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PHOSPHORAMIDES—II†

SYNTHESIS OF 2,4-BIS(DIMETHYLAMINO)QUINOLINES BY HMPT INDUCED RING CLOSURE OF ANTHRANILATES

E. B. PEDERSEN
Department of Chemistry, Odense University, DK-5000 Odense, Denmark

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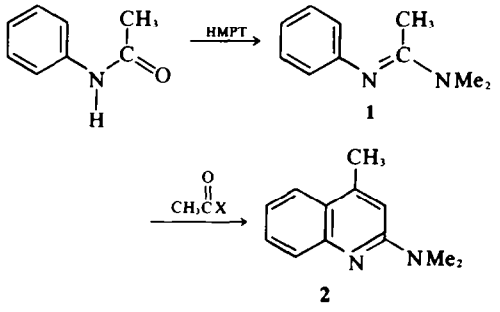
Abstract—6-Chloro-, 7-chloro-, 6-bromo-, 6-methyl-, 6,7-dimethyl-, 7,8-dimethyl- and unsubstituted 2,4-bis-(dimethylamino)quinoline **7** have been prepared by heating appropriately substituted ethyl anthranilates in HMPT at reflux temperature. By heating ethyl N-acetylanthranilate (**3**) at 205–209° in HMPT, N-acetylanthranilic acid (**4**), 2-acetamido-N,N-dimethylbenzamide (**5**) and an acetamidine (**6**) were produced and are belived to be intermediates in the formation of 2,4-bis(dimethylamino)quinoline (**7**) which was produced in trace amounts in the latter reaction.

In earlier investigations it was shown that hexamethylphosphoric triamide (HMPT) could be used as a cyclization reagent in the preparation of aminoquinolines.[1,2] 2 - Dimethylamino - 4 - methyl - quinolines (**2**) were also synthesized simply by refluxing acetanilides and acetic acid derivatives in HMPT.[1]



(1)

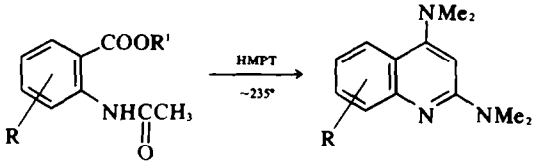
The primarily formed amidine, **1**, was assumed to be in tautomeric equilibrium with an enamine, which may be acetylated by the acetic acid derivative. By this step an acetoacetamidine was obtained which could undergo acid catalyzed cyclization producing the quinoline **2**. In reactions where the acetanilides were also the acetylating reagent (addition of no other acetic acid derivatives to the mixture), the quinolines were obtained in low yields, and the acetamidines, **1**, were then the main products. It was therefore expected that the amidine **1** should also be acetylated by an ortho-carboxy group on the aromatic ring, whereby a quinoline derivative should be produced. As HMPT is known to replace potential OH-groups of heteroaromatic rings with dimethylamino-groups, it could then be foreseen that 2,4-bis(dimethylamino)quinolines should be formed by heating N-acetylanthranilic derivatives in HMPT. These quinolines are of interest, because they can be used as starting materials in a simple synthesis of 1 - alkyl - 4 - dimethylaminocarbostyrils, which are claimed to have analgesic, antiinflammatory, and antipyretic activity, and may be used in treatment of rheumatic disorders.[3]

RESULTS AND DISCUSSION

Esters of anthranilic acids were prepared by heating the acids in EtOH saturated with dry HCl. The esters were then acetylated with acetic anhydride, whereby ethyl N-acetylanthranilates were formed. By heating the so formed carboxamides in HMPT at reflux temperature 2,4-bis(dimethylamino)quinolines were generally formed in 40–70% yield (Table 1). Although the yields are rather high, only a multistep reaction pathway can explain the route from the ethyl N-acetylanthranilate, **3**, to the quinoline **7**.

In order to isolate the intermediates the temperature was lowered from ~235° to 215–218°, but the quinoline **7** was still isolated in 60% yield. The temperature was then lowered a further ten degrees to 205–209°, and the yield of the quinoline dramatically decreased to less than 1%. Instead were N-acetylanthranilic acid, **4**, isolated in 28% yield and 2 - acetamido - N,N - dimethylbenzamide **5** in 29% yield. Furthermore trace amounts of the amidine **6** and the ester **8** were isolated. Based on the knowledge of HMPT-induced reactions, the reaction-path given in Scheme 1 could account for the formation of quinoline **7**. In the first step N-acetylanthranilic acid, **4**, would be formed by a dealkylation of the starting material **3**. It is known that esters in which the alkyl group has a β hydrogen, may be pyrolyzed to give the corresponding acid and an olefin.[4] Although a similar elimination can be expected for **3**, it should nevertheless be remembered that esters like methyl malonate and ethyl malonate can

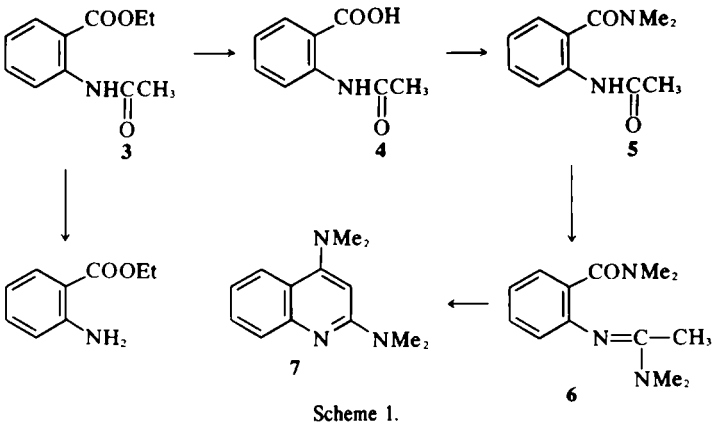
Table 1. Yields of 2,4-bis(dimethylamino)quinolines



R[a]	R'	Quinoline (%)
H	H	41
H	Me	48
H	Et	70
4-Cl	Et	41
5-Cl	Et	52
5-Br	Et	49
5-Me	Et	58
3,4-di-Me	Et	17
4,5-di-Me	Et	66

[a] Substituent of ethyl N-acetylanthranilate.

†Part I, see Ref. 2.



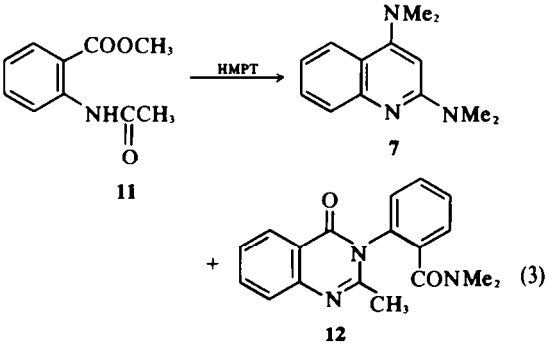
Scheme 1.

behave as simple alkylating reagents in HMPT at reflux temperature.[2] The belief in the ester **3** acting as an alkylating reagent on a nucleophile present in the mixture, by which the acid **4** is produced, is supported by the fact that the quinoline **7** also is produced by heating methyl N-acetylanthranilate in HMPT (Table 1). The latter ester can not produce the acid **4** by the above mentioned pyrolytic reaction. The presence of the carboxylic acid **4** as an intermediate is furthermore supported by the observation that heating **4** under the conditions produced the quinoline **7**. The next step in the sequence given in Scheme 1 is the transformation of the carboxylic acid **4** into the carboxamide **5**. This step is very similar to the very first chemical reaction reported on HMPT, which was the synthesis of N,N - dimethyl - carboxamides by heating the corresponding acids in HMPT.[5,6] The following step would be the production of the amidine **6** from the secondary carboxamide **5**. The transformation of that functional group is also a well established HMPT reaction.[1,7] The so formed amidine **6** could then tautomerize the amidine group to a very reactive enamine, which then could be intramolecularly acylated by the carboxamide group. The ring closure product could then be transformed by HMPT into the quinoline **7**. Ethyl anthranilate, which also was isolated from the mixture, could be formed in a deacylation of the starting material during the reaction, but it could also be an artifact produced by hydrolysis of the starting material in the dilute NaOH used during the work up.

In the reaction of the anthranilic ester **8**, the corresponding amidine **9** was isolated, which gives further evidence for the above mechanism. In this reaction, the quinoline **10** was only isolated in 17% yield. It is obvious that the two ortho substituents to the acetamido group in **8** may cause steric interaction during the reaction either for the formation of the amidine **9** or in the following ring closure reaction of **9** producing the quinoline **10**.

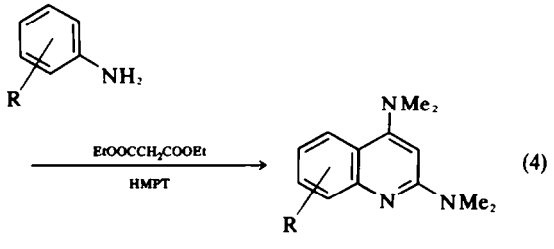
In all reactions great excess of HMPT was used. If a five molar excess was reduced to 1.2 molar excess of HMPT in the reaction with the anthranilic ester 3, the yield of the quinoline **7** was reduced from 70% to 44%. If the ratio of HMPT and the anthranilic ester **3** was further reduced to 3:5 (mol/mol) only trace amounts of the quinoline **7** were isolated. It should be remembered that there are three dimethylamino groups in the HMPT molecule, in this case equivalent to almost two dimethylamino groups per anthranilic ester molecule **3**, and a greater yield of the quinoline **7** could therefore be expected. Instead the carboxamide **5** was isolated in 31% yield. This also supports **5** as a true reaction intermediate, because with deficiency of HMPT the reaction would be expected to stop at one of the reaction intermediates given in Scheme 1.

In the syntheses of the quinolines given in Table 1, a high boiling distillation residue remained in all cases. In the case of methyl N-acetylanthranilate **11** this residue was distilled and the quinazolinone **12** was isolated.

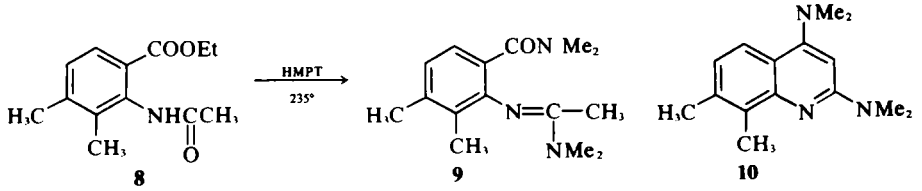


(3)

In the previous paper it was reported that 2,4-bis(dimethylamino)quinolines could be prepared in 23–30% yield simply by heating an appropriate aniline in ethyl malonate and HMPT (eqn 4).



(4)



(2)

Even though the yields are low, it is nevertheless superior to the synthesis reported in this paper for the same quinolines, because substituted N-acetylanthranilic esters in many cases are not easily available. However, substituted quinolines can be envisaged, which cannot be prepared according to eqn (4). These may be synthesized from the appropriate substituted anthranilic derivatives by the method reported in this paper. Therefore it may be concluded that the two synthetic methods are complementary to one another.

In the chemistry of condensed heteroaromatic compounds the synthesis reported in this paper may be of considerable use. Thus many aminoheteroaromatic carboxylic derivatives can be prepared by simple ring closure reactions. From these compounds condensed heteroaromatic pyridines may then be prepared by the HMPT method and the following papers will explain this synthetic approach in detail.

EXPERIMENTAL

In all experiments commercial HMPT (Pierrefitte–Auby) was used.

Synthesis of ethyl anthranilates

General procedure. The 2-aminobenzoic acid and abs EtOH (~1:10 m/m) were saturated with dry HCl and refluxed over night. The EtOH was then stripped off. The mixture made alkaline with dil. NaOH and extracted with ether. The ether was dried over K_2CO_3 and subsequently stripped off. The ester was then distilled at 0.1 mmHg. Correct analyses were in all cases obtained.

Ethyl 5-methylanthranilate, yield 70%; b.p. 90–92°/0.08 mmHg; n_D^{22} = 1.5611. NMR δ ($CDCl_3$): 1.37 (t, J = 7.3 Hz, 3H), 2.26 (s, 3H), 4.30 (q, J = 7.3 Hz, 2H), 5.65 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4 Hz, J = 2.2 Hz, 1H), 7.70 (d, J = 2.2 Hz).

Ethyl 3,4-dimethylanthranilate, distilled 96–114°/0.1 mmHg, recrystallized from petroleum ether 50–70°, yield 33%, m.p. 64°. NMR δ ($CDCl_3$): 1.43 (t, J = 7.2 Hz, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 4.36 (q, J = 7.2 Hz, 2H) 5.81 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H).

Ethyl 4,5-dimethylanthranilate, yield 64%; b.p. 125–130°/0.4 mmHg; m.p. 52–53° (petroleum ether 50–70°). NMR δ ($CDCl_3$): 1.39 (t, J = 7.1 Hz, 3H), 2.20 (s, 3H), 2.22 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 5.39 (s, 2H), 6.43 (s, 1H), 7.57 (s, 1H).

Ethyl 4-chloroanthranilate, yield 68%; b.p. 98–100°/0.07 mmHg; n_D^{21} = 1.5800. NMR δ ($CDCl_3$): 1.42 (t, J = 7.2 Hz, 3H), 4.31 (q, J = 7.2 Hz, 2H) 5.78 (s, 2H), 6.4–6.7 (m, 2H), 7.78 (d, J = 9 Hz, 1H).

Ethyl N-acetylanthranilates

General procedure. These were prepared unless otherwise indicated, by heating the benzoic ester with excess of Ac_2O in anhyd AcOH for 0.5 hr. The mixture was poured into water and the product was collected by filtration, washed with water and recrystallized from EtOH–H_2O. Correct analyses were in all cases obtained.

Ethyl N-acetyl-4-chloroanthranilate, yield 97%; m.p. 75–77°. NMR δ ($CDCl_3$): 1.45 (t, J = 7.3 Hz, 3H), 2.30 (s, 3H), 4.40 (q, J = 7.3 Hz, 2H), 7.05 (dd, J = 8.6 Hz, J = 2.1 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 8.80 (d, J = 2.1 Hz, 1H), 11.18 (s, 1H).

Ethyl N-acetyl-5-bromoanthranilate, yield 86%; m.p. 139–141°. NMR δ ($CDCl_3$): 1.42 (t, J = 7.3 Hz, 3H), 2.24 (s, 3H), 4.39 (q, J = 7.3 Hz, 2H), 7.57 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 8.8 Hz, 1H), 10.89 (s, 1H).

Ethyl N-acetyl-5-methylanthranilate, yield 92%: m.p. 112°. NMR δ ($CDCl_3$): 1.43 (t, J = 7.3 Hz, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 4.35 (q, J = 7.3 Hz, 2H), 7.35 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H), 8.62 (d, J = 8.7 Hz, 1H), 11.00 (s, 1H).

Ethyl N-acetyl-4,5-dimethylanthranilate, yield 90%; m.p. 117–118°. NMR δ ($CDCl_3$): 1.42 (t, J = 7.1 Hz, 3H), 2.23 (s, 6H), 2.30 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 7.71 (s, 1H), 8.47 (s, 1H), 10.89 (s, 1H).

Ethyl N-acetyl-3,4-dimethylanthranilate, ethyl 2 - amino - 3,4 - dimethylbenzoate (3 g), Ac_2O (8 ml) and H_2SO_4 (10 dr.) were refluxed for 10 min. The cooled mixture was poured into 40 ml M HCl, boiled 5 min, and allowed to cool to room temp. The water phase was filtered off and made alkaline with dil. NaOH, which caused a precipitation. Filtration, drying and subsequent recrystallization from petroleum ether 80–100° gave 1.3 g (55%) of the little compound; m.p. 96°. NMR δ ($CDCl_3$): 1.42 (t, J = 7.3 Hz, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 2.40 (s, 3H), 4.31 (q, J = 7.3 Hz, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 9.21 (s, 1H). (Found: C, 66.45; H, 7.34; N, 5.85. $C_{13}H_{17}NO_3$ requires: C, 66.36; H, 7.28; N, 5.95%).

2,4-Bis(dimethylamino)quinoline **7**. Ethyl N-acetylanthranilate (11 g) and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath (250°) for 3 hr. The mixture, which was allowed to cool to ~100°, was then poured into ice and 200 ml 2 M NaOH, and extracted with 3 × 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 120–180°/0.08 mmHg and subsequent recrystallization from petroleum ether 50–70° gave 8.0 g (70%) of the title compound m.p. 78–80°, lit. m.p. 77–78°[2] and 78–78.5°.[8] From 10 g 2-acetamidobenzoic acid in 50 ml HMPT by heating in 5.5 hr, 2,4-bis(dimethylamino)-quinoline was obtained in 41% yield. Using the same procedure the title compound was also obtained in 48% yield by heating methyl 2-acetamidobenzoate (19.4 g) in HMPT (50 ml) for 2.5 hr. From the latter reaction, by distillation at 190–220°/0.1 mmHg of the distillation residue and subsequent crystallization from acetone-petroleum ether, 0.9 g 3 - [2' - (*dimethylcarbamoyl*) - *phenyl*] - 2 - *methyl* - 4 - *oxo* - 3,4 - *dihydroquinazoline* **12** m.p. 141.5–143° (acetone-petroleum ether 80–100°) was obtained, NMR δ ($CDCl_3$): 2.39 (s, 3H), 2.90 and 2.97 (two s, 6H), 7.1–7.8 (m, 7H), 8.1–8.3 (m, 1H). IR CCl_4 (cm^{-1}): 1685 (strong), 1645 (strong), 1600 (strong). UV (96% EtOH): λ_{max} = 225 nm ($\log \epsilon$ = 4.56), λ_{max} = 266 nm ($\log \epsilon$ = 3.93), λ_{max} = 305 nm ($\log \epsilon$ = 3.50), λ_{max} = 316 (sh). MS, *m/e* (%): M^+ 307 (75), 306 (27), 263 (55), 262 (38), 261 (52), 236 (45), 235 (80), 77 (21), 76 (21), 44 (100). (Found: C, 70.00; H, 6.32; N, 13.60. $C_{18}H_{17}N_3O_2$ requires: C, 70.34; H, 5.58; N, 13.67%).

Performance of the above reaction at decreased temperature. Ethyl N-acetylanthranilate (10.4 g) and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath, 220°, (reaction temp. 205–209°) for 3 hr. The mixture, which was allowed to cool to ~100°, was then poured into ice, and extracted with 3 × 100 ml ether. The organic phase was washed with 50 ml H_2O, dried over K_2CO_3 and the ether was stripped off. The residue was subjected to column chromatography using silica gel as supporting material. Elution with 20% ether–petroleum ether afforded 0.18 g ethyl anthranilate, which was treated with Ac_2O in AcOH to give ethyl N-acetylanthranilate m.p. 63–65°.

Further elution with ether yielded 0.1 g 2,4-bis(dimethylamino)quinoline. Then elution with MeOH afforded 0.1 g N,N - dimethyl - N' - [2' - (dimethylcarbamoyl)phenyl] - acetamidine **6**. NMR δ ($CDCl_3$): 1.80 (s, 3H), 2.85, 2.91 and 2.97 (12H, 2.85 and 2.97 due to hindered rotation of C–N bond in the carbamoyl-group); 6.4–7.6 (m, 4H). IR (CCl_4) cm^{-1}: 1638 (strong), 1618 (strong), 1590 (medium). MS, *m/e* (%): M^+ 233 (71), 190 (57), 174 (45), 161 (100), 146 (45), 144 (95), 132 (32), 117 (34), 77 (61), 56 (56), 31 (48). (Found: C, 66.92; H, 8.21; N, 18.01. $C_{13}H_{19}N_3O$ requires: C, 66.20; H, 7.91; N, 17.22%.) The water-phase, which above was extracted with ether, was then extracted with 3 × 100 ml CH_2Cl_2. After drying over K_2CO_3 the CH_2Cl_2 was stripped off, and HMPT was subsequently distilled off at 107°/11 mm. The residuum crystallized on standing over night. Recrystallization from petroleum ether 60–80° and CCl_4 afforded 3.0 g (29%) 2 - acetamido - N,N - dimethylbenzamid **5**. m.p. 104–106°, lit. m.p. 103–106°[10] and 94–96°.[11] The water phase, which was extracted above with CH_2Cl_2, was acidified and filtration yielded 2.5 g (28%) N-acetylanthranilic acid **4**, m.p. 183–185°, lit. m.p. 185°[12] and 184–186°.[13]

Ethyl N-acetylanthranilate (10.4 g) and NMPT (50 ml) were heated in a distillation flask on a silicone oil bath, 230°, (temp. 215–218°) for 3 hr. 6.4 g 60% of 2,4 - bis(dimethylamino) - quinoline **7** could be isolated by using the work up procedure described for that compound.

2,4 - *Bis(dimethylamino)* - 6 - *chloroquinoline*. Using the procedure as described for **7**, ethyl N - acetyl - 5 - chloro - anthranilate (10 g) and HMPT (50 ml) yielded 5.4 g (52%) of the

title compound m.p. 106–108° (petroleum ether 80–100°), lit. m.p. 106–107°.[2]

2,4 - *Bis(dimethylamino)* - 7 - *chloroquinoline.* Using the procedure described for 7, ethyl N - acetyl - 4 - chloroanthranilate (10 g) and HMPT (50 ml) yielded 4.2 g (41%) of the title compound; b.p. 150–152°/0.1 mmHg; $n_D^{25} = 1.6712$. NMR δ ($CDCl_3$): 3.00 (s, 6H), 3.28 (s, 6H), 6.18 (s, 1H), 7.05 (dd, J = 8.6 Hz and J = 2.1 Hz, 1H), 7.6–7.9 (m, 2H). IR (CCl_4) cm^{-1}: 1595 (strong), 1550 (medium), 1500 (medium), 1395 (strong). UV (96% EtOH): $\lambda_{max} = 253$ nm ($\log \epsilon = 4.60$), $\lambda_{max} = 267$ nm (sh), $\lambda_{max} = 307$ nm ($\log \epsilon = 3.80$), $\lambda_{max} = 348$ nm ($\log \epsilon = 3.86$). (Found: C, 62.70; H, 6.60; Cl, 13.95; N, 16.98. $C_{13}H_{16}ClN_3$ requires: C, 62.52; H, 6.46; Cl, 16.86; N, 14.19%).

2,4 - *Bis(dimethylamino)* - 6 - *bromquinoline.* Using the procedure as described for 7, ethyl N - acetyl - 5 - bromoanthranilate (7 g) and HMPT (50 ml) yielded 3.5 g (49%) of the title compound; m.p. 121–122° (petroleum ether 80–100°). NMR δ ($CDCl_3$): 2.98 (s, 6H), 3.27 (s, 6H), 6.23 (s, 1H), 7.5–7.6 (m, 2H), 7.9–8.0 (m, 1H). IR (CCl_4) cm^{-1}; 1590 (strong), 1545 (medium), 1495 (medium), 1395 (strong). UV (96% EtOH): $\lambda_{max} = 248$ nm ($\log \epsilon = 4.50$), $\lambda_{max} = 278$ nm ($\log \epsilon = 4.50$), $\lambda_{max} = 357$ nm ($\log \epsilon = 3.79$). (Found: C, 53.10; H, 5.45; Br, 27.24; N, 14.22. $C_{13}H_{16}BrN_3$ requires: C, 53.07; H, 5.48; Br, 27.16; N, 14.28%).

2.4 - *Bis(dimethylamino)* - 6 - *methylquinoline.* Using the pracedure described for 7, ethyl N - acetyl - 5 - methylanthranilate (11.1 g) and HMPT (50 ml) yielded 6.7 g 58% of the title compound m.p. 77–79° (petroleum ether 80–100°) lit. m.p. 75–77°.[2]

2,4 - *Bis(dimethylamino)* - 6,7 - *dimethylquinoline.* Using the procedure described for 7, ethyl N - acetyl - 4,5 - dimethylanthranilate (8.6 g) and HMPT (50 ml) yielded 5.9 g (66%) of the title compound; m.p. 89–91°. NMR δ ($CDCl_3$): 2.37 (s, 6H), 2.93 (s, 6H), 3.18 (s, 6H), 6.17 (s, 1H), 7.45 (s, 1H), 7.55 (s, 1H). IR (CCl_4) cm^{-1}: 1595 (strong), 1550 (medium), 1500 (medium), 1395 (strong). UV (96% EtOH): $\lambda_{max} = 253$ nm ($\log \epsilon = 4.63$), $\lambda_{max} = 303$ nm ($\log \epsilon = 3.80$), $\lambda_{max} = 346$ nm ($\log \epsilon = 3.85$). (Found: C, 74.00; H, 8.62; N, 17.18. $C_{15}H_{21}N_3$ requires: C, 74.03; H, 8.70; N, 17.21%).

2,4 - *Bis(dimethylamino)* - 7,8 - *dimethylquinoline* **10**. Ethyl N - acetyl - 3,4 - dimethylanthranilate (1.0 g) and HMPT (5 ml) were heated in a distillation flask on a silicone oil bath (250°) for 3 hr. The mixture, cooled to ~ 100°, was then poured into ice and 50 ml 2 M NaOH, and extracted with 3 × 40 ml ether. The organic phase was washed with 2 × 20 ml H_2O, dried over K_2CO_3, and the ether was stripped off. By preparative TLC (silica gel as supporting material and ether for elution) was isolated 0.18 g (17%) of the title compound m.p. 119–120° (petroleum ether 50–70°), lit. m.p. 116–117°.[2] A material was also isolated which on a silica gel column (Merck Fertigsäle B) by elution with MeOH was purified to give 0.08 g N,N - *dimethyl* - N' - [3',4' - *dimethyl* - 2' - (*dimethylcarbamoyl*) - *phenyl*] - *acetamidine* **9**. NMR δ ($CDCl_3$): 1.24 (s, 3H), 2.00 (s, 3H), 2.28 (s, 3H), 2.89, 3.00, and 3.02 (12H, 2.89 and 3.02 due to hindered rotation of C–N bond in carbomoyl group), 6.78 (d, J = 8 Hz, 1H), 6.90 (d, J = 8 Hz, 1H). IR (CCl_4) cm^{-1}: 1638 (strong), 1618 (strong), 1590 (medium). MS, *m/e* (%): $M^+ + 1$ 262 (18), M^+ 261 (100), 260 (16), 246 (25), 217 (55), 215 (19), 201 (27), 189 (60), 175 (19), 174 (17), 172 (44), 146 (25), 105 (16), 56 (17).

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