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Potential Antimalarials. II*
*N*4-Substituted 2-Methoxy(and 2-Hydroxy)-1,5-naphthyridin-4-amines

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Abstract

Several new *N*4-substituted 2-methoxy(and 2-hydroxy)-1,5-naphthyridin-4-amines have been prepared from ethyl 3-aminopyridine-2-carboxylate. 2,4-Dichloro-1,5-naphthyridine with methanolic sodium methoxide gave 4-chloro-2-methoxy-1,5-naphthyridine but with methanolic hydrogen chloride afforded 4-chloro-1,5-naphthyridin-2-ol.

The *N*4-substituted 1,5-naphthyridin-4-amines showed no significant antimalarial activity compared to chloroquine or primaquine in a preliminary *in vivo* screen against *Plasmodium vinckei vinckei* in mice.

Introduction

In an earlier publication[1] we reported the synthesis and preliminary antimalarial screening of a series of 1,8-naphthyridines (1) and (2) against *Plasmodium vinckei vinckei* in mice. We now report the preparation of a series of new 1,5-naphthyridines (3) and the testing, by a more refined test procedure, of these compounds and of the previously described 1,8-naphthyridines.[1]

McCaustland and Cheng[2] synthesized several 1,5-naphthyridines and found that 7-chloro-*N*-(4′-diethylamino-1′-methylbutyl)-1,5-naphthyridin-4-amine (4), '5-aza-chloroquine', possessed very good antimalarial activity against *Plasmodium 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 4- and 8-aminoquinoline drugs. Other potential antimalarial 1,5-naphthyridines have been synthesized by Adams *et al.*[3] and Goldberg *et al.*[4]

Schmidt[5,6] has reported significant radical curative activity by many 8-amino-quinolines[3,4] and also some evidence in derivatives of 4-amino-1,5-naphthyridin-2-ols[6] in tests against *Plasmodium cynomolgi* in Rhesus monkeys.

In a search for curative activity, and because of the obvious similarity of the 1,5-naphthyridin-4-amines to the quinolin-8-amines, we have prepared a number of

* Part I, *Aust. J. Chem.*, 1984, **37**, 1065.

[1] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1984, **37**, 1065.
[2] McCaustland, D. J., and Cheng, C. C., *J. Heterocycl. Chem.*, 1970, **7**, 467.
[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] Schmidt, L. H., *Antimicrob. Agents Chemother.*, 1983, **24**, 615.
[6] Schmidt, L. H., *Am. J. Trop. Med. Hyg.*, 1983, **32**, 231.

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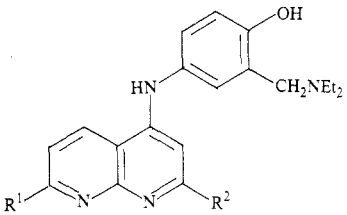
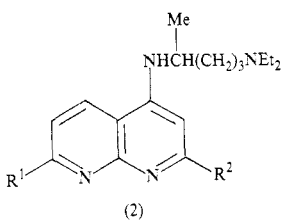
derivatives of 1,5-naphthyridin-4-amines for testing for antimalarial activity. The various amine side chains incorporated in these new compounds were selected from those present in substances which had previously shown activity[5,7] in animal screening experiments and also in clinical use, for example, Amodiaquine.



(1)



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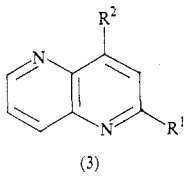

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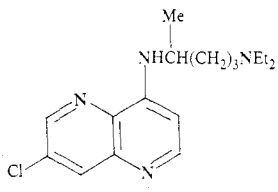

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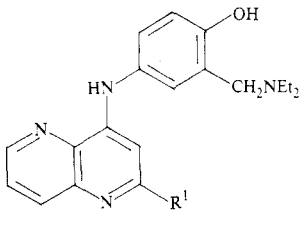

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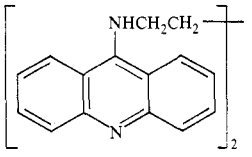

(6)

Synthesis

The 1,5-naphthyridines in this work were prepared initially from ethyl 3-amino-pyridine-2-carboxylate which with diethyl malonate, under conditions modified from those described by Oakes and Rydon,[8] and without isolating the intermediate, gave 1,5-naphthyridine-2,4-diol[8] (3; $R^1 = R^2 = OH$). Treatment of the latter with phosphoryl chloride afforded 2,4-dichloro-1,5-naphthyridine[8] (3; $R^1 = R^2 = Cl$) which with methanolic sodium methoxide at reflux gave 4-chloro-2-methoxy-1,5-naphthyridine (3; $R^1 = OMe$, $R^2 = Cl$) whose structure was established as described below. The reaction of 2,4-dichloro-1,5-naphthyridine with methanolic hydrogen chloride at reflux to give 4-chloro-2-methoxy-1,5-naphthyridine as described by McCaustland and Cheng[2] proved unsatisfactory in our hands. Instead it gave 4-chloro-1,5-naphthyridin-2-ol (3; $R^1 = OH$, $R^2 = Cl$) which was also prepared by hydrolysis of 2,4-dichloro-1,5-naphthyridine with 5 M hydrochloric acid in dioxan,[8] as well as by hydrolysis of 4-chloro-2-methoxy-1,5-naphthyridine with 5 M hydrochloric acid in dioxan. The product from the last reaction was dechlorinated with *p*-toluenesulfonylhydrazide[8] to 1,5-naphthyridin-2-ol (3; $R^1 = OH$, $R^2 = H$). The methoxy compound was therefore 4-chloro-2-methoxy-1,5-naphthyridine.

4-Chloro-2-methoxy-1,5-naphthyridine reacted with 4-amino-2-diethylamino-methylphenol in aqueous solution at 100° to give 2-diethylaminomethyl-4-(2′-methoxy-1′,5′-naphthyridin-4′-ylamino)phenol (5; $R^1 = OMe$) and with a series of amines (namely 2-diethylaminoethylamine, 3-diethylaminopropylamine, propane-1,3-diamine, butane-1,4-diamine, pentane-1,5-diamine and hexane-1,6-diamine) together with

[7] Wiselogle, F. Y., 'A Survey of Antimalarial Drugs 1941–1945' (J. W. Edwards: Ann Arbor, Michigan, 1946).

[8] Oakes, V., and Rydon, H. N., *J. Chem. Soc.*, 1958, 204.

one equivalent of sodium carbonate in n-heptane in an autoclave at 160° for 20 h by replacement of the 4-chloro substituent and formation of the corresponding *N*4-substituted 2-methoxy-1,5-naphthyridin-4-amines [e.g. (3); R^1 = OMe, R^2 = $NHCH_2CH_2NEt_2$].

Brown and Lee[9] have studied the thermal rearrangement of 2- and 4-alkoxypyrimidines to their *N*-alkyl isomers and McCaustland and Cheng[2] have observed *O* to *N* rearrangement in the aminolysis of 4-chloro-2-methoxy-1,5-naphthyridine (3; R^1 = OMe, R^2 = Cl) with novaldiamine but McCaustland and Cheng[2] found that in excess amine with one molar equivalent of potassium carbonate no significant rearrangement took place. In our reactions in the presence of one equivalent of sodium carbonate no sign of rearranged product was detected. The ^1H n.m.r. of the neutral molecules in deuterochloroform showed the methoxy group at δ 4·01–4·02, and should be compared with that of 4-chloro-2-methoxy-1,5-naphthyridine at 4·07; and the ^{13}C n.m.r. spectrum of the products from reaction of 4-chloro-2-methoxy-1,5-naphthyridine with 2-diethylaminoethylamine and propane-1,3-diamine, as dihydrobromides in deuterium oxide, showed resonances at δ 58·40 and 58·28, respectively which are indicative of methoxy groups.[10] The resonance signal due to the carbon of the methoxy group has been found in a variety of heterocycles to occur in the range from δ 53·20 to 61·87 and that of the *N*-methyl group in the range from 34·29 to 49·62.[10]

4-Chloro-1,5-naphthyridin-2-ol (3; R^1 = OH, R^2 = Cl) also reacted with the same series of aliphatic amines as its 2-methoxy analogue but at 180° to give the 4-(*N*-substituted)amino-1,5-naphthyridin-2-ols [e.g. (3); R^1 = OH, R^2 = $NHCH_2CH_2NEt_2$].

Ledóchowski and Chimiak[11] 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 (6); and 3-chloro-7-methoxy-9-phenoxyacridine with the same reagents but at 100° gave both the mono- and bis-acridinyl derivatives. In our reactions, no bis(1,5-naphthyridin-4-yl) compounds were obtained: analyses, integration of the ^1H n.m.r. and mass spectra gave no indication of these products.

4-Chloro-1,5-naphthyridin-2-ol failed to react with 4-amino-2-diethylaminophenol in water at 100°.

Biological Activities

Compounds first reported in this paper and others reported previously were evaluated by a new test procedure for antimalarial activity against *Plasmodium vinckei vinckei* in rodents as described in the Experimental section.

The compounds, already tested for toxicity and safe dosage levels on three mice for each compound and dosage, were administered intraperitoneally to three mice [generally at 10–20% parasitaemia (the mean percentage of parasite-infected red cells)] in normal saline or peanut oil and controls were run against the widely used antimalarials, chloroquine and primaquine, and against the solvents normal saline and peanut oil. Blood counts were made then at various time intervals to determine parasitaemia levels.

[9] Brown, D. J., and Lee, T.-C., *Aust. J. Chem.*, 1968, **21**, 243.
[10] Barlin, G. B., Brown, D. J., and Fenn, M. D., *Aust. J. Chem.*, 1984, **37**, 2391.
[11] Ledóchowski, Z., and Chimiak, A., *Rocz. Chem.*, 1959, **33**, 1207.

In earlier experiments[1] the compounds were administered in 50% dimethylformamide in normal saline to more highly infected mice and tests were thus made over shorter time spans. This was discontinued due to the toxicity of the dimethylformamide, and to the desirability of taking blood counts on mice over a longer time period thus requiring commencement of the tests at lower infection levels.

No significant antimalarial activity was detected in either the 1,5- or 1,8-naphthyridines tested when compared to the progressive increase in the mean percentage of parasite-infected red cells of the control samples injected with normal saline or peanut oil, or when compared to the significant effects of lower dosages of primaquine or chloroquine.

Representative results of the tests on the 1,5-naphthyridines reported in this paper and some 1,8-naphthyridines reported previously[1] are given in Table 1.

Table 1. Preliminary antimalarial screening results against *Plasmodium vinckei vinckei* in mice
For details of test procedures see Experimental section

Compound	Solvent[A]	Dose (mg/kg)	Mean (%) of infected red cells			
			Pre-treatment	Time from dose 6 h	24 h	48 h
(3; R^1 = OH, R^2 = $NH(CH_2)_3NEt_2$)	PO	100	18	27	56	85
(3; R^1 = OH, R^2 = $NH(CH_2)_6NH_2$)	NS	100	10	14	28	67
(5; R^1 = OMe)	PO	100	16	25	41	73
(3; R^1 = OMe, R^2 = $NH(CH_2)_2NEt_2$)[B]	NS	100	13	25	44	80
(3; R^1 = OMe, R^2 = $NH(CH_2)_4NH_2$)[B]	NS	100	20	38	61	87
(1; R^1 = R^2 = H)	PO	100	14	27	53	87
(2; R^1 = R^2 = H)	PO	50	19	34	54	85
(1; R^1 = Me, R^2 = H)	PO	100	11	18	31	68
(1; R^1 = Cl, R^2 = H)	PO	100	12	16	42	76
(2; R^1 = Cl, R^2 = Me)	PO	100	6	13	34	71
Normal saline	—	—	14	19	47	80
Peanut oil	—	—	24	33	63	77
Primaquine[C]	NS	30	9	8	4	2
Chloroquine[C]	NS	20	16	18	8	1

[A] PO, peanut oil; NS, normal saline.
[B] 2HBr.
[C] Diphosphate.

Experimental

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. ^1H and ^{13}C spectra were recorded at 90 MHz and 30° with a JEOL FX90Q 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.

1,5-Naphthyridine-2,4-diol (3; R^1 = R^2 = OH)

1,5-Naphthyridine-2,4-diol was prepared in improved yield as described below from quinolinic acid through quinolinic acid imide,[12] 3-aminopyridine-2-carboxylic acid[13] and its ethyl ester[13]

[12] Sucharda, E., *Ber. Dtsch. Chem. Ges.*, 1925, **58**, 1727.
[13] Oakes, V., Pascoe, R., and Rydon, H. N., *J. Chem. Soc.*, 1956, 1045.

[^{1}H n.m.r. ($CDCl_3$): δ 1·45, t, J 7 Hz, CH_3CH_2; 4·46, q, J 7 Hz, CH_2CH_3; 5·6, b, NH_2; 7·02, q, $J_{4,5}$ 8·5 Hz, $J_{4,6}$ 1·5 Hz, H4; 7·16, q, $J_{4,5}$ 8·5 Hz, $J_{5,6}$ 4·0 Hz, H5; 8·08, q, $J_{5,6}$ 4·0 Hz, $J_{4,6}$ 1·5 Hz, H6] by a modification of the literature[8] procedure which proved troublesome.

Ethyl 3-aminopicolinate (6·0 g) was added in portions over 15 min to diethyl malonate (45 ml) stirred in an open flask at 120° and maintained at that temperature for 5 h. Excess malonic ester was removed under reduced pressure, and the residue refluxed with ethanolic sodium ethoxide (from 1·05 g sodium and 90 ml ethanol) for 5 h, then evaporated to half volume, and diluted with ether (45 ml).

The solid was filtered off, dried, powdered, suspended in water (9·0 ml) and refluxed with 10 M sodium hydroxide (21 ml) until effervescence ceased. Boiling water was then added dropwise to give an almost clear solution which was filtered, and the filtrate adjusted to pH *c.* 5·5 with acetic acid. The dense yellow precipitate was filtered off, washed with water and dried to give 1,5-naphthyridine-2,4-diol (5·7 g), m.p. >360° (lit.[8] >360°). ^{1}H n.m.r. (CD_3SOCD_3): δ 5·91, s, H3; 7·53, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H7; 7·67, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 2 Hz, H8; 8·44, q, $J_{6,7}$ 4 Hz, $J_{6,8}$ 2 Hz, H6.

2,4-Dichloro-1,5-naphthyridine (*3*; $R^1 = R^2 = Cl$)

2,4-Dichloro-1,5-naphthyridine was prepared from 1,5-naphthyridine-2,4-diol (3·0 g) with phosphoryl chloride as described by Oakes and Rydon.[8] The crude product was recrystallized from light petroleum (b.p. 60–80°) to give the dichloro compound as white crystals (2·7 g), m.p. 138–140° (lit.[8] 140°). ^{1}H n.m.r. ($CDCl_3$): δ 7·71, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H7; 7·73, s, H3; 8·32, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 9·05, q, $J_{6,7}$ 4·0 Hz, $J_{6,8}$ 1·5 Hz, H6.

4-Chloro-2-methoxy-1,5-naphthyridine (*3*; $R^1 = OMe$, $R^2 = Cl$)

2,4-Dichloro-1,5-naphthyridine (4·0 g) and methanolic sodium methoxide (from 0·6 g sodium and 180 ml methanol) were refluxed for 1 h. Excess methanol was removed under reduced pressure, and the product purified by column chromatography in ether over silica to give 4-chloro-2-methoxy-1,5-naphthyridine (2·5 g), m.p. 113–114° (lit.[2] 114–115°). ^{1}H n.m.r. ($CDCl_3$): δ 4·07, s, MeO; 7·27, s, H3; 7·59, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 8·16, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 2 Hz, H8; 8·87, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 2 Hz, H6.

4-Chloro-1,5-naphthyridin-2-ol (*3*; $R^1 = OH$, $R^2 = Cl$)

(A) This compound was prepared in quantity from 2,4-dichloro-1,5-naphthyridine as described by Oakes and Rydon.[8] It had m.p. 263° (lit.[8] 263°). ^{1}H n.m.r. ($CDCl_3$): δ 7·13, s, H3; 7·53, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·81, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·71, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

(B) 4-Chloro-2-methoxy-1,5-naphthyridine (0·4 g), 5 M hydrochloric acid (5·0 ml) and dioxan (5·0 ml) were refluxed for 1 h. The mixture was diluted with water, made basic with sodium carbonate, and evaporated to dryness. The residue was boiled with chloroform (3 × 50 ml), and the product extracted was recrystallized from ethyl acetate to give white crystals of 4-chloro-1,5-naphthyridin-2-ol (0·22 g), m.p. 262–263°, not depressed on admixture with the product from (A), and had the same ^{1}H n.m.r. as the product from (A).

This product obtained in (B) was also dechlorinated with *p*-toluenesulfonylhydrazide as described by Oakes and Rydon[8] to give 1,5-naphthyridin-2-ol, m.p. 256–258° (lit. 258°,[8] 259°[14]). 1,5-Naphthyridin-4-ol is reported to have m.p. 340°.[15]

2-Diethylaminomethyl-4-(2′-methoxy-1′,5′-naphthyridin-4′-ylamino)phenol [*5*; $R^1 = OMe$]

4-Chloro-2-methoxy-1,5-naphthyridine (1·0 g), 4-amino-2-diethylaminomethylphenol dihydrochloride (1·37 g), water (20 ml) and ethanol (10 ml) were heated in an oil bath with stirring at 100° for 4 h. The mixture was evaporated under reduced pressure and evaporated three times with water (3 × 20 ml) to remove unchanged chloro compound. The residue was diluted with water (20 ml), adjusted to pH *c.* 7·3 with aqueous ammonia and extracted with chloroform. The extract was dried

[14] Petrow, V., and Sturgeon, B., *J. Chem. Soc.*, 1949, 1157.
[15] Hart, E. P., *J. Chem. Soc.*, 1954, 1879.

(Na_2SO_4) and evaporated to give an oil which was subjected to column and t.l.c. chromatography in chloroform over alumina to give, as a yellow oil, *2-diethylaminomethyl-4-(2′-methoxy-1′,5′-naphthyridin-4′-ylamino)phenol* (0·85 g) (Found: for a sample dried at 20° under vacuum, C, 68·3; H, 6·9. $C_{20}H_{24}N_4O_2$ requires C, 68·2; H, 6·9%). *M* 352. ^{1}H n.m.r. ($CDCl_3$): δ 1·11, t, *J* 7 Hz, CH_3CH_2; 2·63, q, *J* 7 Hz, CH_2CH_3; 3·75, s, CH_2N; 3·99, s, MeO; 6·37, s, H3′; 6·83, d, $J_{5,6}$ 8·5 Hz, H6; 6·96, d, $J_{3,5}$ 2·5 Hz, H3; 7·15, q, $J_{3,5}$ 2·5 Hz, $J_{5,6}$ 8·5 Hz, H5; 7·48, q, $J_{7',8'}$ 8·5 Hz, $J_{6',7'}$ 4·5 Hz, H7; 8·03, q, $J_{7',8'}$ 8·5 Hz, $J_{6',8'}$ 1·5 Hz, H8′; 8·56, q, $J_{6',7'}$ 4·5 Hz, $J_{6',8'}$ 1·5 Hz, H6′; 9·5, b, NH.

The *dipicrate*, prepared in ethanol, had m.p. 200–201° (Found, for sample dried at 100° for 1 h: C, 47·7; H, 3·8; N, 17·1. $C_{32}H_{30}N_{10}O_{16}$ requires C, 47·4; H, 3·7; N, 17·3%).

N-*(2′-Diethylaminoethyl)-2-methoxy-1,5-naphthyridin-4-amine*
[*3*; $R^1 = OMe$, $R^2 = NHCH_2CH_2NEt_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (1·0 g), 2-diethylaminoethylamine (3·0 g), anhydrous sodium carbonate (0·54 g) and n-heptane (20 ml) were heated in an autoclave at 160° for 20 h, then the solvent and excess amine removed under vacuum, and the remaining oil chromatographed in chloroform over alumina.

The product was treated with ethanolic hydrogen bromide and the precipitate recrystallized from ethanol to give white crystals of N-*(2′-diethylaminoethyl)-2-methoxy-1,5-naphthyridin-4-amine dihydrobromide* (1·5 g), m.p. 169–170° (Found: C, 41·5; H, 5·7; Br, 36·6; N, 12·9. $C_{15}H_{24}Br_2N_4O$ requires C, 41·3; H, 5·6; Br, 36·6; N, 12·8%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·04, t, *J* 7 Hz, CH_3CH_2; 2·58, q, *J* 7 Hz, CH_2CH_3; 2·76, t, *J* 5·5 Hz, CH_2NEt_2; 5·62, complex, CH_2NH; 4·01, s, MeO; 5·97, s, H3; 6·81, b, NH; 7·40, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H7; 7·97, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·50, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

^{13}C n.m.r. (dihydrobromide in D_2O): δ 8·15, CH_3CH_2; 37·46, 49·38, $CH_2CH_2NEt_2$; 47·86, CH_2CH_3; 58·40, CH_3O; 82·67, C3; 126·85, C7; 128·50, C8; 129·88, C4; 132·10, C8a; 148·14, C6; 156·70, C4a; 162·03, C2.

N-*(3′-Diethylaminopropyl)-2-methoxy-1,5-naphthyridin-4-amine*
[*3*; $R^1 = OMe$, $R^2 = NH(CH_2)_3NEt_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (0·5 g), 3-diethylaminopropylamine (1·675 g), anhydrous sodium carbonate (0·275 g) and n-heptane were heated at 160° for 20 h as described above. The product was subjected to chromatography in ether over alumina (8 cm) and after elution with ether, the product was eluted with ethanol which was evaporated to give a light yellow oil (0·51 g). *M* 288. ^{1}H n.m.r. ($CDCl_3$): δ 1·03, t, *J* 7 Hz, CH_3CH_2; 1·85, complex, $CH_2CH_2CH_2$; 2·53, q, *J* 7 Hz, CH_2CH_3; 2·57, complex, CH_2NEt_2; 3·32, complex CH_2NH; 4·01, s, MeO; 5·97, s, H3; 7·0, b, NH; 7·42, q, $J_{7,8}$ 8·5 Hz; $J_{6,7}$ 4·5 Hz, H7; 7·98, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·49, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

A sample of this oil was treated with ethanolic picric acid, and the product recrystallized from ethanol to give N-*(3′-diethylaminopropyl)-2-methoxy-1,5-naphthyridin-4-amine dipicrate*, m.p. 185–187° (Found: C, 44·7; H, 4·0; N, 18·4. $C_{28}H_{30}N_{10}O_{15}$ requires C, 45·0; H, 4·0; N, 18·8%).

N-*(3′-Aminopropyl)-2-methoxy-1,5-naphthyridin-4-amine* [*3*; $R^1 = OMe$, $R^2 = NH(CH_2)_3NH_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (0·50 g), propane-1,3-diamine (1·9 g), anhydrous sodium carbonate (0·27 g) and n-heptane (10·0 ml) were heated at 160° for 20 h. Column and thin-layer chromatography (alumina; chloroform) gave a light yellow oil (0·32 g). ^{1}H n.m.r. ($CDCl_3$): δ 1·85, complex, $CH_2CH_2CH_2$; 2·86, t, CH_2NH_2; 3·34, complex, CH_2NH; 4·01, s, MeO; 5·98, s, H3; 6·6, b, NH; 7·43, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H7; 7·99, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·50, q, $J_{6,7}$ 4·0 Hz, $J_{6,8}$ 1·5 Hz, H6.

This oil with ethanolic hydrogen bromide gave bright yellow crystals of N-*(3′-aminopropyl)-2-methoxy-1,5-naphthyridin-4-amine dihydrobromide* (0·45 g) (from ethanol), m.p. >169° (dec.) (Found: C, 36·5; H, 4·7; Br, 40·3; N, 14·0. $C_{12}H_{18}Br_2N_4O$ requires C, 36·6; H, 4·6; Br, 40·5; N, 14·2%).

^{13}C n.m.r. (D_2O): δ 25·54, $CH_2CH_2CH_2$; 37·05, 39·76, $CH_2CH_2CH_2$; 58·28, CH_3O; 81·50, C3; 126·39, C7; 128·28, C8; 129·45, C4; 131·70, C8a; 137·76, C6; 156·32, C4a; 161·44, C2.

N-(*4'-Aminobutyl*)-*2-methoxy-1,5-naphthyridin-4-amine* [*3*; $R^1 = OMe$, $R^2 = NH(CH_2)_4NH_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (0·5 g), butane-1,4-diamine (3·0 g), anhydrous sodium carbonate (0·275 g) and n-heptane (10·0 ml) were heated at 160° for 20 h. Column and thin-layer chromatography (alumina; methanol) gave a light yellow oil (0·4 g). ^{1}H n.m.r. ($CDCl_3$): δ 1·67, complex, $CH_2CH_2CH_2CH_2$; 2·74, t, CH_2NH_2; 3·27, complex, CH_2NH; 4·01, s, MeO; 5·97, s, H 3; 6·5, b, NH; 7·44, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H 7; 7·99, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H 8; 8·50, q, $J_{6,7}$ 4·0 Hz, $J_{6,8}$ 1·5 Hz, H 6.

This oil was treated with ethanolic hydrogen bromide and the product recrystallized from isopropyl alcohol (charcoal) to give N-(*4'-aminobutyl*)-*2-methoxy-1,5-naphthyridin-4-amine dihydrobromide* (0·5 g), which decomposed above 166° (Found: C, 38·6; H, 5·3; N, 13·7. $C_{13}H_{20}Br_2N_4O$ requires C, 38·3; H, 4·9; N, 13·7%).

N-(*5'-Aminopentyl*)-*2-methoxy-1,5-naphthyridin-4-amine* [*3*; $R^1 = OMe$, $R^2 = NH(CH_2)_5NH_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (0·5 g), pentane-1,5-diamine (3·0 g), anhydrous sodium carbonate (0·275 g) and n-heptane (10·0 ml) were heated at 160° for 20 h. Column and thin-layer chromatography (alumina; methanol) gave a yellow oil (0·45 g). ^{1}H n.m.r. ($CDCl_3$): δ 1·57, complex, $CH_2(CH_2)_3CH_2$; 2·68, complex, CH_2NH_2; 3·25, complex, CH_2NH; 4·01, s, MeO; 5·96, s, H 3; 6·5, b, NH; 7·44, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H 7; 7·99, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H 8; 8·50, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H 6.

This oil with ethanolic hydrogen bromide gave a precipitate which was recrystallized from ethanol (charcoal) to give N-(*5'*-aminopentyl)-*2-methoxy-1,5-naphthyridin-4-amine dihydrobromide* (0·6 g) which decomposed above 164° (Found, for product dried at 100° under vacuum: C, 40·1; H, 5·4; N, 13·4. $C_{14}H_{22}Br_2N_4O$ requires C, 39·8; H, 5·3; N, 13·3%).

N-(*6'-Aminohexyl*)-*2-methoxy-1,5-naphthyridin-4-amine* [*3*; $R^1 = OMe$, $R^2 = NH(CH_2)_6NH_2$]

4-Chloro-2-methoxy-1,5-naphthyridine (0·5 g), hexane-1,6-diamine (3·0 g), anhydrous sodium carbonate (0·275 g) and n-heptane (10 ml) were heated at 160° for 20 h. Column and thin-layer chromatography (silica; methanol) gave a yellow oil (0·54 g). ^{1}H n.m.r. ($CDCl_3$): δ 1·44, b, $CH_2(CH_2)_4CH_2$; 2·69, complex, CH_2NH_2; 3·28, complex, CH_2NH; 4·02, s, MeO; 5·98, s, H 3; 6·4, b, NH; 7·45, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·0 Hz, H 7; 8·00, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H 8; 8·51, q, $J_{6,7}$ 4·0 Hz, $J_{6,8}$ 1·5 Hz, H 6.

The free base was treated with ethanolic hydrogen bromide and the yellow solid recrystallized from ethanol (charcoal) to give N-(*6'-aminohexyl*)-*2-methoxy-1,5-naphthyridin-4-amine dihydrobromide* (0·65 g) which decomposed above 163° (Found, for sample dried at 100° under vacuum: C, 41·0; H, 5·7; N, 12·9. $C_{15}H_{24}Br_2N_4O$ requires C, 41·3; H, 5·6; N, 12·9%).

4-(2'-Diethylaminoethylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NHCH_2CH_2NEt_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·5 g), 2-diethylaminoethylamine (1·675 g), anhydrous sodium carbonate (0·3 g) and n-heptane (10·0 ml) were heated in an autoclave at 180° for 20 h. The product was subjected to chromatography in methanol over alumina and recrystallized from ethyl acetate to give white crystals of *4-(2'-diethylaminoethylamino)-1,5-naphthyridin-2-ol* (0·6 g), m.p. 155–156° (Found: C, 64·8; H, 7·9; N, 21·6. $C_{14}H_{20}N_4O$ requires C, 64·6; H, 7·7; N, 21·5%). ^{1}H n.m.r. ($CDCl_3$): δ 1·07, t, J 7 Hz, CH_3CH_2; 2·61, q, J 7 Hz, CH_2CH_3; 2·79, t, CH_2NEt_2; 3·28, complex, CH_2NH; 5·70, s, H 3; 6·98, b, NH; 7·37, q, $J_{7,8}$ 8·0 Hz, $J_{6,7}$ 4·5 Hz, H 7; 7·70, q, $J_{7,8}$ 8·0 Hz, $J_{6,8}$ 1·5 Hz, H 8; 8·39, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H 6.

4-(3'-Diethylaminopropylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NH(CH_2)_3NEt_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·5 g), 3-diethylaminopropylamine (1·8 g), anhydrous sodium carbonate (0·293 g) and n-heptane (10·0 ml) were heated at 180° for 20 h as described above. The yellow solid obtained was subjected to t.l.c. (silica; methanol) and recrystallized from cyclohexane (charcoal) to give white crystals of *4-(3'-diethylaminopropylamino)-1,5-naphthyridin-2-ol* (0·3 g), m.p. 115° (Found, for sample dried at 100° under vacuum: C, 65·7; H, 8·1; N, 20·6. $C_{15}H_{22}N_4O$ requires C, 65·7; H, 8·1; N, 20·4%). ^{1}H n.m.r. ($CDCl_3$): δ 1·05, t, J 7 Hz, CH_3CH_2; 1·87, complex, $CH_2CH_2CH_2$; 2·55, q, J 7 Hz, CH_2CH_3; 2·59, complex, CH_2NEt_2; 3·35, complex,

CH_2NH; 5·68, s, H3; 7·36, q, $J_{7,8}$ 8·0 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·70, q, $J_{7,8}$ 8·0 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·36, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

4-(3′-Aminopropylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NH(CH_2)_3NH_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·5 g), propane-1,3-diamine (2·05 g), anhydrous sodium carbonate (0·3 g) and n-heptane (10·0 ml) were heated at 180° for 20 h. The solid (0·69 g) obtained was subjected to chromatography in methanol over a short column of silica, and recrystallized from a mixture of methanol and ethyl acetate to give light yellow crystals of *4-(3′-aminopropylamino)-1,5-naphthyridin-2-ol* (0·3 g), m.p. 188–189° (Found, for sample dried at 120° under vacuum: C, 61·0; H, 6·7; N, 25·5. $C_{11}H_{14}N_4O$ requires C, 60·5; H, 6·5; N, 25·7%). *M* 218. ^{1}H n.m.r. ($CDCl_3$): δ 1·89, complex, $CH_2CH_2CH_2$; 2·91, t, CH_2NH_2; 3·39, complex, CH_2NH; 5·72, s, H3; 6·8, b, NH; 7·38, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·72, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·37, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

4-(4′-Aminobutylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NH(CH_2)_4NH_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·5 g), butane-1,4-diamine (2·5 g), anhydrous sodium carbonate (0·3 g) and n-heptane (10·0 ml) were heated at 180° for 20 h. The product was recrystallized from water (charcoal) to give light yellow crystals of *4-(4′-aminobutylamino)-1,5-naphthyridin-2-ol* (0·60 g), m.p. 149–150° (Found, for sample dried at 100° under vacuum: C, 61·6; H, 7·0; N, 23·8. $C_{12}H_{16}N_4O$ requires C, 62·0; H, 6·9; N, 24·1%). $M+1$ 233. ^{1}H n.m.r. ($CDCl_3$): δ 1·70, complex, $CH_2(CH_2)_2CH_2$; 2·78, t, CH_2NH_2; 3·32, complex, CH_2NH; 5·71, s, H3; 6·6, b, NH; 7·39, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·75, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·36, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

4-(5′-Aminopentylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NH(CH_2)_5NH_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·5 g), pentane-1,5-diamine (3·0 g), anhydrous sodium carbonate (0·3 g) and n-heptane (10·0 ml) were heated at 180° for 20 h. The product was recrystallized twice from water with charcoal filtration to give white crystals of *4-(5′-aminopentylamino)-1,5-naphthyridin-2-ol* (0·5 g), m.p. 157–159° (Found: C, 63·0; H, 7·3; N, 22·3. $C_{13}H_{18}N_4O$ requires C, 63·4; H, 7·4; N, 22·7%). $M+1$ 247. ^{1}H n.m.r. ($CDCl_3$): δ 1·54, complex, $CH_2(CH_2)_3CH_2$; 2·73, complex, CH_2NH_2; 3·27, complex, CH_2NH; 5·71, s, H3; 6·5, b, NH; 7·38, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·71, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·37, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

4-(6′-Aminohexylamino)-1,5-naphthyridin-2-ol [*3*; $R^1 = OH$, $R^2 = NH(CH_2)_6NH_2$]

4-Chloro-1,5-naphthyridin-2-ol (0·4 g), hexane-1,6-diamine (2·57 g), anhydrous sodium carbonate (0·24 g) and n-heptane (10·0 ml) were heated at 180° for 20 h. The crude product was extracted with ether (3 × 50 ml) and the solid residue was chromatographed in methanol over a short column of silica and recrystallized from water with charcoal filtration to afford white crystals of *4-(6′-aminohexylamino)-1,5-naphthyridin-2-ol* (0·34 g), m.p. 177–178° (Found, for sample dried at 120° under vacuum: C, 64·9; H, 7·9; N, 21·6. $C_{14}H_{20}N_4O$ requires C, 64·6; H, 7·7; N, 21·5%). *M* 260. ^{1}H n.m.r. ($CDCl_3$): δ 1·45, complex, $CH_2(CH_2)_4CH_2$; 2·71, complex, CH_2NH_2; 3·29, complex, CH_2NH; 5·71, s, H3; 6·5, b, NH; 7·39, q, $J_{7,8}$ 8·5 Hz, $J_{6,7}$ 4·5 Hz, H7; 7·72, q, $J_{7,8}$ 8·5 Hz, $J_{6,8}$ 1·5 Hz, H8; 8·37, q, $J_{6,7}$ 4·5 Hz, $J_{6,8}$ 1·5 Hz, H6.

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 level of 100 mg/kg of body weight [except for *N*-(4′-diethylamino-1′-methylbutyl)-1,8-naphthyridin-4-amine which due to toxicity at 100 mg/kg was run at 50 mg/kg]. No apparent ill effects were observed and all mice survived to and beyond 48 h in the above tests and in control experiments with normal saline and peanut oil.

Preliminary Antimalarial Screen

Mice were injected intraperitoneally with 10^6 erythrocytes infected with *Plasmodium vinckei vinckei*. After 5 days (and daily thereafter) each mouse was examined for suitable parasitaemia

levels of 10–20%. In this, thin blood smears were taken, slides were fixed, stained (Giemsa's stain) and the mean percentage of parasite-infected red cells was determined as the average of two or more counts on each slide which varied by no more than ±5% of the mean value.

At infection levels of preferably 10–20% each test chemical at a dosage of 100 mg/kg of body weight [except for *N*-(4′-diethylamino-1′-methylbutyl)-1,8-naphthyridin-4-amine which was at 50 mg/kg] in 0·4 ml of normal saline or peanut oil was given intraperitoneally to three mice whose individual parasitaemia had just previously been determined. Thereafter thin blood smears were taken from each mouse at 6, 24 and 48 h and the parasitaemia assessed as above. The results for the three mice were then averaged at each time point.

Control tests were made against peanut oil and normal saline, and reference tests run against chloroquine and primaquine (as diphosphates).

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