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Potential Antimalarials. IX*
Di-Mannich Bases of 4-(7′-Trifluoromethylquinazolin-4′-ylamino)phenol and 4-(7′-Trifluoromethylquinolin-4′-ylamino)phenol

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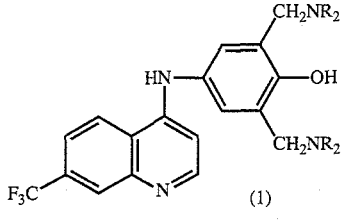
Abstract

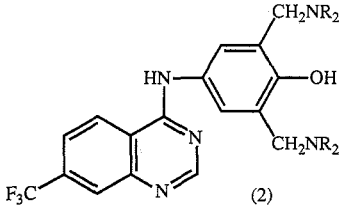
Syntheses are reported for a series of di-Mannich bases of 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol derived from 4-chloro-7-trifluoromethylquinazoline with the di-Mannich bases of 4-aminophenol. Some analogous quinolines were prepared similarly. When tested for antimalarial activity against *Plasmodium falciparum in vitro*, the quinazolines were rather less active than the corresponding quinolines.

Introduction

In recent papers[1–4] we have described the synthesis of di-Mannich bases (1) of 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol and their significant biological activity against *Plasmodium vinkei vinkei* and *P. falciparum*. We now report the synthesis of many 3′-aza analogues, the di-Mannich bases (2) of 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol, and also further quinolines. These compounds were then examined for antimalarial activity in *in vitro* tests against *P. falciparum*.



(1)



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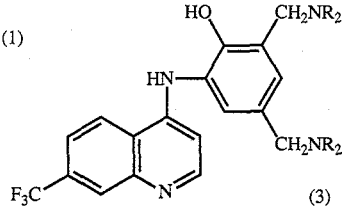

(3)

* Part VIII, *Aust. J. Chem.*, 1989, **42**, 2191.

[1] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1985, **38**, 1827.
[2] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1986, **39**, 51.
[3] Scott, H. V., Tan., W.-L., and Barlin, G. B., *Ann. Trop. Med. Parasitol.*, 1987, **81**, 85.
[4] Scott, H. V., Tan, W.-L., and Barlin, G. B., *Ann. Trop. Med. Parasitol.*, 1988, **82**, 127.

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Syntheses

The necessary intermediate for the preparation of the 4-substituted 7-trifluoromethylquinazolines described below was 2-amino-4-trifluoromethylbenzoic acid. Its preparation has been described by Simet[5] from 1-chloro-2-nitro-4-trifluoromethylbenzene through 2-nitro-4-trifluoromethylphenylacetic acid, 6-trifluoromethyloxindole and 6-trifluoromethylisatin; and by Hauptschein *et al.*[6] from 2-nitro-4-trifluoromethylaniline (prepared from 1-chloro-2-nitro-4-trifluoromethylbenzene by reaction with ethanolic ammonia as described by Pettit and Tatlow[7]) through 2-nitro-4-trifluoromethylbenzonitrile and 2-nitro-4-trifluoromethylbenzoic acid. We found Simet's procedure[5] to be preferable. 4-Hydroxy- and 4-chloro-7-trifluoromethylquinazoline were prepared as outlined by Armarego[8] and Armarego and Smith[9] from the reaction of 2-amino-4-trifluoromethylbenzoic acid with formamide followed by chlorination. The required final compounds were prepared from 4-chloroquinazoline and the preprepared di-Mannich bases of *p*-aminophenol. The latter were obtained by Mannich reactions on *p*-nitrophenol (some preparations were described by one of us previously[10]) followed by catalytic reduction of the nitrophenols to the aminophenols.

Condensation of 4-chloro-7-trifluoromethylquinazoline with these di-Mannich bases in methanol gave the required di-Mannich bases (2) of 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol. *N*-(4′-Diethylamino-1′-methylbutyl)-7-trifluoromethylquinazolin-4-amine, the 3′-aza-7′-trifluoromethyl analogue of chloroquine, was prepared from 4-chloro-7-trifluoromethylquinazoline and N^1, N^1-diethylpentane-1,4-diamine.

In a similar manner to that described above were prepared two di-Mannich bases (1) of 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol.

^{1}H N.M.R. Spectra

The ^{1}H n.m.r. spectra of the compounds synthesized in this work are reported in the Experimental section. In the 4-substituted 7-trifluoromethylquinazolines the signal due to H2 was furthest downfield (except for that in 7-trifluoromethylquinazolin-4-ol), H5 and H6 showed *ortho* coupling and H6 showed *meta* coupling to H8 which resulted in a broadening of the signals to broad singlets or broad doublets except for H8 in 7-trifluoromethylquinazolin-4-ol. The ^{1}H n.m.r. spectra of the 4-substituted 7-trifluoromethylquinolines were consistent with data for analogous compounds reported previously.[1,2,10]

Biological Activities

The new compounds reported in this paper were tested for antimalarial activity by one of us (C.J.) under the kind supervision of Dr G. Butcher, Zoology Department, Australian National University. The procedures for these *in vitro* tests against the FCQ-27 (chloroquine sensitive) strain of the human malaria,

[5] Simet, L., *J. Org. Chem.*, 1963, **28**, 3580.
[6] Hauptschein, M., Nodiff, E. A., and Saggiomo, A. J., *J. Am. Chem. Soc.*, 1954, **76**, 1051.
[7] Pettit, M. R., and Tatlow, J. C., *J. Chem. Soc.*, 1954, 3852.
[8] Armarego, W. L. F., *J. Chem. Soc.*, 1962, 561.
[9] Armarego, W. L. F., and Smith, J. I. C., *J. Chem. Soc. B*, 1967, 449.
[10] Barlin, G. B., and Ireland, S. J., *Aust. J. Chem.*, 1988, **41**, 1727.

Plasmodium falciparum, were as described previously[3,4] except that the initial stock solutions were prepared in ethanol.

The results for these compounds are given in Table 1 together with those for reference quinolines and chloroquine.

Table 1. *In vitro* antimalarial activity of some 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenols and 4-(7′-trifluoromethylquinolin-4′-ylamino)-phenols against the FCQ-27 isolate of *Plasmodium falciparum*

Results are expressed as nmol l^{-1}

Inhibitor	IC_{50}
(2; $NR_2 = NEt_2$)	150
(2; $NR_2 = NPr_2$)	50
(2; NR_2 = NMeBu	30
(2; $NR_2 = N(C_5H_{11})_2$)	90
(2; NR_2 = pyrrolidin-1-yl)	30
(2; NR_2 = piperidin-1-yl)	70
(2; NR_2 = 3-methylpiperidin-1-yl)	12
(2; NR_2 = 3,5-dimethylpiperidin-1-yl)	20
(2; NR_2 = 4-methylpiperidin-1-yl)	40
(2; NR_2 = 4-benzylpiperidin-1-yl)	40
(1; $NR_2 = NEt_2$) (ref. 4)	1·3
(1; $NR_2 = NPr_2$) (ref. 3)	1·7
(1; NR_2 = NMeBu)	10
(1; $NR_2 = N(C_5H_{11})_2$)	175
(1; NR_2 = pyrrolidin-1-yl) (ref. 4)	0·9
(1; NR_2 = piperidin-1-yl) (ref. 4)	0·7
(1; NR_2 = 3-methylpiperidin-1-yl)[A]	1·6
(1; NR_2 = 3,5-dimethylpiperidin-1-yl) (ref. 4)	1·4
(1; NR_2 = 4-methylpiperidin-1-yl)[A]	1·5
(3; $NR_2 = NEt_2$)[B]	49·8
(3; NR_2 = 4-methylpiperidin-1-yl)[B]	42
Chloroquine	15

[A] Scott, H. V., Barlin, G. B., and Ireland, S. J., unpublished data.
[B] Barlin, G. B., and Yan, J.-H., *Aust. J. Chem.*, 1989, **42**, 2191.

Six of the di-Mannich derivatives of 4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol (2) gave IC_{50} values of less than 50 nM, and the two most active compounds, those from 3-methylpiperidine and 3,5-dimethylpiperidine, gave IC_{50} values of 12 and 20 nM respectively. The di-Mannich base from diethylamine (2; $NR_2 = NEt_2$) was appreciably less active with an IC_{50} value of 150 nM.

Comparison of the quinazolines (2) with the quinolines (1) listed in Table 1 reveals that with the exception of the dipentylamino compound (2; $NR_2 = N(C_5H_{11})_2$) the quinazolines were less active than the corresponding quinolines. This lower activity of the quinazolines varied from *c.* 110-fold for the diethylamino compound (2; $NR_2 = NEt_2$) (in which it was most marked) to *c.* threefold for (2; NR_2 = NMeBu).

The di-Mannich base from 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol with butylmethylamine gave an IC_{50} value of 10 indicating it was less active than its diethylamino analogue,[4] a trend continuing in the corresponding dipentylamino compound with an IC_{50} value of 175 nM.

The isomeric di-Mannich bases derived from 2-(7′-trifluoromethylquinazolin-4′-ylamino)phenol were not prepared because we have recently shown[11] that the compounds (3) (Table 1), di-Mannich bases of 2-(7′-trifluoromethylquinolin-4′-ylamino)phenol, were less active than the corresponding compounds (1), di-Mannich bases derived from 4-(7′-trifluoromethylquinolin-4′-ylamino)phenol.

Experimental

Solids for analysis were dried at 100°/0·2 mmHg for 6 h unless specified otherwise. Melting points were taken in Pyrex capillaries. Analyses were performed by the Australian National University Analytical Services Unit. ^{1}H n.m.r. spectra were generally recorded at 90 MHz and 30° with a Jeol FX90Q Fourier-transform spectrometer in $CDCl_3$ solutions unless otherwise stated (e.g. CD_3SOCD_3) with tetramethylsilane as internal standard. In cases where greater peak dispersion was required, spectra were also recorded at 200 or 300 MHz on Varian XL200 or XL300 spectrometers. I.r. spectra were recorded in potassium bromide discs with a Unicam SP1050 infrared spectrometer. The following compounds were required for the preparation of 2-amino-4-trifluoromethylbenzoic acid. Details of variations to literature procedures and the physical properties of the intermediates are recorded below.

2-Nitro-4-trifluoromethylphenylacetic acid, m.p. 143–145° (lit.[5] 145–146·5°). ^{1}H n.m.r. δ 4·15, s, CH_2; 6·35, br, COOH; 7·54, d, $J_{5,6}$ 8 Hz, H6; 7·89, br d, $J_{5,6}$ 8 Hz, H5; 8·42, br s, H3.

6-Trifluoromethyloxindole, m.p. 186–188° (lit.[5] 186–188°). ^{1}H n.m.r. δ 3·63, s, CH_2; 7·18, s, H7; 7·33, q, $J_{5,6}$ 8 Hz, H5,6; 8·70, br, NH. I.r. ν_{max} 3160 (NH st), 1710 (C=O st), 1640, 1470, 1329, 1309, 1265, 1170, 1120, 1055 cm^{-1}.

6-Trifluoromethylisatin, m.p. 193–195° (lit.[5] 192–194·5°) (Found, for a sample dried at 80°/0·2 mmHg for 4 h: C, 50·4; H, 1·8; F, 26·5; N, 6·4. Calc. for $C_9H_4F_3NO_2$: C, 50·2; H, 1·9; F, 26·5; N, 6·5%). ^{1}H n.m.r. (CD_3SOCD_3) δ 4·5, br, NH; 7·12, s, H7; 7·41, d, $J_{4,5}$ 8 Hz, H5(4); 7·71, d, $J_{4,5}$ 8 Hz, H4(5). I.r. ν_{max} 3140 (NH st), 1780 and 1765 and 1730 (C=O st), 1650 (C=O st?), 1468, 1330, 1190, 1145, 1065 cm^{-1}.

2-Nitro-4-trifluoromethylaniline

This compound was prepared from 1-chloro-2-nitro-4-trifluoromethylbenzene with ethanolic ammonia at 120° as described by Pettit and Tatlow.[7] It had m.p. 105–107° (lit.[1] 106–107°). ^{1}H n.m.r. δ 6·45, br s, NH_2; 6·91, d $J_{5,6}$ 8·5 Hz, H6; 7·56, dd, $J_{5,6}$ 8·5, $J_{3,5}$ 2 Hz, H5; 8·43, s, H3. I.r. ν_{max} 3518 (NH st), 3390 (NH sym st), 1667 (NO_2 st?), 1590 (ar skeleton st), 1340 (NO_2 st), 1290, 1130, 916, 840, 700, 630 cm^{-1}.

2-Nitro-4-trifluoromethylbenzonitrile

This compound was prepared from 2-nitro-4-trifluoromethylaniline as described below involving diazotization in glacial acetic acid/concentrated sulfuric acid as described for the isomer, 4-nitro-3-trifluoromethylbenzonitrile.[12] The preparation of the title compound described by Hauptschein, Nodiff and Saggiomo,[6] involving diazotization in aqueous sulfuric acid, was found to be less satisfactory.

A solution of 2-nitro-4-trifluoromethylaniline (7·0 g, 0·034 mol) in glacial acetic acid (54 ml) was gradually poured into a stirred solution of sodium nitrite (2·58 g, 0·037 mol) in concentrated sulfuric acid (18 ml) maintained at 10–20°. The excess nitrous acid was decomposed with urea, and then the diazonium solution was then treated with potassium nickel cyanide as described[6] and the product isolated by steam distillation to give the title compound (2·30 g) as a low melting solid (Found: C, 44·9; H, 1·4; N, 12·7. Calc. for $C_8H_3N_2O_2$: C, 44·4; H, 1·4, N, 12·9%). ^{1}H n.m.r. ($CDCl_3$) δ 8·14, s, H5,6; 8·62, s, H3.

[11] Barlin, G. B., and Yan, J.-H., *Aust. J. Chem.*, 1989, **42**, 2191.
[12] Caldwell, W. T., and Sayin, A. N., *J. Am. Chem. Soc.*, 1951, **73**, 5125.

2-Nitro-4-trifluoromethylbenzoic Acid

This compound was prepared as described by Hauptschein *et al.*[6] and recrystallized from a mixture of methylene chloride and benzene. It had m.p. 132–134° (lit.[6] 140–140·5°) (Found, for a sample dried at 20° under vacuum for 2 h: C, 40·8; H, 1·4; N, 5·9. Calc. for $C_8H_4F_3NO_4$: C: 40·8; H, 1·7; N, 6·0%). ^{1}H n.m.r. δ 8·02, s, H5,6; 8·20. s, H3; 8·81, br s, COOH. I.r. ν_{max} 3300–2300 (OH st), 3140 (CH st), 1732 (C=O st), 1570 (NO_2 st?), 1370, 1340 (NO_2 st), 1190, 1100, 875, 780, 710 cm^{-1}.

2-Amino-4-trifluoromethylbenzoic Acid

This compound was best prepared according to Simet[5] and recrystallized from aqueous methanol. It had m.p. 174–176° (lit.[5] 175–177°) (Found, for a sample dried at 20° under vacuum for 2 h: C, 46·7; H, 2·9; F, 28·1; N, 6·8. Calc. for $C_8H_6F_3NO_2$: C, 46·8; H, 2·9; F, 27·8; N, 6·8%). ^{1}H n.m.r. (CD_3SOCD_3) δ 6·76, dd, $J_{5,6}$ 8·5, $J_{3,5}$ 1·5 Hz, H5; 7·11, br s, H3; 7·87, d, $J_{5,6}$ 8·5 Hz, H6. I.r. ν_{max} 3550 (NH asym st), 3430 (NH sym st), 3100br (OH st), 1706 (C=O st), 1610, 1350, 1250, 1190, 1100, 940, 790 cm^{-1}. It was also prepared from 2-nitro-4-trifluoromethylbenzoic acid as described by Hauptschein *et al.*[6] but in our hands this method was less satisfactory.

4-Chloro- and 4-Hydroxy-7-trifluoromethylquinazoline

2-Amino-4-trifluoromethylbenzoic acid (1·705 g) was mixed with formamide (1·4 ml) and heated at 125° for 45 min, and then at 171° for 2·5 h. After cooling, the mixture was diluted with water and the product filtered and washed. It was recrystallized from ethanol with charcoal filtration to give 7-trifluoromethylquinazolin-4-ol (1·24 g), m.p. 225–227° (lit.[9] 227°) (Found: C, 50·8; H, 2·3; F, 27·0; N, 13·1. Calc. for $C_9H_5F_3N_2O$: C, 50·5; H, 2·3; F, 26·6; N, 13·1%). ^{1}H n.m.r. (CD_3SOCD_3) δ 7·83, br d, $J_{5,6}$ 8 Hz, H6; 7·98, br s, H8; 8·24, s, H2; 8·33, br d, $J_{5,6}$ 8 Hz, H5. I.r. ν_{max} 2900br (NH st), 1720 (C=O st), 1620, 1455, 1330, 1265, 1200, 1140, 890, 800 cm^{-1}.

4-Chloro-7-trifluoromethylquinazoline was prepared from the quinazolin-4-ol by a literature procedure[8,9] but the mixture of the quinazolin-4-ol (2·35 g), phosphorus pentachloride (4·86 g) and phosphoryl chloride (15 ml) was refluxed for 3 h after all the solid had dissolved. After chromatography in benzene over alumina (15 cm) and recrystallization from light petroleum (b.p. 60–80°) the 4-chloro-7-trifluoromethylquinazoline (1·56 g) had m.p. 62–64° (lit.[1] 62°). ^{1}H n.m.r. δ 7·91, dd, $J_{5,6}$ 8·5, $J_{6,8}$ 1·5 Hz, H6; 8·36, br s, H8; 8·41, d, $J_{5,6}$ 8·5 Hz, H5; 9·14, s, H2. I.r. ν_{max} 3080 (CH st), 1580, 1330, 1235, 1150, 1075, 845, 690 cm^{-1}.

2,6-Bis(dipentylaminomethyl)-4-nitrophenol

Dipentylamine (2·10 g, 0·013 mol) was added to a chilled mixture of paraformaldehyde (0·40 g, 0·013 mol) in ethanol (1·0 ml), *p*-nitrophenol (0·46 g, 0·0033 mol) added and the mixture refluxed in an oil bath at 90–95° for 18 h. The solvent was then evaporated under vacuum and the crude product chromatographed in dichloromethane over a column of alumina to give as an oil *4,6-bis(dipentylaminomethyl)-4-nitrophenol* (0·905 g) (Found: C, 70·4; H, 10·6. $C_{28}H_{51}N_3O_3$ requires C, 70·4; H, 10·8%). ^{1}H n.m.r. δ 0·88, t, *J* 7 Hz, Me; 1·26, complex, $NCH_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$; 2·50, t, NCH_2; 3·71, s, $ArCH_2N$; 8·05, s, H3,5.

2,6-Bis(N-butyl-N-methylaminomethyl)-4-nitrophenol

N-Butylmethylamine (5·06 g), paraformaldehyde (1·74 g), ethanol (4·0 ml) and *p*-nitrophenol (2·0 g) were allowed to react in a manner similar to that described above. The product was chromatographed in chloroform over a column of alumina and gave as an oil *2,6-bis(N-butyl-N-methylaminomethyl)-4-nitrophenol* (4·592 g) (Found: C, 64·3; H, 9·3. $C_{18}H_{31}N_3O_3$ requires C, 64·1; H, 9·3%). ^{1}H n.m.r. δ 0·91, complex, $CH_2\mathbf{Me}$; 1·46, complex, $NCH_2C\mathbf{H}_2C\mathbf{H}_2$; 2·28, s, NMe; 2·50, t, *J* 7 Hz, $NC\mathbf{H}_2CH_2$; 3·66, s, $ArCH_2N$; 8·02, s, H3,5.

2,6-Bis(4′-benzylpiperidin-1′-ylmethyl)-4-nitrophenol

4-Benzylpiperidine (4·98 g), paraformaldehyde (0·86 g), ethanol (5·0 ml) and *p*-nitrophenol (1·0 g) were allowed to react as above. After cooling, the mixture was diluted with hexane and the yellow solid was filtered off and recrystallized from a mixture of dichloromethane and light petroleum (b.p. 60–80°) to give the *title compound* (2·416 g), m.p. 110–111·5° (Found, for a sample dried at 78°/0·2 mmHg for 5 h: C, 72·9; H, 8·1; N, 8·0. $C_{32}H_{39}N_3O_3.0·8H_2O$ requires C, 72·8; H, 7·8; N, 8·0%). ^{1}H n.m.r. δ 1·12–2·21, complex, 2·95, m, H2′,3′,4′,5′,6′; 2·53, br s, CH_2Ph; 3·66, s, $ArCH_2N$; 7·22, complex, Ph; 8·00, s, H3,5.

2,6-Bis(dimethylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol

A mixture of 4-amino-2,6-bis(dimethylaminomethyl)phenol[10] (0·214 g), 4-chloro-7-trifluoromethylquinazoline (0·223 g), methanol (1·5 ml), water (0·4 ml) and concentrated hydrochloric acid (2 drops) was refluxed in an oil bath at 90° for 5 h. The solvent was evaporated under reduced pressure and the residue diluted with water and neutralized with dilute ammonium hydroxide. The product was extracted into chloroform, the extract dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by t.l.c. (alumina, 0·5% methanol in chloroform) to give *2,6-bis(dimethylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol* (0·262 g) as an oil (Found, for a sample dried at 120°/0·2 mmHg for 5 h: C, 60·4; H, 6·1; N, 16·8. $C_{21}H_{24}F_3N_5O$ requires C, 60·1; H, 5·8; N, 16.7%). ^{1}H n.m.r. δ 2·28, s, Me; 3·55, s, CH_2N; 7·36, s, H3,5; 7·64, br d, $J_{5',6'}$ 8·5 Hz, H6′; 8·11, br s, H8′; 8·16, br d, $J_{5',6'}$ 8·5 Hz, H5′; 8·73, s, H2′. I.r. ν_{max} 3700–2400 (OH st and NH st), 1580, 1485, 1465, 1320, 1145 cm^{-1}.

2,6-Bis(diethylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol

4-Amino-2,6-bis(diethylaminomethyl)phenol[10] (0·117 g) and 4-chloro-7-trifluoromethylquinazoline (0·097 g) were allowed to react as for the analogue above. The crude product was purified by t.l.c. (alumina, 7% methanol in methylene chloride) and the product (0·154 g) was crystallized from a mixture of methylene chloride and light petroleum (b.p. 60–80°) to give the *title compound*, m.p. 75–85° (Found, for a sample dried at 20° under vacuum for 24 h: C, 62·3; H, 7·0, N, 14·4. $C_{25}H_{32}F_3N_5O.0·3H_2O$ requires C, 62·4; H, 6·8; N, 14·5%). ^{1}H n.m.r. δ 1·07, t, *J* 7 Hz, Me; 2·61, q, *J* 7 Hz, C**H**$_2$Me; 3·69, s, $ArCH_2N$; 7·40, s, H3,5; 7·65, br d, $J_{5',6'}$ 8·5 Hz, H6′; 8·09, br d, $J_{5',6'}$ 8·5 Hz, H5′; 8·13, br s, H8′; 8.73, s, H2′.

2,6-Bis(dipropylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol

4-Amino-2,6-bis(dipropylaminomethyl)phenol[1] (0·123 g) and 4-chloro-7-trifluoromethylquinazoline (0·086 g) were allowed to react as above. The crude product was purified by t.l.c. (alumina, chloroform, developed twice and then alumina, 1% methanol in choloroform) to give the *title compound* (0·156 g) (Found, for a sample dried at 80°/0·2 mmHg for 18 h: C, 64·3; H, 7·8; N, 12·8. $C_{29}H_{40}F_3N_5O.0·5H_2O$ requires C, 64·4; H, 7·6; N, 12·9%). ^{1}H n.m.r. δ 0·87, t, *J* 7 Hz, Me; 1·49, complex, C**H**$_2$Me; 2·48, complex, NC**H**$_2$CH$_2$; 3·69, s, $ArCH_2N$; 7·42, s, H3,5; 7·66, br d, $J_{5',6'}$ 8·5 Hz, H6′; 7·84, br s, NH; 8·07, br d, $J_{5',6'}$ 8·5 Hz, H5′; 8·14, br s, H8′, OH; 8·74, s, H2′. I.r. ν_{max} 3500 (H_2O), 2970 (CH aliph st), 1580, 1480, 1130 cm^{-1}.

2,6-Bis(dipentylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol

2,6-Bis(dipentylaminomethyl)-4-nitrophenol (0·400 g) was dissolved in a mixture of ethanol (15 ml) and saturated ethanolic ammonia (15 ml), Raney nickel added and the mixture shaken with hydrogen until uptake ceased. The catalyst was filtered off on celite and the product subjected to t.l.c. (alumina, chloroform) to give the amine (0·370 g) which was used directly in the next reaction. It had ^{1}H n.m.r. δ 0·87, br t, Me; 1·28, complex, $NCH_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$; 2·46, t, *J* 7 Hz, NC**H**$_2$CH$_2$; 3·58, s, $ArCH_2N$; 6·50, s, H3,5.

Treatment of this product (0·131 g) and 4-chloro-7-trifluoromethylquinazoline (0·068 g) as described above (but refluxed for 8 h) gave a crude product which was purified by t.l.c. (alumina, ethyl acetate/hexane, 3 : 7) to give the *title compound* (0·053 g) as an oil which

solidified on standing (Found, for a sample dried at 65°/0·2 mmHg for 18 h: C, 68·9; H, 8·7. $C_{37}H_{56}F_3N_5O$ requires C, 69·0; H, 8·8%). ^{1}H n.m.r. δ 0·89, complex, Me; 1·27, complex, $NCH_2CH_2\mathbf{CH_2}CH_2CH_2$; 2·54, complex, $NC\mathbf{H_2}CH_2$; 3·72, s, $ArCH_2N$; 7·43, s, H3,5; 7·59, br, OH, NH; 7·71, dd, $J_{5',6'}$ 8·5, $J_{6',8'}$ 1·5 Hz, H6′; 8·01, d, $J_{5',6'}$ 8·5 Hz, H5′; 8·18, br s, H8′; 8·76, s, H2′.

2,6-Bis(N-butyl-N-methylaminomethyl)-4-(7′-trifluoromethylquinazolin-4′-ylamino)phenol

2,6-Bis(*N*-butyl-*N*-methylaminomethyl)-4-nitrophenol (0·80 g) was reduced with hydrogen over Raney nickel as for the dipentylamino analogue above. After column chromatography (alumina, chloroform) it gave as an oil 4-amino-2,6-bis(*N*-butyl-*N*-methylaminomethyl)phenol (0·552 g) which was used directly in the reaction below. It had ^{1}H n.m.r. δ 1·68, br t, $CH_2\mathbf{Me}$; 2·22, complex, $NCH_2(\mathbf{CH_2})_2$; 3·01, s, NMe; 3·20, t, J 7 Hz, $NC\mathbf{H_2}CH_2$; 4·30, s, $ArCH_2N$; 7·22, s, H3,5.

The above crude phenol (0·149 g) and 4-chloro-7-trifluoromethylquinazoline (0·113 g) [under similar reaction conditions to those described above but refluxed for 10 h and the crude product purified by t.l.c. (alumina, ethyl acetate/hexane, 1 : 3, developed twice)] gave the *title compound* (0·102 g) (Found, for a sample dried at 65°/0·2 mmHg for 18 h: C, 64·3; H, 7·5. $C_{27}H_{36}F_3N_5O$ requires C, 64·4, H, 7·2%). ^{1}H n.m.r. δ 0·93, complex, $CH_2\mathbf{Me}$; 1·50, complex, $NCH_2C\mathbf{H_2}C\mathbf{H_2}$; 2·29, s, NMe; 2·51, complex $NC\mathbf{H_2}CH_2$; 3·62, s, $ArCH_2N$; 7·42, s, H3,5; 7·57, br, OH, NH; 7·70, dd, $J_{5',6'}$ 8·5, $J_{6',8'}$ 1·5 Hz, H6′; 7·99, d, $J_{5',6'}$ 8·5 Hz, H5′; 8·16, s, H8′; 8·75, br s, H2′.

2,6-Bis(pyrrolidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

A similar reaction of 4-amino-2,6-bis(pyrrolidin-1′-ylmethyl)phenol[10] (0·139 g) and 4-chloro-7-trifluoromethylquinazoline (0·118 g), but refluxed for 6 h, gave a crude product which was purified by t.l.c. (alumina, chloroform) to give the *title compound* as a yellow oil (0·083 g) (Found: C, 63·7; H, 6·2, F, 11·9; N, 14·5. $C_{25}H_{28}F_3N_5O$ requires C, 63·7; H, 6·0; F, 12·1; N, 14·8%). ^{1}H n.m.r. δ 1·79, complex, H3′,4′; 2·60, complex, H2′,5′; 3·74, s, $ArCH_2N$; 7·37, s, H3,5; 7·64, br d, $J_{5'',6''}$ 9 Hz, H6″; 8·10, br d, $J_{5'',6''}$ 9 Hz, H5″; 8·14, br s, H8″; 8·36, br, OH, NH; 8·72, s, H2″. I.r. ν_{max} 3320br (OH st and NH st), 2970 (CH_2 st), 1580, 1480, 1320, 1130 cm^{-1}.

2,6-Bis(piperidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

The product from 4-amino-2,6-bis(piperidin-1′-ylmethyl)phenol[10] (0·240 g) and 4-chloro-7-trifluoromethylquinazoline (0·184 g) when refluxed as above (but for 5 h) and purified by t.l.c. (alumina, chloroform and alumina, 0·5% methanol in chloroform) gave as an oil the *title compound* (0·197 g) (Found: C, 62·9; H, 6·8; N, 13·3. $C_{27}H_{32}F_3N_5O.H_2O$ requires C, 62·6; H, 6·6; N, 13·5%). ^{1}H n.m.r. δ 1·51, complex, H3′,4′,5′; 2·49, complex, H2′,6′; 3·60, s, $ArCH_2N$; 7·37, s, H3,5; 7·67, br d, $J_{5'',6''}$ 8·5 Hz, H6″; 7·79, br s, OH, NH; 8·03, br d, $J_{5'',6''}$ 8·5 Hz, H5″; 8·15, br s, H8″; 8·74, s, H2″. I.r. ν_{max} 3360 (OH st and NH st), 2940 (CH_2 st), 1580, 1480, 1320, 1130 cm^{-1}.

2,6-Bis(3′-methylpiperidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

This compound was prepared similarly from 4-amino-2,6-bis(3′-methylpiperidin-1′-ylmethyl)phenol[10] (0·227 g) and 4-chloro-7-trifluoromethylquinazoline (0·159 g) and the crude yellow solid was subjected to t.l.c. (alumina, 0·3% methanol in chloroform) to give the *title compound* (0·318 g) (Found, for a sample dried at 120°/0·2 mmHg for 5 h: C, 64·7; H, 7·0; N, 12·8. $C_{29}H_{36}F_3N_5O.0·65H_2O$ requires C, 64·6; H, 7·0; N, 13·0%). ^{1}H n.m.r. δ 0·86, d, J 5·5 Hz, Me; 1·65, complex, H3′,4′,5′; 2·85, complex, H2′,6′; 3·62, s, $ArCH_2N$; 7·38, s, H3,5; 7·67, br d, $J_{5'',6''}$ 9 Hz, H6″; 7·67, br, OH, NH; 8·02, br d, $J_{5'',6''}$ 9 Hz, H5″; 8·15, br s, H8″; 8·75, s, H2″. I.r. ν_{max} 3400 (H_2O), 2940 (CH aliph st), 1580, 1480, 1320, 1130 cm^{-1}.

2,6-Bis(4′-methylpiperidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

The 4-methyl isomer was prepared similarly from 4-amino-2,6-bis(4′-methylpiperidin-1′-ylmethyl)phenol[10] (0·309 g) and 4-chloro-7-trifluoromethylquinoline (0·217 g); it precipitated

as a yellow solid, and was purified by t.l.c. (alumina, 25% ethyl acetate in hexane) to give the *title compound* (0·182 g) (Found: C, 65·9; H, 7·1; F, 10·4; N, 13·0. $C_{29}H_{36}F_3N_5O$ requires C, 66·0; H, 6·9; F, 10·8; N, 13·3%). A sample of this product was dissolved in dilute hydrochloric acid and reprecipitated by addition of ammonium hydroxide to pH 9. The solid was filtered off, washed with water and dried in the air. It melted at *c.* 130° (Found: C, 64·0; H, 7·4; N, 12·7. $C_{29}H_{36}F_3N_5O.H_2O$ requires C, 63·8; H, 7·0; N, 12·8%). ^{1}H n.m.r. δ 0·91, br s, Me; 1·47, complex, 2·04, br t, *J* 11 Hz, 2·93, br d, *J* 11 Hz, H2′,3′,4′,5′,6′; 3·59, s, $ArCH_2N$; 7·35, s, H3,5; 7·64, br d, $J_{5'',6''}$ 8·5 Hz, H6″; 8·08, br d, $J_{5'',6''}$ 8·5 Hz, H5″; 8·04, br s, OH, NH; 8·13, br s, H8″; 8·72, s, H2″. I.r. ν_{max} 2980 and 2950 (CH aliph st), 1590, 1485, 1330, 1140 cm^{-1}.

4,6-Bis(3′,5′-dimethylpiperidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

The 3′,5′-dimethyl analogue was prepared from 4-amino-2,6-bis(3′,5′-dimethylpiperidin-1′-ylmethyl)phenol[10] (0·290 g) and 4-chloro-7-trifluoromethylquinazoline (0·188 g). The product was subjected to t.l.c. (alumina, 20% ethyl acetate in hexane) to give the *title compound* (0·223 g) (Found: C, 66·8; H, 7·6; N, 12·5. $C_{31}H_{40}F_3N_5O$ requires C, 67·0; H, 7·3; N, 12·6%). ^{1}H n.m.r. δ 0·85, complex, Me; 1·65, complex, H3′,4′,5′; 2·90, complex, H2′,6′; 3·60, s, $ArCH_2N$; 7·36, s, H3,5; 7·65, br d, $J_{5'',6''}$ 8·5 Hz, H6″; 8·09, br d, $J_{5'',6''}$ 8·5 Hz, H5″; 8·14, br s, H8″; 8·72, s, H2″. I.r. ν_{max} 2960 (CH aliph st), 1580, 1475, 1320, 1130 cm^{-1}.

4,6-Bis(4′-benzylpiperidin-1′-ylmethyl)-4-(7″-trifluoromethylquinazolin-4″-ylamino)phenol

2,6-Bis(4′-benzylpiperidin-1′-ylmethyl)-4-nitrophenol (0·26 g) in ethanolic ammonia was reduced as described above to give the corresponding amino compound (0·127 g). ^{1}H n.m.r. δ 1·16–2·37, complex, 2·95, m, H2′,3′,4′,5′,6′; 2·52, br s, C**H**$_2$Ph; 3·53, s, $ArCH_2N$; 6·46, s, H3,5; 7·21, complex, Ph.

The above crude phenol (0·127 g) and 4-chloro-7-trifluoromethylquinazoline (0·061 g) were allowed to react under conditions similar to those described above and the crude product was purified by t.l.c. (alumina, dichloromethane) to give the *title compound* (0·085 g), m.p. 98–102° (Found, for a sample dried at 75°/0·2 mmHg for 24 h: C, 72·2; H, 6·8, N, 10·1. $C_{41}H_{44}F_3N_5O.0·2H_2O$ requires C, 72·1; H, 6·6; N, 10·2%). ^{1}H n.m.r. δ 1·12–2·23, complex, 2·98, m, H2′,3′,4′,5′,6′; 2·54, br s, C**H**$_2$Ph; 3·64, s, $ArCH_2N$; 7·22, complex CH_2**Ph**; 7·40, s, H3,5; 7·68, br d, $J_{5'',6''}$ 8·5 Hz, H6″; 8·00, br d, $J_{5'',6''}$ 8·5 Hz, H5″; 8·16, br s, H8″; 8·74, s, H2″.

N-*(4′-Diethylamino-1′-methylbutyl)-7-trifluoromethylquinazolin-4-amine*

A mixture of 4-chloro-7-trifluoromethylquinazoline (0·070 g), N^1,N^1-diethylpentane-1,4-diamine (0·6 ml, 0·49 g) and *n*-heptane (1·4 ml) was heated in a Teflon lined screw-top reaction vessel at 140° for 20 h. The solvent was evaporated and the product subjected to t.l.c. (alumina, 30% ethyl acetate in hexane, developed twice) to give the *title compound* (0·082 g), m.p. 89–91° (Found, for a sample dried at 70°/0·2 mmHg for 20 h: C, 60·8; H, 7·1; N, 15·6. $C_{18}H_{25}F_3N_4$ requires C, 61·0; H, 7·1; N, 15·8%). ^{1}H n.m.r. δ 1·03, t, *J* 7 Hz, **Me**CH_2; 1·34, d, *J* 6·5 Hz, **Me**CH; 1·68, complex, C**H**$_2$C**H**$_2$$CH_2$N; 2·47, complex, CH_2CH_2C**H**$_2$N; 2·55, q, *J* 7 Hz, MeC**H**$_2$; 4·50, complex, MeC**H**; 6·75, br d, NH; 7·59, dd, $J_{5,6}$ 9, $J_{6,8}$ 1·5 Hz, H6; 7·93, br d, $J_{5,6}$ 9 Hz, H5; 8·09, br s, H8; 8·69, s, H2.

2,6-Bis(dipentylaminomethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol

4-Amino-2,6-bisdipentylaminomethylphenol (0·37 g, see above), 4-chloro-7-trifluoromethylquinoline (0·15 g), methanol (3·0 ml), water (1·0 ml) and concentrated hydrochloric acid (0·1 ml) were refluxed in an oil bath at 90° for 18 h. The methanol was evaporated under reduced pressure, the residue diluted with water and adjusted with ammonium hydroxide to pH 7 and the mixture extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give an oil which was subjected to t.l.c. (alumina, dichloromethane) to give *2,6-bis(dipentylaminomethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol* (0·243 g) (Found: C, 70·2; H, 9·1; F, 8·7; N, 8·5. $C_{38}H_{57}F_3N_4O.0·5H_2O$ requires C, 70·0; H, 9·0; F, 8·7; N, 8·6%). ^{1}H n.m.r. δ 0·87, t, *J* 7 Hz, Me; 1·26, complex, NCH_2C**H**$_2$C**H**$_2$$CH_2$; 2·5, t, *J* 7 Hz,

$NC\mathbf{H}_2CH_2$; 3·69, s, $ArCH_2N$; 6·74, d, $J_{2',3'}$ 5·5 Hz, H 3′; 7·07, s, H 3,5; 7·63, br d, $J_{5',6'}$ 9 Hz, H 6′; 8·04, d, $J_{5',6'}$ 9 Hz, H 5′; 8·31, br s, H 8′; 8·54, d, $J_{2',3'}$ 5·5 Hz, H 2′.

*2,6-Bis(*N*-butyl-*N*-methylaminomethyl)-4-(7′-trifluoromethylquinolin-4′-ylamino)phenol*

4-Amino-2,6-bis(*N*-butyl-*N*-methylaminomethyl)phenol (0·55 g, see above) and 4-chloro-7-trifluoromethylquinoline (0·413 g) as for the analogue above gave a crude product which was purified by t.l.c. (alumina, ethyl acetate/hexane, 1 : 5) to yield the *title compound* (0·352 g) (Found: C, 60·4; H, 6·1; N, 16·8. $C_{21}H_{24}F_3N_5O$ requires C, 60·1; H, 5·8; N, 16·7%). ^{1}H n.m.r. δ 0·90, t, J 7 Hz, **Me**CH_2; 1·45, complex, $NCH_2(C\mathbf{H}_2)_2$; 2·26, s, NMe; 2·46, t, J 7 Hz, $NC\mathbf{H}_2CH_2$; 3·61, s, NCH_2Ar; 6·74, d, $J_{2',3'}$ 5 Hz, H 3′; 7·04, s, H 3,5; 7·30, br s, NH; 7·58, br d, $J_{5',6'}$ 9 Hz, H 6′; 8·12, br d, $J_{5',6'}$ 9 Hz, H 5′; 8·28, br s, H 8′; 8·54, d, $J_{2,3}$ 5 Hz, H 2′. I.r. ν_{max} 2960, 1580, 1480, 1125 cm^{-1}.

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