

# Phosphoramides. X.\* Phosphorus Pentaoxide Amine Mixtures and HMPT as Reagents in the Synthesis of 4-Amino- and 4-Dimethylamino-2,3-polymethylenequinolines

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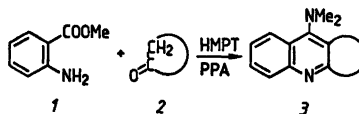
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4-Dimethylamino-2,3-polymethylenequinolines *3a–g* have been prepared by heating appropriate cycloalkanones with methyl anthranilate *1* in HMPT at reflux temperature. 6,12-Bis(dimethylamino)dibenzo[*b,f*][1,5]diazocine *10* and 2,3,5,6-bis(polymethylene)pyridines *11* were isolated as by-products. 4-Amino-2,3-polymethylenequinolines *16a–d* were prepared by heating cyclohexanone or cycloheptanone and methyl anthranilates with a phosphorus pentaoxide, diethylamine, and diethylamine hydrochloride reagent system. Using diethylamine or dibutylamine without the corresponding hydrochlorides 11-ethylamino- and 11-butylamino-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoline *14* were isolated in low yields. In many of the above reactions 2,3-polymethylene-4(1*H*)-quinolinones could be isolated and were believed to be reaction intermediates.

pounds can be obtained by a one-step procedure from simple starting materials.

## HEXAMETHYLPHOSPHORIC TRIAMIDE AS RING CLOSURE AND DIMETHYLAMINATION REAGENT

4-Dimethylamino-2,3-polymethylenequinolines *3* were prepared in 13–65 % yield by heating methyl anthranilate *1* and cycloalkanones *2* in hexamethylphosphoric triamide, HMPT, with addition of a catalytic amount of polyphosphoric acid, PPA, at 260–270 °C for 2–20 h, Table 1. In Scheme 1 possible



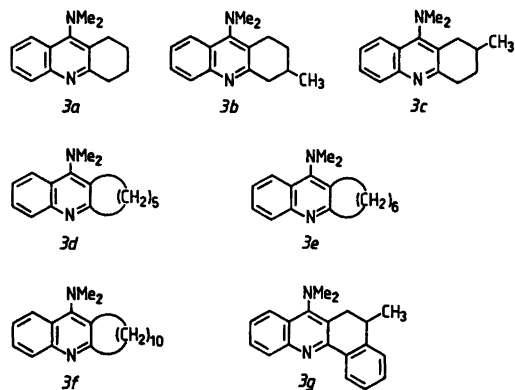
mechanisms for formation of 9-dimethylamino-1,2,3,4-tetrahydroacridine *3a* are suggested. The intermediate quinolinones *7* were isolated in low yields in the synthesis of the quinolines *3*, when cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, and cycloheptanone were used. It was possible to separate the solvent and reagent function of HMPT by lowering the reaction temperature, because elevated temperature is required to put the dimethylamino group onto the quinoline ring. In this manner 42–70 % yield of 2,3-tetra- and 2,3-pentamethylene-4(1*H*)-quinolinones *7* were obtained. It was not possible to isolate the anil *4*, which is believed to be an intermediate in the corresponding Tiedtke reaction.<sup>8</sup> Instead,

Many 4-substituted-2,3-polymethylenequinolines possess a wide spectrum of pharmacological activities. 9-Amino-1,2,3,4-tetrahydroacridine (Tacrine) is a potent anticholinesterase inhibitor,<sup>1,2</sup> and some 4-*N*-substituted-amino-2,3-polymethylenequinolines are analeptics, respiratory stimulants and analgetics.<sup>3–5</sup>

The usual synthetic routes to these compounds proceed *via* 4-chloro-2,3-polymethylenequinolines, which were prepared from the corresponding hydroxy compounds by treatment with POCl<sub>3</sub>. By reaction of the chloro compounds with appropriate amines in phenol at normal pressure the required 4-amino-2,3-polymethylenequinolines were obtained.<sup>3,6,7</sup> In this investigation it is shown that these com-

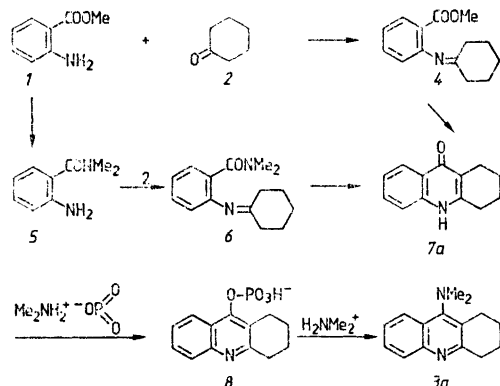
\* Part IX, cf. Ref. 9.

**Table 1.** 4-Dimethylamino-2,3-polymethylenequinolines prepared from methyl anthranilate and cycloalkanones.



Product	Ketone	Reaction time (h)	Yield (%)
3a	Cyclohexanone	2	40
3b	3-Methylcyclohexanone	2½	33
3c	4-Methylcyclohexanone	2½	28
3d	Cycloheptanone	17	65
3e	Cyclooctanone	20	37
3f	Cyclododecanone	17	13
3g	4-Methyltetralone	17	28

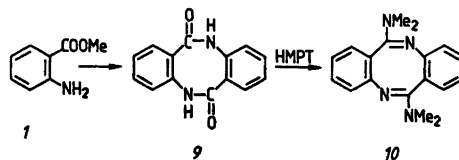
*o*-amino-*N,N*-dimethylbenzamide **5** was detected in the reaction mixture after heating for 1 h. **5** was also synthesized from **1** under the same reaction conditions as above, but without addition of **2**. Refluxing the benzamide **5** and cyclohexanone with a catalytic amount of *p*-toluenesulfonic acid afforded **6**, which was heated in HMPT to give **3a**. This indicates



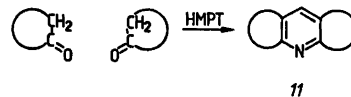
**Scheme 1.**

a pathway in which the benzamide derivative **5** is involved, cf. Scheme 1. The acridine **3a** was also synthesized from **7a** by heating in HMPT to reflux temperature. When HMPT is used as a reagent for replacing a hydroxy group with a dimethylamino group, it has been shown that the metaphosphate ion is transiently formed,<sup>9</sup> which here leads to the formation of **8**.

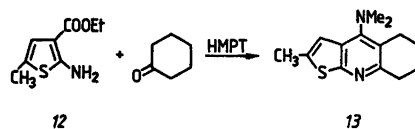
Some by-products were isolated from the reaction mixtures. HMPT reacted with **1** to produce the dibenzodiazocine **10**, probably via **9**.



Other by-products were 2,3,5,6-bis(polymethylene)pyridines **11** which were isolated in the reaction of cyclooctanone and cyclododecanone with **1** and HMPT. Analogous products have previously been obtained in low yields by refluxing cycloalkanones in HMPT.<sup>10</sup>

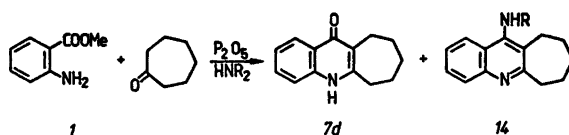


The synthesis described here also gives a simple route to the corresponding thienopyridines. Then aminothiophenecarboxylates are used instead of **1**, exemplified by the synthesis of the thienopyridine **13** from the thiophene derivative **12**.



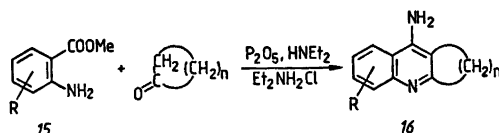
#### PHOSPHORUS PENTAOXIDE AMINE MIXTURES AS RING CLOSURE AND AMINATION REAGENTS

Phosphorus pentaoxide amine mixtures have recently been observed to undergo reactions at 200–250°C similar to those of HMPT.<sup>11</sup> Heating **1** and cycloheptanone in a mixture of phosphorus pentaoxide and diethylamine was



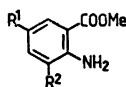
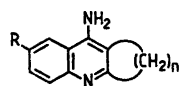
expected to produce 11-diethylamino-7,8,9,10-tetra-hydro-6H-cyclohepta[b]quinoline. Instead the cyclohepta[b]quinolinone **7d** was isolated in 66 % yield. Also ethylaminoquinoline **14** (R=Et) was isolated in 5 % yield. Using a phosphorus pentoxide dibutylamine reagent system, **7d** was also isolated in high yield. In the latter reaction the quinolines **14** (R=H) and **14** (R=butyl) were produced in 1 and 12 % yield, respectively. Obviously the severe reaction conditions cause dealkylation reactions of the intermediately formed dialkylaminoquinolines with formation of **14**. Contrary to that, demethylation was never observed in the preparation of the 4-dimethylaminoquinolines **3** by the HMPT method. When phosphorus pentoxide dialkylamine mixtures are used as reagents, a mechanism similar to that given in Scheme 1 may be suggested for replacing the oxo group of **7d** with a dialkylamino group. Sterical repulsion is increased in the nucleophilic aromatic substitution reaction of the

4-quinolinyl phosphate using diethylamine or dibutylamine, in comparison with the attack of dimethylamine on the same substrate, which can then explain that only 4-dimethylaminoquinolines can be prepared in good yields.



Dialkylamine hydrochloride was added to the reaction mixture in order to catalyze the formation of the aminoquinolines. 4-Amino-2,3-polymethylenequinolines **16** ( $n=4, 5$ ) were then prepared at 260 °C in 11–51 % yield from **15** and cycloalkanones, cf. Table 2. The severe reaction conditions also caused dehalogenation, which was observed for methyl 5-iodoanthranilate and methyl 3,5-dichloroanthranilate. The ring size of the cycloalkanone influenced the yield of the 4-amino-2,3-polymethylenequino-

Table 2. 4-Amino-2,3-polymethylenequinolines prepared from methyl anthranilates and cycloalkanones  $O=C(CH_2)_nCH_2$ .



Product	R	n	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	M.p. (lit. m.p.)
<b>16a</b>	H	4	H	H	16	182–183°C (183–184°C) <sup>15</sup>
<b>16b</b>	H	5	H	H	51	176–177°C (176–177°C) <sup>6</sup>
<b>16b</b>	H	5	I	H	31	
<b>16c<sup>a</sup></b>	Cl	5	Cl	H	32	241–242°C
<b>16c</b>	Cl	5	Cl	Cl	34	
<b>16d</b>	CH <sub>3</sub>	5	CH <sub>3</sub>	H	29	207–208°C (209–210°C) <sup>6</sup>

<sup>a</sup> <sup>1</sup>H NMR  $\delta$ (CDCl<sub>3</sub>): 1.9–2.1 (6 H, m), 2.8–3.0 (2 H, m), 3.1–3.3 (2 H, m), 4.7 (2 H, s), 7.5–8.0 (3 H, m). IR (KBr) cm<sup>-1</sup>: 3490, 3340. UV,  $\lambda_{max}$  (96 % EtOH) (log  $\epsilon$ ): 220 (4.63), 255 (4.55), 322.5 (3.85) nm. Anal. C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>Cl: C, H, N.

lines 16 enormously. Using cyclooctanone, 16 (R=H and  $n=6$ ) was not isolated at all. It was attempted to increase the yield of 16 (R=H and  $n=4$ ) using a phosphorus pentoxide, dibutylamine, and dibutylamine hydrochloride reagent system, but almost an identical yield of 16 (R=H) was obtained as above. The 4-aminquinoline 16 was prepared from 7d using the phosphorus pentoxide, diethylamine, and diethylamine hydrochloride reagent system, making 2,3-polymethylene-4(1H)-quinolinones possible intermediates in the above reactions.

## EXPERIMENTAL

Commercial HMPT (Pierreite Auby) was used. Warning: Nasal tumours are observed in rats exposed daily to 400 and 4000 parts per billion (ppb) HMPT after 8 months of exposure.<sup>16</sup>

**2-Amino-N,N-dimethylbenzamide 5.** Methyl anthranilate 1 (15.1 g), PPA (1.0 g), and HMPT (50 ml) were heated for 3 h in a distillation flask on an oil bath (260°C). The mixture, allowed to cool to 100°C, was poured onto ice, 200 ml of 2 M NaOH were added and then was extracted with 3×300 ml ether. The organic phase was washed with 50 ml 2 M NaOH, dried over  $K_2CO_3$  and the ether was stripped off. Distillation at 120–160°C/0.4 mmHg gave 6.6 g (40%) of the title compound, which was redistilled at 125–130°C/0.6 mmHg, picrate m.p. 150.5–151.5°C, lit.<sup>12</sup> m.p. 151–152°C.

**2-Cyclohexylideneamino-N,N-dimethylbenzamide 6.** 2-Amino-N,N-dimethylbenzamide 5 (5 g), cyclohexanone (3.6 g), *p*-toluenesulfonic acid (0.2 g) and benzene (100 ml) were refluxed for 70 h using a Dean-Stark water separator. The benzene was then stripped off and subsequent distillation at 135–140°C/0.25 mmHg gave 4.5 g (60%) of 6, <sup>1</sup>H NMR,  $\delta(CDCl_3)$ : 1.4–2.0 (6 H, m), 2.0–2.3 (2 H, m), 2.3–2.6 (2 H, m), 3.0 (6 H, d, hindered rotation of  $NMe_2$ ), 6.6–6.8 (1 H, m), 7.1–7.5 (3 H, m). MS, Found: *m/e* 244.1569. Calc. for  $C_{15}H_{20}N_2O$ : *m/e* 244.1575.

**1,2,3,4-Tetrahydro-9-acridanone 7a.** Methyl anthranilate 1 (15.1 g), cyclohexanone (9.8 g), PPA (1.0 g), and HMPT (50 ml) were heated for 3 h in a distillation flask on a silicone oil bath (230°C). The mixture, allowed to cool to 100°C, was then poured onto ice and 200 ml of 2 M NaOH were added. The precipitate was recrystallized from pyridine to give 8.4 g (42%) of the title compound, m.p. >365°C, lit. m.p. 370°C.<sup>18</sup> Picrate m.p. 197–198°C, lit. m.p. 198°C.<sup>18</sup>

**2-Methyl-1,2,3,4-tetrahydro-9-acridanone 7c.** Methyl anthranilate 1 (15.1 g), 4-methylcyclohexanone (11.2 g), PPA, (1.0 g), and HMPT

(50 ml) were reacted as above to give 11.3 g (53%) of the title compound, m.p. 345–346°C, lit. m.p. >350°C.<sup>14</sup>

**5,6,7,8,9,10-Hexahydro-11H-cyclohepta[b]quinoline-11-one 7d.** Methyl anthranilate 1 (15.1 g), cycloheptanone (13.4 g), PPA (1.0 g), and HMPT (50 ml) were reacted as above at 240°C to give 15 g (70%) of the title compound, m.p. 347–348°C (pyridine), lit. m.p. 330°C.<sup>4</sup>

**9-Dimethylamino-1,2,3,4-tetrahydroacridine 3a.** (i) Methyl anthranilate 1 (15.1 g), cyclohexanone (11 g), PPA (0.5 g), and HMPT (50 ml) were heated for 2 h in a distillation flask on an oil bath (250°C). The mixture, allowed to cool to 100°C was then poured into ice and 200 ml 2 M NaOH and extracted with 3×300 ml ether. The organic phase was washed with 50 ml 2 M NaOH, dried over  $K_2CO_3$  and the ether was stripped off. Distillation of the organic phase at 120–170°C/0.15 mmHg and subsequent recrystallization from ligroin (80–100°C) gave 9.1 g (40%) of the title compound m.p. 113–114°C. <sup>1</sup>H NMR  $\delta(CDCl_3)$ : 1.7–2.1 (4H, m), 2.7–3.2 (4H, m), 3.0 (6H, s), 7.1–7.7 (2H, m), 7.8–8.0 (2H, m). UV,  $\lambda_{max}$  (96% EtOH) (log  $\epsilon$ ): 205 (4.52), 229 (4.56), 250 (3.44), 295 (3.44), 308 (3.60), 321 (3.76), 340 (3.66). IR (KBr)  $cm^{-1}$ : 1610, 1570, 1560, 1500. Anal.  $C_{15}H_{18}N_2$ : C, H, N. The mother liquid from the crystallization was chromatographed on a silica gel column. Using ether–light petroleum (1:5), 0.1 g of 6,12-bis(dimethylamino)dibenzo-[b, f][1,5]diazocine 10 was isolated, m.p. 144–145°C (ligroin (80–100°C)). <sup>1</sup>H NMR  $\delta(CDCl_3)$ : 2.9 (12 H, s), 6.7–7.5 (8 H, m). MS, *m/e* 292 M<sup>+</sup>. Anal.  $C_{18}H_{20}N_4$ : C, H, N. In another experiment the reaction was stopped after 1 h. The mixture was then worked up as above and upon distillation of the organic phase at 120–160°C/0.4 mmHg 2.1 g of 2-amino-N,N-dimethylbenzamide 5 was isolated. (ii) 1,2,3,4-Tetrahydro-9-acridanone 7a (6.6 g), PPA (0.3 g), and HMPT (20 ml) were heated for 3 h in a distillation flask on an oil bath (260°C). The mixture was then worked up as above. Distillation at 130–190°C/0.2 mmHg and subsequent crystallization gave 2.1 g (28%) of 3a. (iii) 2-Cyclohexylideneamino-N,N-dimethylbenzamide 6 (2 g), PPA (0.2 g), and HMPT (6 ml) were heated for 4½ h in a distillation flask on an oil bath (260°C). The mixture allowed to cool to 100°C was poured into ice and 25 ml 2 M NaOH and extracted with 3×25 ml ether. The organic phase was washed with 25 ml 2 M NaOH, dried over  $K_2CO_3$ , and the ether stripped off. Preparative silica gel TLC with ether for elution afforded 0.5 g (27%) of 3a ( $R_F=0.43$ ).

**9-Dimethylamino-3-methyl-1,2,3,4-tetrahydroacridine 3b.** Methyl anthranilate 1 (15.1 g), 3-methylcyclohexanone (11.7 g), PPA (1.0 g), and HMPT (50 ml) were heated for 2½ h in a distillation flask on an oil bath (260°C). The mixture allowed to cool to 160°C, was then poured into ice and 200 ml 2 M NaOH and extracted with 3×300 ml ether. The organic

phase was washed with 50 ml 2M NaOH, dried over  $K_2CO_3$ , and the ether was stripped off. Distillation at 150–190°C/0.7 mmHg gave 8.0 g (35 %) of the title compound, m.p. 84.5–86°C (light petroleum).  $^1H$  NMR  $\delta(CDCl_3)$ : 1.1 (3H, d,  $J=6$  Hz), 1.3–3.3 (7H, m), 3.0 (6H, s), 7.2–7.6 (2H, m), 7.8–8.1 (2H, m). Anal.  $C_{15}H_{20}N_2$ : C, H, N. *3-Methyl-1,2,3,4-tetrahydro-9-acridanone* 7b precipitated after acidifying the alkaline water phase. It was recrystallized from pyridine to give 2.1 g (10 %), m.p. 361.5–362.5°C, lit. m.p. 362°C.<sup>13</sup>

*9-Dimethylamino-2-methyl-1,2,3,4-tetrahydro-acridine* 3c. Methyl anthranilate 1 (15.1 g), 4-methylcyclohexanone (11.2 g), PPA (0.8 g), and HMPT (50 ml) were heated for 2½ h in a distillation flask on an oil bath (260°C). The mixture was then worked up as above for 3b. Distillation at 120–190°C/0.09 mmHg and subsequent recrystallization from light petroleum afforded 6.7 g (28 %) of the title compound 3c, m.p. 98–99°C.  $^1H$  NMR  $\delta(CDCl_3)$ : 1.1 (3H, d,  $J=6$  Hz), 1.5–3.2 (7 H, m), 3.0 (6 H, s), 7.2–7.6 (2H, m), 7.8–8.1 (2H, m). Anal.  $C_{15}H_{20}N_2$ : C, H, N. Upon acidifying the alkaline waterphase 1.9 g (9 %) of *2-methyl-1,2,3,4-tetrahydro-9-acridanone* 7c precipitated.

*11-Dimethylamino-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline* 3d. Methyl anthranilate 1 (15.1 g), cycloheptanone (13.4 g), PPA (1.0 g), and HMPT (50 ml) were heated for 17 h in a distillation flask on an oil bath (260°C). The mixture was then worked up as above for 3b. Distillation at 120–170°C/0.03 mmHg and subsequent redistillation at 145–150°C/0.3 mmHg gave 15.6 g (65 %) of the title compound,  $n_D^{25}=1.6125$ , picrate m.p. 172–173°C.  $^1H$  NMR  $\delta(CDCl_3)$ : 1.6–2.0 (6H, m), 2.7–3.3 (4H, m), 3.0 (6H, s), 7.3–7.7 (2H, m), 7.9–8.2 (2H, m). Found: C 79.95; H 8.66; N 11.20. Calc. for  $C_{15}H_{20}N_2$ : C 79.95; H 8.39; N 11.66. From the waterphase 1.1 g (5 %) *5,6,7,8,9,10-hexahydro-11H-cyclohepta[b]quinoline-11-one* 7d precipitated upon acidifying.

*12-Dimethylamino-6,7,8,9,10,11-hexahydro-cycloocta[b]quinoline* 3e. Methyl anthranilate 1 (15.1 g) cyclooctanone (15.1 g), PPA (1.0 g), and HMPT (50 ml) were heated for 20 h in a distillation flask on a silicone oil bath (260°C). The mixture was then worked up as above for 3b. Distillation at 120–180°C/0.2 mmHg and subsequent recrystallization from ligroin (80–100°C) gave 1.1 g (8 %) *1,2,3,4,5,6,8,9,10,11,12,13-dodecahydrodicycloocta[b,e]pyridine*, m.p. 143–144°C.  $^1H$  NMR  $\delta(CDCl_3)$ : 1.0–1.6 (8H, m), 1.6–2.1 (8H, m), 2.6–3.1 (8H, m), 7.0 (1H, s). UV,  $\lambda_{max}$  (96 % EtOH) (log  $\epsilon$ ): 218 (3.96), 235 (3.45), 272 (3.80), 275 (3.87), 279 (3.86), 284 (3.84). Anal.  $C_{17}H_{22}N_2$ : C, H, N. Redistillation of the mother liquid at 140–145°C/0.15 mmHg gave 9.3 (37 %) of the title compound 3e, m.p. 71–72.5°C (light petroleum).  $^1H$  NMR  $\delta(CDCl_3)$ : 1.2–1.6 (4 H, m), 1.6–2.1 (4 H, m), 2.9–3.3 (4 H, m), 3.0

(6 H, s), 7.3–7.7 (2 H, m), 7.8–8.1 (2 H, m). Found: C 80.15; H 8.74; N 10.39. Calc. for  $C_{17}H_{22}N_2$ : C 80.27; H 8.72; N 11.01.

*16-Dimethylamino-6,7,8,9,10,11,12,13,14,15-decahydrocyclo-dodeca[b]quinoline* 3f. Methyl anthranilate 1 (15.1 g) cyclo-dodecanone (21.8 g), PPA (1.0 g), and HMPT (50 ml) were heated for 17 h in a distillation flask on a silicone oil bath (260°C). The mixture was then worked up as above for 3b. Distillation at 160–205°C/0.6 mmHg gave 6.9 g. From this fraction there was isolated, by preparative silica gel TLC with ether–light petroleum (1:1) for elution: (i) 1.5 g (10 %) *1,2,3,4,5,6,7,8,9,10,12,13,14,15,16,17,18,19,20,21-eicosahydrodicyclo-dodeca[b,e]pyridine* ( $R_F=0.48$ ), m.p. 139–140°C.  $^1H$  NMR  $\delta(CDCl_3)$ : 1.2–1.6 (24 H, m), 1.6–2.1 (8 H, m), 2.4–3.1 (8 H, m), 7.2 (1 H, s). MS,  $m/e$  355.32397. Calc. for  $C_{25}H_{41}N$ :  $m/e$  355.32388. (ii) 3.9 g (13 %) of the title compound 3f ( $R_F=0.57$ ), b.p. 185–190°C/0.55 mmHg, m.p. 69.5–71°C (light petroleum).  $^1H$  NMR  $\delta(CDCl_3)$ : 1.4–1.8 (12 H, m), 1.8–2.3 (4 H, m), 2.8–3.3 (4 H, m), 3.1 (6 H, s), 7.3–7.7 (2 H, m), 7.9–8.2 (2 H, m). Found: C 81.15; H 9.88; N 8.27. Calc. for  $C_{15}H_{20}N_2$ : C 81.23; H 9.74; N 9.02.

*7-Dimethylamino-5-methyl-5,6-dihydrobenz[c]-acridine* 3g. Methyl anthranilate 1 (15.1 g), 4-methyltetralone (19.2 g), PPA (1.0 g), and HMPT (50 ml) were heated for 17 h in a distillation flask on an oil bath (260°C). The mixture was then worked up as above for 3b. Distillation at 175–210°C/0.6 mmHg gave 8.0 g (28 %) of the title compound 3g. By preparative silica gel TLC with ether–light petroleum (1:4) for elution 3g was further purified ( $R_F=0.47$ ), b.p. 190°C/0.35 mmHg picrate m.p. 217–218°C.  $^1H$  NMR  $\delta(CDCl_3)$ : 1.3 (3 H, d,  $J=7$ Hz), 3.0–3.3 (3 H, m), 3.1 (6 H, s), 7.3–7.8 (5 H, m), 8.0–8.3 (2 H, m), 8.3–8.6 (1 H, m). UV,  $\lambda_{max}$  (96 % EtOH) (log  $\epsilon$ ): 213 (4.56), 223 (4.44), 250 (4.49), 264 (4.52), 276 (4.30), 289 (4.25), 315 (3.95), 330 (4.06), 343 (4.06). Picrate found: C 59.80; H 4.27; N 13.10. Calc for  $C_{26}H_{23}N_5O_7$ : C 60.34; H 4.48; N 13.53.

*4-Dimethylamino-2-methyl-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline* 13. Ethyl 2-amino-5-methyl-3-thiophenecarboxylate 12 (18.5 g), cyclohexanone (11.0 g), PPA (0.7 g), and HMPT (50 ml) were heated for 3 h in a distillation flask on an oil bath (250°C). The mixture was then worked up as above for 3b. Distillation at 139–141°C/0.08 mmHg gave 7.8 g (30 %) of the title compound  $n_D^{25}=1.6222$ .  $^1H$  NMR  $\delta(CDCl_3)$ : 1.8 (4 H, m), 2.52 (3 H, d,  $J=1.2$  Hz), 2.7 (4H, m), 2.98 (6 H, s), 7.01 (1 H, q,  $J=1.2$  Hz). IR ( $CCl_4$ )  $cm^{-1}$ : 1550, 1520. UV,  $\lambda_{max}$  (96 % EtOH) (log  $\epsilon$ ): 230 (4.29), 250 (4.31), 306 (3.96). Found: C 68.50; H 7.19; N 11.25; S 12.85. Calc. for  $C_{14}H_{16}N_2S$ : C 68.27; H 6.37; N 11.37; S 13.00.

## PREPARATION OF 4-AMINO-2,3-POLY-METHYLENEQUINOLINES 16.

*General procedure.*  $P_2O_5$  (0.31 mol) and diethylamine hydrochloride (0.4 mol) were mixed. To this mixture methyl anthranilate (0.1 mol) and cycloalkanone (0.12 mol) were added. Then diethylamine (0.4 mol) was added dropwise under stirring. The reaction mixture was heated on an oil bath at 260°C (reaction temperature 250–255°C) for 21 h with stirring. The mixture was then poured onto ice and 2 M NaOH (200 ml) was added. The water phase was extracted with 3 × 200 ml ether. The combined ether phases were washed with 50 ml 2 M NaOH, dried over  $K_2CO_3$  and the ether was stripped off. The residue was triturated with ether and the precipitate 16 was recrystallized from ethyl acetate.

*Preparation of 16b from 5,6,7,8,9,10-Hexahydro-11H-cyclohepta[b]quinoline-11-one 7d.* 7d (4.8 g),  $P_2O_5$  (3.4 g), and diethylamine hydrochloride (5 g) were heated on an oil bath at 270°C until melting. The mixture was cooled to 100°C and diethylamine (4.6 ml) was added dropwise. The reaction mixture was then refluxed under stirring on an oil bath at 270°C for 21 h. The mixture was then worked up as above in the general procedure to give 2.1 g (44%) of 16b.

*11-Ethylamino-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline 14 (R=Et).* To  $P_2O_5$  (20 g) diethyl amine (30 g) was added dropwise under stirring. To this mixture methyl anthranilate (15.1 g) and cycloheptanone (11.1 g) were added. The mixture was heated with stirring on an oil bath at 260°C (reaction temperature 100–150°C) for 26 h. The mixture was then worked up as above for 16. The ether was stripped off and preparative silica gel TLC with ether for elution afforded: 1.1 g (5%) of the title compound ( $R_F=0.4$ ), MS, found:  $m/e$  240.1620. Calc. for  $C_{18}H_{20}N_2$ :  $m/e$  240.1626. From the water phase 14.1 g (66%) of 5,6,7,8,9,10-hexahydro-11H-cyclohepta[b]quinoline-11-one 7d was isolated upon acidifying.

*11-Butylamino-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline 14 (R=Bu).* To  $P_2O_5$  (25 g) dibutylamine (51.6 g) was added dropwise with stirring. To this mixture methyl anthranilate (15.1 g) and cycloheptanone (11.2 g) were added. The mixture was heated with stirring on an oil bath at 260°C (reaction temperature 150°C) for 3½ h. Then further  $P_2O_5$  (10 g) was added and the reaction temperature was increased to 220°C. The reaction mixture was now refluxed under stirring on an oil bath at 260°C for 17½ h. The mixture was then worked up as above for 16. The ether was stripped off and the residue was distilled. Distillation 150–180°C/0.09 mmHg gave 5.3 g of a material, which was subjected to preparative TLC, using silica gel as supporting material and ether for elution.

(i) 3.1 g (12%) of the title compound was isolated, ( $R_F=0.44$ )  $n_D^{27}=1.6021$ , b.p. 180°C/0.15 mmHg.  $^1H$  NMR  $\delta(CDCl_3)$ : 0.7–2.1 (13 H, m), 2.7–3.5 (6 H, m), 4.05 (1 H, s), 7.3–7.8 (2 H, m), 7.8–8.2 (2 H, m). IR (film)  $cm^{-1}$ : 3350. UV,  $\lambda_{max}$  (96% EtOH) (log  $\epsilon$ ): 226 (4.18), 235 (4.12), 307.5 (3.49), 320 (3.52). Found: C 80.00; H 8.77; N 10.26. Calc. for  $C_{18}H_{20}N_2$ : C 80.55; H 9.01; N 10.44.

(ii) 0.2 g (1%) of 16b. From the alkaline water phase 15.1 g (71%) of 5,6,7,8,9,10-hexahydro-11H-cyclohepta[b]quinoline-11-one 7d precipitated upon acidifying.

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