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# Potential Antimalarials. III*
# $N^4$-Substituted 7-Bromo-1,5-naphthyridin-4-amines

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*Abstract*

A series of new $N^4$-substituted 7-bromo-1,5-naphthyridin-4-amines has been prepared from nicotinic acid through 3-bromo-8-chloro-1,5-naphthyridine by nucleophilic replacement of the 8-chloro substituent with appropriate amines.

Several of these compounds, namely 7-bromo-*N*-(4′-diethylamino-1′-methylbutyl)-1,5-naphthyridin-4-amine ('5-azabromoquine'), 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)phenol and 7-bromo-*N*-(2′-diethylaminoethyl)-1,5-naphthyridin-4-amine showed significant antimalarial acivity. Apparent cures were effected when these test chemicals were injected intraperitoneally in a single dose of 200 mg/kg to mice infected with *Plasmodium vinckei vinckei*.

## Introduction

In earlier parts[1,2] of this series we described the synthesis and testing against *Plasmodium vinckei vinckei* of a series of 1,8-naphthyridines[1] and $N^4$-substituted 2-methoxy(and 2-hydroxy)-1,5-naphthyridin-4-amines.[2] We now report the preparation of a new series of $N^4$-substituted 7-bromo-1,5-naphthyridin-4-amines and testing against *P. vinckei vinckei* in mice in which some of these compounds showed significant antimalarial activity.

1,5-Naphthyridines have been examined previously for antimalarial activity by Adams *et al.*,[3] Goldberg *et al.*,[4] McCaustland and Cheng,[5] and Chen *et al.*[6] McCaustland and Cheng[5] found that 7-chloro-*N*-(4′-diethylamino-1′-methylbutyl)-1,5-naphthyridin-4-amine ('5-azachloroquine') possessed very good antimalarial activity against *P. berghei* in mice. It was comparable to chloroquine in activity when screened for blood schizontocidal activity, and was much less toxic than chloroquine and the existing 4- and 8-aminoquinoline drugs. Chen *et al.*[6] have prepared from 4-(1′,5′-naphthyridin-4′-ylamino)phenol (also with 2′-methyl and 6′-methoxy groups) a series of compounds with double Mannich basic chains of the

* Part II, *Aust. J. Chem.*, 1984, **37**, 2469.

[1] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1984, **37**, 1065.
[2] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1984, **37**, 2469.
[3] Adams, J. T., Bradsher, C. K., Breslow, D. S., Amore, S. T., and Hauser, C. R., *J. Am. Chem. Soc.*, 1946, **68**, 1317.
[4] Goldberg, A. A., Theobald, R. S., and Williamson, W., *J. Chem. Soc.*, 1954, 2357.
[5] McCaustland, D. J., and Cheng, C. C., *J. Heterocycl. Chem.*, 1970, **7**, 467.
[6] Chen, C., Zheng, X., Zhu, P., and Guo, H., *Yaoxue Zuebao*, 1982, **17**(2), 112 (*Chem. Abstr.*, 1982, **97**, 6191n).

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*p*-aminophenol, and report them to be effective antimalarials. In view of this activity, and the absence of activity in 2-methoxy(and 2-hydroxy)-1,5-naphthyridin-4-amines,[2] we have prepared a number of derivatives of 7-bromo-1,5-naphthyridin-4-amine (1; R = NHR′). This series, rather than the corresponding 7-chloro-1,5-naphthyridin-4-amines, was examined because 3-bromo-8-chloro-1,5-naphthyridine was more readily available than its 3,8-dichloro analogue. The diverse amine side chains incorporated in these new compounds varied from the branched alkyl diamine of chloroquine, and the straight-chain aliphatic diamines with chain length of 2–6 carbons which had previously been incorporated in substances showing antimalarial activity,[7] to the aromatic amine of amodiaquine.

## Synthesis

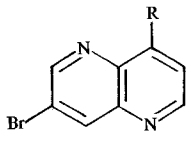
Compounds reported in this paper were prepared from the known ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate[8] (2; R = OH, R′ = Et) (see Experimental section) by hydrolysis in aqueous sodium hydroxide to the corresponding acid followed by decarboxylation in refluxing quinoline to 7-bromo-1,5-naphthyridin-4-ol (1; R = OH). Chlorination of this hydroxy compound by refluxing for 10 h with phosphoryl chloride gave 3-bromo-8-chloro-1,5-naphthyridine (1; R = Cl) in good yield.

The 3-bromo-8-chloro-1,5-naphthyridine reacted with 4-amino-2-(diethylaminomethyl)phenol hydrochloride in water at 100° to give 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)phenol (1b), but with one equivalent of benzene-1,4-diamine in aqueous methanol at 100° it gave *N*,*N*′-bis(7″-bromo-1″,5″-naphthyridin-4″-yl)benzene-1,4-diamine (3) hydrochloride as the major product and 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)aniline (1i) as shown by analyses, and $^1$H n.m.r. and mass spectral data. Ledóchowski and Chimiak[9] report that 9-chloroacridine with butane-1,4-diamine (hydrochloride) in phenol at 200° gave *N*,*N*′-di(acridin-9″-yl)butane-1,4-diamine; and 3-chloro-7-methoxy-9-phenoxyacridine with the same reagents but at 100° gave both the mono- and bis-acridinyl derivatives. 3-Bromo-8-chloro-1,5-naphthyridine reacted with 5-diethylaminopentan-2-amine, 2-diethylaminoethylamine, 3-diethylaminopropylamine, butane-1,4-diamine, pentane-1,5-diamine, hexane-1,6-diamine, and 3-dimethylaminopropylamine each in n-heptane at 160° for 20 h by replacement of the 8-chloro substituent and formation of the corresponding $N^4$-substituted 7-bromo-1,5-naphthyridin-4-amines (1a,c–h). 3-Bromo-8-chloro-1,5-naphthyridine with methanolic sodium methoxide at reflux readily gave 3-bromo-8-methoxy-1,5-naphthyridine.

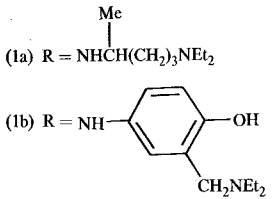
## Biological Activities

*In vivo* evaluation of the compounds described in this paper for antimalarial activity against *P. vinckei vinckei* in preliminary screening in rodents was examined, and the results are summarized in Table 1. Prior to these antimalarial studies each compound was examined for toxicity and safe dosage levels.

[7] Wiselogle, F. Y., 'A Survey of Antimalarial Drugs 1941–1945' (J. W. Edwards: Ann Arbor, Michigan, 1946).
[8] Heindl, J., Kelm, H.-W., Dogs, E., Seeger, A., and Herrmann, Ch., *Eur. J. Med. Chem.—Chim. Ther.*, 1977, **12**, 549.
[9] Ledóchowski, Z., and Chimiak, A., *Rocz. Chem.*, 1959, **33**, 1207.



(1)



(1a) R = $NHCH(CH_2)_3NEt_2$

(1b) R = NH– (OH, $CH_2NEt_2$)

(1c) R = $NH(CH_2)_2NEt_2$

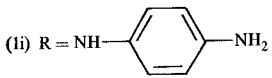
(1d) R = $NH(CH_2)_3NEt_2$

(1e) R = $NH(CH_2)_4NH_2$

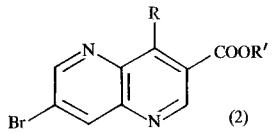
(1f) R = $NH(CH_2)_5NH_2$

(1g) R = $NH(CH_2)_6NH_2$

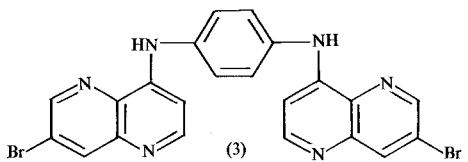
(1h) R = $NH(CH_2)_3NMe_2$



(1i) R = NH– ($NH_2$)



(2)



(3)

**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

| Compound | Solvent | Dose (mg/kg) | Mean percentage of parasite-infected red cells | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pretreatment | 9 h | 24 h | 48 h | 3 days | 6 days | 10 days | 13 days | 14 weeks |
| (1a) | peanut oil | 200 | 4 | 2 | 1 | <1 | <1 | <1 | <1 | <1 | [A] |
| (1b) | peanut oil | 200 | 11 | 10 | 1 | <1 | <1 | <1 | <1 | <1 | [A] |
| (1c)[B] | normal saline | 200 | 10 | 9 | <1 | <1 | <1 | <1 | 0 | 0 | [A] |
| (1d)[B] | normal saline | 100 | 11 | 12 | 6 | 22 | 48 | | | | |
| (1e)[B] | normal saline | 200 | 6 | 3 | <1 | <1 | 22 | | | | |
| (1f)[B] | normal saline | 200 | 6 | 7 | 12 | 36 | 59 | | | | |
| (1g)[B] | normal saline | 200 | 6 | 7 | 25 | 55 | 85 | | | | |
| (1h)[B] | normal saline | 200 | 12 | 13 | 1 | 5 | 18 | | | | |
| (1i) | normal saline | 200 | 3 | 13 | 34 | 76 | 80 | | | | |
| (3)[C] | peanut oil | 200 | 8 | 20 | 29 | 59 | 65 | | | | |
| Chloroquine[D] | normal saline | 20 | 14 | 11 | 2 | <1 | <1 | 7 | | <1 | [A] |
| Normal saline | — | — | 4 | 7 | 19 | 40 | 77 | | | | |
| Peanut oil | — | — | 14 | 25 | 42 | 77 | 82 | | | | |

[A] Mice alive after 14 weeks. [B] Hydrobromide. [C] Hydrochloride. [D] Diphosphate.

The results in Table 1 reveal that 7-bromo-*N*-(4′-diethylamino-1′-methylbutyl)-1,5-naphthyridin-4-amine (1a) ('5-azabromoquine'), 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminomethyl)phenol (1b), and 7-bromo-*N*-(2′-diethylaminoethyl)-1,5-naphthyridin-4-amine (1c) at a dosage of 200 mg/kg had very good antimalarial activity, comparable to that shown by chloroquine at a dosage of 20 mg/kg; a count of the mean percentage of parasite-infected red cells at 24 h after administration of the chemical showed less than 1% infection, and no increase was detected during the 13-day test. These counts were lower than for infected mice treated with chloroquine. Each of these test mice remained alive and healthy at 14 weeks.

7-Bromo-*N*-(3′-diethylaminopropyl)-1,5-naphthyridin-4-amine (1d) and 7-bromo-*N*-(3′-dimethylaminopropyl)-1,5-naphthyridin-4-amine (1h) showed some antimalarial activity at the dosages employed.

Of the naphthyridines with terminal primary amino groups, the highest activity was shown by 4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)butylamine (1e) which decreased to no significant activity in 6-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-hexylamine (1g) at the test concentrations of 200 mg/kg.

Relative to 'bromoquine'[10] which has an $LD_{50}$ of 72 mg/kg for a single intraperitoneal dose, '5-azabromoquine' (1a) is much less toxic with no apparent ill effects at a dosage of 200 mg/kg. This observation is consistent with the report by McCaustland and Cheng[5] that '5-azachloroquine' is less toxic than chloroquine. It appears therefore that aza substitution also decreases toxicity.

## Experimental

*General*

Solids for analysis were dried in an oven at 100° unless otherwise specified, and 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 $CD_3SOCD_3$ and sodium 3-trimethylsilylpropanesulfonate (in $D_2O$) as internal standards. Mass spectra were recorded on an Incos data system attached to a VG Micro Mass 7070F spectrometer with perfluorokerosene as standard.

*Ethyl 7-Bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate* (*2*; *R* = *OH*, *R′* = *Et*)

This compound was prepared from nicotinic acid through 5-bromonicotinic acid,[11,12] its amide,[12] and 5-bromopyridin-3-amine[12,13] which was condensed with diethyl ethoxymethylenemalonate and ring-closed in boiling diphenyl ether (not Dowtherm$^R$A as in ref.[8]) to the known ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate.[8]

*7-Bromo-4-hydroxy-1,5-naphthyridine-3-carboxylic Acid* (*2*; *R* = *OH*, *R′* = *H*)

Ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate (10·0 g) and 2·5 M sodium hydroxide (100 ml) were refluxed for 1 h. The solid dissolved and a gelatinous precipitate was produced. This mixture was diluted with boiling water (300 ml) and filtered with charcoal; the filtrate was acidified with glacial acetic acid. After cooling, the precipitate (8·0 g) was filtered off, washed with water and dried. A sample was purified by reprecipitation from aqueous sodium hydroxide with glacial

[10] Wiselogle, F. Y., 'A Survey of Antimalarial Drugs 1941–1945' p. 387 (J. W. Edwards: Ann Arbor, Michigan, 1946).
[11] Backman, G. B., and Micucci, D. D., *J. Am. Chem. Soc.*, 1948, **70**, 2381.
[12] Garcia, E. E., Greco, C. V., and Hunsberger, I. M., *J. Am. Chem. Soc.*, 1960, **82**, 4430.
[13] Ziegler, F. E., and Bennett, G. B., *J. Am. Chem. Soc.*, 1973, **95**, 7461.

acetic acid to give *7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylic acid*, m.p. >295° (dec.) (Found: C, 40·2; H, 2·0; Br, 29·6; N, 10·3. $C_9H_5BrN_2O_3$ requires C, 40·2; H, 1·9; Br, 29·7; N, 10·4%). $^1$H n.m.r. (NaOD): $\delta$ 8·22, d, $J_{6,8}$ 1·0 Hz, H 8; 8·60, br, H 2,6.

*7-Bromo-1,5-naphthyridin-4-ol* (*1*; *R* = *OH*)

7-Bromo-4-hydroxy-1,5-naphthyridine-3-carboxylic acid (8·0 g) was added in portions over 10 min to stirred refluxing quinoline (400 ml), and the mixture refluxed for 1 h. The mixture was cooled and diluted with acetone (1200 ml), and the precipitate was filtered off, washed with acetone and dried. The product was reprecipitated from aqueous sodium hydroxide with glacial acetic acid to give a white solid (6·0 g). A sample was purified for analysis by sublimation and gave *7-bromo-1,5-naphthyridin-4-ol*, m.p. >360° (Found: C, 43·1; H, 2·3; N, 12·2. $C_8H_5BrN_2O$ requires C, 42·7; H, 2·2; N, 12·4%). $^1$H n.m.r. (NaOD; 90°): $\delta$ 6·64, d, $J_{2,3}$ 6 Hz, H 3; 8·29, d, $J_{2,3}$ 6·0 Hz, H 2; 8·33, d, $J_{6,8}$ 2 Hz, H 8; 8·65, d, $J_{6,8}$ 2 Hz, H 6.

*3-Bromo-8-chloro-1,5-naphthyridine* (*1*; *R* = *Cl*)

7-Bromo-1,5-naphthyridin-4-ol (7·0 g) and phosphoryl chloride (200 ml) were refluxed for 10 h; excess phosphoryl chloride was distilled under reduced pressure and the residue poured onto ice. This cold mixture was neutralized with aqueous ammonia, and the solid was filtered off, washed with water and dried. It was recrystallized from n-heptane to give white needles of *3-bromo-8-chloro-1,5-naphthyridine* (6·4 g), m.p. 181–183° (Found: C, 39·7; H, 1·6; N, 11·3. $C_8H_4BrClN_2$ requires C, 39·4; H, 1·7; N, 11·5%). $^1$H n.m.r. ($CDCl_3$): $\delta$ 7·77, d, $J_{6,7}$ 5·0 Hz, H 7; 8·62, d, $J_{2,4}$ 2·0 Hz, H 4; 8·85, d, $J_{6,7}$ 5·0 Hz, H 6; 9·07, d, $J_{2,4}$ 2 Hz, H 2.

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

3-Bromo-8-chloro-1,5-naphthyridine (0·3 g, 0·0013 mol), 4-amino-2-(diethylaminomethyl)phenol dihydrochloride (0·33 g, 0·0013 mol) and water (45·0 ml) were heated with stirring in an oil bath at 100° for 2 h. The cooled reaction mixture was adjusted with aqueous ammonia to pH 7–8, and the dense yellow precipitate was filtered off, washed with water and dried. It was recrystallized from cyclohexane to give yellow crystals of *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)-2-(diethylaminoethyl)phenol* (0·4 g), m.p. 163–165° (Found: C, 56·6; H, 5·3; Br, 20·0; N, 13·7. $C_{19}H_{21}BrN_4O$ requires C, 56·9; H, 5·3; Br, 19·9; N, 14·0%). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·14, t, *J* 7 Hz, $CH_3CH_2$; 2·67, q, *J* 7 Hz, $CH_2CH_3$; 3·80, s, $CH_2N$; 6·86, d, $J_{2',3'}$ 5·5 Hz, H 3′; 6·87, d, $J_{5,6}$ 8 Hz, H 6; 6·99, d, $J_{3,5}$ 2·5 Hz, H 3; 7·17, q, $J_{3,5}$ 2·5, $J_{5,6}$ 8 Hz, H 5; 8·2, br, NH; 8·44, d, $J_{6',8'}$ 2 Hz, H 8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H 2′; 8·74, d, $J_{6',8'}$ 2 Hz, H 6′.

*7-Bromo*-N-(*4′-diethylamino-1′-methylbutyl*)-*1,5-naphthyridin-4-amine* (*1a*)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (0·5 g), 5-diethylaminopentan-2-amine (3·25 g) and n-heptane were heated in an autoclave at 160° for 20 h. The reaction mixture was washed out with methanol and the solvent evaporated. The excess of amine was then removed by distillation at *c.* 100°/0·5 mm. The residue was subjected to thin-layer chromatography (alumina; chloroform), and gave the product as a light yellow oil (0·5 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·01, t, *J* 7 Hz, $CH_3CH_2$; 1·33, d, *J* 6·5 Hz, $CH_3CH$; 1·62, complex, $CH_2CH_2CHMe$; 2·52, q, *J* 7 Hz $CH_2CH_3$; 2·50, complex, $CH_2NEt_2$; 3·62, complex, CH; 6·52, d, $J_{2,3}$ 5·5 Hz, H 3; 8·36, d, $J_{6,8}$ 2 Hz, H 8; 8·48, d, $J_{2,3}$ 5·5 Hz, H 2; 8·65, d, $J_{6,8}$ 2 Hz, H 6.

The *7-bromo*-N-(*4′-diethylamino-1′-methylbutyl*)-*1,5-naphthyridin-4-amine dipicrate*, prepared in and recrystallized from ethanol, had m.p. 220–222° (Found: C, 42·3; H, 3·8; Br, 9·9; N, 16·8. $C_{29}H_{31}BrN_{10}O_{14}$ requires C, 42·3; H, 3·8; Br, 9·7; N, 17·0%).

*7-Bromo*-N-(*2′-diethylaminoethyl*)-*1,5-naphthyridin-4-amine* (*1c*)

3-Bromo-8-chloro-1,5-naphthyridine (0·5 g), 2-diethylaminoethylamine (2·5 g) and n-heptane (10·0 ml) were heated at 160°, and the product was purified as described above to give a yellow oil (0·6 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·08, t, *J* 7 Hz, $CH_3CH_2$; 2·63, q, *J* 7 Hz, $CH_2CH_3$; 2·81, complex, $CH_2NEt_2$; 3·33, complex, $CH_2NH$; 6·50, d, $J_{2,3}$ 5·5 Hz, H 2; 7·0, br, NH; 8·37, d, $J_{6,8}$ 2 Hz, H 8; 8·51, d, $J_{2,3}$ 5·5 Hz, H 3; 8·69, d, $J_{6,8}$ 2·0 Hz, H 6.

This oil with ethanolic hydrogen bromide gave *7-bromo*-N-(*2'-diethylaminoethyl*)-*1,5-naphthyridin-4-amine dihydrobromide*, m.p. 274–276° (from ethanol) (Found: C, 34·9; H, 4·4; Br, 49·4; N, 11·2. $C_{14}H_{21}Br_3N_4$ requires C, 34·7; H, 4·4; Br, 49·4; N, 11·5%).

*7-Bromo*-N-(*3'-diethylaminopropyl*)-*1,5-naphthyridin-4-amine* (*1d*)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (0·5 g), 3-diethylaminopropylamine (3·0 g) and n-heptane (10·0 ml) was heated at 160° to give a light yellow oil (0·6 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·06, t, $J$ 7 Hz, $CH_3CH_2$; 1·88, complex, $CH_2CH_2CH_2$; 2·57, q, $J$ 7 Hz, $CH_2CH_3$; 2·61, complex, $CH_2NEt_2$; 3·36, complex, $CH_2NH$; 6·48, d, $J_{2,3}$ 5·5 Hz, H3; 7·6, br, NH; 8·35, d, $J_{6,8}$ 2 Hz, H8; 8·48, d, $J_{2,3}$ 5·5 Hz, H2; 8·65, d, $J_{6,8}$ 2 Hz, H6.

A portion of this oil with ethanolic hydrogen bromide gave *7-bromo*-N-(*3'-diethylaminopropyl*)-*1,5-naphthyridin-4-amine dihydrobromide*, m.p. 214–216° (from ethanol) (Found: C, 36·6; H, 4·7; Br, 48·1; N, 11·5. $C_{15}H_{21}BrN_4.2HBr$ requires C, 36·1; H, 4·6; Br, 48·0; N, 11·2%).

*4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)butylamine* (*1e*)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (0·5 g), butane-1,4-diamine (4·0 g) and n-heptane (10·0 ml) was heated at 160°, and the product was purified as described above to give a low-melting semisolid (0·45 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·71, complex, $CH_2(CH_2)_2CH_2$; 2·78, complex, $CH_2NH_2$; 3·31, complex, $CH_2NH$; 6·49, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·6, br, NH; 8·36, d, $J_{6',8'}$ 2·0 Hz, H8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·65, d, $J_{6',8'}$ 2·0 Hz, H6′. M+1, 296.

This product with ethanolic hydrogen bromide gave *4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-butylamine dihydrobromide*, m.p. 225–227° (from ethanol) (Found: C, 32·3; H, 3·9; N, 12·4. $C_{12}H_{15}BrN_4.2HBr$ requires C, 31·5; H, 3·8; N, 12·3%).

*5-(7'-Bromo-1',5'-naphthyridin-4'-ylamino) pentylamine* (*1f*)

3-Bromo-8-chloro-1,5-naphthyridine (0·5 g) with pentane-1,5-diamine (4·0 g) and n-heptane (10·0 ml) gave a low-melting semisolid (0·3 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·45, complex, $CH_2(CH_2)_3CH_2$; 2·73, complex, $CH_2NH_2$; 3·30, complex, $CH_2NH$; 6·49, d, $J_{2',3'}$ 5·5 Hz, H3′; 6·6, br, NH; 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′. M+1, 310.

The *5-(7'-bromo-1',5'-naphthyridin-4'-ylamino) pentylamine dihydrobromide*, prepared in and recrystallized from ethanol, had m.p. 244–246° (Found: C, 33·4; H, 4·1; N, 11·4. $C_{13}H_{19}Br_3N_4$ requires C, 33·1; H, 4·1; N, 11·9%).

*6-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)hexylamine* (*1g*)

6-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)hexylamine (1g) was prepared from 3-bromo-8-chloro-1,5-naphthyridine (0·5 g) and hexane-1,6-diamine (5·0 g) in n-heptane (10·0 ml). The product was obtained as a low-melting semisolid (0·45 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·60, complex, $CH_2(CH_2)_4CH_2$; 2·70, complex, $CH_2NH_2$; 3·29, complex, $CH_2NH$; 6·50, d, $J_{2',3'}$ 5·5 Hz, H3′; 8·37, d, $J_{6',8'}$ 2·0 Hz, H8′; 8·50, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·66, d, $J_{6',8'}$ 2·0 Hz, H6′. M, 323.

This product with ethanolic hydrogen bromide gave *6-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-hexylamine dihydrobromide*, m.p. 195–197° (from ethanol) (Found: C, 35·2; H, 4·5; N, 11·4. $C_{14}H_{19}BrN_4.2HBr$ requires C, 34·7; H, 4·4; N, 11·6%).

*7-Bromo*-N-(*3'-dimethylaminopropyl*)-*1,5-naphthyridin-4-amine* (*1h*)

7-Bromo-*N*-(3′-dimethylaminopropyl)-1,5-naphthyridin-4-amine (1h) was prepared from 3-bromo-8-chloro-1,5-naphthyridine (0·5 g) and 3-dimethylaminopropylamine (2·0 g) in n-heptane (10·0 ml). The product was obtained as a yellow oil (0·6 g). $^1$H n.m.r. ($CDCl_3$): $\delta$ 1·88, complex, $CH_2CH_2CH_2$; 2·26, s, $Me_2N$; 2·43, complex, $CH_2NMe_2$; 3·36, complex, $CH_2NH$; 6·51, d, $J_{2,3}$ 5·5 Hz, H3; 7·1, br, NH; 8·35, d, $J_{6,8}$ 2 Hz, H8; 8·49, d, $J_{2,3}$ 5·5 Hz, H2; 8·65, d, $J_{6,8}$ 2 Hz, H6.

*7-Bromo*-N-(*3'-dimethylaminopropyl*)-*1,5-naphthyridin-4-amine dihydrobromide* prepared in, and recrystallized from, ethanol had m.p. 258–260° (Found: C, 33·2; H, 4·2; N, 11·8. $C_{13}H_{19}Br_3N_4$ requires C, 33·1; H, 4·1; N, 11·9%).

*4-(7′-Bromo-1′,5′-naphthyridin-4′-ylamino)aniline (1i), and N,N′-Bis(7″-bromo-1″,5″-naphthyridin-4″-yl)benzene-1,4-diamine (3) as the Hydrochloride*

3-Bromo-8-chloro-1,5-naphthyridine (0·5 g, 0·002 mol), benzene-1,4-diamine dihydrochloride (0·38 g, 0·002 mol), water (20·0 ml) and methanol (5·0 ml) were heated with stirring in an oil bath at 100° for 2 h. After cooling the reaction mixture, the yellow precipitate was filtered off and recrystallized from water (which was adjusted with hydrochloric acid to pH 2) to give yellow crystals of *N,N′-bis(7″-bromo-1″,5″-naphthyridin-4″-yl)benzene-1,4-diamine hydrochloride* (0·30 g), m.p. > 360° (Found: C, 47·5; H, 2·7; N, 15·2. $C_{22}H_{14}Br_2N_6$.HCl requires C, 47·3; H, 2·7; N, 15·1%). M, 522. $^1$H n.m.r. ($CD_3SOCD_3$): $\delta$ 4·69, d, $J_{2'',3''}$ 6·5 Hz, H3″; 5·17, s, H2,3,5,6; 6·12, d, $J_{2'',3''}$ 6·5 Hz, H2″; 6·25, d, $J_{6'',8''}$ 2 Hz, H8″; 6·63, d, $J_{6'',8''}$ 2 Hz, H6″.

The filtrate from the reaction mixture above was adjusted to pH 8–9; the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give yellow needles of *4-(7′-bromo-1′,5′-naphthyridin-4′-ylamino)aniline* (0·2 g), m.p. 215–216° (Found: C, 53·4; H, 3·6; N, 17·6. $C_{14}H_{11}BrN_4$ requires C, 53·4; H, 3·5; N, 17·8%). M+1, 316. $^1$H n.m.r. ($CDCl_3$): $\delta$ 6·75, d, $J_{2,3}$ 8·5 Hz, H2,6; 6·84, d, $J_{2',3'}$ 5·5 Hz, H3′; 7·16, d, $J_{2,3}$ 8·5 Hz, H3,5; 8·14, br, NH; 8·41, d, $J_{6',8'}$ 2·0 Hz, H8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·74, d, $J_{6',8'}$ 2 Hz, H6′.

*3-Bromo-8-methoxy-1,5-naphthyridine (1; R = OMe)*

3-Bromo-8-chloro-1,5-naphthyridine (0·2 g) was refluxed with methanolic sodium methoxide (from 0·2 g sodium and 20 ml methanol) for 2 h, then the solvent was evaporated. The product was extracted into chloroform and subjected to thin-layer chromatography (alumina; chloroform), and recrystallized from cyclohexane to give white needles of *3-bromo-8-methoxy-1,5-naphthyridine* (0·12 g), m.p. 167–169° (Found: C, 45·1; H, 2·9; N, 11·7. $C_9H_7BrN_2O$ requires C, 45·2; H, 2·9; N, 11·7%). $^1$H n.m.r. ($CDCl_3$): $\delta$ 4·15, s, MeO; 7·00, d, $J_{6,7}$ 5·5 Hz, H7; 8·54, d, $J_{2,4}$ 2·0 Hz, H4; 8·82, d, $J_{6,7}$ 5·5 Hz, H6; 8·95, d, $J_{2,4}$ 2 Hz, H2.

*Toxicity Testing*

Each naphthyridine was tested for acute toxicity in three mice by injection intraperitoneally, each with a single dose in normal saline or peanut oil, at a dose of 200 mg/kg of body weight [except for 7-bromo-*N*-(3′-diethylaminopropyl)-1,5-naphthyridin-4-amine (1d) which due to toxicity at 200 mg/kg was run at 100 mg/kg]. No apparent ill effects were observed, and all mice survived to and beyond 8 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] except that each test chemical was given at a dosage of 200 mg/kg of body weight [except for 7-bromo-*N*-(3′-diethylaminopropyl)-1,5-naphthyridin-4-amine (1d) which was at 100 mg/kg], and blood counts were made at 9, 24, 48 h and thence daily.

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