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Phosphoramides. I. Hexamethylphosphoric Triamide as a Reagent in a New Synthesis of 2,4-Bis(dimethylamino)quinolines

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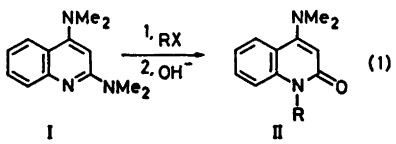
6-Methyl-, 6-methoxy-, 8-methoxy-, 6-chloro-, 7,8-dimethyl-, and unsubstituted 2,4-bis(dimethylamino)quinoline have been prepared in 23 – 30 % yield by heating the appropriate aniline and diethyl malonate in hexamethylphosphoric triamide (HMPT) to reflux temperature.

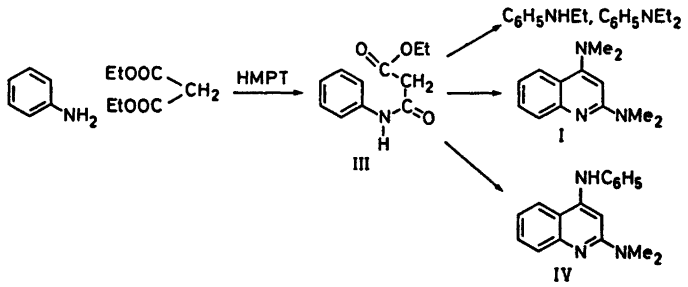
The carbostyrils II have been prepared[1] by heating 2,4-bis(dimethylamino)quinoline (I) with a primary alkyl halide, and treating the resulting 1-alkyl quaternary ammonium compound with dilute aqueous alkali, eqn. 1. They are claimed to have analgesic, antiinflammatory, and antipyretic activity, and may be used



in the treatment of rheumatic disorders.[1] Unfortunately, I is only available by a multistep synthesis; it was prepared by heating the corresponding 2,4-dichloroquinoline in an ethanolic solution of dimethylamine. This paper states that 2,4-bis(dimethylamino)quinolines are easily available by a one step synthesis from very simple starting materials.

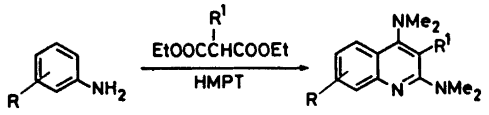
RESULTS AND DISCUSSION

Recently, HMPT has been used as a cyclization reagent in a new synthesis of 2-dimethylaminoquinolines.[2] It was therefore conceivable, that the quinoline I could be produced by heating the amide III in HMPT. I and not the corresponding 4-hydroxycarbostyril should be expected, because HMPT is known to replace potential hydroxy-groups with dimethylamino-groups.[3] As carboxamides may be prepared by heating appropriate esters with amines, it was thus attempted to prepare I simply by heating aniline and ethyl malonate in HMPT. For those anilines investigated in which steric hindrance could be excluded, the corresponding 2,4-bis(dimethylamino)quinolines were produced in yields of 23 – 30 % (Table 1). Steric hindrance seems to play an important role



Scheme 1.

Table 1. Yields of 2,4-bis(dimethylamino)quinolines.



R	R^1	Quinoline (%)
H	H	30
p-Me	H	25
p-OMe	H	26
o-OMe	H	25
p-Cl	H	29
2,3-di-Me	H	23
2,5-di-Me	H	< 1
H	Et	5

in the success of the ring closure reaction. Thus, the yield of the corresponding quinoline was only 5 %, when diethyl ethylmalonate was heated with aniline in HMPT. A methyl group in the 5-position of the aniline ring gave rise to almost complete steric hindrance, so that in the reaction of 2,5-dimethylaniline the yield of the corresponding 2,4-bis(dimethylamino)quinoline was estimated to be less than 1 % and it was in fact not isolated in the pure state. Steric hindrance is evident in the case of 2,5-dimethylaniline, as the isomeric 2,3-dimethylaniline produced the corresponding quinoline in a yield of 23 %. These findings are also in accordance with the general rule of electrophilic aromatic substitution saying that a third substituent does not enter the 2-position of 1,3-disubstituted benzenes.

In all the investigated reactions of anilines with diethyl malonate in HMPT at reflux temperature, a lower boiling fraction could be isolated. This fraction was, in the case of aniline, separated by preparative TLC, and *N*-ethyl- and *N*,*N*-diethylaniline could be isolated in pure state, In fact for all other anilines the NMR spectra of the low boiling fractions also showed a mixture of the corresponding *N*-ethyl- and *N*,*N*-diethylanilines. The alkylating power of diethyl malonate in HMPT at high temperature was confirmed by heating *N*-methylaniline in this medium at reflux temperature, whereupon *N*-ethyl-*N*-methylaniline was produced in 67 % yield. In the reactions of anilines with diethyl malonate in HMPT a very high boiling fraction of a glassy substance was isolated in all cases. When the cyclization was carried out with aniline the glassy substance could be induced to crystallize and was identified as 4-anilino-2-dimethylaminoquinoline (IV). Similarly, crystalline 4-(*p*-anisidino)-2-dimethylamino-6-methoxyquinoline was isolated, when *p*-anisidine was reacted with diethyl malonate and HMPT.

In order to increase the yield of the quinoline I, attempts were made using methyl instead of ethyl malonate, and also the malonic ester and aniline were heated in HMPT in the ratios 1:2, 1:1, and 2:1, but in all cases 25 – 30 % yields of I were obtained. It was then expected that the quinoline I would be produced in high yield by heating in HMPT the amide III, which was thought to be an intermediate in the reaction. However, the quinoline I was formed in the same yield (29 %) as before, but a mixture of *N*-ethyl- and *N*,*N*-diethylaniline, and the quinoline IV were also isolated. This strongly indicated that very fast equilibria exist at the prevalent reaction temperature of ~230 °C, so that the use of aniline and malonic ester or the amide III as starting materials in the quinoline synthesis has almost no effect on the product distribtution.

EXPERIMENTAL

In all experiments commercial HMPT (Pierrefitte-Auby) was used. The microanalyses were performed by the Microanalytical Laboratory, University of Copenhagen. IR-spectra were recorded on a Perkin Elmer Model 457, UV spectra on a Beckmann ACTA III, and NMR spectra on a Jeol C-60HL spectrometer.

2,4-Bis(dimethylamino)quinoline. Aniline (9.3 g), ethyl malonate (16 g) and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath at 210 °C for 1 h and then at 250 °C for 2. During the reaction EtOH distilled off. The residue, allowed to cool to 100 °C, was then poured into ice and 200 ml 2 N NaOH, and extracted with 4 × 100 ml ether. The organic phase was washed with 50 ml H_2O, dried over K_2CO_3, and the ether was stripped off. Distillation gave:

1. 1.4 g of a fraction, b.p. 80 – 100 °C/10 mmHg. From this fraction were isolated, by PLC using siliga gel as the supporting material and elution with ether-light petroleum (1:9), *N*-ethylaniline, $n_D^{20} = 1.5534$, lit.[4] $n_D^{20} = 1.55397$, and *N*,*N*-diethylaniline, $n_D^{20} = 1.5412$, lit.[4] $n_D^{20} = 1.5418$. Both compounds gave NMR

spectra identical with spectra of authentic samples.

2. A fraction, b.p. 100 – 150 °C/0.05 mmHg, which on subsequent recrystallization from petroleum ether gave 6.5 g (30 %) of 2,4-bis(dimethylamino)quinoline, m.p. 77 – 78 °C, lit. m.p. 78 – 78.5 °C [5] and 68 – 70 °C;[1] NMR δ ($CDCl_3$): 2.83 (s, 6 H), 3.08 (s, 6 H), 6.10 (s, 1 H), 6.8 – 7.9 (m, 4 H).

3. A fraction, b.p. 180 – 220 °C/0.03 mmHg, which crystallized by treatment with boiling benzine (80 – 100 °C) to give 1,9 g of 4-anilino-2-dimethylaminoquinoline, m.p. 121 – 125 °C (subl.); NMR δ ($CDCl_3$): 3.05 (s, 6 H), 6.48 (s, 2H), 6.8 – 7.8 (m, 9 H); UV (EtOH): λ_{max} = 243 nm (log ε = 4.51) 320 nm (log ε = 4.08). (Found: C 77.40; H 6.63; N 16.02. $C_{17}H_{17}N_3$ requires: C 77.53; H 6.51; N 15.96).

2,4-Bis(dimethylamino)-6-methoxyquinoline. *p*-Anisidine (12.3 g), ethyl malonate (16 g), and HMPT (50 ml) were heated as above and the mixture was then worked up in a similar way. Distillation gave:

1. A fraction, b.p. 120 – 180 °C/0.05 mmHg, which on subsequent recrystallization from petroleum ether gave 6.4 g (26 %) of the title compound, m.p. 96 – 98 °C; NMR δ ($CDCl_3$): 2.91 (s, 6 H), 3.15 (s, 6 H), 3.86 (s, 3 H), 6.25 (s, 1 H), 6.9 – 7.3 (m, 2 H), 7.4 – 7.7 (m, 1 H); UV (EtOH): λ_{max} = 240 nm (log ε = 4.58), 267 nm (log ε = 4.45), 360 nm (log ε = 3.67). (Found: C 68.77; H 8.39; N 17.06. $C_{14}H_{19}N_3O$ requires: C 68.54; H 7.81; N 17.13).

2. A fraction b.p. 220 – 270 °C/0.05 mmHg, which crystallized by treatment with boiling benzine (80 – 100 °C) to give 2.3 g of 4-(*p*-anisidino)-2-dimethylamino-6-methoxy-quinoline, m.p. 144 – 148 °C; NMR δ ($CDCl_3$): 3.00 (s, 6 H), 3.77 (s, 6 H), 6.19 (broad singlet, 2 H), 6.6 – 7.3 (m, 6 H), 7.4 – 7.7 (m, 1 H); UV (EtOH): 240 nm (log ε = 4.52), 315 nm (log ε = 3.99), 340 nm (sh). (Found: C 70.10; H 7.12; N 12.96. $C_{19}H_{21}N_3O_2$ requires: C 70.56; H 6.55; N 13.00).

2,4-Bis(dimethylamino)-8-methoxyquinoline. *o*-Anisidine (12.3 g), ethyl malonate (16 g), and HMPT (50 ml) were heated as above and the mixture was then worked up in a similar way. Distillation 100 – 200 °C/0.04 mmHg and subsequent recrystallization from petroleum ether gave 6.2 g (25 %) of the title compound, m.p. 104 – 106 °C; NMR δ ($CDCl_3$): 2.90 (s, 6 H), 3.19 (s, 6 H), 3.97 (s, 3 H), 6.20 (s, 1H), 6.7 – 7.5 (m, 3H); UV (EtOH): 263 nm (log ε = 4.49), 346 nm (log ε = 3.67). (Found: C 68.40; H 7.98; N 16.98. $C_{14}H_{19}N_3O$ requires: C 68.54; H 7.81; N 17.13).

2,4-Bis(dimethylamino)-6-methylquinoline. *p*-Toluidine (10.7 g), ethyl malonate (16.0 g), and HMPT (50 ml) were heated as above and the mixture was then worked up in a similar way. Distillation 100 – 170 °C/0.1 mmHg and subsequent recrystallization from light petroleum gave 5.8 g (25 %) of the title compound m.p. 75 – 77 °C; NMR δ ($CDCl_3$): 2.42 (s, 3 H), 2.90 (s, 6 H), 3.14 (s, 6 H), 6.18 (s, 1 H), 6.9 – 7.6 (m, 3 H); UV (EtOH): 247 nm (log ε = 4.52), 302 nm (log ε = 3.75), 348 (log ε = 3.76). (Found: C 73.15; H 7.93; N 18. 26. $C_{14}H_{19}N_3$ requires: C 73.52; H 8.35; N 18.33).

7,8-Dimethyl-2,4-bis(dimethylamino)quinoline. 2,3-Dimethylaniline (12.1 g), ethyl malonate (16.0 g), and HMPT (50 ml) were heated as above, and the mixture was then worked up in a similar way. Distillation 100 – 200 °C/0.1 mmHg and subsequent recrystallization from petroleum ether gave 5.6 g (23 %) of the title compound m.p. 116 – 117 °C; NMR δ ($CDCl_3$): 2.39 (s, 3 H), 2.60 (s, 3 H), 2.86 (s, 6 H), 3.13 (s, 6 H), 6.14 (s, 1 H), 6.89 (d, J = 9 Hz, 1 H), 7.53 (d, J = 9 Hz, 1 H); UV (EtOH): 255 nm (log ε = 4.58), 345 nm (log ε = 3.71). (Found: C 73.80; H 8.83; N 17.18. $C_{15}H_{21}N_3$ requires: C 74.03; H 8.70; N 17.27).

2,4-Bis(dimethylamino)-5,8-dimethylquinoline. 2,5-Dimethylaniline (12.1 g), ethyl malonate (16 g), and HMPT (50 ml) were heated as above and the mixture was worked up in a similar way. For a fraction (1.3 g), b.p. 145 – 150 °C/0.05 mmHg an NMR spectrum was obtained with big singlets at 2.60 and 3.05, and a small singlet at δ 6.15 ($CDCl_3$), which should be expected for the title compound. From this fraction 0.4 g of an oil with the same characteristic NMR signals as the title compound was obtained by preparative TLC, using acetone-ether (2:3) for eluation and silica gel as supporting material. As this fraction also was very impure no further purification was attempted.

6-Chloro-2,4-bis(dimethylamino)quinoline. *p*-Chloroaniline (12.8 g), ethyl malonate (16.0 g), and HMPT (50 ml) were heated as above, and the mixture was then worked up in a similar way. Distillation 100 – 200 °C/0.1 mmHg and subsequent recrystallization from petroleum ether gave 7.3 g (29 %) of the title compound m.p. 106 – 107 °C; NMR δ ($CDCl_3$): 2.87 (s, 6 H), 3.12 (s, 6 H), 6.15 (s, 1 H), 7.1 – 7.8 (m, 3 H); UV (EtOH): 244 nm (log ε = 4.43), 274 nm (log ε = 4.42), 355 nm (log ε = 3.74). (Found: C 62.60; H 7.07; N 16.88. $C_{13}H_{16}ClN_3$ requires: C 62.52; H 6.46; N 16.86).

2,4-Bis(dimethylamino)-3-ethyl-quinoline. Aniline (9.3 g), diethyl ethylmalonate (18.8 g), and HMPT (50 ml) were heated as above, and the mixture was then worked up in a similar way. Distillation 100 – 160 °C/0.05 mmHg gave a fraction which was subjected to separation on a silica gel column. Elution with ether gave 1.2 g (5 %) of the title compound, which was then distilled at 0.05 mmHg to give the analytically pure compound; NMR δ ($CDCl_3$): 1.05 (t, J = 7Hz, 3H), 2.80 [q, J = 7Hz; this signal overlaps the singlets of the two dimethylamino groups at 2.83 and 2.97 (a total of 14 H)], 6.5 – 7.9 (m, 4 H); UV (EtOH): 252 nm (log ε = 4.37), 327 nm (log ε = 3.85). (Found: C 74.10; H 8.72; N 16.40. $C_{15}H_{21}N_3$ requires; C 74.03; H, 8.70; N, 17.27).

N-*Ethyl*-N-*methylaniline*. *N*-Methylaniline (10.7 g), ethyl malonate (16.0 g), and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath (250 °C) for 3 h and a low boiling material was allowed to distill off. The residue was allowed to cool to 100 °C, and was then poured into ice and 200 ml 2 N NaOH and extracted with 4 × 100 ml ether. The organic phase was washed with 50 ml H_2O, dried over K_2CO_3, and the ether was stripped off. Distillation 82 – 83 °C/11 mmHg, gave 9.0 g (67 %) of the title compound, $n_D^{20} = 1.5459$ lit.[6] $n_D^{20} = 1.5450$; NMR δ ($CDCl_3$): 0.98 (t, $J = 7$ Hz, 3 H), 2.70 (s, 3 H), 3.22 (q, $J = 7$ Hz, 2 H), 6.3 – 7.3 (m, 5 H).

REFERENCES

1. J. R. Geigy A.-G., Belg. 636,867 (1964); *Chem. Abstr. 62* (1965) 536a.
2. Pedersen, E. B. and Lawesson, S.-O. *Acta Chem. Scand. B 28* (1974) 1045.
3. Pedersen, E. B. and Lawesson, S.-O. *Tetrahedron 30* (1974) 875.
4. Vogel, A. I. *J. Chem. Soc.* (1948) 1825.
5. Fatutta, S., Mauro, M. and Pasin, C. *Ric. Sci Parte 2: Sez. A 8* (1965) 736.
6. Arbuzov, B. A. and Guzhavina, L. M. *Zh. Fiz. Khim. 23* (1949) 1070; Beilstein XII[3] 259.

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