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PHOSPHORAMIDES—V†

SYNTHESIS OF 4,6-BIS(DIMETHYLAMINO)THIENO[2,3-b]PYRIDINES BY AN HMPT INDUCED RING CLOSURE REACTION

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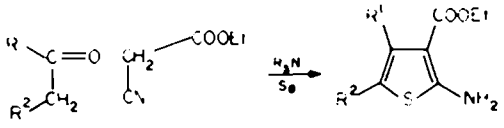
Abstract—2-Acetamido-3-thiophenecarboxylic acid ethyl esters **1** have been heated in HMPT to reflux temperature to produce 4,6-bis(dimethylamino)thieno[2,3-b]pyridines **7**. Substituents in the 4 position of the thiophene ring were found to exert steric hindrance on the reaction. Only a multistep mechanism can account for the product **7**. The intermediates **2–5** were also isolated in the reaction of **1a** with HMPT.

In earlier investigations it was shown that 2,4-bis(dimethylamino)quinolines could be obtained directly by two different ring closure reactions. They were prepared in 23–30% yield simply by heating an appropriate aniline in ethyl malonate and HMPT[1] (Scheme 1).

The alternative procedure was to heat N-acetylanthranilic esters in HMPT to reflux temperature.[2] Even though the yields were rather small in the first reaction, it seems nevertheless to be superior to the latter, because substituted N-acetylanthranilic esters in many cases are not easily available.

However, the two synthetic methods are complementary to one another. For syntheses of thieno[2,3-b]pyridines simple 2-aminothiophenes are unsuitable starting materials as they are quoted to be very unstable.[3] On the other hand ethyl 2-acetamido-3-thiophenecarboxylates are easily available from the corresponding aminocompounds, which can be synthesized directly from sulphur and ethyl cyanoacetate[4] (Eq. 1).

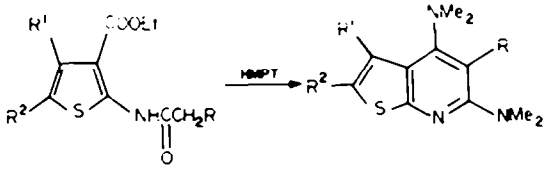


RESULTS AND DISCUSSION

4,6-Bis(dimethylamino)thieno[2,3-b]pyridines were produced by heating ethyl 2-acetamido-3-thiophencarboxylates in HMPT to reflux temperature (Table 1). 35–48% Yields were obtained for starting materials substituted with an alkyl or a phenyl group in the 5-position (**1a–1d**). For substitution in the 4-position with methylene or methyl groups (**1f** and **1g**) the yields dramatically decreased to less than 10%, which probably was due to steric hindrance. With a phenyl group in the 4-position of the thiophene ring (**1e**) this effect was even more pronounced as the corresponding thieno[2,3-b]pyridine could not be isolated.

In order to isolate the intermediates in the reaction of **1a** with HMPT, the temperature was lowered from ~235° to 207–9° and the thienol[2,3-b]pyridine **7a** could not then be isolated. The 3-thiophenecarboxylic acid **2** was isolated in 2% yield, the 3-thiophenecarboxamide **3**

Table 1.



1 **7**

Starting material	R	R^1	R^2	Product	%
1a	H	H	CH_3	**7a**	48
1b	H	H	CH_2CH_3	**7b**	35
1c	H	H	$CH(CH_3)_2$	**7c**	37
1d	H	H	C_6H_5	**7d**	39
1e	H	C_6H_5	H	**7e**	0
1f	H	$-CH_2-CH_2-CH_2-$		**7f**	6
1g	H	CH_3	CH_3	**7g**	10
9	CH_2CH_3	H	CH_3	**10**	24

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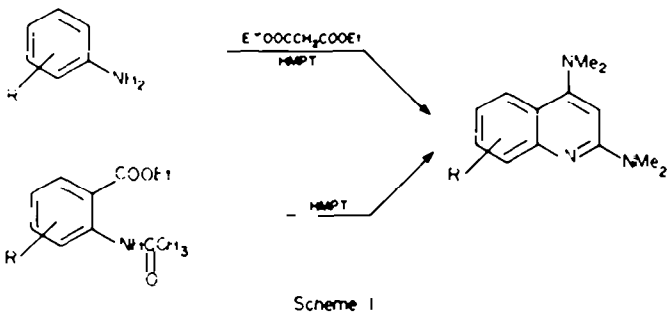
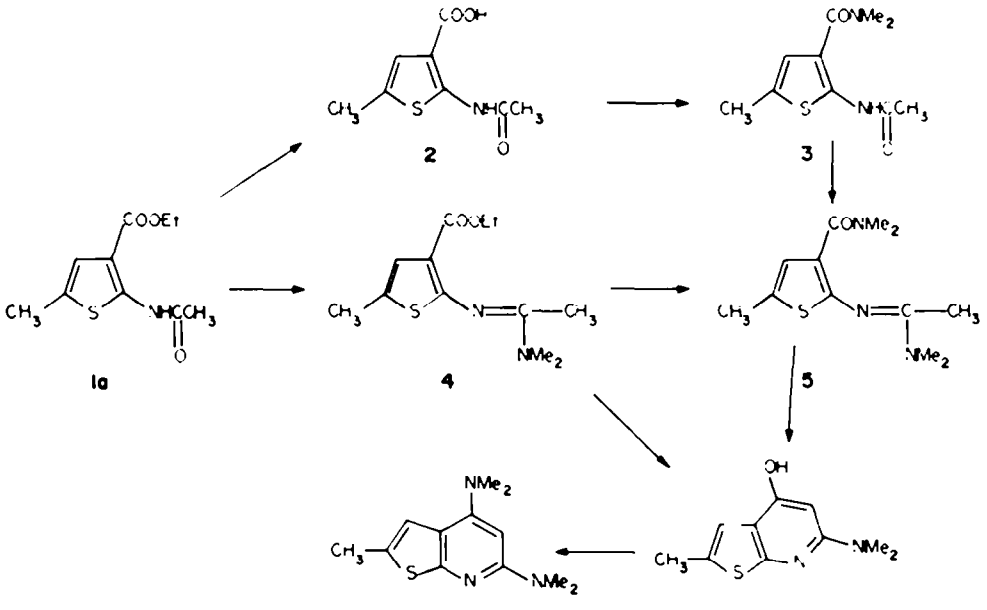


Scheme 1



Scheme 2

in 1% yield, the amidine **5** in 1% yield. These intermediates suggest a multistep reaction pathway, which is like the one found for reaction of 2-acetamidobenzoates with HMPT, whereby 2,4-bis-dimethylaminoquinolines were formed[2] (Scheme 2). In the first step, the starting material **1** is dealkylated to produce the carboxylic acid **2**, which is transformed into the carboxyamide **3**. The latter step is very likely, as the synthesis of N,N-dimethylcarboxamides by heating the corresponding carboxylic acids in HMPT is well known.[5,6] Also it is known that N,N-dimethylamidines are produced when secondary carboxamides are heated in HMPT.[7,8] Therefore, it may be assumed that the amidine **6** is formed in the next step by reaction of the amide **3** with HMPT. The 1-dimethylamino)ethyleneamino group is then believed to tautomerize to a reactive enamine, which may be intramolecularly acylated by the carbamoyl group to give the 4-hydroxythieno[2,3-b]pyridine **6**. The last step is then replacement of the OH group with a dimethylamino group. Also this transformation is very likely as HMPT has been shown to replace OH groups of heterocyclic aromatics with dimethylamino groups at elevated temperature.[9] In the reaction of the thiophene **1a** with HMPT, the amidine **4** also was isolated in 14% yield. This indicates an alternative pathway to the product **7**. The amidine may be formed from the starting material. The ester **4** is then supposed to undergo a dealkylation reaction. The acid formed by that, is transformed into the carboxamide **5** and the reaction proceeds further forward as above. Alternatively the amidine **4** may undergo a direct ring closure reaction to the 4-hydroxyquinoline **6**, which then as above is assumed to undergo further reaction.

As mentioned above substitution at the 4-position caused steric hindrance to the formation of the thieno-[2,3-b]pyridines. In the reaction of the carboxamide **1e** in HMPT at reflux temperature only the amidine **8** could be isolated in 47% yield and 4,6-bis(dimethylamino)-3-phenyl-thieno[2,3-b]pyridine could not be detected in any fraction obtained by chromatography of the reaction mixture. By comparison with Scheme 2 it is seen that the amidine **8** is the intermediate which should undergo the ring closure reaction, if the thieno[2,3-b]pyridine was formed. However, as the reaction stopped at **8** it may be concluded that it is the very ring closure reaction which can be sterically detained by substitution on the 4-position of the thiophene ring.

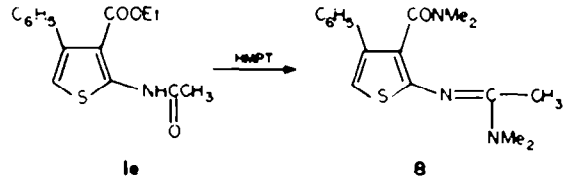
In compound **9**, where the acetyl group of **1a** is replaced by butyryl, the corresponding thieno[2,3-b]pyridine **10** was produced in 24% yield, Scheme 3. The dithienodiazocine **11** also was isolated in that reaction and it may be assumed that this ring system is formed from two molecules of 2-amino-5-methyl-3-thiophenecarboxylic acid ethyl ester, which may be formed by deacylation of the starting material.

EXPERIMENTAL

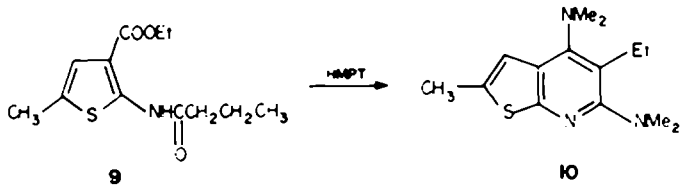
In all experiments commercial HMPT (Pierrefitte-Auby) was used.

2-Amino-2-thiophenecarboxylic esters were prepared as described by Gewald *et al.*[4]

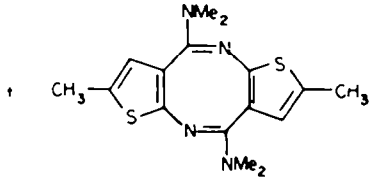
2-Amino-5-isopropyl-3-thiophenecarboxylic acid ethyl ester. To ethyl cyanoacetate (45.3 g) and S (12.8 g) in DMF (80 ml),



(2)



9 10



11

Scheme 3

triethylamine (30 ml) was added under stirring. To this soln 3-methyl-butanal (34.5 g), was added dropwise and the temp. increased to 55°. After stirring 1 hr, the mixture was poured into 600 ml H_2O, which was extracted with ether. The ether phase was dried over K_2CO_3. Distillation 104–110°/0.08 gave 34.4 g (40%) of the title compound; n_D^{23} = 1.5507. NMR δ ($CDCl_3$): 1.25 (d, J = 6.7 Hz, 6H), 1.35 (t, J = 7.0 Hz, 3H), 2.87 (h, d, J = 6.7 Hz and J = 1.2 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H) 6.00 (broad s, 2H), 6.61 (d, J = 1.2 Hz, 1H). IR (CCl_4) cm $^{-1}$: 3490 (NH), 3320 (NH), and 1675 (C = 0). UV (96% EtOH): λ_{max} = 225 nm (log ε = 4.51), λ_{max} = 261 nm (log ε = 3.70). λ_{max} = 305 nm (log ε = 3.79). (Found: C, 56.30; H, 7.11; N, 6.51; S, 14.94. $C_{10}H_{15}NO_2S$ requires: C, 56.32; H, 7.09; N, 6.57; S, 15.00%).

2-Acetamido-3-thiophenecarboxylic acid ethyl esters (General procedure). These were prepared by refluxing the corresponding amino compound with excess Ac_2O in anhyd AcOH for 1 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 obtained in all cases.

2 - *Acetamido* - 5 - *methyl* - 3 - *thiophenecarboxylic acid ethyl ester* **1a**. Yield 78%; m.p. 75–6°. NMR δ ($CDCl_3$): 1.40 (t, J = 7.5 Hz, 3H), 2.30 (s, 3H), 2.40 (d, J = 1.2 Hz, 3H) 4.34 (q, J = 7.5 Hz, 2H), 6.87 (q, J = 1.2 Hz, 1H).

2 - *Acetamido* - 5 - *iso* - *propyl* - 3 - *thiophenecarboxylic acid ethyl ester* (**1c**). Yield 89%; m.p. 54–5°. NMR δ($CDCl_3$): 1.30 (d, J = 6.9 Hz, 6H), 1.36 (t, J = 7.0 Hz, 3H), 2.25 (s, 3H), 3.04 (h, J = 6.9 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 6.79 (d, J = 1.0 Hz, 1H), 10.80 (broad s, 1H).

2 - *Acetamido* - 5 - *phenyl* - 3 - *thiophenecarboxylic acid ethyl ester* (**1d**). Yield 81%; m.p. 103–6°. NMR δ($CDCl_3$): 1.41 (t, J = 7 Hz, 3H), 2.32 (s, 3H), 4.39 (q, J = 7 Hz, 2H) 7.2–7.8 (m, 6H), 11.0 (broad s, 1H).

2 - *Acetamido* - 4,5 - *trimethylene* - 3 - *thiophenecarboxylic acid ethyl ester* (**1f**). Yield 89%; m.p. 96–9°. NMR δ($CDCl_3$): 1.38 (t, J = 7.3 Hz, 3H) 2.30 (s, 3H), 2.2–2.6 (m, 2H), 2–65–3.0 (m, 4H) 4.30 (q, J = 7.3 Hz, 2H), 11.0 (broad s, 1H).

2 - *Butyramido* - 5 - *methyl* - 3 - *thiophenecarboxylic acid ethyl ester* (**9**). 2 - Amino - 5 - methyl - 3 - thiophenecarboxylic acid ethyl ester (32 g), butyric anhydride (34 g), and butyric acid (50 ml) were heated to 140° for 1 hr. The reaction mixture was poured into water and extracted with ether. The ether phase was washed with 3 × 100 ml 2 M NaOH. Distillation 134–8/0.06 mm gave 40 g (88%) of the title compound; m.p. 33° (petroleum ether). NMR δ($CDCl_3$): 1.01 (t, J = 7 Hz, 3H), 1.36 (t, 7.1 Hz, 3H). 1.80 (sextet, J = 7 Hz, 2H), 2.38 (d, J = 1.2 Hz, 3H), 2.48 (t, J = 7 Hz, 2H), 4.30 (q, J = 7.1, 2H) 6.77 (q, J = 1.2 Hz, 1H), 10.77 (broad s, 1H).

4,6 - *Bis(dimethylamino)* - 2 - *methylthieno*[2,3-b]*pyridine* (**7a**). **1a** (10 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 3 × 100 ml ether. The ether phase was extracted with 4 M HCl. The water phase was then made alkaline with 2 M NaOH and extracted with ether. The organic phase was dried over K_2CO_3 and the ether was stripped off. Sublimation of 0.05 mm Hg gave 5.0 g (48%) **7a**, m.p. 134° (petroleum ether 60–80°–CCl_4). NMR δ($CDCl_3$): 2.48 (d, J = 1.3 Hz, 3H), 3.00 (s, 6H), 3.06 (s, 6H), 5.73 (s, 1H), 6.86 (q, J = 1.3 Hz, 1H). IR (CCl_4) cm $^{-1}$: 1575 (strong), 1560 (shoulder), 1530 (strong), 1400 (strong), 1140 (strong), 740 (strong). UV (96% EtOH): λ_{max} = 213 nm (log ε = 4.24), λ_{max} = 265 nm (log ε = 4.44), λ_{max} = 293 nm (log ε = 4.21). (Found: C, 61.15; H, 7.11; N, 17.70; S, 13.67. $C_{12}H_{17}N_3S$ requires: C, 61.25; H, 7.28; N, 17.86; S, 13.60%).

Performance of the above reaction at decreased temperature. **1a** (10.7 g) and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath, 230° (reaction temp. 207–9°) 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. The residue was treated with petroleum ether and 4.5 g (42%) of the *starting material* **1a** precipitated. The mother liquor was subjected to preparative TLC. Using silica gel as supporting material and ether for elution; (a) 0.15 g (2%) 2 - *amino* - 5 - *methyl* - 3 - *thiophenecarboxylic acid* ethyl ester R_f = 0.78. (b) 0.6 g (6%) **1a**, R_f = 0.69; (c) 1.7 g (14%) 2 - [1' - (*dimethylamino*)*ethylideneamino*] - 5 - *methyl* - 3 - *thiophenecarboxylic acid ethyl ester* **4**, R_f = 0.49, b.p. 127/0.08; n_D^{23} = 1.5744. NMR δ($CDCl_3$): 1.25 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 2.30 (d, J = 1.2 Hz, 3H), 3.07 (s, 6H) 4.15 (q, J = 7.2 Hz, 2H), 6.76 (q, J = 1.2 Hz, 1H). IR (CCl_4) cm $^{-1}$: 1700 (strong), 1595 (strong), 1395 (strong), 1235 (strong), 1150 (strong). UV (96% EtOH): λ_{max} = 225 nm (log ε = 4.49), λ_{max} = 308 nm (log ε = 3.88). MS. *m/e* (%): M^+ 254 (100), 209 (20), 208 (34), 182 (35), 164 (20), 152 (21), 140 (31), 138 (24), 70 (23), 56 (76); (d) 0.15 g (1%) N,N - *dimethyl* - 2 - *acetamido* - 5 - *methyl* - 3 - *thiophenecarboxamide* **3**, R_f = 0.26, m.p. 147–8°. NMR δ($CDCl_3$): 2.20 (s, 3H), 2.40 (d, J = 1.2 Hz, 3H), 3.12 (s, 6H), 6.06 (q, J = 1.2 Hz, 1H) 10.78 (broad s, 1H). IR (CCl_4) cm $^{-1}$: 1690 (strong), 1605 (strong), 1560 (medium), 1525 (strong), 1390 (strong), 1150 (strong). UV (96% EtOH): 221 nm (log ε = 4.22), 294 nm (log ε = 3.91). MS *m/e* (%): M^+ 226 (52), 184 (77), 141 (15), 140 (100), 139 (78), 112 (12), 72 (17). 46 (23), 44 (21), 43 (48). (e) 0.14 g (1%) N,N - *dimethyl* - 2[1' - *dimethylamino*)*ethylidenamino*] - 5 - *methyl* - 3 - *thiophenecarboxamide* **5** (liquid), R_f 0.05. NMR δ($CDCl_3$): 2.00 (s, 3H), 2.33 (d, J = 1.0 Hz, 3H), 3.00 (s, 6H), 3.07 (s, 6H), 6.48 (q, J = 1.0 Hz, 1H). MS: M^+ = 253.1262. $C_{12}H_{19}N_3OS$ requires M^+ = 253.1249. The water phase, which above was extracted with ether, was then extracted with 3 × 50 ml $CHCl_3$. $CDCl_3$ was stripped off, and HMPT subsequently distilled off at ~60°/0.1 mm. By treatment of the residuum with ether further 0.46 g (4%) of crystalline **3** was obtained. The water phase, which was extracted above with $CDCl_3$, was acidified, and extracted with ether. Evaporation of the ether yielded 0.15 g (2%) of 2 - *acetamido* - 5 - *methyl* - 3 - *thiophenecarboxylic acid* **2** m.p. 194–6 (H_2O–EtOH). NMR ($CDCl_3$–MeOD): 2.27 (s, 3H), 2.38 (d,

J = 1.2 Hz, 3H), 6.82 (q, J = 1.2 Hz, 1H). IR (KBr) cm^{-1}: 2500–3500 (medium) 1670 (strong), 1640 (strong), 1250 (strong). UV (96% EtOH): 222 nm (log ε = 4.27), 301 nm (log ε = 3.96). MS *m/e* (%): M^+ 199 (37), 157 (50), 141 (6), 140 (11), 139 (100), 111 (12), 84 (7), 59 (8), 72 (6), 43 (40).

4,6 - *Bis(dimethylamino)* - 2 - *ethylthieno*[2,3 - b]*pyridine* **7b**. **1b** (7.4 g)[11] and HMPT (50 ml) were heated in a distillation flash 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 combined ether phases were dried over K_2CO_3. Distillation 136–170°/0.08 nm gave a fraction, which was subjected to silica gel column chromatography using ether-petroleum ether (1:4) for elution. 2.7 g (35%) **7b** were obtained; b.p. 165–7°/0.15 mm, m.p. 41–3°. NMR δ($CDCl_3$): 1.31 (t, J = 7.5 Hz, 3H), 2.83 (qd, J = 7.5 Hz and J = 1.2 Hz, 2H), 3.02 (s, 6H), 3.10 (s, 6H), 5.74 (s, 1H), 6.84 (t, J = 1.2 Hz, 1H). IR (CCl_4) cm^{-1}: 1575 (strong), 1560 (shoulder), 1525 (strong), 1400 (strong), 1130 (strong). UV (96% EtOH): λ_{max} = 215 nm (log ε = 4.23), λ_{max} = 265 nm (log ε = 4.46), λ_{max} = 292 nm (log ε = 4.23). (Found: C, 62.85; H, 6.80; N, 16.92; S, 13.05. $C_{13}H_{19}N_3S$ requires: C, 63.14; H, 6.93; N, 16.99; S, 12.94%).

4,6 - *Bis(dimethylamino)* - 2 - *isopropylthieno*[2,3 - b]*pyridine* **7c** was obtained from **1c** (13 g) and HMPT (50 ml) as described for **7b**, yield 5.0 g (38%); b.p. 146–156/0.06 mm; n_D^{23} = 1.6241. NMR δ (CCl_4): 1.35 (d, J = 7.1 Hz, 6H), 2.93 (s, 6H), 2.99 (s, 6H), 5.58 (s, 1H), 6.68 (d, J = 0.9 Hz, 1H). IR (CCl_4) cm^{-1}: 1575 (strong), 1560 (shoulder), 1520 (strong), 1400 (strong), 1135 (strong), 740 (strong). UV (96% EtOH): λ_{max} = 213 nm (log ε = 4.23), λ_{max} = 265 nm (log ε = 4.45), λ_{max} = 293 nm (log ε = 4.22). (Found: C, 63.75; H, 8.02; N, 15.72; S, 12.08. $C_{14}H_{21}N_3S$ requires: C, 63.85; H, 8.04; N, 15.96; S, 12.15%).

4,6 - *Bis(dimethylamino)* - 2 - *phenylthieno*[2,3 - b]*pyridine* **7d** was obtained from **1d** (10 g) and HMPT (50 ml) as described for **7b**. However, column chromatography was performed without preceeding distillation, yield 4.0 g (39%); m.p. 128–131°. NMR δ($CDCl_3$): 3.03 (s, 6H), 3.08 (s, 6H), 5.65 (s, 1H), 7.2–7.8 (m, 6H). IR (CCl_4) cm^{-1}: 1570 (strong), 1545 (shoulder), 1400 (strong), 1135 (strong). UV (96% EtOH): λ_{max} = 219 nm (log ε = 4.40), λ_{max} = 280 nm (log ε = 4.20), λ_{max} = 346 nm (log ε = 4.45). (Found: C, 68.60; H, 6.33; N, 14.02; S, 10.88. $C_{17}H_{19}N_3S$ requires: C, 68.66; H, 6.44; N, 14.13; S, 10.76%).

4,6 *Bis(dimethylamino)* - 2,3 - *trimethylenethieno*[2,3 - b]*pyridine* **7f** was obtained from **1f** (6 g) and HMPT (50 ml) as described for **7b**, yield 0.35 g (6%); m.p. 96–101° (petroleum ether 50–70°). NMR δ ($CDCl_3$): 2.2–2.7 (m, 2H), 2.7–3.2 (m, 4H), 2.87 (s, 6H), 3.13 (s, 6H), 5.99 (s, 1H). IR (CCl_4) cm^{-1}: 1575 (strong), 1550 (shoulder), 1520 (strong), 1395 (strong), 1140 (medium). UV (96% EtOH): λ_{max} = 218 nm (log ε = 4.20), λ_{max} = 270 nm (log ε = 4.40), λ_{max} = 298 nm (log ε = 4.17). (Found: C, 64.00; H, 7.18; N, 15.19; S, 12.21. $C_{14}H_{19}N_3S$ requires: C, 64.34; H, 7.33; N, 16.08; S, 12.25%).

4,6 - *Bis(dimethylamino)* - 2,3 - *dimethylthieno*[2,3 - b]*pyridine* **7g** was prepared from **1g** (10.3 g)[11] and HMPT (50 ml) as described for **7b**, yield 1.1 g (10%); m.p. 95–9° (petroleum ether 50–70°). NMR δ ($CDCl_3$): 2.34 (s, 3H), 2.41 (s, 3H), 2.76 (s, 6H), 3.09 (s, 6H), 6.00 (s, 1 H). IR (CCl_4) cm^{-1}: 1575 (strong), 1550 (strong), 1515 (strong), 1390 (strong), 1140 (strong), 970 (strong). UV (96% EtOH): λ_{max} = 214 nm (log ε = 4.17), λ_{max} = 269 nm (log ε = 4.37), λ_{max} = 295 nm (log ε = 4.12). (Found: C, 62.20; H, 7.34; N, 16.29; S, 13.57. $C_{13}H_{19}N_3S$ requires: C, 62.62; H, 7.68; N, 16.86; S, 12.84%).

4,6 - *Bis(dimethylamino)* - 5 - *ethyl* - 2 - *methylthieno*[2,3 - b]*pyridine* **10** was prepared from **9** (10.0 g) and HMPT (50 ml) as described for **7b**, yield 2.5 g (24%); b.p. 120–2/0.1 mm; n_D^{23} = 1.6032. NMR δ($CDCl_3$): 1.07 (t, J = 7.7 Hz, 3H), 2.53 (d, J = 1.2 Hz, 3H), 2.81 (s, 6H), 2.93 (s, 6H), CH_2 of the Et group is overlapped by the two dimethylamino groups, 6.94 (q, J = 1.2 Hz, 1H). IR (CCl_4) cm^{-1}: 1550 (strong), 1515 (strong), 1080 (strong). UV (96% EtOH): λ_{max} = 227 nm (log ε = 4.20), λ_{max} = 276 nm (log ε = 4.24), λ_{max} = 300 nm (shoulder). (Found: C, 63.90; H, 8.11; N, 15.98; S, 12.35. $C_{14}H_{21}N_3S$ requires: C, 63.85; H, 8.04; N, 15.96; S, 12.15%). During work up there was also by distillation obtained a high boiling fraction 180–240/0.1 mm. By treatment of this fraction with a small amount of ether 0.6 g (9%) of 4,9 - *bis(dimethylamino)* - 2,7 - *dimethyl* - *dithieno*[2,3 - b:2',3' - f][1,5]*diazocine* **11** precipitated; m.p. 224–5° (benzin 80–100–xylene). NMR δ ($CDCl_3$): 2.30 (d, J = 1.2 Hz, 6H), 2.98 (s, 12H), 6.12 (q, J = 1.2 Hz, 2H). IR (CCl_4) cm^{-1}: 1585 (strong), 1550 (strong), 1495 (strong), 1090 (strong). UV (96% EtOH): λ_{max} = 234 nm (log ε = 4.35), λ_{max} = 292 (shoulder). MS (%): M^+ + 2 334 (13), M^+ + 1 333 (26), M^+ 332 (100), 288 (10), 247 (10), 245 (11), 233 (28), 220 (11), 166 (10). (Found: C, 57.65; H, 6.14; N, 16.93; S, 19.11. $C_{16}H_{20}N_4S_2$ requires: C, 57.82; H, 6.07; N, 16.86; S, 19.26%).

N,N - *Dimethyl* - 2 - [1' - (*dimethylamino*)*ethyleneamino*] - 4 - *phenyl* - 3 - *thiophenecarboxamide* **8**. **1e** (10 g)[11] and HMPT (50 ml) were heated in a distillation flask on a silicone oil bath, 250°, for 5 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 combined ether phases were dried over K_2CO_3. Silica gel column chromatography using ether-petroleum ether (1:1), ether, and at last MeOH for elution gave in the MeOH phase 5.6 g (55%) of **8** (oil). NMR δ ($CDCl_3$): 2.10 (s, 3H), 2.86 (d, hindered rotation about C-N bond in the carbamoyl group, J = 9 Hz, 6H) 3.02 (s, 6H), 6.71 (s, 1H), 7.1–7.5 (m, 5H). MS: M^+ = 315.1390. $C_{17}H_{21}N_3OS$ requires M^+ = 315.1405.

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