody>
<tr>
<td>CH₃</td>
<td>NMe₂</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OC₆H₅</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>p-CH₃C₆H₅NH</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>CH₃O</td>
<td>p-CH₃OC₆H₅NH</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>Cl</td>
<td>p-ClC₆H₅NH</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

KINETICS

The reaction given in eqn. 3, which is observed when no DMF is added, is also the first step in the quinoline synthesis, Scheme 1.

\[ p-R-C_6H_5NHCOC_6H_5 \xrightarrow{\text{HMPA}} \]

\[ \begin{array}{c}
\text{I} \\
\text{II} \quad \text{III}
\end{array} \]

\[ p-R-C_6H_5N=CCH_3+\text{HOP}(\text{NMe}_2)_2 \]

\[ t=0\text{ min} \]

\[ t=166\text{ min} \]

\[ t=274\text{ min} \]

*Fig. 1. Reaction of p-acetotoluidide with HMPA followed by NMR of aromatic hydrogen atoms.*

should be noted that the number of aromatic hydrogens is constant during the reaction. An example is given in Fig. 1 for the reaction of p-acetotoluidide with HMPA at 210 °C. At this temperature only traces of dimethylamine could be detected. This indicates that almost no OMPA is formed by the reaction of III with HMPA at this temperature as dimethylamine is produced in this reaction, (Scheme 1).

The most simple approach to the kinetics of the reaction given in eqn. 3 is to assume that the reaction is pseudo first order with regard to the amide I if excess of HMPA is used. However, if log $a_0/(a_0-x)$, where $a_0$ is starting concentration of I and x the consumption of I, is plotted against the time, (Fig. 2), this reaction order is easily ruled out as no linear correlation is found. Instead if it is assumed that the reaction is autocatalysed the rate equations will be as follows:

$$\frac{d(a_0-x)}{dt} = -k(a_0-x)(x+c_0)$$

or

$$\frac{1}{a_0+c_0} \ln \frac{x+c_0}{a_0-x} = kt + K$$

where $a_0$ is initial concentration of I, $x$ consumption of I as well as concentration of the catalyst produced during the reaction, $c_0$ is initial concentration of the catalyst, $k$ rate constant, $t$ time, and $K$ constant. For p-acetotoluidide heated in HMPA, $c_0=0$, at 210 °C there is then found an excellent linear correlation when log $x/(a_0-x)$ is plotted against $t$, (Fig. 3).

At the start of the reaction where no catalyst is present this correlation is obviously not found. An induction period of 50–60 min was needed to produce the amount of catalyst, about 0.1 equivalent, necessary for the good linear correlation.

The rate constants for the reaction of para substituted acetanilides with HMPA at 210 °C were calculated by the least squares method (para-substituent, rate constant mol$^{-1}$ kg min$^{-1}$ given): CI, $2.28 \times 10^{-2}$; H, $2.31 \times 10^{-3}$; CH$\_3$, $2.22 \times 10^{-3}$; OCH$\_3$, $2.11 \times 10^{-4}$. These rate constants can be correlated with $\sigma^+$ values but the found Hammett $\rho$-value is so close to zero as 0.05 that no reasonable conclusion about the mechanism can be drawn.

In order to find out if III was the catalyst in the reaction it was prepared in situ.

from (Me₂N)₂P(O)Cl and powdered NaOH (1:1) in HMPA and then combined with p-acetotoluolide and heated. In fact if the reaction was followed by NMR and c₀ was assumed to be equal to the initial concentration of (Me₂N)₂P(O)Cl and NaOH in eqn. 5, a linear correlation was obtained between \( \log (x + c₀)/(a₀ - x) \) and \( t \), (Fig. 4). Furthermore the rate constant, \( 2.19 \times 10^{-2} \) mol⁻¹ kg min⁻¹ calculated by the least squares method was very close to the one obtained when no catalyst was added. Interestingly when the catalyst was added no induction period was needed, instead 10% of p-acetotoluolide was converted to the corresponding amidine even before the reaction temperature of 210 °C was reached. As the kinetics shows that the phosphoric acid derivative III is formed and also acts as a catalyst in the reaction of secondary carboxamides with HMPA, two mechanisms can easily be set up for the formation of the amidines; Schemes 4 and 5. In the first HMPA and the carboxamide are in equilibrium with the additions complex XIII, which in the rate determining step reacts with III to give XIV and III is then recovered. Compound XIV then produces the amidine II by an elimination reaction. In the other mechanism the carboxamide by reaction with III forms the additions complex XV, which by reaction with HMPA also produces XIV and III. The last step is then the same as above. The phosphoric acid derivative III is probably partly deprotonated by the amidine formed during the reaction or by HMPA. The nucleophilicity of the dimethylamino-groups of III is then increased compared to those of HMPA. As the first step in both mechanisms depends on the nucleophilicity of a dimethylamino-group in HMPA and III, respectively, the latter mechanism seems to be the most probable one.

CONCLUSION

2-Dimethylamino-quinoline has earlier been prepared from a variety of quinoline derivatives³⁻¹³ and thus from not easily available starting materials. Also many step-ring-closure reactions have been used for the synthesis of, e.g. 2-dimethylamino-4-methyl-quinolines.¹³ In this paper a method is presented giving the same types of quinolines as mentioned above³⁻¹³ but with easily available, simple and cheap starting materials and with a one-pot reaction. We thus strongly feel, that the dimethylaminoquinoline synthesis presented here seems to be the method of choice and, to the best of our knowledge and judgement, superior to all known procedures.

EXPERIMENTAL

In all experiments commercial HMPA dried over molecular sieves (3A) was used. NMR spectra were recorded on a Varian A-60 spectrometer (\( s = \) singlet, \( d = \) doublet, \( t = \) triplet, \( q = \) quartet and \( m = \) multiplet). The microanalyses were performed by Løvens Kemiske Fabrik, Copenhagen.

2-Dimethylamino-quinoline. Acetanilide (13.5 g), 10 ml DMF and 50 HMPA were heated on a silicon-oil bath (250 °C) for 16 h. The reflux temperature increased during this time from 205 °C to 240 °C. The reaction mixture was

allowed to cool to 100 °C and was then poured into 400 ml 2 M NaOH and extracted with 3 x 200 ml diethyl ether. The organic phase was washed with 2 x 100 ml H₂O, dried over K₂CO₃ and the ether was stripped off. Distillation 95 – 110 °C/0.01 mmHg followed by recrystallization from light petroleum (60 – 80 °C) gave 11.5 g (67 %) of the title compound, m.p. 70 – 71 °C, lit. ¹¹ m.p. 70 – 71 °C. Preparative TLC of the mother liquid using silica gel as the supporting material and elution with ether – light petroleum (1:4) gave further 0.93 g (5 %) of the title compound, RₑF=0.18, and 0.1 g (< 1 %) of N,N-dimethyl-N'-phenylformamidine, RₑF=0.06.  

2-Dimethylamino-8-methyl-quinoline. o-Azetotoluidide (14.9 g), 10 ml DMF and 50 ml HMPA were heated as above and worked up as above. Distillation 100 – 110 °C/0.07 mmHg gave a fraction, which was chromatographed on a silica gel column. Using ether – light petroleum (1:10) for elution 14.1 g (76 %) of the title compound was obtained; b.p. 94 – 96 °C/0.05 mmHg; νₚₑ₄=1.6367; NMR δ (CDCl₃): 2.65 (s, 3 H), 3.08 (s, 6 H), 6.72 (d, J=9 Hz, 1 H), 6.9 – 7.5 (m, 3 H), 7.73 (d, J=9 Hz, 1 H); IR(Film): 1610 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=250 nm (log ε=4.55) and 354 nm (log ε=3.80). (Found: C 77.34; H 7.54; N 15.07. C₁₄H₁₄N₃ requires: C 77.38; H 7.88; N 15.04). Further elution with ether gave 0.43 g (3 %) of N,N-dimethyl-N'-otolylformamidine; b.p. 128 – 130 °C/12 mmHg; νₚₑ₄=1.5772; NMR δ (CDCl₃): 2.26 (s, 3 H), 2.93 (s, 6 H), 6.4 – 7.2 (m, 4 H), 7.38 (s, 1 H); IR(Film): 1640 cm⁻¹ (strong). (Found: C 73.98; H 8.65; N 16.81. C₁₀H₁₆N₄ requires: C 74.03; H 8.70; N 17.27).  

2-Dimethylamino-6-methylquinoline. p-Azetotoluidide (14.9 g), 10 ml DMF and 50 ml HMPA were heated as above. The reaction mixture was allowed to cool to 100 °C and was then poured into 400 ml 2 M NaOH and extracted with 3 x 200 ml ether. The combined ether phases were washed with 2 x 100 ml water, dried over K₂CO₃ and the ether was stripped off. Distillation 118 – 122 °C/0.3 mmHg and subsequent recrystallization from light petroleum (60 – 80 °C) gave 11.3 g (61 %) of the title compound; m.p. 78 – 79 °C; NMR δ (CDCl₃): 2.38 (s, 3 H), 3.10 (s, 6 H), 6.72 (d, J=9 Hz, 1 H), 7.1 – 7.8 (m, 4 H); IR(CCl₄): 1610 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=250 nm (log ε=4.54), 357 nm (log ε=3.77). (Found: C 77.50; H 7.64; N 15.06. C₁₄H₁₄N₃ requires: C 77.38; H 7.58; N 15.04). The combined water phases were then extracted with 3 x 100 ml CHCl₃ and distillation 112 – 118 °C/0.1 mmHg gave 5.2 g OMPA.  

2-Dimethylamino-6-methoxyquinoline. p-Azetanisidine (16.5 g), 10 ml DMF and 50 ml HMPA were heated as above for 16 h and worked up in a similar way. The ether extract gave by distillation at 134 – 142 °C/0.1 mmHg and subsequent recrystallization from light petroleum (60 – 80 °C) 10.3 g (51 %) of the title compound; m.p. 71 – 72 °C; NMR δ (CDCl₃): 3.11 (s, 6 H), 3.60 (s, 3 H), 6.7 – 7.9 (m, 5 H); IR(CCl₄): 1615 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=243 nm (log ε=4.54) and 366 nm (log ε=3.70). (Found: C 71.23; H 7.02; N 13.97. C₁₄H₁₂N₃O requires: C 71.26; H 6.98; N 13.85). Preparative TLC of the distillation residue using silica gel as supporting material and ether for elution gave 1.46 g (5 %) of 6-bis(dimethylamino)-phosphinyloxy-2-dimethylaminoquinoline; m.p. 80 – 82 °C; NMR δ (CDCl₃): 7.27 (d, J=10 Hz, 12 H), 3.16 (s, 6 H), 6.85 (d, J=9 Hz, 1 H), 7.2 – 7.9 (m, 4 H); IR(KBr): 1620 cm⁻¹ (strong). (Found: H 7.01; N 17.10. C₁₄H₁₄N₃O requires: H 7.19; N 17.38). From the CHCl₃ extract there was obtained 3.5 g OMPA by distillation 118 – 122 °C/0.2 mmHg.  

2-Dimethylamino-6-methoxyquinoline. o-Azetanisidine (16.5 g), 10 ml DMF and 50 ml HMPA were heated as above for 16 h. Work up as for 2-dimethylaminoquinoline followed by distillation 130 – 140 °C/0.1 mmHg and subsequent recrystallization from light petroleum (60 – 80 °C) gave 8.0 g (40 %) of the title compound; m.p. 105 – 107 °C; NMR δ (CDCl₃): 3.17 (s, 6 H), 3.97 (s, 3 H), 6.7 – 7.3 (m, 4 H), 7.78 (d, J=9 Hz, 1 H); IR(CH₃Cl): 1610 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=260 nm (log ε=4.43) and 356 nm (log ε=3.59). (Found: C 71.12; H 6.93; N 13.86. C₁₄H₁₄N₃O requires: C 71.26; H 6.98; N 13.85). Preparative TLC of the distillation residue using silica gel as supporting material and acetone – CHCl₃ (1:9) for elution gave 1.77 g (5 %) of 8-bis(dimethylamino)phosphinyloxy-2-dimethylamino-quinoline; NMR δ (CDCl₃): 2.78 (d, J=10 Hz, 12 H), 3.17 (s, 6 H), 6.85 (d, J=9 Hz, 1 H), 7.0 – 7.7 (m, 3 H), 7.80 (d, J=9 Hz, 1 H); IR(CCl₄): 1620 and 1630 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=260 nm (log ε=4.46) and 353 nm (log ε=3.68). (Found: C 55.63; H 7.38; N 17.12. C₁₄H₁₄N₃O requires: C 55.58; H 7.19; N 17.38).  

2-Dimethylamino-benzo[h]quinoline. N-α-Naphthylacetamide (18.5 g), 10 ml DMF and 50 ml HMPA were heated as above for 16 h. Work up as for 2-dimethylaminoquinoline and followed by recrystallization, gave 13.0 g (59 %) of the title compound; m.p. 92 – 93 °C; NMR δ (CDCl₃): 3.12 (s, 6 H), 6.68 (d, J=9 Hz, 1 H), 7.4 – 7.9 (m, 6 H), 9.17 (m, 1 H); IR(CCl₄): 1610 cm⁻¹ (strong); UV (C₆H₅Cl): λₑₓₘₐₓ=241 nm (log ε=4.72), 2.91 nm (log ε=4.26), 321 nm (log ε=3.05), 363 nm (log ε=3.81) and 382 nm (log ε=3.81). (Found: C 81.02; H 6.35; N 12.57. C₁₄H₁₂N₃ requires: C 81.05; H 6.35; N 12.60).  

2-Dimethylamino-3-methylquinoline. N-Phenylpropionamide (14.9 g), 10 ml DMF and 50 ml HMPA were heated as above for 25 h. Work up as above gave by distillation 86 – 110 °C/0.15 mmHg a fraction, which was subjected to chromatography on a silica gel column. Elution with ether – light petroleum (40 – 60 °C) (1:1) gave 9.8 g (53 %) of the title compound; b.p. 158 – 160 °C/11 mmHg; νₚₑ₄=1.6161; NMR δ
(CDCl₃): 2.35 (d, J = 1.0 Hz, 3 H), 2.95 (s, 6 H), 7.1 – 8.0 (m, 5 H); IR(CCl₄): 1615 cm⁻¹ (strong), 1635 cm⁻¹ (strong); UV (CH₃OH): 253 nm (log ε = 4.33) and 333 nm (log ε = 3.72). (Found: C 77.21; H 7.72; N 15.09. C₁₅H₂₃N₅ requires: C 77.38; H 7.58; N 15.09). Further elution with ether gave 0.94 g (5%) of N,N-dimethyl-N'-phenylformamidine.

2-Dimethylamino-3-ethyl-quinoline. N-Phenylbutyramide (8.15 g), 5 ml DMF and 25 ml HMPA were heated as above for 12 h. Work up as above gave by distillation a fraction 60 – 100 °C/0.07 mmHg which was subjected to chromatography on a silica gel column. Elution with ether – light petroleum (40 – 60 °C) (1:1) gave 2.6 g (26%) of the title compound; b.p. 167 – 169 °C/14 mmHg; ν_D₄ = 1.0132; NMR δ (CDCl₃): 1.28 (t, J = 7 Hz, 3 H), 2.78 (q, J = 7 Hz, 2 H), 2.93 (s, 6 H), 7.1 – 8.0 (m, 5 H); IR(CCl₄): 1610 cm⁻¹ (strong), 1630 cm⁻¹ (strong); UV (CH₃OH): 253 nm (log ε = 4.34), 333 nm (log ε = 3.74). (Found: C 77.64; H 8.20; N 13.97. C₁₅H₂₃N₅ requires: C 77.96; H 8.05; N 13.99). Further elution with ether gave 3.7 g of a fraction which was estimated by NMR and GLC to contain about 50% N,N-dimethyl-N'-phenylformamidine, corresponding to ~10% yield.

Attempted preparation of 2-dimethylamino-3-isopropylquinoline. N-Phenyl-isovaleramide (17.7 g), 10 ml DMF and 50 ml HMPA were heated as above for 18 h. The reaction mixture was taken up in 400 ml 2 M NaOH and extracted with 3 × 200 ml ether. The combined ether phases were washed with 2 × 100 ml H₂O, dried over K₂CO₃ and the ether stripped off. Distillation at 90 – 120 °C/0.1 mmHg, and subsequent recrystallization from light petroleum gave 3.6 g (39%) of the title compound, m.p. 47 – 48 °C, lit.¹⁰ m.p. 47 – 50 °C.

2-Dimethylamino-4,6-dimethyl-quinoline. p-Toluidine (5.4 g), acetic acid (10 g) and 50 ml HMPA were heated as above. Work up as above gave after distillation 100 – 140 °C/0.1 mmHg and subsequent recrystallization from light petroleum 5.4 g (54%) of the title compound m.p. 85 – 87 °C; NMR δ (CDCl₃): 2.43 (s, 3 H), 2.50 (d, J = 1.0 Hz, 3 H), 3.11 (s, 6 H), 6.68 (q, J = 1.0 Hz, 1 H), 7.1 – 7.8 (m, 3 H); IR(CCl₄): 1620 cm⁻¹ (strong); UV (CH₃OH): 254 nm (log ε = 4.50), 356 nm (log ε = 3.78). (Found: C 78.08; H 8.21; N 14.00. C₁₃H₁₄N₂ requires: C 77.96; H 8.05; N 13.90).

2-Dimethylamino-4,8-dimethyl-quinoline. o-Toluidine (5.4 g) acetic acid (10 g) and 50 ml HMPA were heated as above for 16 h. Work up as above gave after distillation 80 – 130 °C/0.05 mmHg and subsequent recrystallization from light petroleum 3.5 g (35%) of the title compound; m.p. 58 – 60 °C, lit.¹³ m.p. 60 – 62 °C.

6-Chloro-2-dimethylamino-4-methyl-quinoline. p-Chloroaniline (6.4 g) acetic acid (10 g) and 50 ml HMPA were heated as above for 16 h. Work up as above gave after distillation 110 – 150 °C/0.15 mmHg and subsequent recrystallization from light petroleum 4.4 g (40%) of the title compound; m.p. 81 – 83 °C; NMR δ (CDCl₃): 2.43 (d, J = 1.0 Hz, 3 H), 3.12 (s, 6 H), 6.65 (q, J = 1.0 Hz, 1 H), 7.2 – 7.8 (m, 3 H); IR(CCl₄): 1620 cm⁻¹ (strong); UV (CH₃OH): 252 nm (log ε = 4.53), 280 nm (log ε = 4.23), 288 nm (log ε = 4.10), 359 nm (log ε = 3.82). (Found: C 65.28; H 5.94; N 12.86. C₁₃H₁₂ClN₄ requires: C 65.30; H 5.94; N 12.69).

2-Dimethylamino-6-methoxy-4-methyl-quinoline. p-Anisidine (6.2 g) acetic acid (10 g) and 50 ml HMPA were heated as above. Work up as above gave after distillation 130 – 180 °C/0.2 mmHg and subsequent recrystallization from light petroleum 2.5 g (23%) of the title compound m.p. 84 °C lit.¹³ m.p. 87 – 89 °C.

2-Dimethylamino-4-ethyl-3-methyl-quinoline. Aniline (4.7 g), propionic acid (12.8 g) and 50 ml HMPA were heated as above. Work up as above gave the title compound, which was purified on a silica gel column using ether – light petroleum (1:4) for elution to give 1.78 g (17%) of pure title compound; b.p. 154 – 156 °C/2 mmHg; ν_D₄ = 1.6085; NMR δ (CDCl₃): 1.20 (t, J = 8 Hz, 3 H), 2.37 (s, 3 H), 2.90 (s, 6 H), 3.00 (q, J = 8 Hz, 2 H), 7.1 – 8.0 (m, 4 H); IR(CCl₄): 1595 cm⁻¹ (strong); UV (CH₃OH): 252 nm (log ε = 4.37), 333 cm⁻¹ (log ε = 3.70). (Found: C 78.67; H 8.49; N 12.96. C₁₃H₁₅N₂ requires: C 78.46; H 8.47; N 13.07).

N,N-Dimethyl-N’-p-tolyl-acetamide. p-Acetotoluidide (29.8 g) and 100 ml HMPA were heated as above at 230 °C for 6 h. Work up as for 2-dimethylaminoquinoline and subsequent fractionated distillation gave: I. 15.6 g (44%) of...
the title compound, b.p. 80—82 °C/0.05 mmHg, nD20 = 1.5670; NMR δ (CDCl3): 1.82 (s, 3 H), 2.27 (s, 3 H), 2.97 (s, 6 H), 6.3—6.7 (m, 2 H), 6.8—7.2 (m, 2 H); IR (CCl4): 1625 cm⁻¹ (strong); UV (CH3OH): 241 nm (log ε = 4.14). (Found: C 74.98; H 9.22; N 16.02. C14H17N4O requires: C 74.95; H 9.15; N 15.90). 2. 3.6 g (18 %) 2-dimethylamino-4,6-dimethyl-quinoline b.p. 129—131 °C/0.1 mmHg.

N,N-Dimethyl-N-(p-methoxyphenyl)-acetanilide. Acetanilide 33 g and 100 ml HMPA were heated at 225 °C for 4 h. and the reaction mixture was worked up as above. Distillation 105—110 °C/0.2 mmHg gave 29 g, 76 % of the title compound, nD20 = 1.5717; NMR δ (CDCl3): 1.82 (s, 3 H), 2.87 (s, 6 H), 3.73 (s, 3 H), 6.5—6.9 (m, 4 H); IR (CCl4): 1620 cm⁻¹ (strong); UV (CH3OH): 241 nm (log ε = 4.14). (Found: C 68.95; H 8.44; N 14.56. C11H12N2O requires: C 68.72; H 8.99; N 14.68). Further distillation 160—170 °C/0.1 mmHg and subsequent recrystallization from light petroleum gave 1.38 g (6 %) 2-dimethylamino-6-methoxy-4-methylquinoline.

N¹-(p-Chlorophenyl)-N,N-dimethyl-acetanilide. p-Chloroacetanilide (30 g) and 100 ml HMPA were heated at 225 °C for 5 h. and the reaction mixture was worked up as above. Distillation 90—100 °C/0.05 mmHg gave 22.3 g (64 %) of the title compound, nD20 = 1.5656; NMR δ (CDCl3): 1.83 (s, 3 H), 2.98 (s, 6 H), 6.4—6.7 (m, 2 H), 7.0—7.3 (m, 2 H); IR (CCl4): 1620 cm⁻¹ (strong); UV (CH3OH): 248 nm (log ε = 4.14). (Found: C 61.27; H 6.75; N 14.13. C13H12ClN2 requires: C 61.06; H 6.66; N 14.24).

p-Acetotoluidide (14.9 g) + N,N-dimethyl-acetanilide (12 g) and 50 ml HMPA were heated on a silicone-oil (250 °C) bath for 16 h. and the reaction mixture was worked up as above. Distillation 120—160 °C/0.3 mmHg and subsequent recrystallization from light petroleum gave 2.9 g (43 %) of 2-dimethylamino-4,6-dimethyl-quinoline.

Acetanilide (13.5 g) + phenylacetate (16 g) and 50 ml HMPA were treated as above for 16 h. The cooled reaction mixture is poured into 400 ml 2 M NaOH and extracted with 4 × 200 ml ether. To the combined ether phases (ether phase 1) was added 150 ml 2 M HCl. The precipitate was filtered off and the ether phase 1 was separated. The precipitate was taken up in the acidic water phase, which then was made alkaline and extracted with ether. This ether phase was dried over Na2SO4 and distillation at 110—120 °C/0.2 mmHg and subsequent recrystallization from light petroleum gave 9.7 g (52 %) 2-dimethylamino-4,6-methyl-quinoline. The ether phase 1 was dried over Na2SO4 and by distillation at 100—150 °C/0.05 mmHg a fraction was obtained, which was subjected to column chromatography using silica gel as the supporting material. Elution with ether gave 1.67 g dimethylamidodiphenyl phosphate; b.p. 137—140 °C/0.05 mmHg, lit.5 b.p. 154 °C/0.2 mmHg; nD20 = 1.5402; lit.6 nD20 = 1.5407. Further elution with MeOH gave 3.36 g bis(dimethylamido)phenyl phosphate; b.p. 160—161 °C/10 mmHg, lit.5 b.p. 154—155 °C/9 mmHg; nD20 = 1.5061; lit.6 nD20 = 1.5037.

N,N-Dimethylpropionamide + acetanilide. To a solution of N,N-dimethylpropionamide in HMPA (prepared by heating propionic acid (5.7 g) in HMPA (50 ml) at reflux temperature for 2 h) acetanilide (6.75 g) was added. The mixture was heated for 17 h on a silicon oil-bath (250 °C), poured into 400 ml 2 M NaOH and extracted with 4 × 200 ml ether. The combined ether phases were washed with 2 × 100 ml H2O and dried over K2CO3. Distillation 86—150 °C/0.05 mmHg gave a fraction which was subjected to column chromatography using silica gel as the supporting material.

1. Elution with ether—light petroleum (1:4) gave 1.9 g of a mixture of XI and XII (1:1) which could be separated by preparative GLC (Perkin-Elmer F 21, 5 % Se 30). 3,4-Dimethyl-2-dimethylamino-quinoline (XII), NMR (CDCl3): 2.35 (s, 3 H), 2.60 (s, 3 H), 2.90 (s, 6 H), 7.1—8.0 (m, 4 H); IR (CCl4): 1610 cm⁻¹ (strong); UV (CH3OH): 250 nm (log ε = 4.38), 334 nm (log ε = 3.68).

2. Further elution with ether—light petroleum (2:3) gave 3.2 g of a mixture of IX and X (1:3) which could be separated by preparative GLC as above. 2-Dimethylamino-4-ethyl-quinoline (X), NMR (CDCl3): 1.31 (t, J = 7 Hz, 3 H), 2.93 (q, J = 7 Hz, 2 H), 3.15 (s, 6 H), 6.70 (s, 1 H), 7.0—7.9 (m, 4 H); IR (CCl4): 1620 cm⁻¹ (strong); UV (CH3OH): 250 nm (log ε = 4.55), 350 nm (log ε = 3.77).

REFERENCES


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