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Potential Antimalarials. IV*
4-[7′-Bromo(and chloro)-1′,5′-naphthyridin-4′-ylamino]phenols and N^4-Substituted 7-Chloro-1,5-naphthyridin-4-amines

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Abstract

A series of nine mono- and di-Mannich bases, for example 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dimethylaminomethyl)phenol derived from 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol and several other N^4-substituted 7-bromo- and 7-chloro-1,5-naphthyridin-4-amines have been prepared.

All these compounds showed significant antimalarial activity when injected intraperitoneally in a single dose of 100–200 mg/kg to mice infected with *Plasmodium vinckei vinckei*. The di-Mannich bases appeared to be the most potent and effective in parasite control; however, no deaths were observed in infected mice treated with the mono-Mannich compounds.

Introduction

In Parts I[1] and II[2] of this series we described the synthesis and testing against *P. vinckei vinckei* in mice of a series of 1,8-naphthyridines and N^4-substituted 2-methoxy(and 2-hydroxy)-1,5-naphthyridin-4-amines, and in Part III[3] the preparation and antimalarial activity of some N^4-substituted 7-bromo-1,5-naphthyridin-4-amines.

In this paper we report the preparation of 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol (1a) and a series of mono- and di-Mannich bases (1b–j) derived therefrom; together with some chloro analogues (2c–e) of the active bromo compounds described here and in Part III.[3] This series of mono- and di-Mannich bases were prepared because of the relatively high activity of 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol observed by us[3] and the existence of such structures in amodiaquine (Camoquin)[4,5] and amopyroquine.[5,6] Chen *et al.*[7] also report good antimalarial activity in a series of di-Mannich bases derived from

* Part III, *Aust. J. Chem.*, 1985, **38**, 459.

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4-(1′,5′-naphthyridin-4′-ylamino)phenol and 4-(6′-methoxy-2′-methyl-1′,5′-naphthyridin-4′-ylamino)phenol.

Testing of these bromo- and chloro-1,5-naphthyridines against *P. vinckei vinckei* in mice confirmed the very significant antimalarial activity of these compounds.

Synthesis

3-Bromo-8-chloro-1,5-naphthyridine,[3] when heated with aqueous methanolic *p*-aminophenol hydrochloride at 100°, gave 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol (1a). This product with formalin in ethanol and a moderate amount of dimethylamine, dipropylamine or pyrrolidine at reflux gave the mono-Mannich bases (1b–d) respectively. 4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol with ethanolic formalin and a large excess of dimethylamine, diethylamine, dipropylamine, pyrrolidine, piperidine or morpholine at reflux for 20 h gave the di-Mannich bases (1e–j). 7-Bromo-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine (2b) and *N*,*N*-diethyl-2-(7′-bromo-1′,5′-naphthyridin-4′-ylthio)ethylamine (2a) were prepared from 3-bromo-8-chloro-1,5-naphthyridine with 4-diethylaminobutylamine in n-heptane at 160°, and refluxing aqueous sodium 2-diethylaminoethanethiolate, respectively.

4,7-Dichloro-1,5-naphthyridine with 4-amino-2-diethylaminomethylphenol dihydrochloride in aqueous methanol at 100°, and with 2-diethylaminoethylamine or 4-diethylaminobutylamine in n-heptane at 160° gave the compounds (2c), (2d) and (2e).

Biological Activities

Compounds reported in this paper were examined for antimalarial activity against *P. vinckei vinckei* in mice and the results, averaged for the three mice at each time point, are summarized in Table 1. Each compound was examined for toxicity and for safe dosage levels prior to the antimalarial studies. The substituted 4-amino-1,5-naphthyridines reported here, with one exception only, showed strong antimalarial activity leading to significantly reduced parasitaemia 24 h after treatment, and a reduction in most cases to less than 1% at 48 h.

The results reveal that, whereas 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol (1a) showed no antimalarial activity, each of its mono-Mannich bases (1b–d) showed good activity with a low parasite count at 2–3 days, followed by a rise and then a reduction (presumably due to the immunological response) to $<1\%$ at 14–19 days after treatment. This behaviour was similar to that shown by chloroquine in our previous paper.[3]

The di-Mannich bases (1e), (1g) and (1h) showed even higher activity with a reduction of parasite levels to $<1\%$ within 48 h of treatment and no observed increase thereafter to 4 weeks.

Compounds (1f), (1i) and (1j) produced similar reductions but at 14 days an increase was observed (further details are recorded in Table 1).

7-Bromo-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine (2b) appeared to be more effective than its diethylaminopropyl analogue reported previously.[3]

The sulfide (2a), *N*,*N*-diethyl-2-(7′-bromo-1′,5′-naphthyridin-4′-ylthio)ethylamine, unlike its nitrogen analogue,[3] 7-bromo-*N*-(2′-diethylaminoethyl)-1,5-naphthyridine, showed no antimalarial activity (compare Schönhöfer's hypothesis[8,9]).

[8] Schönhöfer, F., *Hoppe-Seyler's Z. Physiol. Chem.*, 1942, **274**, 1.

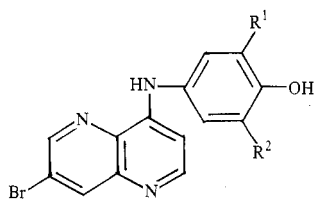
[9] Thompson, P. E., and Werbel, L. M., in '*Antimalarial Agents*' (Medicinal Chemistry Vol. 12) (Ed. G. deStevens) pp. 103, 161 (Academic Press: New York 1972).

Table 1. Preliminary antimalarial screening results against *Plasmodium vinckei vinckei* in mice

For details of test procedures see Experimental section. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0 h denotes pretreatment

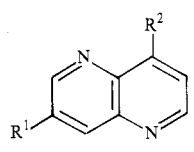
Compound	Solvent[A]	Dose (mg/kg)	Mean percentage of parasite-infected red cells 0 h	9 h	24 h	48 h	3 d	6 d	8 d	9 d	14 d	19 d	4 w
(1a)	PO	200	16	34	62	88	[B]						
(1b)[C]	NS	200	27	30	9	<1	<1	11	8	4	<1	<1	<1
(1c)	PO	200	16	27	16	3	5	26	14	5	<1	<1	<1
(1d)[C]	NS	200	19	26	3	<1	<1	25	28	18	<1	<1	<1
(1e)	PO	200	18	24	5	<1	<1	<1	<1	<1	<1	<1	<1
(1f)[C]	NS	100	10	9	<1	<1	<1	<1	<1	<1	16	<1	<1
(1g)	PO	200	22	32	7	<1	<1	<1	<1	<1	<1	<1	<1
(1h)	PO	100	11	11	1	<1	<1	<1	<1	<1	<1	<1	<1
(1i)	PO	200	17	13	1	<1	<1	<1	<1	<1	63	[D]	
(1j)	PO	200	15	15	<1	<1	<1	<1	<1	<1	16	[E]	
(2a)	PO	200	9	14	29	65	83	[B]					
(2b)[C]	NS	100	13	17	4	7	12	35	9	5	<1	<1	<1
(2c)	PO	200	14	12	1	<1	<1	3	15	21	<1	<1	<1
(2d)[C]	NS	200	17	20	5	<1	4	34	19	7	<1	<1	<1
(2e)[C]	NS	100	13	17	5	2	4	56	22	10	<1	<1	<1
NS	—	—	27	45	63	88	[F]						
PO	—	—	19	42	66	85	[F]						
Chloroquine[G]	NS	40	28	30	4	<1	<1	10	71	82[H]			

[A] PO, peanut oil; NS, normal saline.
[B] All three mice dead.
[C] Dihydrobromide.
[D] Two mice dead, parasitaemia of third mouse < 1%.
[E] One mouse dead, parasitaemia of remaining two mice < 1%.
[F] Two of the three mice dead at 3 days.
[G] Diphosphate.
[H] All mice dead at 10 days.



	R^1	R^2
(1a)	H	H
(1b)	H	CH_2NMe_2
(1c)	H	CH_2NPr_2
(1d)	H	CH_2N
(1e)	CH_2NMe_2	CH_2NMe_2
(1f)	CH_2NEt_2	CH_2NEt_2
(1g)	CH_2NPr_2	CH_2NPr_2

	R^1	R^2
(1h)	CH_2N	CH_2N
(1i)	CH_2N	CH_2N
(1j)	CH_2N O	CH_2N O



	R^1	R^2
(2a)	Br	$SCH_2CH_2NEt_2$
(2b)	Br	$NH(CH_2)_4NEt_2$
(2c)	Cl	NH, OH, CH_2NEt_2

	R^1	R^2
(2d)	Cl	$NH(CH_2)_2NEt_2$
(2e)	Cl	$NH(CH_2)_4NEt_2$

The three *N*-substituted 7-chloro-1,5-naphthyridin-4-amines (2c–e) produced similar antimalarial effects: the initial knockdown was followed by a rise in parasitaemia which then fell to <1% at 14–19 days, through to 4 weeks.

Comparison of the test results for the chloro compound (2e) with its bromo analogue (2b) did not reveal any significant differences; but the chloro compounds (2c) and (2d), from the evidence presented in Table 1, were apparently less effective than their bromo analogues (described in Part III[3]) which also reduced parasitaemia levels to <1% within 48 h, but maintained it at that level through to 13 days.

In control experiments it was found that infected mice injected with a single does of chloroquine diphosphate (LD_{50} 63 mg/kg) at 40 mg/kg initially produced significantly lower parasitaemia levels decreasing to <1% at 2 days but this then increased and the mice died at 10 days. This contrasts with our earlier experiments[3] with a dosage of 20 mg/kg in which the mice survived to and beyond 14 weeks.

These results at different dose levels may indicate that the variations observed between the mono- and di-Mannich bases are due to non-optimal dose levels; these differences may be significant in the control of parasitaemia.

Experimental

General

Solids and oils for analysis were dried in an oven at 100° unless otherwise specified. 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 recorded at 90 MHz and 30° with a Jeol FX90 and Fourier transform spectrometer with digital resolution of 0·12 Hz with tetramethylsilane in $CDCl_3$ or CD_3SOCD_3.

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (*1a*)

3-Bromo-8-chloro-1,5-naphthyridine[3] (2·0 g), *p*-aminophenol hydrochloride (1·2 g), water (40·0 ml) and methanol (20·0 ml) were heated with stirring in an oil bath at 100° for 2 h. The methanol was then evaporated under reduced pressure and the remaining aqueous solution was adjusted to pH 8 with ammonium hydroxide. The yellow precipitate which formed was filtered off, washed with water, dried and recrystallized from methanol to give *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)phenol* (2·5 g), m.p. 245–247° (Found: C, 53·6; H, 3·2; N, 13·2. $C_{14}H_{10}BrN_3O$ requires C, 53·2; H, 3·2; N, 13·3%). ^{1}H n.m.r. (CD_3SOCD_3): δ, 6·86, d, $J_{2,3}$ 9 Hz, H2,6; 6·86, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·23, d, $J_{2,3}$ 9 Hz, H3,5; 8·44, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·48, d, $J_{6',8'}$ 2 Hz, H8′; 8·88, d, $J_{6',8'}$ 2 Hz, H6′; 9·2, br, NH; 9·4, br, OH.

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2-dimethylaminomethylphenol (*1b*)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (2·0 ml; 36%), and ethanolic dimethylamine (1·0 ml; 33%) in ethanol (10·0 ml) were refluxed with stirring for 20 h. The reaction mixture was evaporated under reduced pressure and the residue purified by t.l.c. (silica; methanol) to give an oil (0·25 g). ^{1}H n.m.r. ($CDCl_3$): δ, 2·37, s, Me_2N; 3·66, s, CH_2N; 6·85, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·88, d, $J_{5,6}$ 8·5 Hz, H6; 6·97, d, $J_{3,5}$ 3 Hz, H3; 7·18, q, $J_{3,5}$ 3 Hz, $J_{5,6}$ 8·5 Hz, H5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2·0 Hz, H8′; 8·47, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·71, d, $J_{6',8'}$ 2 Hz, H6′; 9·8, br, OH.

This oil was treated with ethanolic hydrogen bromide and the product recrystallized from ethanol to give yellow crystals of *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-dimethylaminomethylphenol dihydrobromide* (0·3 g), m.p. >305° (dec.) (Found: C, 38·4; H, 3·7; N, 10·4. $C_{17}H_{19}Br_3N_4$ requires C, 38·2; H, 3·6; N, 10·5%).

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2-(N,N-dipropylaminomethyl)phenol (*1c*)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), dipropylamine (0·48 g), formalin (2·0 ml; 36%) and ethanol (10·0 ml) were refluxed with stirring for 20 h and the mixture worked up as described above. The product was purified by t.l.c. (alumina; chloroform then silica; ethanol)

and recrystallized from light petroleum (b.p. 60–80°) to give yellow crystals of *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-*(N,N-*dipropylaminomethyl)phenol* (0·15 g), m.p. 138–139° (Found: C, 58·7; H, 5·9; N, 13·2. $C_{21}H_{25}BrN_4O$ requires C, 58·7; H, 5·9; N, 13·1%). ^{1}H n.m.r. ($CDCl_3$): δ, 0·92, t, J 7 Hz, $CH_3CH_2CH_2$; 1·60, complex, $CH_3CH_2CH_2$; 2·47, complex, $CH_3CH_2CH_2$; 3·79, s, CH_2N; 6·87, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·87, d, $J_{5,6}$ 8·5 Hz, H6; 6·97, d; $J_{3,5}$ 2·5 Hz, H3; 7·17, q, $J_{3,5}$ 2·5 Hz, $J_{5,6}$ 8·5 Hz, H5; 8·2, br, NH; 8·42, d, $J_{6',8'}$ 2 Hz, H8′, 8·49, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·73, d, $J_{6',8'}$ 2 Hz, H6′; 9·4, br, OH.

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2-pyrrolidin-1″-ylmethylphenol (1d)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), pyrrolidine (0·15 g), formalin (2·0 ml; 36%) and ethanol (10·0 ml) were refluxed with stirring for 10 h and worked up as described above. The crude product was purified by t.l.c. (silica; methanol) and the oil (0·27 g) [^{1}H n.m.r. ($CDCl_3$): δ, 1·86, complex, H3″,4″; 2·66, complex, H2″,5″; 3·83, s, CH_2N; 6·84, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·86, d, $J_{5,6}$ 9 Hz, H6; 6·96; d, $J_{3,5}$ 2·5 Hz, H3; 7·15, q, $J_{3,5}$ 2·5 Hz, $J_{5,6}$ 9 Hz, H5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2 Hz, H8′; 8·47, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·70, d, $J_{6',8'}$ 2 Hz, H6′; 9·5, br, OH] was treated with ethanolic hydrogen bromide and the solid recrystallized from ethanol to give *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-pyrrolidin-1″-ylmethylphenol dihydrobromide*, m.p. 318° (dec.) (Found: C, 41·0; H, 3·8; Br, 42·8; N, 9·6. $C_{19}H_{21}Br_3N_4O$ requires C, 40·7; H, 3·8; Br, 42·7; N, 10·0%).

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dimethylaminomethyl)phenol (1e)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (10 ml; 36%) and ethanolic dimethylamine (30 ml; 33%) were refluxed with stirring for 20 h. The product was isolated as described above and purified by t.l.c. (alumina; chloroform) to give *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(dimethylaminomethyl)phenol* (0·5 g) as a yellow oil (Found: C, 55·4; H, 5·8; N, 16·0. $C_{20}H_{24}BrN_5O$ requires C, 55·8; H, 5·6; N, 16·3%). ^{1}H n.m.r. ($CDCl_3$): δ, 2·33, s, Me_2N; 3·57, s, CH_2N; 5·36, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·06, s, H3,5; 8·2, br, NH; 8·41, d, $J_{6',8'}$ 2 Hz, H8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·73, d, $J_{6',8'}$ 2 Hz, H6′.

The *tripicrate* was prepared in, and recrystallized from, ethanol. It had m.p. 152–153° (Found: C, 41·0; H, 3·1; N, 17·1. $C_{20}H_{24}BrN_5O.3(C_6H_3N_3O_7)$ requires C, 40·8; H, 3·0; N, 17·5%).

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(diethylaminomethyl)phenol (1f)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (5·0 ml; 36%), diethylamine (5·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 20 h. The product was purified by t.l.c. (silica; methanol) to give a yellow oil (0·7 g). ^{1}H n.m.r. ($CDCl_3$): δ, 1·10, t, J 7 Hz, CH_3CH_2; 2·62, q, J 7 Hz, CH_3CH_2; 3·71, s, CH_2N; 6·89, d, $J_{2',3'}$ 5 Hz, H3′; 7·12, s, H3,5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2 Hz, H8′; 8·48, d, $J_{2',3'}$ 5 Hz, H2′; 8·72, d, $J_{6',8'}$ 2 Hz, H6′.

A sample of this oil with ethanolic picric acid gave a yellow precipitate which was recrystallized from ethanol to yield *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(diethylaminomethyl)phenol tripicrate*, m.p. 191–193° (Found: C, 42·6; H, 3·4; N, 16·4. $C_{24}H_{32}BrN_5O.3(C_6H_3N_3O_7)$ requires C, 43·0; H, 3·5; N, 16·7%).

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(N,N-*dipropylaminomethyl)phenol (1g)*

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenyl (0·5 g), formalin (5·0 ml; 36%), dipropylamine (5·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 20 h. The *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis*(N,N-*dipropylaminomethyl)phenol* (0·5 g) was isolated as a yellow oil after t.l.c. (alumina; ethanol) (Found: C, 61·8; H, 7·5; N, 12·7. $C_{28}H_{40}BrN_5O$ requires C, 62·0; H, 7·4; N, 12·9%). ^{1}H n.m.r. ($CDCl_3$): δ, 0·89, t, J 7 Hz, $CH_3CH_2CH_2$; 1·55, complex, $CH_3CH_2CH_2$; 2·45, complex, $CH_3CH_2CH_2N$; 3·71, s, CH_2N; 6·90, d, $J_{2',3'}$ 5 Hz, H3′; 7·13, s, H3,5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2 Hz, H8′; 8·47, d, $J_{2',3'}$ 5 Hz, H2′; 8·73, d, $J_{6',8'}$ 2 Hz, H6′.

The *tripicrate* was prepared in, and recrystallized from, ethanol. It had m.p. 176–178° (Found: C, 45·0; H, 4·0; N, 15·7. $C_{28}H_{40}BrN_5O.3(C_6H_3N_3O_7)$ requires C, 44·9; H, 4·0; N, 15·9%).

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(pyrrolidin-1″-ylmethyl)phenol (1h)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (5·0 ml; 36%), pyrrolidine (5·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 20 h. Excess reagents were distilled

and the product purified by t.l.c. (silica; methanol) to give as a yellow oil *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(pyrrolidin-1″-ylmethyl)phenol* (0·64 g) (Found: C, 59·9; H, 6·2; N, 14·0. $C_{24}H_{28}BrN_5O$ requires C, 59·8; H, 5·9; N, 14·5%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·83, complex, H3″ 4″; 2·63, complex, H2″,5″; 3·77, s, CH_2N; 6·86, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·08, s, H3,5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2 Hz, H8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·72, d, $J_{6',8'}$ 2 Hz, H6′.

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(piperidin-1″-ylmethyl)phenol (*1i*)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (5·0 ml; 36%), piperidine (5·0 ml) and ethanol (10·0 ml) were refluxed with stirring for 20 h. Workup was as described above to give *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(piperidin-1″-ylmethyl)phenol* (0·6 g) as a yellow oil which became a semi-solid (Found: C, 61·5; H, 6·5; N, 13·5. $C_{26}H_{32}BrN_5O$ requires C, 61·2; H, 6·3; N, 13·7%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·55, complex, H3″,4″,5″; 2·51, complex, H2″,6″; 3·62, s, CH_2N; 6·89, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·08, s, H3,5; 8·2, br, NH; 8·40, d, $J_{6',8'}$ 2 Hz, H8′; 8·49, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·72, d, $J_{6',8'}$ 2 Hz, H6′.

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(morpholin-4″-ylmethyl)phenol (*1j*)

4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)phenol (0·5 g), formalin (5·0 ml; 36%), morpholine (5·0 ml) and ethanol (10·0 ml) were refluxed as described above. The product was purified by t.l.c. (alumina; chloroform) to give as a yellow oil *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(morpholin-4″-ylmethyl)phenol* (0·56 g) (Found: C, 56·4; H, 5·7; N, 13·2. $C_{24}H_{28}BrN_5O_3$ requires C, 56·0; H, 5·5; N, 13·6%). ^{1}H n.m.r. ($CDCl_3$): δ, 2·57, complex, H2″,6″; 3·67, s, CH_2N; 3·76, complex, H3″,5″; 6·87, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·12, s, H3,5; 8·2, br, NH; 8·42, d, $J_{6',8'}$ 2 Hz, H8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·74, d, $J_{6',8'}$ 2 Hz, H6′.

The *dipicrate* was prepared in and recrystallized from ethanol. It had m.p. 216–218° (Found: C, 44·5; H, 3·5; N, 15·6. $C_{24}H_{28}BrN_5O_3.2(C_6H_3N_3O_7)$ requires C, 44·5; H, 3·5; N, 15·8%).

N,N-*Diethyl-2-(7′-bromo-1′,5′-naphthyridin-4′-ylthio)ethylamine* (*2a*)

3-Bromo-8-chloro-1,5-naphthyridine (0·3 g) and 2-diethylaminoethylmercaptan hydrochloride (0·25 g) in a solution of sodium hydroxide (0·12 g) in ethanol (15 ml) were refluxed for 3 h. The mixture was evaporated, the product extracted into chloroform, and subjected to t.l.c. (alumina; chloroform). It gave N,N-*diethyl-2-(7′-bromo-1′,5′-naphthyridin-4′-ylthio)ethylamine* (0·33 g) as a brownish yellow oil which slowly crystallized on standing. It had m.p. 64–65° (Found: C, 49·3; H, 5·4; N, 12·3. $C_{14}H_{18}BrN_3S$ requires C, 49·4; H, 5·3; N, 12·3%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·08, t, J 7 Hz, CH_3CH_2; 2·64, q, J 7 Hz, CH_3CH_2; 3·05, complex, CH_2CH_2; 7·37, d, $J_{2,3}$ 5 Hz, H3′; 8·51, d, $J_{6,8}$ 2 Hz, H8′; 8·72, d, $J_{2,3}$ 5 Hz, H2′; 8·91, d, $J_{6,8}$ 2 Hz, H6′.

*7-Bromo-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine* (*2b*)

3-Bromo-8-chloro-1,5-naphthyridine (0·5 g), 4-diethylaminobutylamine (1·5 g) and n-heptane (10·0 ml) were heated in an autoclave at 160° for 20 h and the product purified as described above. The *7-bromo-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine* (0·58 g) was obtained as a yellow oil (Found: C, 55·0; H, 6·8; N, 16·0. $C_{16}H_{23}BrN_4$ requires C, 54·7; H, 6·6; N, 16·0%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·02, t, J 7 Hz, CH_3CH_2; 1·70, complex, $CH_2(CH_2)_2CH_2$; 2·49, q, J 7 Hz, CH_3CH_2; 2·50, complex, CH_2NEt_2; 3·34, complex, $NHCH_2$; 6·50, d, $J_{2,3}$ 5·5 Hz, H3; 8·36, d, $J_{6,8}$ 2 Hz, H8; 8·50, d, $J_{2,3}$ 5·5 Hz; H2; 8·65, d, $J_{6,8}$ 2 Hz, H6.

The *dihydrobromide*, prepared in and recrystallized from ethanol, had m.p. 237–239° (Found: C, 37·5; H, 4·8; N, 10·9. $C_{16}H_{23}BrN_4.2HBr$ requires C, 37·5; H, 4·9; N, 10·9%).

4-(7′-Chloro-1′,5′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol ('*5-azaamodiaquine*') (*2c*)

4,7-Dichloro-1,5-naphthyridine[10] (0·2 g), 4-amino-2-diethylaminomethylphenol dihydrochloride (0·27 g) water (15·0 ml) and methanol (5·0 ml) were heated with stirring in an oil bath at 100° for 2 h. The methanol was then evaporated under reduced pressure and the aqueous solution adjusted with ammonium hydroxide to pH 7–8. The yellow precipitate was collected, washed, dried, and recrystallized from cyclohexane to give *4-(7′-chloro-1′,5′-naphthyridin-4′-ylamino)-2-diethylamino-*

[10] McCaustland, D. J., and Cheng, C. C., *J. Heterocycl. Chem.*, 1970, **7**, 467.

methylphenol (0·28 g), m.p. 167–169° (Found: C, 64·0; H, 6·0; N, 15·5. $C_{19}H_{21}ClN_4O$ requires C, 64·0; H, 5·9; N, 15·7%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·14, t, J 7 Hz, CH_3CH_2; 2·66, q, J 7 Hz, CH_3CH_2; 3·79, s, CH_2N; 6·85, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·86, d, $J_{5,6}$ 8 Hz, H6; 6·98, d, $J_{3,5}$ 3 Hz, H3; 7·17, q, $J_{5,6}$ 8 Hz, $J_{3,5}$ 3 Hz, H5; 8·2, br, NH; 8·23, d, $J_{6',8'}$ 2 Hz, H8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·65, d, $J_{6',8'}$ 2 Hz, H6′.

7-Chloro-N-(*2-diethylaminoethyl*)-*1,5-naphthyridin-4-amine* (*2d*)

4,7-Dichloro-1,5-naphthyridine (0·4 g), 2-diethylaminoethylamine (1·2 g) and n-heptane (10 ml) were heated in an autoclave at 160° for 20 h. Solvent and excess amine were then removed under reduced pressure and the product purified by t.l.c. (alumina; chloroform) to give *7-chloro*-N-(*2-diethylaminoethyl*)-*1,5-naphthyridin-4-amine* (0·48 g) as a brownish orange oil (Found: C, 60·5; H, 7·1; N, 20·0. $C_{14}H_{19}ClN_4$ requires C, 60·3; H, 6·9; N, 20·1%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·06, t, J 7 Hz, CH_3CH_2; 2·61, q, J 7 Hz, CH_3CH_2; 2·79, t, J 6 Hz, CH_2NEt_2; 3·34, complex, CH_2NH; 6·48, d, $J_{2,3}$ 5·5 Hz, H3; 7·0, br, NH; 8·17, d, $J_{6,8}$ 2 Hz, H8; 8·51, d, $J_{2,3}$ 5·5 Hz, H2; 8·60, d, $J_{6,8}$ 2 Hz, H6.

The *dihydrobromide*, prepared in and recrystallized from ethanol, had m.p. 265–267° (Found: C, 38·2; H, 4·8; N, 12·4. $C_{14}H_{19}ClN_4.2HBr$ requires C, 38·2; H, 4·8; N, 12·7%).

7-Chloro-N-(*4′-diethylaminobutyl*)-*1,5-naphthyridin-4-amine* (*2e*)

4,7-Dichloro-1,5-naphthyridine (0·4 g), 4-diethylaminobutylamine (1·5 g) and n-heptane (10·0 ml) were heated at 160° for 20 h as described above. The product was purified by t.l.c. (alumina; chloroform) and gave *7-chloro*-N-(*4′-diethylaminobutyl*)-*1,5-naphthyridin-4-amine* (0·47 g) as a brownish yellow oil (Found: C, 62·6; H, 7·8; N, 18·0. $C_{16}H_{23}ClN_4$ requires C, 62·6; H, 7·6; N, 18·3%). ^{1}H n.m.r. ($CDCl_3$): δ, 1·02, t, J 7 Hz, CH_3CH_2; 1·70, complex, $CH_2(CH_2)_2CH_2$; 2·53, q, J 7 Hz, CH_3CH_2; 2·57, complex, CH_2NEt_2; 3·33, complex, CH_2NH; 6·47, d, $J_{2,3}$ 5·5 Hz, H3; 6·7, br, NH; 8·16, d, $J_{6,8}$ 2 Hz, H8; 8·50, d, $J_{2,3}$ 5·5 Hz, H2; 8·54, d, $J_{6,8}$ 2 Hz, H6.

The *dihydrobromide*, prepared in ethanolic hydrogen bromide and recrystallized from propan-2-ol, had m.p. 210–212° (Found: C, 40·8; H, 5·4; N, 11·7. $C_{16}H_{23}ClN_4.2HBr$ requires C, 41·0; H, 5·4; N, 11·9%).

Toxicity Testing

The naphthyridines were tested for acute toxicity in mice by intraperitoneal injection in normal saline or peanut oil. Each test chemical was injected in a single dose of 200 mg/kg of body weight [except for 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2,6-bis(diethylamino and pyrrolidin-1″-yl)-methylphenol and 7-bromo(and chloro)-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine which, due to toxicity at 200 mg/kg, were run at 100 mg/kg] to three mice. No apparent ill effects were observed and all mice survived to and beyond 4 days in the above tests and in control experiments with normal saline and peanut oil.

Preliminary Antimalarial Screen

This was carried out as described previously.[2,3] Each test chemical was given at a dosage of 200 mg/kg of body weight except for 4-(7′-bromo-1′-5′-naphthyridin-4′-ylamino-2,6-bis(diethylamino and pyrrolidin-1″-yl)methylphenol and 7-bromo(and chloro)-*N*-(4′-diethylaminobutyl)-1,5-naphthyridin-4-amine which were at 100 mg/kg).

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