SYNTHESIS AND ANTIMALARIAL ACTIVITY OF SOME NITROGENOUS HETEROCYCLIC COMPOUNDS

A Thesis

Submitted to

The Australian National University

for the Degree of

Doctor of Philosophy

by

WENG LAI TAN

Medical Chemistry Group

The John Curtin School of Medical Research

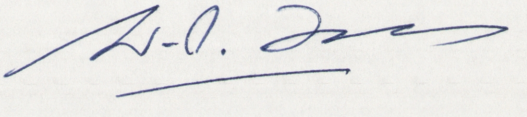
The Australian National University

Canberra

September, 1985

CERTIFICATE OF ORIGINALITY

The work described in this thesis was carried out by the candidate at The Australian National University. Where the work of others was employed or quoted, appropriate references have been included.



ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to Dr G. B. Barlin for advice, encouragement and supervision and to thank Dr D. J. Brown for his personal interest in this work. Thanks also go to Drs W. L. F. Armarego, W. B. Cowden, M. D. Fenn, P. Waring for helpful discussions and to all members of the Medical Chemistry Group for their help and support. I am indebted to Mrs R. Enge for kindly typing this thesis.

A particular word of thanks to Dr N. H. Hunt for providing rodent malaria parasites, Professor A. W. Pound and Dr I. A. Clark for advice on the preliminary antimalarial screening and Mr S. J. Ireland for assistance with this operation. I also thank Mr H. V. Scott and others at the Army Malaria Research Unit, Ingleburn, N.S.W. for performing the *in vitro* antimalarial tests.

Grateful acknowledgement is made to The Australian National University for the award of a Post-graduate Research Scholarship.

Last, but not least, to Miss Lim Chuat-Tien from afar, I offer my sincere thanks for her enormous support and encouragement throughout the preparation of this thesis.

SUMMARY

A series of $\underline{N}^4$-substituted 7-halogeno-1,5-naphthyridin-4-amines have been prepared from 5-halogeno-pyridin-3-amines through 4-chloro-7-halogeno-1,5-naphthyridines. Mono- and di-Mannich bases derived from 4-(7'-halogeno-1',5'-naphthyridin-4'-ylamino)phenol were prepared from the above 4-chloro compound by reaction with p-aminophenol followed by the Mannich reaction, or from the chloro compound with 4-amino-2-diethylaminomethylphenol.

General synthetic routes to various $\underline{N}^4$-substituted 2-methoxy (and 2-hydroxy)-1,5-naphthyridin-4-amines and 1,8-naphthyridines from ethyl 3-aminopyridine-2-carboxylate and 6-substituted pyridin-2-amine, respectively, are also reported.

Whereas a mono-Mannich base was prepared directly from the commercially available 4-chloro-7-trifluoromethyl-quinoline and 4-amino-2-diethylaminomethylphenol, a series of di-Mannich bases was prepared via the key intermediate 4-(7'-trifluoromethyl-4'-ylamino)phenol. Analogous mono- and di-Mannich bases derived from 4-[2',7'- and 2',8'-bis-(trifluoromethyl)quinolin-4'-ylamino]phenols were prepared through the known 4-bromoquinolines.

The above compounds were evaluated for antimalarial activity in a preliminary *in vivo* screen against *Plasmodium vinckei vinckei* in mice. Those showing significant activity in this preliminary rodent screen were examined (by others) against both chloroquine-sensitive (FCQ-27) and chloroquine-resistant (K-1) strains of *Plasmodium falciparum*

(a human Plasmodium species) in an *in vitro* test.

Three di-Mannich bases derived from 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)phenol were found to be highly effective against *P. vinckei vinckei* and to have a potency approaching, and not significantly differing from that of the new antimalarial agent, mefloquine, in the *in vitro* screen described above.

The N^4-substituted 7-bromo (and chloro)-1,5-naphthyridin-4-amines were active in the *P. vinckei vinckei* - mouse model but, unfortunately, all showed significant cross-resistance with chloroquine against *P. falciparum in vitro*.

The series of N^4-substituted 2-methoxy (and 2-hydroxy)-1,5-naphthyridin-4-amines and 1,8-naphthyridines were found to be totally inactive as blood schizontocides in the preliminary screen but the efficacy of the first series (also considered as derivatives of 8-aminoquinolines) as tissue schizontocides (active against hepatic stages of malaria parasites) is yet to be evaluated.

Not only were all the seven mono- and di-Mannich bases of 4-(7'-trifluoromethylquinolin-4'-ylamino)phenols highly effective against *P. vinckei vinckei* in mice, but they were also far superior in activity to the classical antimalarial agent, chloroquine in the *in vitro* screen; several appeared to be significantly better than either amodiaquine or mefloquine against both FCQ-27 and K-1 isolates of *P. falciparum*, as measured by their ID_{50} (concentration of a drug causing 50% inhibition of ^{3}H-hypoxanthine uptake) values.

The above three 1,5-naphthyridines and the seven active quinolinylaminophenols are compounds worthy of further study especially when their preliminary *in vivo* rodent screens indicated much lower toxicity than the widely used 4-aminoquinoline drug, chloroquine. Furthermore, their ID_{50} values for both the FCQ-27 and K-1 isolates are essentially the same, strongly indicating minimal or no cross-resistance with chloroquine. The latter phenomenon coincides with the call for a search for new drugs which would overcome or at least alleviate the ever increasing problem of the parasites' resistance to antimalarial agents.

CONTENTS

CHAPTER I

INTRODUCTION

I-1 Malaria - Historical Background

Malaria, derives its name from mala aria - the Italian for bad air. It was also known as AGUE, PALUDISM, JUNGLE FEVER, MARSH FEVER or PERIODIC FEVER. In 1880, the causative agent of malaria was discovered by Alphonse Laveran[1] when he observed the presence of minute parasites in the corpuscles of blood of soldiers in Algeria. Golgi[2] in 1889 produced clear evidence of the existence of multiple species of malaria parasites by defining the characteristic periodicity of the fever in relation to the rupture of schizonts in the blood. An all-important discovery was made in 1897 and 1898 when Sir Ronald Ross[3] was able to demonstrate the genus Anopheles as the insect in which development of the malaria parasite takes place. The four species of malaria parasites affecting man are all members of the subphylum Sporozoa, the family Plasmodiidae, and the genus Plasmodium. It was not until 1954 that they received official validation as Plasmodium falciparum, P. vivax, P. ovale and P. malariae.

Through the use of such antimosquito measures as drainage and the application of larvicides and short-acting insecticides, considerable reduction in malaria was accomplished in many of the temperate and more highly developed areas of the world, particularly where transmission was of short duration. Even so, malaria, as late as 1943, still caused at least 3,000,000 deaths and

300,000,000 cases of fever annually.[4] Today, this parasitic disease is world-wide covering vast areas in Africa, Asia and Latin America[5] and it has been estimated that more than 200 million people are affected each year.[6]

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases has given malaria the highest priority because of its immense public impact over a large area of the world and because the efficacy of current control measures is being increasingly compromised by the emergence and spread of resistance of Plasmodium falciparum to drugs and of resistance of the mosquito vector to commonly used insecticides.

I-2 General Life Cycle of Human Malaria Parasites

A conception of the life cycles of the Plasmodium species is not only essential knowledge in chemotherapy but also in epidemiology, pathogenesis and immunology. The general structure of the malaria parasite life cycle is shown diagrammatically in Fig. I.1 and relates specifically to P. vivax and P. ovale in which true relapses of malaria occur. The exoerythrocytic stages 6-9 are absent in P. falciparum and P. malariae.

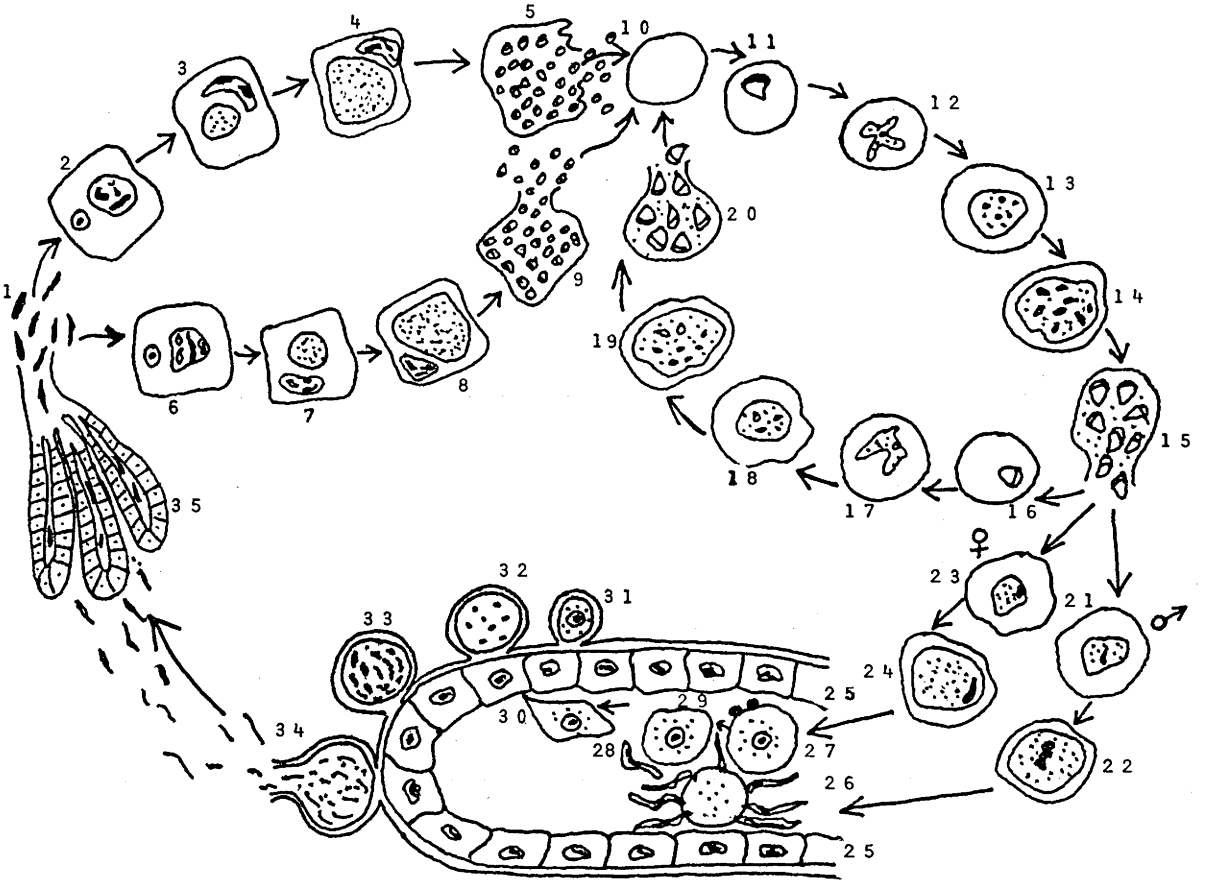


Fig. I.1. Life cycle of human Plasmodium species. Various stages of the parasite life cycle are illustrated above from the introduction of sporozoites into man by infected mosquitoes. The steps in this cycle are described as follows:

1. Sporozoites of two types penetrating the parenchymatous cells of the liver.

2-4. One initiates immediate exoerythrocytic schizogony.

5. Mature and rupturing exoerythrocytic schizont releasing merozoites.

6. The other type of sporozoites becomes hypnozoites, and eventually relapse forms (6-9).

7-9. Activated and mature hypnozoites.

9. Mature hypnozoites rupture liver cell to release merozoites.

10. Merozoites enter red blood cells (RBCs).

11-12. Trophozoites in RBC.

13-14. Immature schizonts in RBCs.

15. Mature erythrocytic schizont discharging merozoites.

16-20. Merozoite re-establishes blood cycle. Asexual cycles in RBCs require approximately 3 days in the case of P. malariae and 2 days for the other plasmodia of man. Episodes of chill and fever follow the massive release of merozoites from ruptured RBCs.

21-22. Developing microgametocytes in blood.

23-24. Developing macrogametocytes in blood.

25. Entry of gametocytes into midgut of Anopheles.

26. Exflagellation of microgametocyte with production of eight microgametes.

27. Macrogamete released from RBC.

28. Free microgamete.

29. Macrogamete about to be fertilized by 28.

30. Zygote elongating into ookinete.

31-33. Oocysts on surface of midgut.

34. Rupture of mature oocyst and discharge of sporozoites into haemocoele.

35. Invasion of salivary glands by sporozoites.

The phenomena of periodicity during different stages of the life cycle are highly significant and provide criteria for the preliminary diagnosis into quotidian, tertian or quartan groups as regards the blood cycles.

I-3 Acquired and Natural Immunity

The development of resistance to malaria in man depends on the frequency and duration of exposure to the parasite.[7,8] The acquired immunity keeps parasite levels very low but this is maintained only if sporozoite challenge continues. In areas where transmission is irregular, an effective immunity may never be attained. Patients may sometimes be classified as non-immune if they have not previously or recently been exposed to Plasmodium infection and as semi-immune or immune if they have a history of prolonged exposure.

Natural resistance to malaria in man is well known and has been shown to be due to various genetic traits, of which the following three examples are the most common and the best substantiated:

(a) Haemoglobin S. Possession of the sickle-cell gene confers a strong resistance against P. falciparum malaria.[9]

(b) Glucose-6-phosphate dehydrogenase (G6PD) deficiency limits the multiplication of P. falciparum and reduces this infection in the community.[10]

(c) The absence of the Duffy blood group inhibits invasion of erythrocytes by merozoites of P. vivax. The pure negroes of West Africa exhibit this character and are totally immune to benign tertian malaria, as was first demonstrated by Miller et al.[11] in 1975.

I-4 Development of Antimalarial Agents

Two and a half centuries before the causative agent of malaria was known, the curative property of the bark of the Cinchona tree had already been exploited. Today, 350 years later, modern medicine must still rely on quinine (I.1), the major alkaloid constituent of the bark, as a life-saving medicament in severe cases of falciparum malaria.

Chloroquine (I.2a) is generally considered to be one of the most fascinating, useful and versatile antimalarial drugs developed during the modern era of synthetic organic chemistry.[12] It was first prepared in 1934 by H. Andersag as part of a programme which included the synthesis of such important compounds as mepacrine (I.3), pentaquine (I.4a), isopentaquine (I.4b), pamaquine (I.4c), primaquine (I.4d), and sontoquine (I.2b).[13] The objective of this programme was to develop substitutes for quinine.

The development of amodiaquine (I.5a), a Mannich base-type antimalarial, and related compounds[14,15] was first initiated when a search for 4-aminoquinolines

superior to chloroquine during the World War II antimalarial drug development programme led to the incorporation of a 4-aminoquinoline moiety into a Mannich base. Because of the apparent structural relationship and an outstanding similarity in antimalarial activity, these Mannich base antimalarials are considered by most workers as 4-aminoquinolines.

Schmidt et al.[16] highlighted the usefulness of amodiaquine (I.5a) and amopyroquine (I.5b) (also a Mannich base antimalarial) against chloroquine-resistant strain of P. falciparum in Aotus monkeys. Ren et al.[17] in China observed the superiority in both antimalarial activity and toxicity in the di-Mannich base (I.5c) over chloroquine. More recently, reports[18,19] of Mannich bases WR 194,965 (I.6) and WR 228,258 (I.7), as being highly active in both rodent malaria and P. falciparum in vitro, further expanded the scope of Mannich base compounds in the clinical treatment of malaria.

Curd et al.[20] first claimed certain biguanides as possessing good activity against Plasmodium gallinaceum in chicks. The biguanide, proguanil (I.8) and its active metabolite, cycloguanil[21] (I.9) like pyrimethamine (I.10), all share the powerful selective inhibition of the activity of malarial dihydrofolate reductase.[22] The sulphonamides, notably sulphadiazine (I.11) and sulphadoxine (I.12) and sulphones such as dapsone (I.13) have been used as antimalarials in combination with pyrimethamine. The regimen which has replaced sulphadoxine-pyrimethamine in areas where malaria parasites' resistance to this

combination is problematic includes tetracycline (I.14), a highly effective but slow blood schizontocide, in association with a short course of quinine.[23] Early work establishing the efficacy of the tetracycline antibiotics was provided by Clyde et al.[24]

The antimalarial development programme of the U.S. Army Research and Development Command, based on the Walter Reed Army Institute of Research (WRAIR) has carried out, since its inception in 1964, an unprecedented volume of research involving not only the mass primary screening of over 300,000 candidate compounds, but also basic studies on the biology and immunology of malaria. From this programme has emerged mefloquine (I.15), (a 4-quinoline-methanol which has an unusually long half-life in man) which is in an advanced state of clinical trial particularly in areas of Asia[25] and South America[26] where multiple drug-resistant P. falciparum is a major problem, and in parts of Africa[27] where the problem is rapidly becoming established. While various other compounds have been described in recent literature, very few outside the WRAIR programme[28] have passed their preclinical trial stage. New developments were recently reviewed[29,30] and have been further detailed by various authors.[31] Among the newer compounds, hydroxypiperaquine (I.16), pyronaridine (I.17) and halofantrene (I.18) are known to be in clinical trial.[32-35]

Artemisinine (I.19) (Qinghaosu),[36] an endoperoxide of a sesquiterpenoid lactone, is a natural constituent of the plant Artemesia annua. This novel compound is a potent

blood schizontocide which bears no structural resemblance to any other antimalarial agent. In view of the poor solubility of artemisinine, semi-synthetic derivatives of this lactone are being evaluated. Two of these, artesunate (I.19a) and artemether (I.19b) are more soluble and active, and artesunate is currently being developed for further clinical trials in i.v. therapy of cerebral malaria.[37,38]

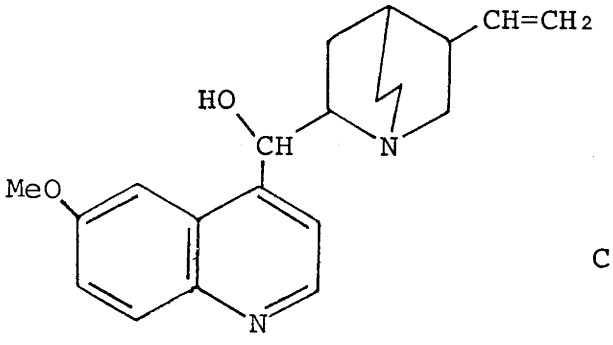
Several new 8-aminoquinolines that are being evaluated as possible replacements for primaquine show promise in having a strong blood schizontocidal as well as tissue schizontocidal effect. Such a compound is WR 225,448 (I.20).

Hanson[39] has drawn attention to an area of possible interaction between chemotherapy and immunological resistance that deserves further investigation, namely the combination of antimalarial therapy with compounds that enhance immunity. A recent report on the combined use of chloroquine and glucan is strong support for this approach. Glucan is a known immunopotentiating agent, again when given alone or as an adjuvant.[40] Against P. bergei malaria, it is not very effective when used alone but Bliznakiv (1980, cited by Hanson[39]) has reported that glucan combined with chloroquine was much more active against P. bergei in mice than either compound used separately.

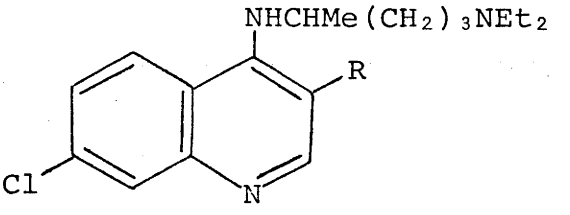
With the progressive recognition of deficiencies in control programs based upon insecticides, drugs have become more important in prevention while continuing their

vital roles in the specific treatment of clinical attacks. This increased reliance upon drugs is hampered by two important limitations, namely (a) no single compound is suitable for all purposes and (b) the efficacy of available agents suffers from the widespread and, evidently increasing, occurrence of drug-resistant parasites.

Structures of antimalarial compounds



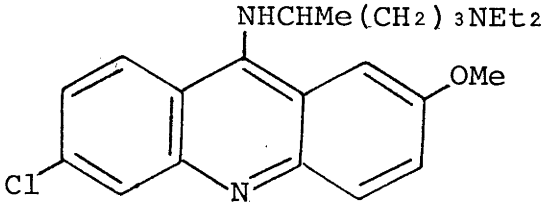
(I.1)



(I.2)

(a) R = H

(b) R = Me



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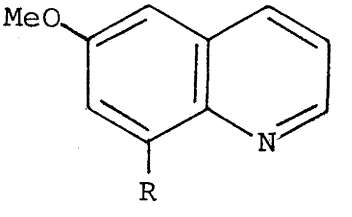


(I.4)

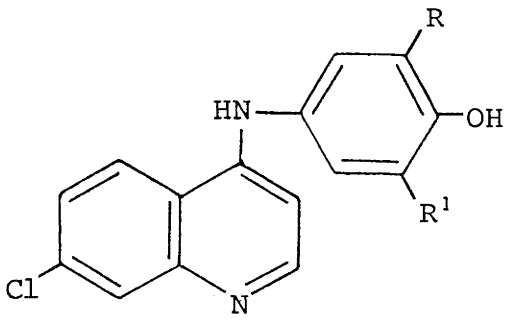
(a) R = $NH(CH_2)_5NHCHMe_2$

(b) R = $NHCHMe(CH_2)_3NHCHMe_2$

(c) R = $NHCHMe(CH_2)_3NEt_2$

(d) R = $NHCHMe(CH_2)_3NH_2$

(e) R = $NH(CH_2)_3CHMeNH_2$



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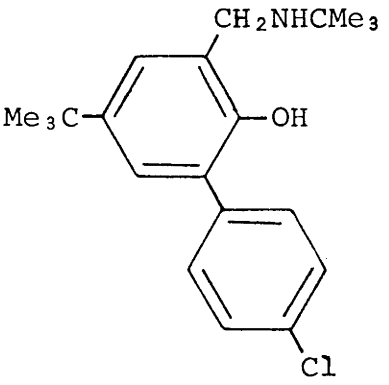
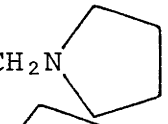
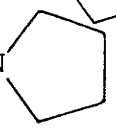
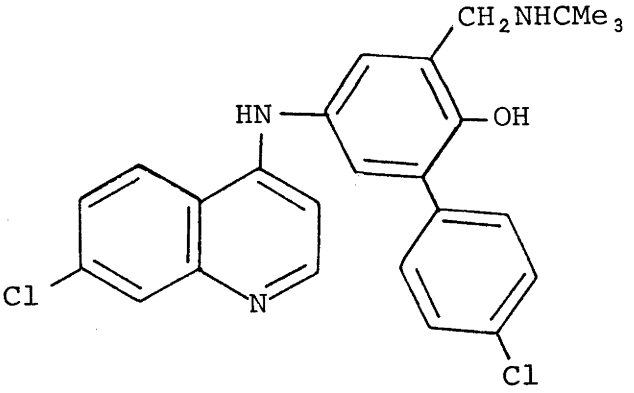


(I.6)

(a) R = H, R^1 = CH_2NEt_2

(b) R = H, R^1 = 

(c) R = R^1 = 



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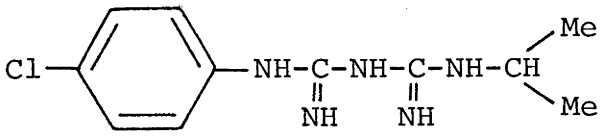

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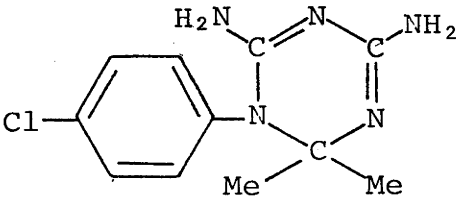

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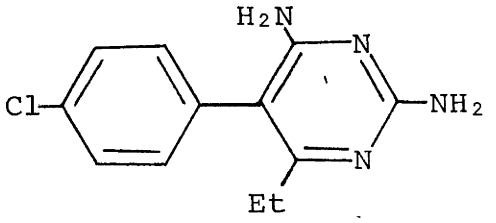

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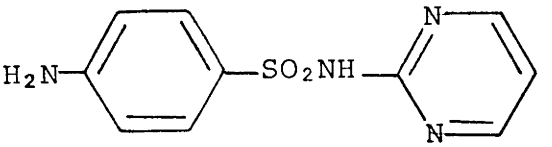

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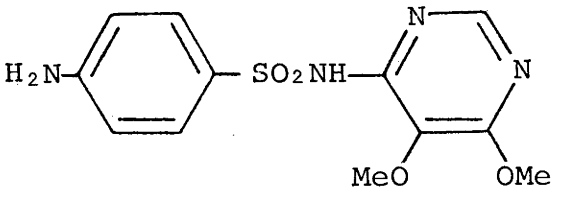

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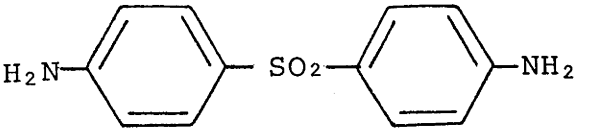

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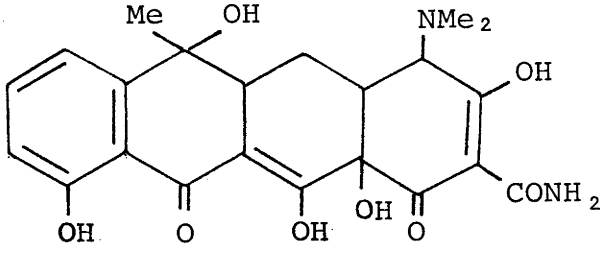

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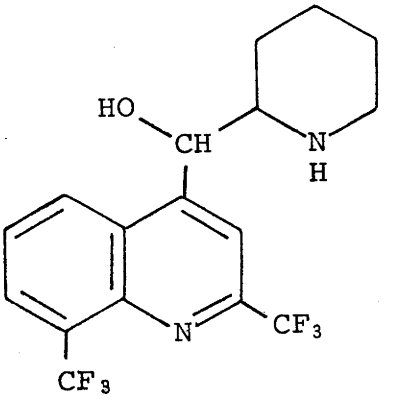

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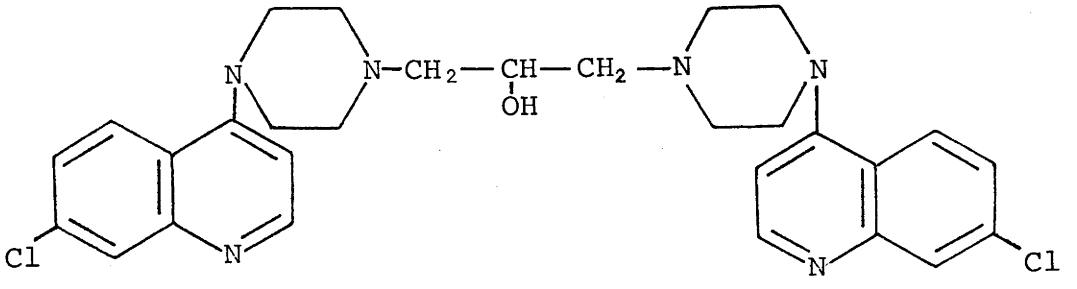

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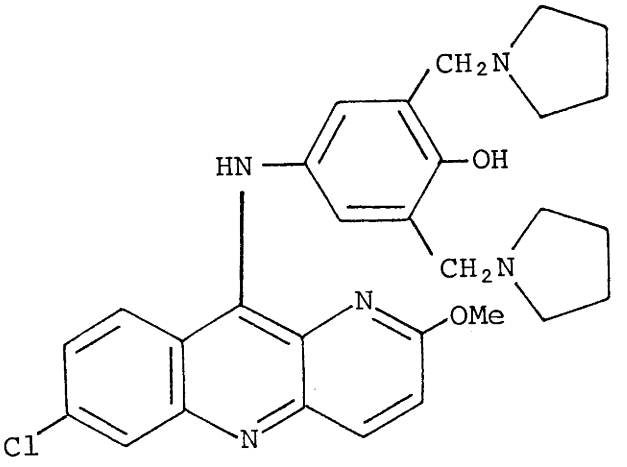

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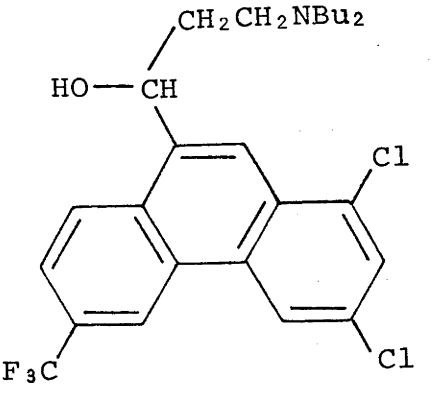

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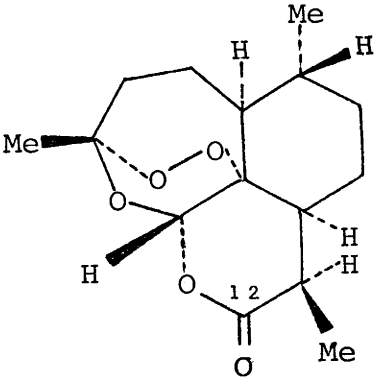

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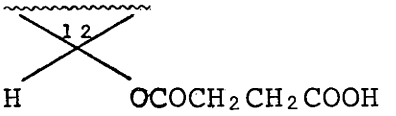
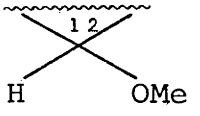
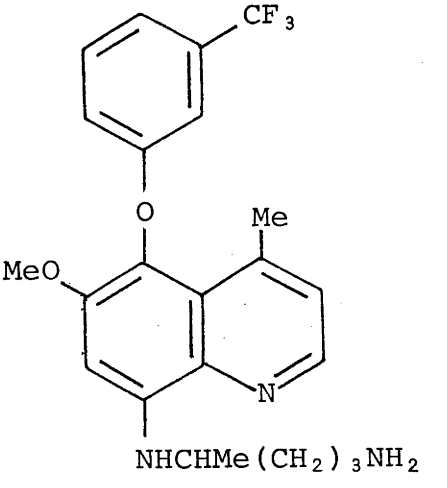
(a) 

(b) 



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I-5 Immunization and Vaccination

Recent advances in biochemistry, molecular biology, cell culture, and the monoclonal antibody development have provided new tools for immunologists and parasitologists for the identification of target antigens for immune effector mechanisms. Considerable effort is now being directed towards the production of vaccines for malaria. The three main approaches are development of an anti-sporozoite vaccine to abort the infection at its source,[41] an antimerozoite vaccine to alleviate clinical disease,[42] and an antigamete vaccine which blocks transmission.[43] Reducing transmission is an essential part of any vaccination programme and one could envisage appropriate combinations of a vaccine to stop transmission and chemotherapy to suppress clinical malaria.

The present limitations concern the purification of adequate quantities of potentially 'protective' antigens for immunization studies. The recent successful cloning of the genes coding respectively for surface antigens of *P. knowlesi* and *P. falciparum*[44,45] and of the genes expressing *P. falciparum* schizont and merozoite specific polypeptides[46,47] may solve the problem in the near future and render possible the mass production of malaria antigens either using the DNA recombinant technology or biochemical synthesis of polypeptides after elucidation of the DNA sequence of the malaria cloned genes. Despite encouraging perspectives, several problems remain to be solved before an effective anti-malaria vaccine can be developed for human use, such as the development of adjuvants acceptable

for human use, the production on a large scale of adequate malarial antigens, the definition of the role of antigenic diversity among various isolates of P. falciparum, and the extent of cross-protection with other plasmodia species infecting man.

I-6 Classification of Antimalarials

The existing antimalarial drugs may be divided into the following categories according to the sites at which they act to interrupt the life cycle of plasmodia.

(a) Causal prophylactic agents

Strictly speaking these agents bring about total prevention of the infective stages, the sporozoites, from developing into pre-erythrocytic schizonts (see Fig. I.1; 2-4) or, in P. vivax and P. ovale, hypnozoites (Fig. I.1; 6-9). In practice the term 'causal prophylaxis' is taken to mean the blockage of development of these intrahepatic stages. The antifolates proguanil (I.8) and pyrimethamine (I.10) effectively block pre-erythrocytic schizogony, certainly of P. falciparum and P. malariae and probably of P. vivax and P. ovale. It is questionable whether they influence the establishment and survival of hypnozoites of the latter two species when used in the normal manner. Primaquine (I.4d), although fulfilling all the above three roles is, unfortunately, too toxic to be deployed as a causal prophylactic.

(b) Anti-relapse drugs (acting against latent tissue stages, Fig. I.1; 6-9)

This group of drugs effect radical cure, in which the latent tissue stages (hypnozoites) that are responsible for true relapses of P. vivax and P. ovale in the blood, sometimes years after the initial infection, are eliminated. At the present time the only compound used for this purpose is the 8-aminoquinoline, primaquine (I.4d), although some of its more toxic analogues such as pamaquine (I.4c) are also available.

(c) Blood schizontocides

Quinine (I.1) and the 4-aminoquinolines, chloroquine (I.2a) and amodiaquine (I.5a), all act against erythrocytic schizonts, as does the obsolete agent mepacrine (I.3) (Fig. I.1; 11-15). Mefloquine (I.15) and Qinghaosu (I.19) act exclusively as blood schizontocides. Pyrimethamine (I.10) and proguanil (I.8) are both slowly active against blood schizonts. The sulfas (sulphadiazine and sulphadoxine) are only moderately active when given alone but highly effective when administered in synergistic combination with the antifolate pyrimethamine. Primaquine (I.4d) also has schizontocidal activity, but only at toxic doses.

(d) Gametocytocides

The gametocytes (Fig. I.1; 21-24) of P. vivax, P. malariae and presumably P. ovale, are killed by usual doses of the effective blood schizontocides, but mature gametocytes of P. falciparum are not affected. Primaquine (I.4d) and quinocide (I.4e) which kill gametocytes of all

species, are particularly useful for interrupting transmission of P. falciparum.

(e) Sporontocides

Primaquine (I.4d) as well as pyrimethamine (I.10) and proguanil (I.8) when given to a gametocyte carrier, are known to prevent or inhibit the development of oocysts (Fig. I.1; 31-34) in mosquitoes feeding on that carrier. They thus prevent the formation of sporozoites and thereby transmission of the disease.

I-7 Drug Resistance in Malaria

Resistance of Plasmodium falciparum to antimalarial drugs is emerging as one of the two most important technical factors obstructing the world-wide effort to eradicate, or at least control, the disease. The other major factor is entomological - viz. the diminishing efficacy of residual insecticidal spraying of dwellings. There are two reasons for the diminishing impact of spraying on vector populations: physiological resistance of certain mosquito vectors to insecticides and strain differences or adaptive mechanisms in some anophelines resulting in the avoidance of sprayed surfaces.

The earliest reports of antimalarial drug resistance came from Brazil in 1910,[48] when failures of quinine were suspected. Details of the dates of introduction of antimalarials and the first recognition of resistance to them are shown in Table I.1 (data from ref. 49).

Table I.1 Dates of introduction of antimalarials and the first recognition of resistance to them.

Compound	Year first used in therapy	Year resistance first strongly suspected or confirmed		
		Therapy in man		
		P. falciparum	P. vivax	P. malariae
Quinine	c. 1630	Brazil 1910[a] Malaya 1967	Macedonia 1918[a]	
Methylene blue	1891			
Pamaquine	1926			
Mepacrine	1935	New Guinea 1946		
Chloroquine	1945	Venezuela 1960[a] Colombia 1961[b]		
Proguanil	1948	Liverpool 1949	Liverpool 1949	Java 1950
Primaquine	1951	Colombia 1963	New Guinea 1958	
Pyrimethamine	1952	Gambia 1952	United States 1953	Kenya and Tanzania 1954
Cycloguanil embonate	1963	S. Rhodesia 1964		
Sulphadiazine	1964			
Sulphadoxine	1964	Cambodia 1968		
Dapsone	1965	Cambodia 1968		
Mefloquine	?	?Thailand 1980		

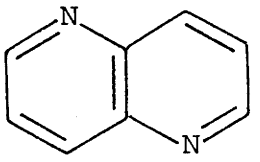
[a] Only suspected [b] First confirmation

To date, the exact mechanism as to how malaria parasites become resistant to various drugs is still unclear. However, several postulates have been put forward which include three major categories of change,[50] namely (a) inactivation of drug by the microorganism, (b) decreased penetration of drug into the cell, (c) alteration of microbial metabolism so as to eliminate the step or steps previously susceptible to the drug.

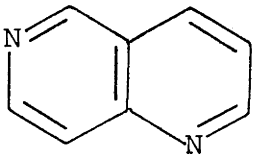
An appropriately selected drug combination can be useful in protecting the individual components against resistance. Merkli et al.[51] have shown that the triple combination of mefloquine, pyrimethamine and sulphadoxine is extremely effective in delaying the emergence of resistance to any of the three in malaria infected mice. Further details on the use of drug combinations in the prevention of resistance have been discussed.[52]

I-8 Naphthyridines as Potential Antimalarials

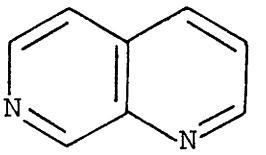
Naphthyridines are diazanaphthalenes or pyridopyridines in which one nitrogen atom is present in each six-membered ring and none at the bridgehead positions. There are six possible isomers as shown:



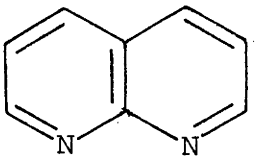
1,5-Naphthyridine



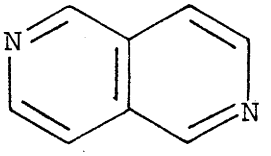
1,6



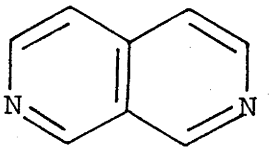
1,7



1,8



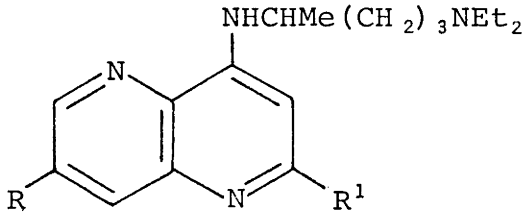
2,6



2,7

I-8-A 1,5-Naphthyridine Derivatives

Interest in the 4-amino-1,5-naphthyridines as potential prophylactic antimalarial agents has been generated by the structural similarity of this ring system to both 4- and 8-aminoquinolines. Earliest report in the literature[53,54] confirmed the interesting antimalarial activity of 4-(4'-diethylamino-1'-methylbutylamino)-1,5-naphthyridine (I.21a) comparable to quinine itself.



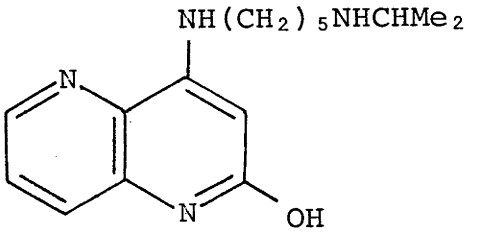
(I.21)

(a) $R = R^1 = H$
(b) $R = H$, $R^1 = OMe$
(c) $R = Cl$, $R^1 = H$
(d) $R = Cl$, $R^1 = OMe$

Goldberg et al.[55] disclosed significant antimalarial activity for the 4-amino-1,5-naphthyridines which are substituted with alkoxy groups in both 2- and 6-positions. McCaustland and Cheng[56] in 1970 reported the synthesis of 7-chloro-4-(4'-diethylamino-1'-methylbutylamino)-2-methoxy-1,5-naphthyridine (I.21d) in which the structural features of both chloroquine (I.2a) and pamaquine (I.4c) were incorporated. Analogous compounds "5-azachloroquine" (I.21c) and "5-azapamaquine" (I.21b) were also reported and their antimalarial activities evaluated. "5-Azachloroquine" (I.21c) was found to be comparable to chloroquine in activity when screened for blood schizontocidal activity in the P. bergei - mouse model; it was however much less toxic than chloroquine. No acute toxicity was noted at a dose of 640 mg/kg whereas chloroquine was 100% lethal at a dose of 320 mg/kg.[56] Compounds (I.21d) and (I.21b) were however less active

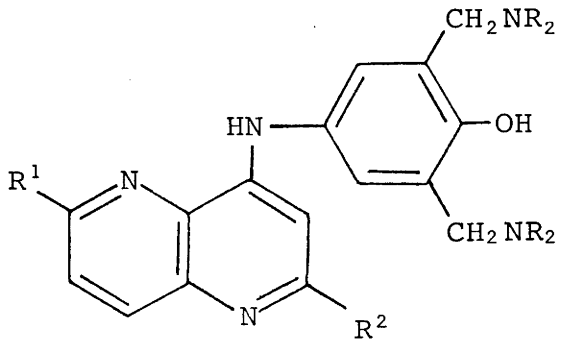
than "5-azachloroquine". Nevertheless, Schmidt[57] later confirmed compound (I.21c) was devoid of radical curative activity in a P. cynomolgi - Rhesus monkey model.

In a programme to expand upon the derivatives of 4-amino-1,5-naphthyridines in an effort to secure an optimal prophylactic antimalarial drug, the Exxon Research and Engineering Company, sponsored by the U.S. Army Medical Research and Development Command, furnished a total of 26 naphthyridine target and 145 naphthyridine intermediates for biological testing.[58] One of the target structures, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (I.22), proved to be curative in the Rhesus monkey infected with sporozoites of the B strain of P. cynomolgi at a dosage level of 10 mg/kg.[57,58]



(I.22)

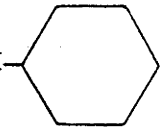
Several unsubstituted and 2,6-disubstituted 1,5-naphthyridine compounds carrying double Mannich basic chains of p-aminophenol were explored by Chen et al.[59] in China. Some of these (I.23a), (I.23b) and (I.23c), were rather effective in a P. bergei - mouse model.



(I.23)

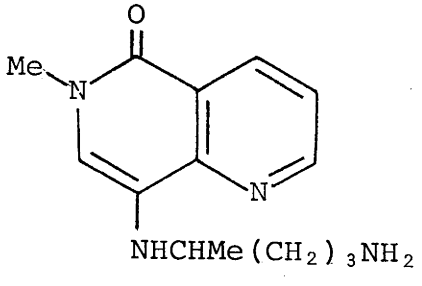
(a) $R^1 = R^2 = H$, NR_2 = 

(b) $R^1 = OMe$, $R^2 = Me$, $NR_2 = N(Et)_2$

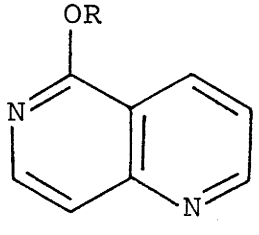
(c) $R^1 = OMe$, $R^2 = Me$, $NR_2 = NH$- 

I-8-B 1,6-Naphthyridine Derivatives

Carroll et al.[60] in 1981 described the synthesis of several 1,6-naphthyridine derivatives, (I.24), (I.25a) and (I.25b).



(I.24)



(I.25)

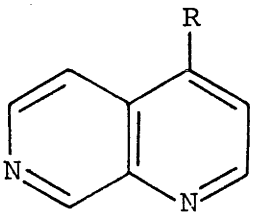
(a) R = H

(b) R = CH_2CF_3

Both (I.24) and (I.25b) were found to be toxic at the minimal dose tested (40 mg/kg) when evaluated for antimalarial activity in the P. bergei - mouse model. When assayed for radical curative activity in the P. cynomolgi - Rhesus monkey model, (I.25b) was inactive at the maximal dose tested (10 mg/kg per day) and (I.24) was found to be less active than primaquine.

I-8-C 1,7-Naphthyridine Derivatives

Chien and Cheng[61] reasoned that the electron-withdrawing effect produced by the Cl substituent in the chloroquine (I.2a) molecule may also be produced by a nitrogen in the ring in the place of the C-Cl group. If so, the 1,7-naphthyridine analogues of the 4-amino-quinolines may retain similar antimalarial activity. To test this hypothesis, they synthesized the 7-aza congeners of chloroquine, (I.26a), (I.26b) and an amodiaquine (I.5a) - related analogue (I.26c).

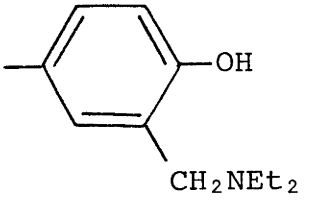


(I.26)

(a) R = $NHCHMe(CH_2)_3NEt_2$

(b) R = $NH(CH_2)_3NEt_2$

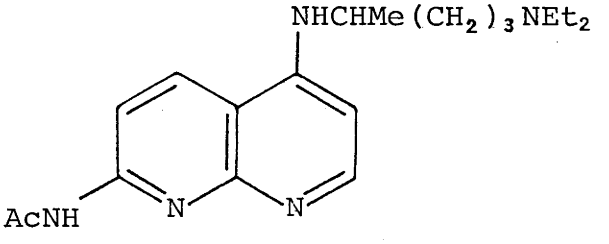
(c) R =



When evaluated for blood schizontocidal activity in the P. bergei - mouse model, (I.26b) was devoid of activity; (I.26a) and (I.26c) produced only a slight extension in survival time of the treated mice compared with the untreated controls. Neither (I.26a) nor (I.26c) approached the potency of chloroquine or amodiaquine.

I-8-D 1,8-Naphthyridine Derivatives

Antimalarial compounds with 1,8-naphthyridine as the heterocyclic nucleus have not been examined extensively in the past. However, Adams et al.[54] in 1946 first reported the synthesis of 7-acetamido-4-(4'-diethylamino-1'-methylbutylamino)-1,8-naphthyridine (I.27) as a potential antimalarial agent, but no biological activity was described.

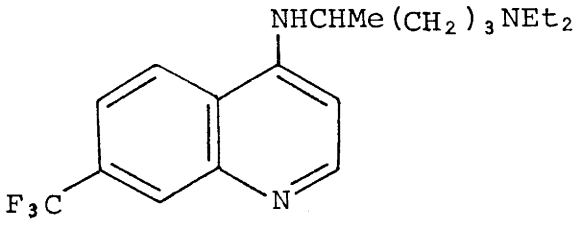


(I.27)

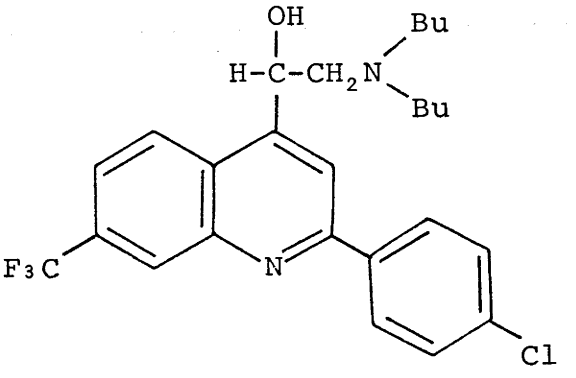
I-9 Trifluoromethylquinolines as Potential Antimalarials

The replacement of the 7-halogeno substituent in the quinoline nucleus of known antimalarials by a trifluoromethyl group gives compounds which retain their potent activities. This was first shown[62] in compound (I.28). Soon thereafter, various fluorine-containing α-dialkylaminomethyl-2-phenyl-4-quinolinemethanol derivatives were prepared[63] for evaluation against Plasmodium bergei in mice and the preliminary biological data indicated the fluoro compounds to be more potent at comparable doses than the corresponding chloro derivatives. 2-(4-Chlorophenyl)-α-dibutylaminomethyl-7-trifluoromethyl-4-quinolinemethanol (I.29) when administered to mice in a single subcutaneous dose was curative at 40 mg/kg.[63] Pinder and Burger[64] also observed antimalarial activity in the series of α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols carrying OCH_3, CH_3, or Cl in positions 6 or 8. However, these compounds were moderately phototoxic.

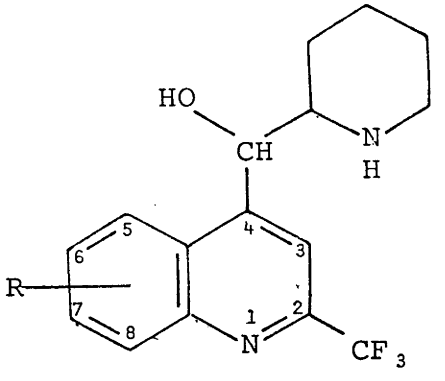
With the support from the U.S. Army Medical Research and Development Command, the synthesis of several bis-(trifluoromethyl) analogues of the above soon followed[65] in which all four target compounds (I.30a), (I.30b), (I.15) and (I.30c) were found to be curative against P. bergei in mice at 160 mg/kg or lower. Further toxicological, pharmacological and clinical data for compound (I.15) (mefloquine) were established and results show that it is therapeutically effective in single doses against both chloroquine-resistant and chloroquine-sensitive P. falciparum, with a cure rate approaching 100%.[66]



(I.28)



(I.29)



(I.30)

(a) R = 6-CF_3

(b) R = 7-CF_3

(c) R = 8-CF_3 with 6-OMe

R = 8-CF_3 (I.15)

CHAPTER II

SYNTHESIS OF SOME $\underline{N}^4$-SUBSTITUTED 2-METHOXY (AND 2-HYDROXY)-1,5-NAPHTHYRIDIN-4-AMINES, $\underline{N}^4$-SUBSTITUTED 7-BROMO (AND CHLORO)-1,5-NAPHTHYRIDIN-4-AMINES AND 4-[7'-BROMO (AND CHLORO)-1',5'-NAPHTHYRIDIN-4'-YLAMINO]PHENOLS.

II-1 Introduction

In view of the strong blood schizontocidal property and curative activity of several 1,5-naphthyridine derivatives, coupled with the low toxicity of "5-azachloroquine" described in CHAPTER I, it was decided to prepare further derivatives of this heterocyclic nucleus. Thus, it was resolved to prepare 2-methoxy (and 2-hydroxy)-1,5-naphthyridin-4-amines with various aminoalkyl side chains attached at N4 and similar $\underline{N}^4$-substituted 7-bromo (and chloro)-1,5-naphthyridin-4-amines as well as mono- and di-Mannich bases derived from 4-[7'-bromo (and chloro)-1',5'-naphthyridin-4'-ylamino]phenols.

In practice the starting materials for the 7-bromo-1,5-naphthyridin-4-amines were obtained in much higher overall yield than their chloro analogues, and past experience[15] had also shown that bromo- and chloro-analogues generally exhibit comparable antimalarial activity.

II-2 General Methods for Synthesis of 1,5-Naphthyridines

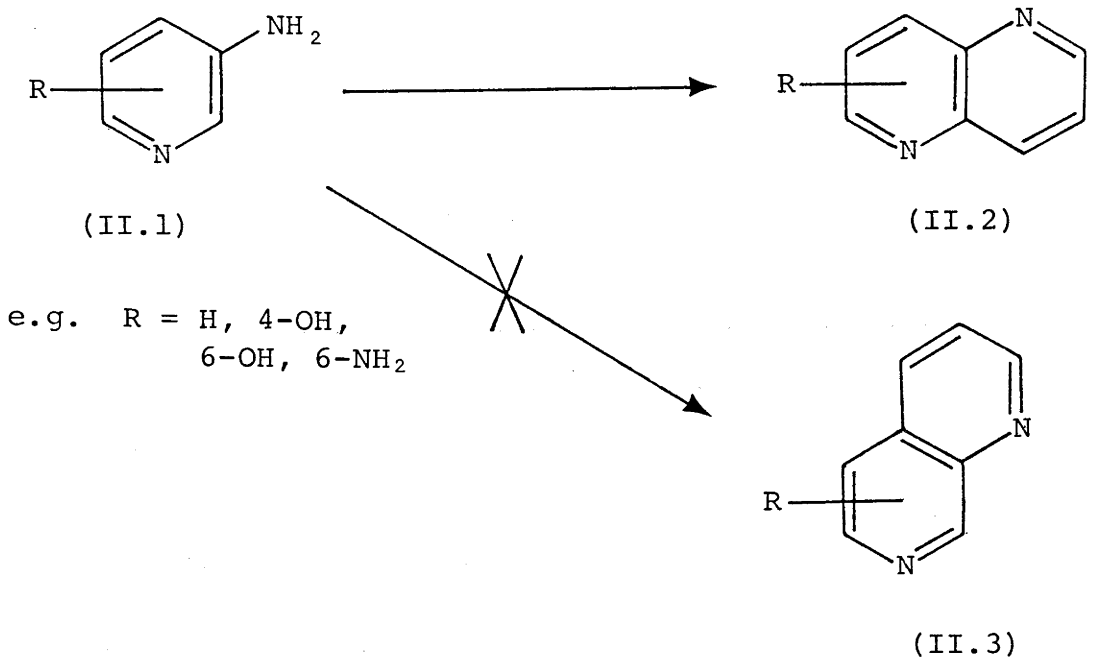
Two principal methods are generally employed in the synthesis of 1,5-naphthyridines; namely the Skraup reaction and the ethoxymethylenemalonic ester method.

(a) The Skraup Reaction

Various unsubstituted and substituted 1,5-naphthyridines (II.2) can be prepared from pyridin-3-amines (II.1) by application of the Skraup reaction (with glycerol) or modified Skraup reaction (with other condensing reagents such as methylacrolein and acetaldehyde). Unfortunately, these syntheses do not lead to the 4-halogeno- or 4-hydroxy-1,5-naphthyridines required in this work.

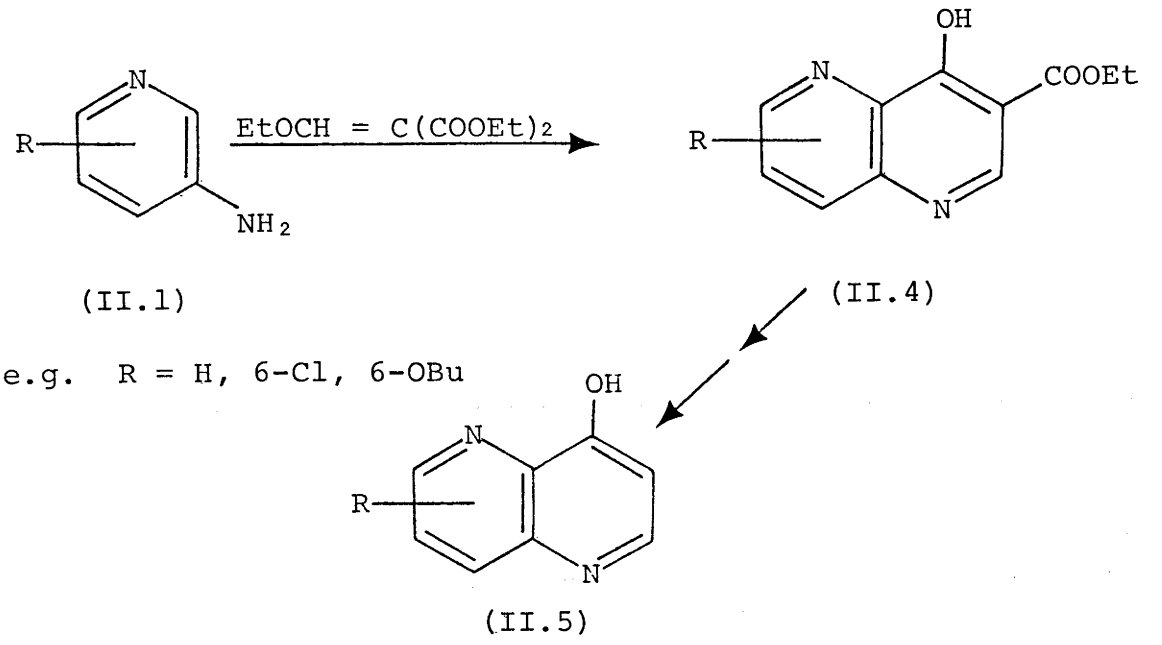
Rapoport and Batcho,[67] starting from pyridin-3-amine with glycerol under the conditions of the Skraup reaction, prepared 1,5-naphthyridine but no 1,7-naphthyridine (II.3, R = H) was observed. When a blocking group was present in the 2-position of the pyridin-3-amine(s) differing results were observed leading to the formation of 1,5- or 1,7-naphthyridines. 2-Halogenopyridin-3-amines gave 1,5-naphthyridine[68] and 2-hydroxypyridin-3-amine gave 8-hydroxy-1,7-naphthyridine.[69]

Pyridin-3-amines with groups other than halogeno or hydroxy in the 2-position gave only tarry products.[68]



(b) Ethoxymethylenemalonic Ester (EMME) Method

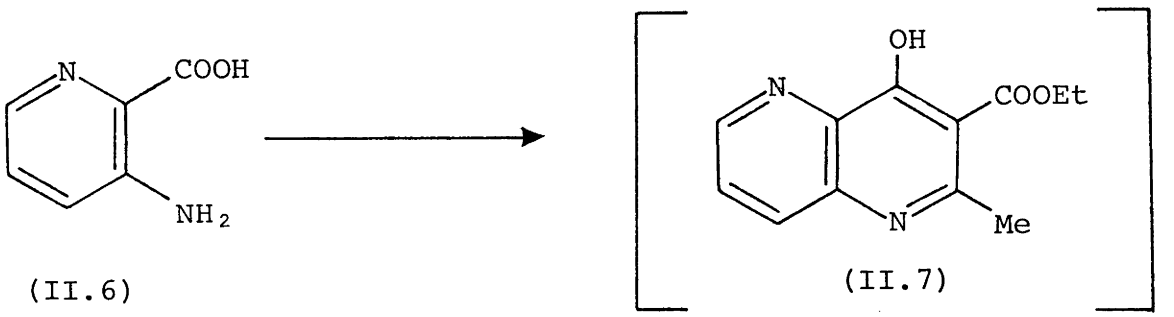
Adaptation of the excellent quinoline synthesis of Adams et al.[54] and Price and Roberts[70] is the most practical preparative method for the synthesis of substituted 1,5-naphthyridines. This requires the heating of the condensation product of pyridin-3-amine or a substituted pyridin-3-amine with diethyl ethoxymethylene-malonate (EMME) in refluxing "Dowtherm A" to afford the ethyl 4-hydroxy-1,5-naphthyridine-3-carboxylate(s) (II.4). This product can be hydrolysed and decarboxylated to form the 1,5-naphthyridin-4-ol(s) (II.5) in good yield.[54,55,70]



In this way, the 1,5-naphthyridin-4-ols required in this work were prepared.

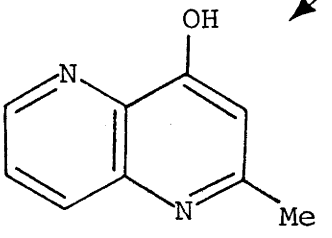
(c) Miscellaneous Preparations

Several 2,4-disubstituted-1,5-naphthyridines can be prepared from 3-aminopicolinic acid or its ester with suitable condensing agents. Baumgarten, Su and Barkley[71] claimed that 3-aminopicolinic acid (II.6) was converted by ethyl acetoacetate into the intermediate (II.7), which then underwent hydrolysis and decarboxylation to give 2-methyl-1,5-naphthyridin-4-ol (II.8) but in low yield. In an attempt to prepare 2,4-dichloro-1,5-naphthyridine (II.12), Oakes and Rydon[72] reported that ethyl 3-amino-picolinate (II.9) condensed with malonic ester to give the intermediate (II.10) which readily underwent Dieckmann cyclization; hydrolysis and decarboxylation of the cyclized product then gave the dihydroxy-compound (II.11), which with phosphoryl chloride readily yielded the dichloro-compound (II.12).

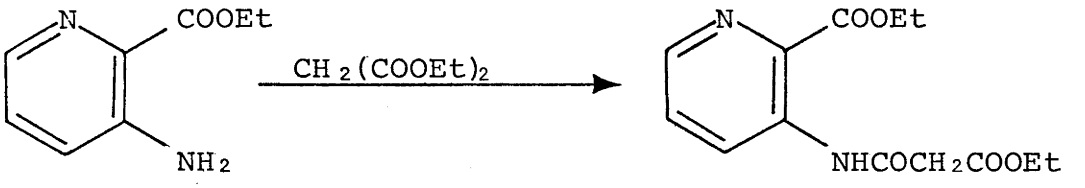


(II.6)

(II.7)

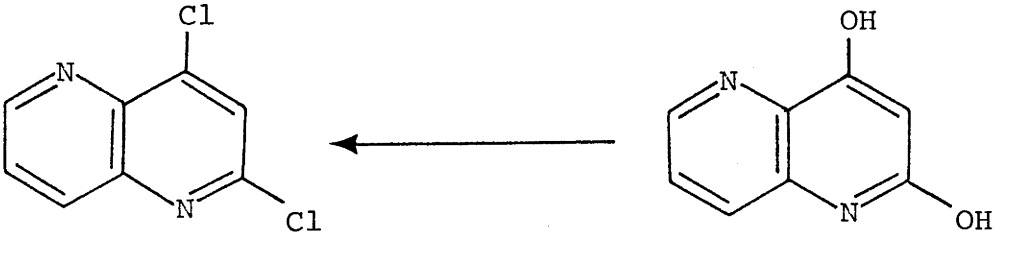


(II.8)



(II.9)

(II.10)



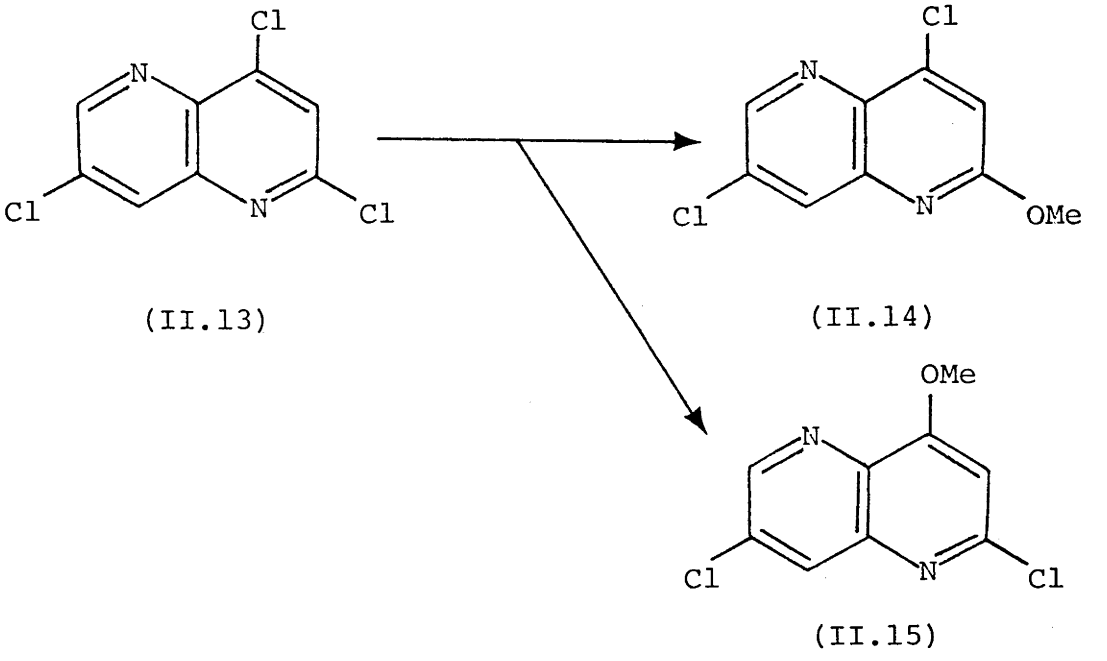
(II.12)

(II.11)

II-3 Reactivity of Halogeno-substituents in 1,5-Naphthyridine

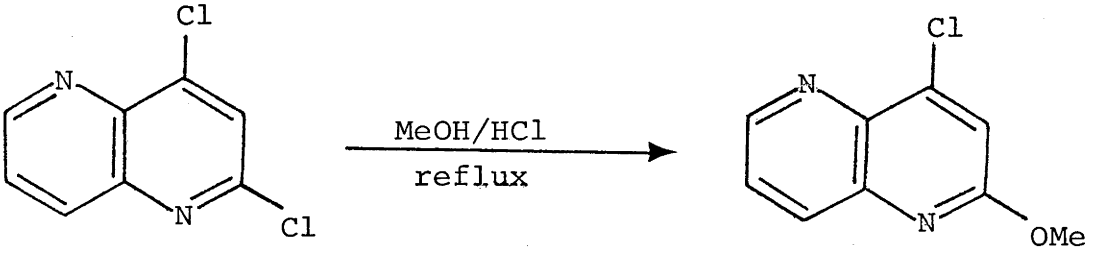
Kinetic data for nucleophilic substitution of various halogeno-1,5-naphthyridine compounds are not available to date. However Oakes and Rydon,[72] by application of an approximate quantum-mechanical treatment, were able to calculate that in 2,4-dichloro-1,5-naphthyridine (II.12), the 2-chloro substituent is more reactive towards nucleophiles than the chloro substituent at the 4-position. The predicted preferential reactivity of the 2-chloro substituent in (II.12) towards nucleophilic reagents was exhibited in its reactions with ammonia, water and hydrazine, in all of which only the 4-chloro-2-substituted-1,5-naphthyridines were obtained. The structures of the products derived from reaction with ammonia and water were established by subsequent conversion into 1,5-napthyridin-2-ol through the 4-(p-toluenesulfonylhydrazide).[72]

In a study of nucleophilic substitution of 2,4,7-trichloro-1,5-naphthyridine (II.13) with one equivalent of sodium methoxide in methanol, McCaustland and Cheng[56] were able to use ^{1}H n.m.r. data to prove that the structure of the major product was 4,7-dichloro-2-methoxy-1,5-naphthyridine (II.14) rather than its 4-methoxy isomer (II.15).



(II.13) (II.14) (II.15)

Methanolysis of 2,4-dichloro-1,5-naphthyridine (II.12) in the presence of an acid catalyst has also been found to favour reaction at the 2-position[56] so giving rise to 4-chloro-2-methoxy-1,5-naphthyridine (II.16) in good yield. In addition, the nucleophilic substitution of 3-bromo-8-chloro-1,5-naphthyridine with sodium methoxide in methanol (as described in the Experimental Section of this Chapter) gave the expected 3-bromo-8-methoxy-1,5-naphthyridine, leaving the bromo-substituent untouched (confirmed by ^{1}H n.m.r. and analyses data).



(II.12) (II.16)

From these data it would appear that 4,7-dihalogeno-1,5-naphthyridines react with nucleophiles by replacement of the 4-halogeno substituent but that differences in reactivity of halogeno substituents in the 2,4-dihalogeno-1,5-naphthyridine would be significantly less and, moreover, apparently favour reaction at the 2-position with either methanolic hydrogen chloride or sodium methoxide in methanol.

II-4 Preparation of $\underline{N}^4$-Substituted 2-Methoxy (and 2-Hydroxy)-1,5-naphthyridin-4-amines

The method employed for the preparation of 2,4-disubstituted-1,5-naphthyridines involved the condensation of diethyl malonate with a 2-substituted pyridin-3-amine. Thus, ethyl 3-aminopyridine-2-carboxylate (II.9) with diethyl malonate, under conditions modified from those described by Oakes and Rydon[72] for the preparation of 2,4-dichloro-1,5-naphthyridine and without isolating the intermediate, gave 1,5-naphthyridine-2,4-diol (II.11). Treatment of the latter with phosphoryl chloride afforded 2,4-dichloro-1,5-naphthyridine[72] (II.12) which with methanolic sodium methoxide at reflux gave 4-chloro-2-methoxy-1,5-naphthyridine (II.16) (SCHEME II-1), the structure of which was established as described below. The reaction of (II.12) with methanolic hydrogen chloride at reflux, as described by McCaustland and Cheng,[56] to give (II.16) proved unsatisfactory. Instead it gave 4-chloro-1,5-naphthyridin-2-ol (II.17) which was also

prepared by hydrolysis of (II.12) with 5 M hydrochloric acid in dioxan,[72] as well as by hydrolysis of (II.16) with 5 M hydrochloric acid in dioxan. Compound (II.17), when dechlorinated through the p-toluenesulfonylhydrazide[72] gave 1,5-naphthyridin-2-ol (II.18) (SCHEME II-2).

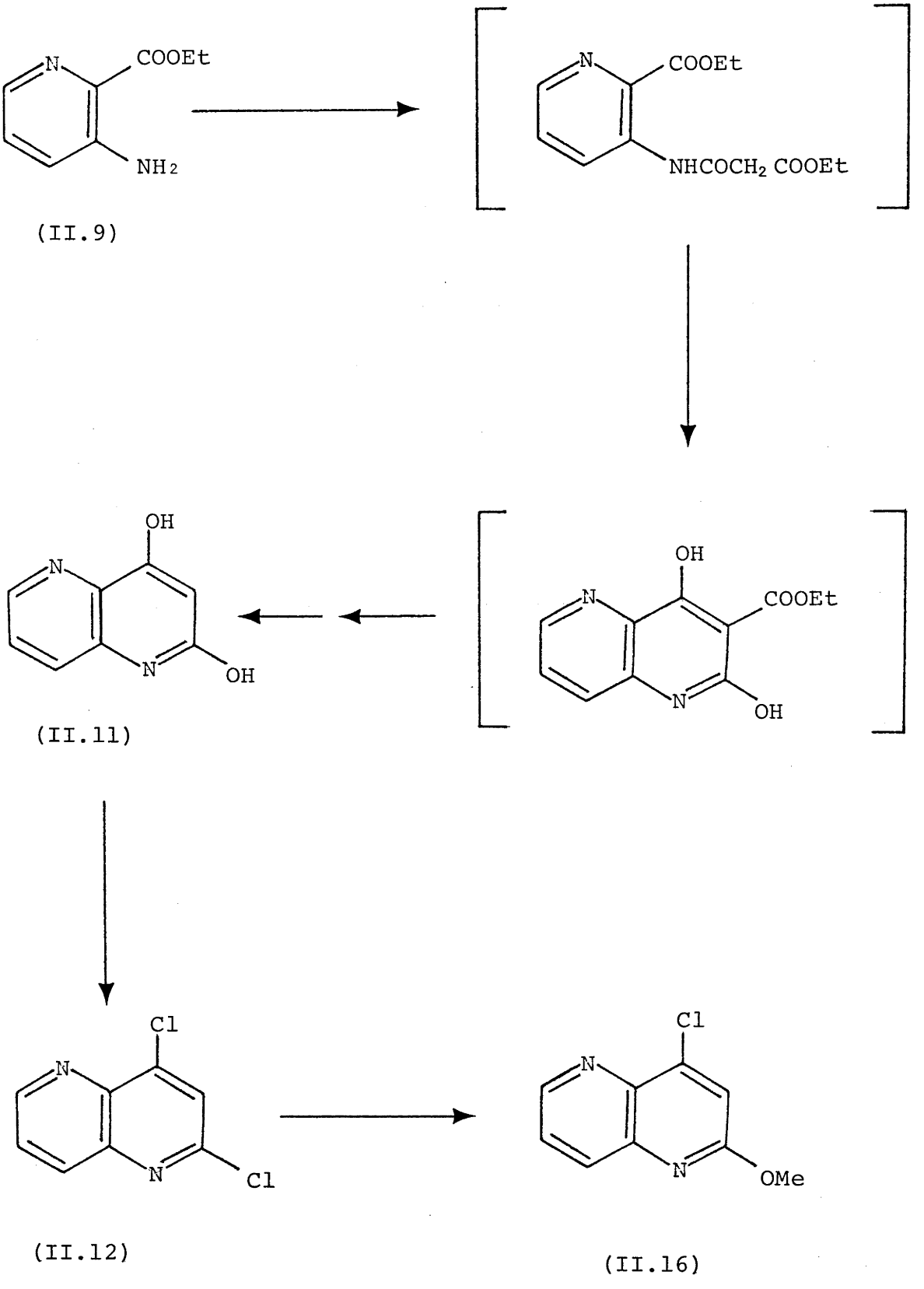
4-Chloro-2-methoxy-1,5-naphthyridine (II.16) reacted with 4-amino-2-diethylaminomethylphenol in aqueous solution at 100° to give 2-diethylaminomethyl-4-(2'-methoxy-1',5'-naphthyridin-4'-ylamino)phenol (II.19) and with a series of amines (namely 2-diethylaminoethylamine, 3-diethylaminopropylamine, propane-1,3-diamine, butane-1,4-diamine, pentane-1,5-diamine and hexane-1,6-diamine) together with one equivalent of sodium carbonate in heptane in an autoclave at 160° for 20 h by replacement of the 4-chloro substituent and formation of the corresponding N4-substituted 2-methoxy-1,5-naphthyridin-4-amines (II.20a-f) (SCHEME II-3).

Brown and Lee[73] have studied the thermal rearrangement of 2- and 4-alkoxypyrimidines to their N-alkyl isomers and McCaustland and Cheng[56] have observed O to N rearrangement in the aminolysis of (II.16) with novaldiamine [$NH_2CHMe(CH_2)_3NEt_2$] alone. However the latter authors also found that in excess amine with one molar equivalent of potassium carbonate no significant rearrangement took place. Aminolyses, as illustrated in (SCHEME II-3), were carried out in the presence of one equivalent of sodium carbonate and 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

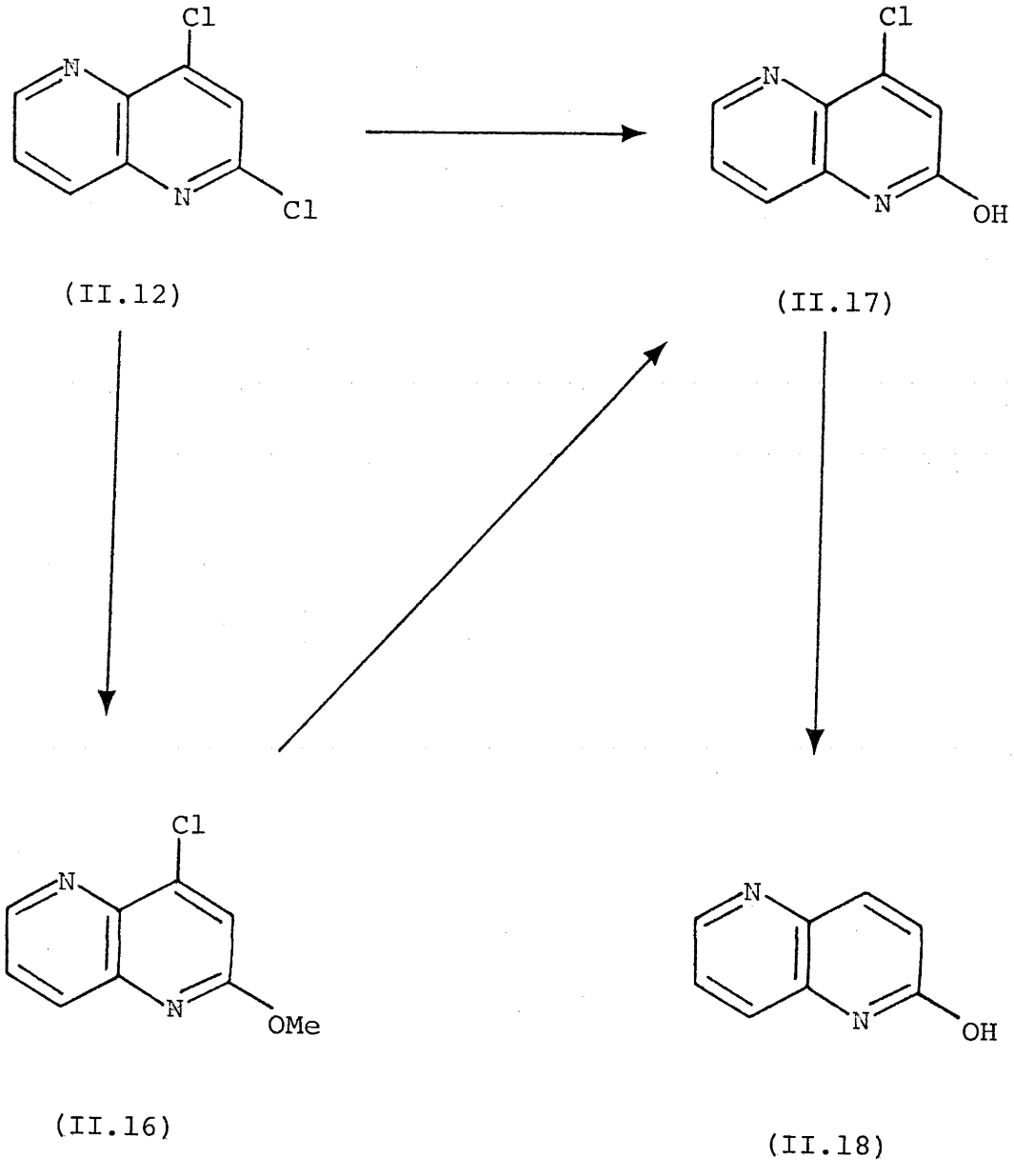
compared with that of (II.16) at 4.07 (N-methyl groups of various heterocycles have shown resonances between δ 3.35 to 4.43[74]); and the ^{13}C n.m.r. spectra of the products (II.20a) and (II.20c) as dihydrobromides in deuterium oxide, showed resonances at δ 58.40 and 58.28 respectively which are indicative of methoxy groups.[74] The resonance signal due to the carbon of the methoxy group has been found in a variety of heterocycles to occur in the range δ 53.20 to 61.87 and that of the N-methyl group in the range from 34.29 to 49.62.[74]

4-Chloro-1,5-naphthyridin-2-ol (II.17)[72] also reacted with the same series of aliphatic amines in the presence of sodium carbonate (as its 2-methoxy analogue but at the higher temperature of 180°) to give the 4-(N-substituted) amino-1,5-naphthyridin-2-ols (II.21a-f); but (II.17) failed to react with 4-amino-2-diethylaminophenol in water at 100° (SCHEME II-4).

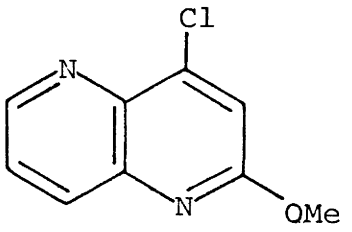
Ledóchowski and Chimiak[75] reported that 9-chloroacridine with butane-1,4-diamine (hydrochloride) in phenol at 200° gave N,N'-bis(acridin-9'-yl)butane-1,4-diamine; and 3-chloro-7-methoxy-9-phenoxyacridine with the same reagents (at 100°) gave both the mono- and bis-acridinyl derivatives. However in the reactions illustrated in both SCHEME II-3 and SCHEME II-4, no bis(1,5-naphthyridin-4-yl)compounds were obtained: analyses, integration of the ^{1}H n.m.r. and mass spectra gave no indication of any of these products.


COOEt
NH2
(II.9)
COOEt
NHCOCH2 COOEt
OH
COOEt
OH
OH
OH
(II.11)
Cl
Cl
(II.12)
Cl
OMe
(II.16)

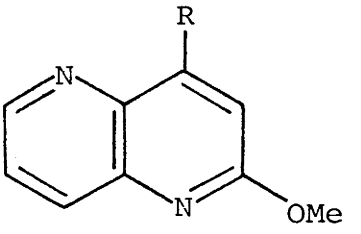
SCHEME II-1



SCHEME II-2



(II.16)



(II.20)

(a) R = $NH(CH_2)_2NEt_2$

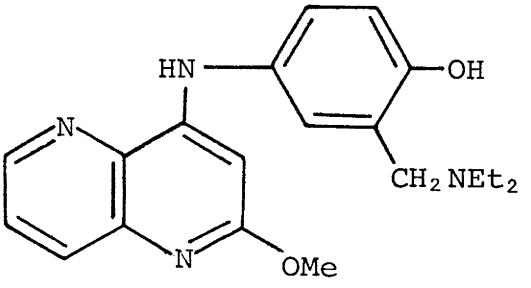
(b) R = $NH(CH_2)_3NEt_2$

(c) R = $NH(CH_2)_3NH_2$

(d) R = $NH(CH_2)_4NH_2$

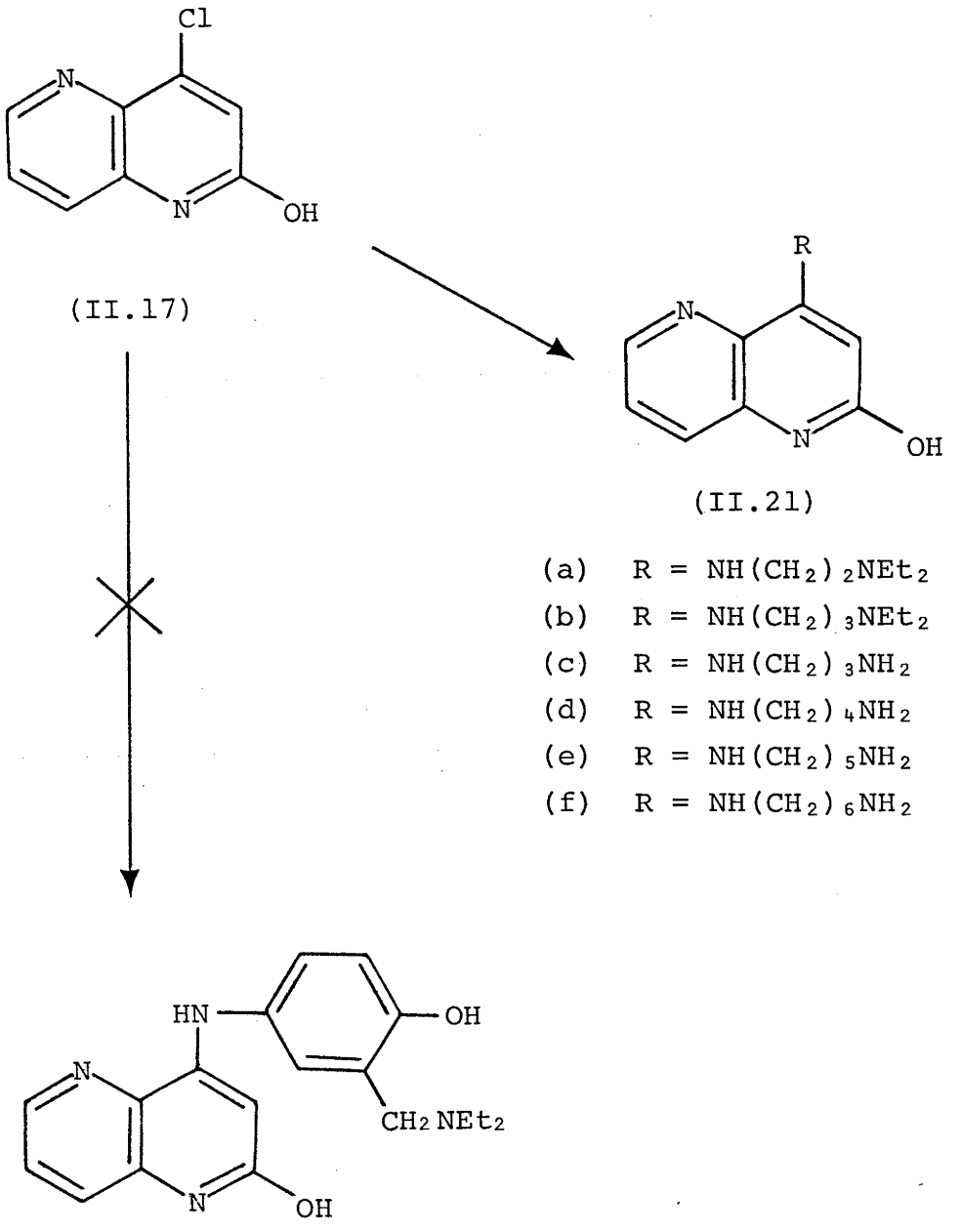
(e) R = $NH(CH_2)_5NH_2$

(f) R = $NH(CH_2)_6NH_2$



(II.19)

SCHEME II-3


Cl
N
N
OH
(II.17)
R
N
N
OH
(II.21)
(a) R = NH(CH2)2NEt2
(b) R = NH(CH2)3NEt2
(c) R = NH(CH2)3NH2
(d) R = NH(CH2)4NH2
(e) R = NH(CH2)5NH2
(f) R = NH(CH2)6NH2
HN
OH
CH2 NEt2
N
N
OH

SCHEME II-4

II-5 Preparation of $\underline{N}^4$-Substituted 7-Bromo (and Chloro)-1,5-naphthyridin-4-amines

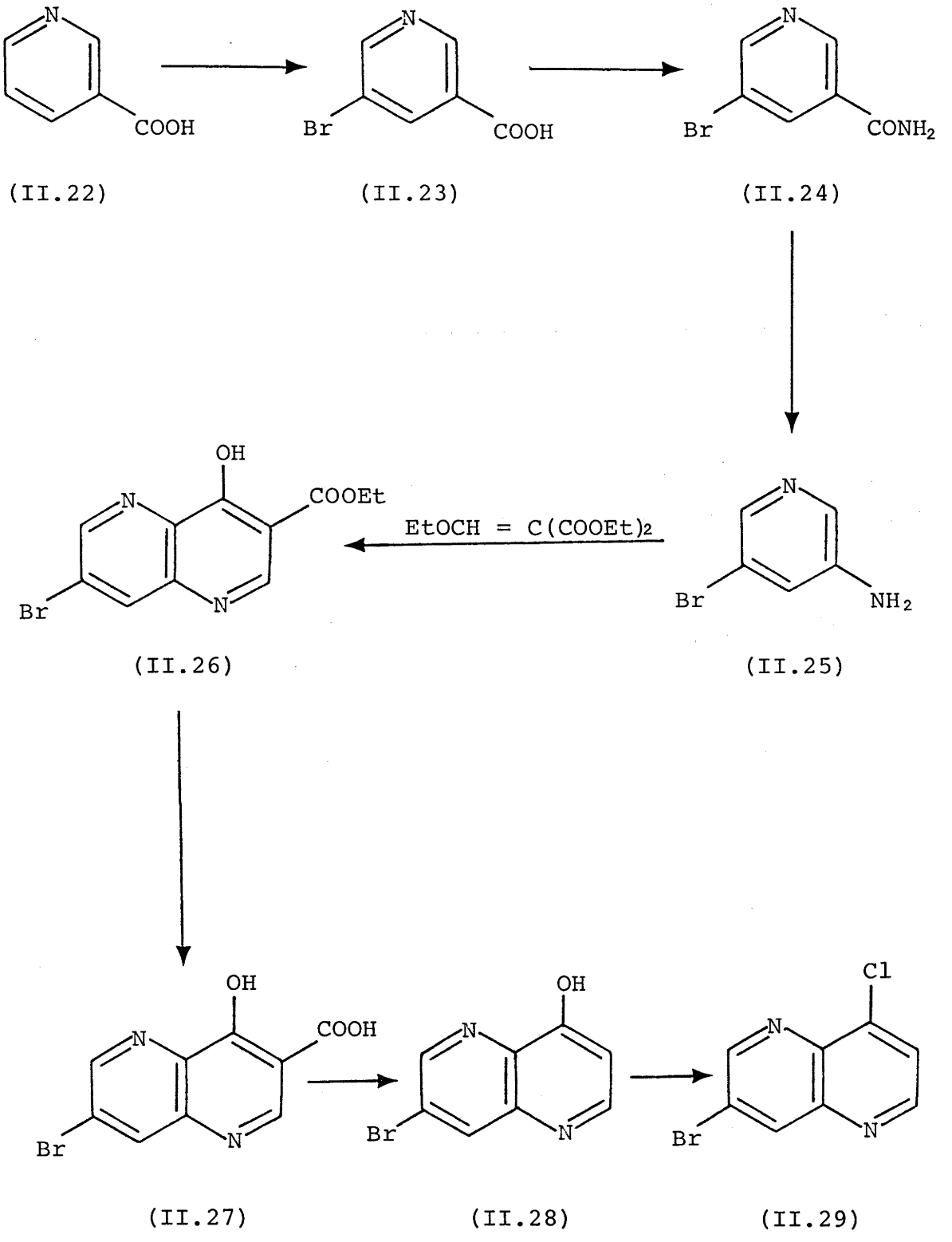
Ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate[76] (II.26) was prepared from nicotinic acid (II.22) through 5-bromonicotinic acid (II.23),[77,78] its amide (II.24)[78] and 5-bromopyridin-3-amine (II.25)[78,79] which was condensed with diethyl ethoxymethylenemalonate and ring-closed in boiling diphenyl ether (not "Dowtherm A" as in ref.[76]) to the known ester (II.26). The latter (II.26), in aqueous sodium hydroxide was hydrolysed to the corresponding acid (II.27) which in turn was decarboxylated in refluxing quinoline to give 7-bromo-1,5-naphthyridin-4-ol (II.28). Chlorination of this hydroxy compound (II.28) gave 3-bromo-8-chloro-1,5-naphthyridine (II.29) in excellent yield (SCHEME II-5).

Ethyl 7-chloro-4-hydroxy-1,5-naphthyridine-3-carboxylate[56] was prepared similarly from nicotinic acid but the 5-bromonicotinic acid (II.23) was converted to 5-aminonicotinic acid (II.30)[77] and thence *via* a diazonium salt to the required intermediate 5-chloro-nicotinic acid (II.31).[77] The amide, 5-chloronicotinamide,[80] also undergoes Hofmann reaction to 5-chloropyridin-3-amine[81] as for the bromo-analogue but in poor yield. The ester, ethyl 7-chloro-4-hydroxy-1,5-naphthyridine-3-carboxylate,[56] was saponified, decarboxylated and finally chlorinated to the required 4,7-dichloro-1,5-naphthyridine (II.32).[56]

Both bromochloronaphthyridine (II.29) and the dichloro-naphthyridine (II.32) with a series of amines in heptane at 160° for 20 h, gave the $\underline{N}^4$-substituted 7-bromo (and chloro)

-1,5-naphthyridin-4-amines (II.33a-h) and (II.34a-b) (SCHEME II-6).

The bromochloronaphthyridine (II.29) with aqueous sodium 2-diethylaminoethanethiolate or methanolic sodium methoxide at reflux, undergoes nucleophilic substitution with the replacement of its 4-chloro substituent to give N,N-diethyl-2-(7'-bromo-1',5'-naphthyridin-4'-ylthio)-ethylamine (II.35) or 3-bromo-8-methoxy-1,5-naphthyridine (II.36) respectively. Nevertheless 3-bromo-8-chloro-1,5-naphthyridine (II.29) with one equivalent of benzene-1,4-diamine in aqueous methanol at 100° gave N,N'-bis(7"-bromo-1",5"-naphthyridin-4"-yl)benzene-1,4-diamine (II.37) hydrochloride as the major product and some 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)aniline (II.38) as shown by analyses, ^{1}H n.m.r. and mass spectral data (SCHEME II-7).

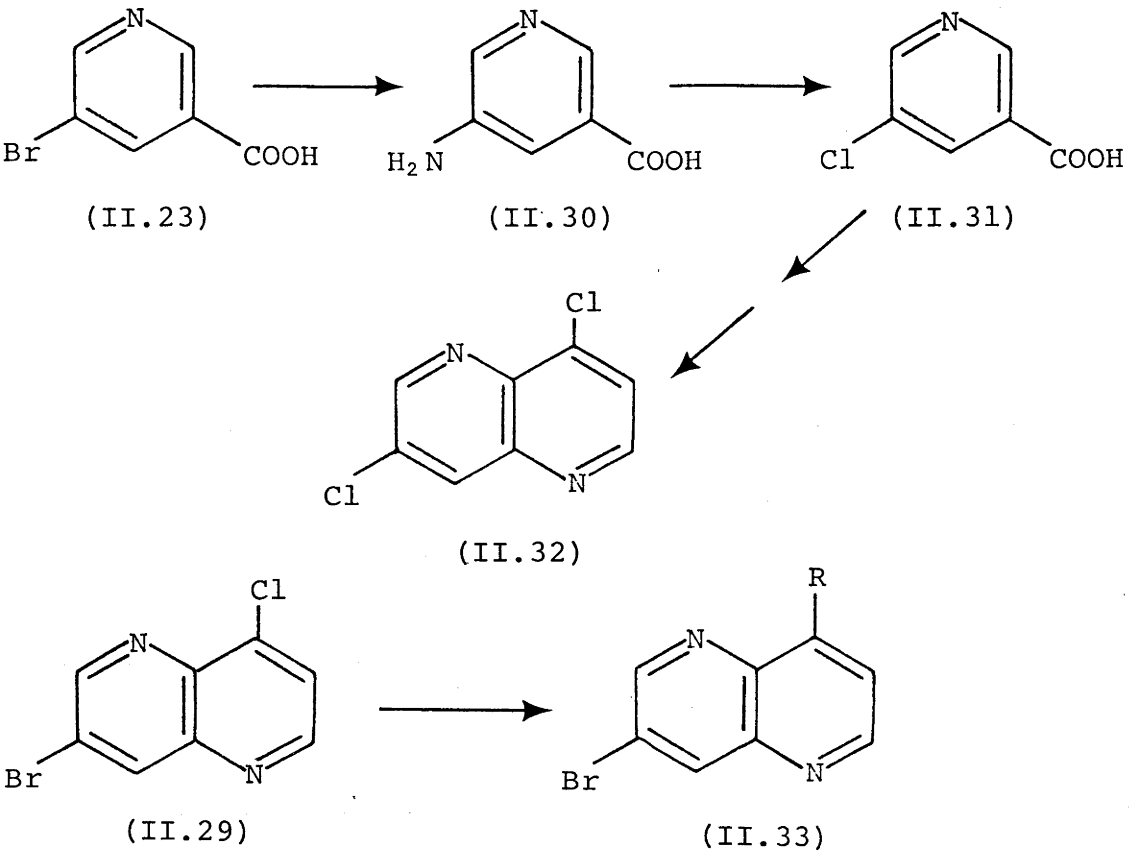


(II.22) (II.23) (II.24)

(II.26) (II.25)

(II.27) (II.28) (II.29)

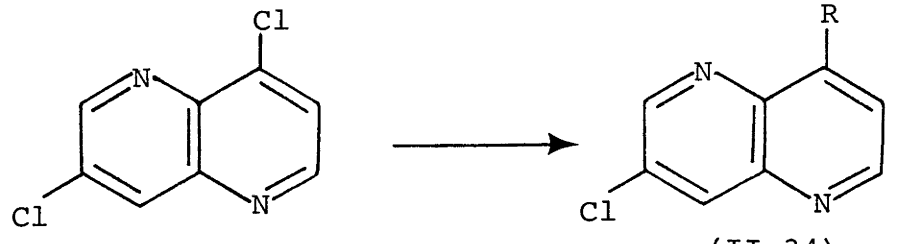
SCHEME II-5



(II.23) (II.30) (II.31) (II.32)

(II.29) (II.33)

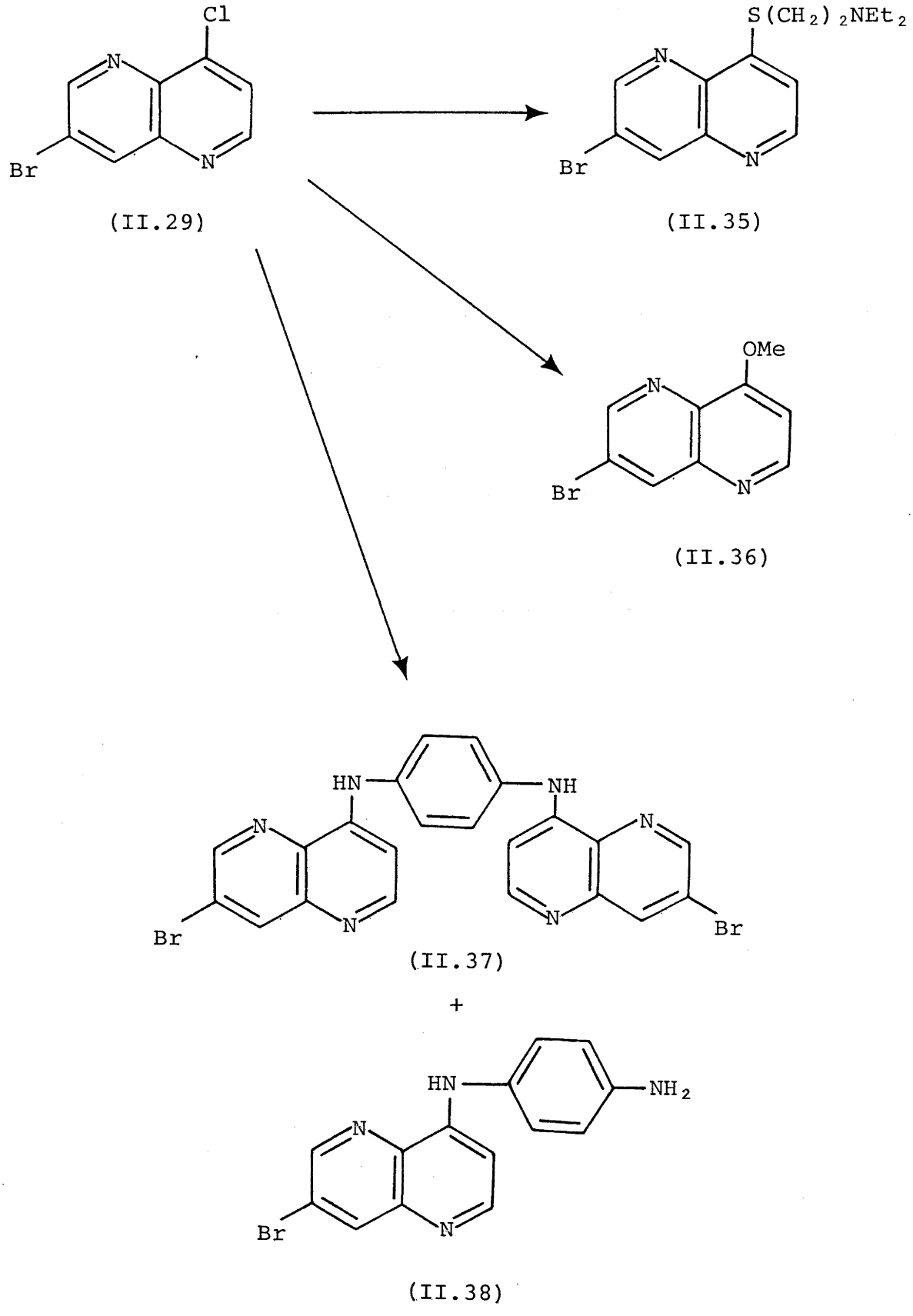
(a) R = $NHCHMe(CH_2)_3NEt_2$
(b) R = $NH(CH_2)_2NEt_2$
(c) R = $NH(CH_2)_3NEt_2$
(d) R = $NH(CH_2)_4NEt_2$
(e) R = $NH(CH_2)_4NH_2$
(f) R = $NH(CH_2)_5NH_2$
(g) R = $NH(CH_2)_6NH_2$
(h) R = $NH(CH_2)_3NMe_2$



(II.32) (II.34)

(a) R = $NH(CH_2)_2NEt_2$
(b) R = $NH(CH_2)_4NEt_2$

SCHEME II-6



(II.29)

(II.35)

(II.36)

(II.37)

+

(II.38)

SCHEME II-7

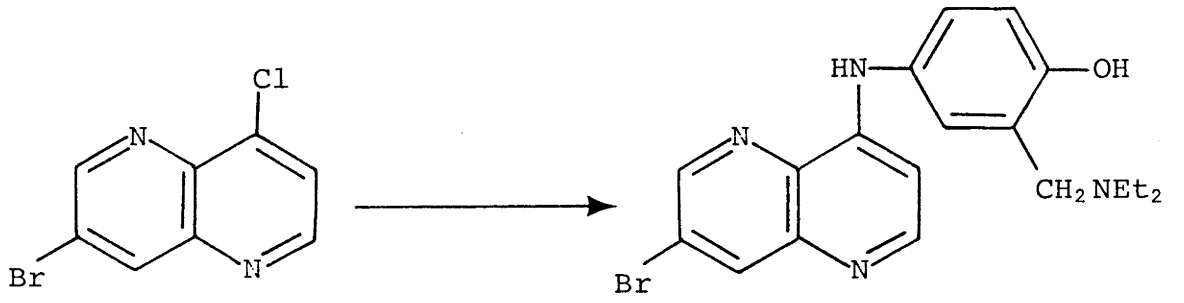
II-6 Preparation of 4-[7'-Bromo (and Chloro)-1',5'-naphthyridin-4'-ylamino]phenols

3-Bromo-8-chloro-1,5-naphthyridine (II.29), when heated with aqueous 4-amino-2-diethylaminomethylphenol at 100°, gave 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (II.39). Similarly, the bromochloronaphthyridine (II.29) by reaction with p-aminophenol hydrochloride in aqueous methanol afforded 4-(7'-bromo-1',5'-naphthyridine-4'-ylamino)phenol (II.40) in good yield. This product, with formalin in ethanol and a moderate amount of dimethylamine, dipropylamine or pyrrolidine at reflux gave the mono-Mannich bases (II.41a-c) respectively (SCHEME II-8).

Nevertheless, 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)phenol (II.40) with ethanolic formalin and a large excess of dimethylamine, diethylamine, dipropylamine, pyrrolidine, piperidine, 2-methylpiperidine, 3,5-dimethylpiperidine, morpholine or N-methylpiperazine at reflux for 20 h gave the di-Mannich bases (II.41d-l). 4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2-pyrrolidin-1"-ylmethylphenol (II.41c) when refluxed with ethanolic dimethylamine and formalin for 10 h afforded 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-6-dimethylaminomethyl-2-pyrrolidin-1"-ylmethylphenol (II.42) (SCHEME II-9). However transaminations rendered unsatisfactory the attempted preparation of 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-(diethylaminomethyl)-6-(pyrrolidin-1"-ylmethyl)phenol from 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-(diethylaminomethyl)phenol by reflux with formalin and pyrrolidine

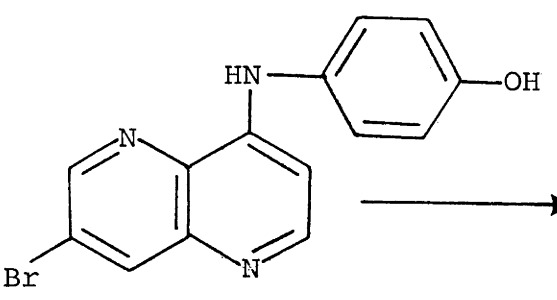
in ethanol; and the attempted preparation of 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-(diethylaminomethyl)-6-(dimethylaminomethyl)phenol from 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-(diethylaminomethyl)phenol with formalin and dimethylamine, or from 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2-(dimethylaminomethyl)phenol with formalin and diethylamine in ethanol.

Similarly, 4,7-dichloro-1,5-naphthyridine[56] (II.32) with 4-amino-2-diethylaminomethylphenol gave 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (II.43) and with aqueous methanolic p-aminophenol hydrochloride gave 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)phenol (II.44) which when refluxed with ethanolic formalin in large excess of dimethylamine, diethylamine, dipropylamine or pyrrolidine afforded the di-Mannich bases (II.45a-d), respectively (SCHEME II.10).

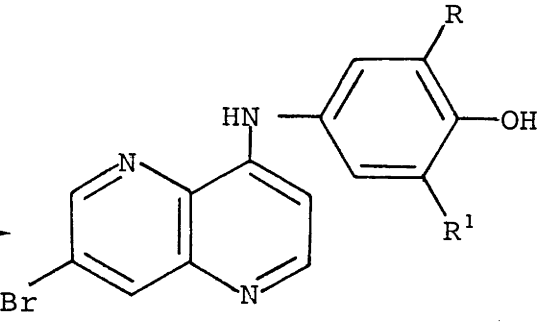


(II.29)

(II.39)



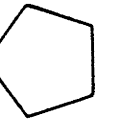
(II.40)



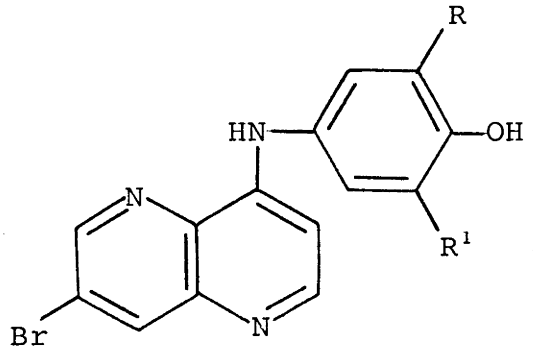
(II.41)

(a) R = H, R^1 = CH_2NMe_2

(b) R = H, R^1 = CH_2NPr_2

(c) R = H, R^1 = 

SCHEME II-8

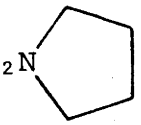


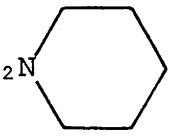
(II.41)

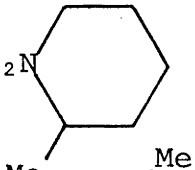
(d) $R = R^1 = CH_2NMe_2$

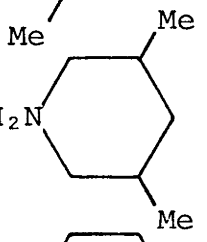
(e) $R = R^1 = CH_2NEt_2$

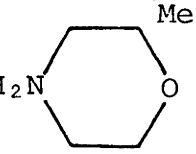
(f) $R = R^1 = CH_2NPr_2$

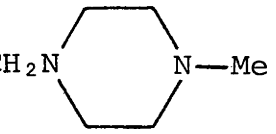
(g) $R = R^1 =$ 

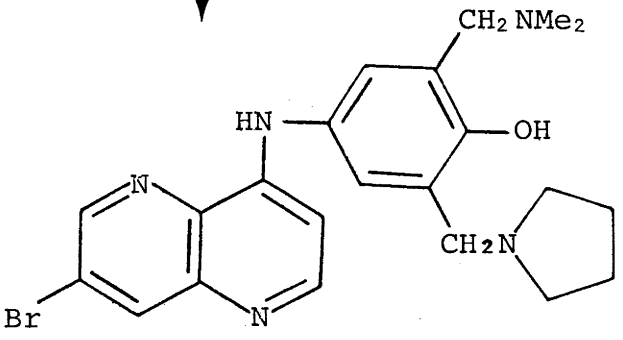
(h) $R = R^1 =$ 

(i) $R = R^1 =$ 

(j) $R = R^1 =$ 

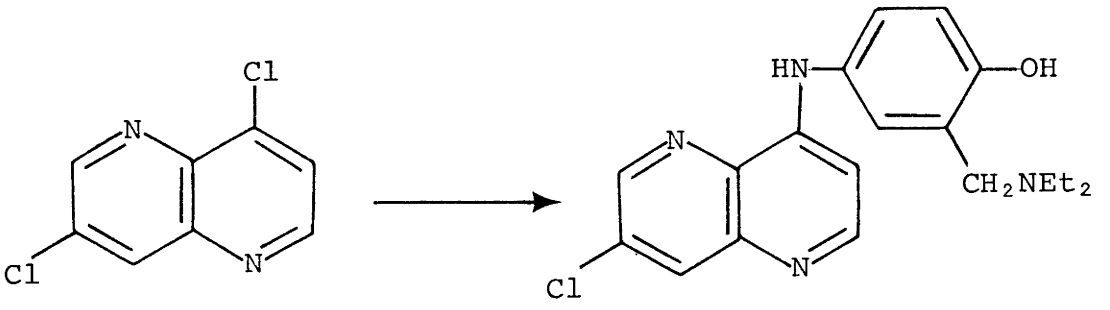
(k) $R = R^1 =$ 

(l) $R = R^1 =$ 



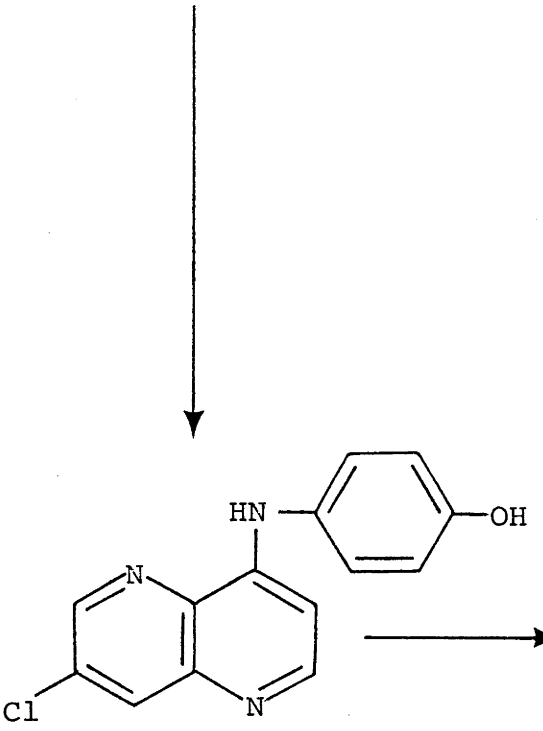
(II.42)

SCHEME II-9

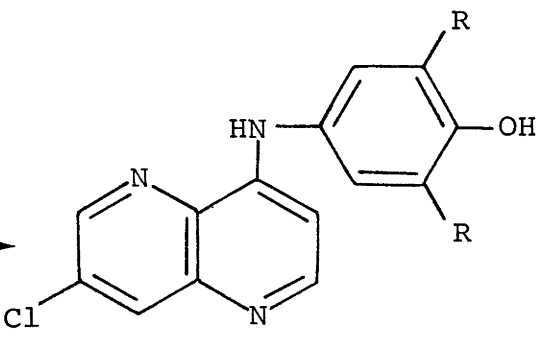


(II.32)

(II.43)



(II.44)

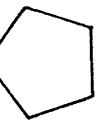


(II.45)

(a) R = CH_2NMe_2

(b) R = CH_2NEt_2

(c) R = CH_2NPr_2

(d) R = CH_2N 

SCHEME II-10

II-7 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. ^{1}H and ^{13}C n.m.r. Spectra were recorded (by Dr M. D. Fenn) at 90 M Hz and 30° with a Jeol FX 90 Q 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 7070 F spectrometer with perfluorokerosene as standard.

1,5-Naphthyridine-2,4-diol (II.11)

1,5-Naphthyridine-2,4-diol was prepared in improved yield as described below from quinolinic acid through quinolinic acid imide,[82] 3-aminopyridine-2-carboxylic acid[83] and its ethyl ester[83] [^{1}H n.m.r. ($CDCl_3$): δ 1.45, t, J 7 Hz, $C\underline{H}_3CH_2$; 4.46, q, J 7 Hz, $CH_2\underline{C}H_3$; 5.6, b, NH_2; 7.02, q, $J_{4,5}$ 8.5 Hz, $J_{4,6}$ 1.5 Hz, H 4; 7.16, q, $J_{4,5}$ 8.5 Hz, $J_{5,6}$ 4.0 Hz, H 5; 8.08, q, $J_{5,6}$ 4.0 Hz, $J_{4,6}$ 1.5 Hz, H 6] by a modification of the troublesome literature[72] procedure.

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.[72] >360°). ^{1}H n.m.r. (CD_3SOCD_3): δ 5.91, s, H 3; 7.53, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.0 Hz, H 7; 7.67, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 2 Hz, H 8; 8.44, q, $J_{6,7}$ 4 Hz, $J_{6,8}$ 2 Hz, H 6.

2,4-Dichloro-1,5-naphthyridine (II.12)

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.[72] 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.[72] 140°). ^{1}H n.m.r. ($CDCl_3$): δ 7.71, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.0 Hz, H 7; 7.73, s, H 3; 8.32, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 9.05, q, $J_{6,7}$ 4.0 Hz, $J_{6,8}$ 1.5 Hz, H 6.

4-Chloro-2-methoxy-1,5-naphthyridine (II.16)

2,4-Dichloro-1,5-naphthyridine[72] (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.[56] 114-115°). ^{1}H n.m.r. ($CDCl_3$): δ 4.07, s, MeO; 7.27, s, H 3; 7.59, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 8.16, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 2 Hz, H 8; 8.87, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 2 Hz, H 6.

4-Chloro-1,5-naphthyridin-2-ol (II.17)

(A) This compound was prepared in quantity from 2,4-dichloro-1,5-naphthyridine as described by Oakes and Rydon.[72] It has m.p. 263° (lit.[72] 263°). ^{1}H n.m.r. ($CDCl_3$): δ 7.13, s, H 3; 7.53, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.81, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.71, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

(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 x 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 with the same ^{1}H n.m.r. spectrum as the product from (A).

This product obtained in (B) was also dechlorinated through the p-toluenesulfonylhydrazide as described by Oakes and Rydon[72] to give 1,5-naphthyridin-2-ol (II.18), m.p. 256-258° (lit. 258°,[72] 259°[84]). 1,5-Naphthyridin-4-ol is reported to have m.p. 340°.[85]

2-Diethylaminomethyl-4-(2'-methoxy-1',5'-naphthyridin-4'-ylamino)phenol (II.19)

4-Chloro-2-methoxy-1,5-naphthyridine (II.16) (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 then evaporated three times with water (3 x 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 (Na_2SO_4) and evaporated to give an oil which was subjected to column and thin-layer 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, H 3'; 6.83, d, $J_{5,6}$ 8.5 Hz, H 6; 6.96, d, $J_{3,5}$ 2.5 Hz, H 3; 7.15, q, $J_{3,5}$ 2.5 Hz, $J_{5,6}$ 8.5 Hz, H 5; 7.48, q, $J_{7',8'}$ 8.5 Hz, $J_{6',7'}$ 4.5 Hz, H 7'; 8.03, q, $J_{7',8'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 8'; 8.56, q, $J_{6',7'}$ 4.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 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 (II.20a)

4-Chloro-2-methoxy-1,5-naphthyridine (II.16) (1.0 g), 2-diethylaminoethylamine (3.0 g), anhydrous sodium carbonate (0.54 g) and 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, $C\underline{H}_3CH_2$; 2.58, q, J 7 Hz, $CH\underline{H}_2CH_3$; 2.76, t, J 5.5 Hz, $CH\underline{H}_2NEt_2$; 5.62, complex, $CH\underline{H}_2NH$; 4.01, s, MeO; 5.97, s, H 3; 6.81, b, NH; 7.40, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.0 Hz, H 7; 7.97, 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.

^{13}C n.m.r. (dihydrobromide in D_2O): δ 8.15, $\underline{C}H_3CH_2$; 37.46, 49.38, $\underline{C}H_2\underline{C}H_2NEt_2$; 47.86, $\underline{C}H_2CH_3$; 58.40, CH_3O; 82.67, C 3; 126.85, C 7; 128.50, C 8; 129.88, C 4; 132.10, C 8a; 148.14, C 6; 156.70, C 4a; 162.03, C 2.

N-(3'-Diethylaminopropyl)-2-methoxy-1,5-naphthyridin-4-amine (II.20b)

4-Chloro-2-methoxy-1,5-naphthyridine (0.5 g), 3-diethylaminopropylamine (1.68 g), anhydrous sodium carbonate (0.28 g) and heptane were heated at 160° for

20 h as for compound (II.20a). 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, $C\underline{H}_3CH_2$; 1.85, complex, $CH_2C\underline{H}_2CH_2$; 2.53, q, J 7 Hz, $C\underline{H}_2CH_3$; 2.57, complex, $C\underline{H}_2NEt_2$; 3.32, complex, $C\underline{H}_2NH$; 4.01, s, MeO; 5.97, s, H 3; 7.0, b, NH; 7.42, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.98, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.49, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

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 (II.20c)

4-Chloro-2-methoxy-1,5-naphthyridine (0.50 g), propane-1,3-diamine (1.9 g), anhydrous sodium carbonate (0.27 g) and 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, $CH_2C\underline{H}_2CH_2$; 2.86, t, $C\underline{H}_2NH_2$; 3.34, complex, $C\underline{H}_2NH$; 4.01, s, MeO; 5.98, s, H 3; 6.6, b, NH; 7.43, 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 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. $C_{12}H_{16}N_4O.2HBr$ requires C, 36.6; H, 4.6; Br, 40.5; N, 14.2%). ^{13}C n.m.r. (D_2O): δ 25.54, $CH_2\underline{C}H_2CH_2$; 37.05, 39.76, $\underline{C}H_2CH_2\underline{C}H_2$; 58.28, CH_3O; 81.50, C 3; 126.39, C 7; 128.28, C 8; 129.45, C 4; 131.70, C 8a; 137.76, C 6; 156.32, C 4a; 161.44, C 2.

N-(4'-Aminobutyl)-2-methoxy-1,5-naphthyridin-4-amine (II.20d)

4-Chloro-2-methoxy-1,5-naphthyridine (0.5 g), butane-1,4-diamine (3.0 g), anhydrous sodium carbonate (0.28 g) and heptane (10.0 ml) were heated at 160° for 20 h. Column and thin-layer chromatograph (alumina; methanol) gave a light yellow oil (0.4 g). ^1H n.m.r. ($CDCl_3$): δ 1.67, complex, $CH_2\underline{C}H_2\underline{C}H_2CH_2$; 2.74, t, $\underline{C}H_2NH_2$; 3.27, complex, $\underline{C}H_2NH$; 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 (II.20e)

4-Chloro-2-methoxy-1,5-naphthyridine (0.5 g), pentane-1,5-diamine (3.0 g), anhydrous sodium carbonate (0.28 g) and 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 (II.20f)

4-Chloro-2-methoxy-1,5-naphthyridine (0.5 g), hexane-1,6-diamine (3.0 g), anhydrous sodium carbonate (0.28 g) and 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 (II.21a)

4-Chloro-1,5-naphthyridin-2-ol (II.17) (0.5 g), 2-diethylaminoethylamine (1.68 g), anhydrous sodium carbonate (0.3 g), and heptane (10.0 ml) were heated in an autoclave at 180° for 20 h. The product was subjected to column 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 (II.21b)

4-Chloro-1,5-naphthyridin-2-ol (0.5 g), 3-diethylamino-propylamine (1.8 g), anhydrous sodium carbonate (0.29 g),

and heptane (10.0 ml) were heated at 180° for 20 h as described above. The yellow solid obtained was subjected to thin-layer chromatography (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, $C\underline{H}_3CH_2$; 1.87, complex, $CH_2C\underline{H}_2CH_2$; 2.55, q, J 7 Hz, $C\underline{H}_2CH_3$; 2.59, complex, $C\underline{H}_2NEt_2$; 3.35, complex, $C\underline{H}_2NH$; 5.68, s, H 3; 7.36, 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; 8.36, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

4-(3'-Aminopropylamino)-1,5-naphthyridin-2-ol (II.21c)

4-Chloro-1,5-naphthyridin-2-ol (0.5 g), propane-1,3-diamine (2.05 g), anhydrous sodium carbonate (0.3 g) and 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, $CH_2C\underline{H}_2CH_3$; 2.91, t, $C\underline{H}_2NH_2$; 3.39, complex, $C\underline{H}_2NH$; 5.72, s, H 3; 6.8, b, NH; 7.38, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.72, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.37, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

4-(4'-Aminobutylamino)-1,5-naphthyridin-2-ol (II.21d)

4-Chloro-1,5-naphthyridin-2-ol (0.5 g), butane-1,4-diamine (2.5 g), anhydrous sodium carbonate (0.3 g) and 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, $CH_2(C\underline{H}_2)_2CH_2$; 2.78, t, $C\underline{H}_2NH_2$; 3.32, complex, $C\underline{H}_2NH$; 5.71, s, H 3; 6.6, b, NH; 7.39, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.75, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.36, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

4-(5'-Aminopentylamino)-1,5-naphthyridin-2-ol (II.21e)

4-Chloro-1,5-naphthyridin-2-ol (0.5 g), pentane-1,5-diamine (3.0 g), anhydrous sodium carbonate (0.3 g) and 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, $CH_2(C\underline{H}_2)_3CH_2$; 2.73, complex, $C\underline{H}_2NH_2$; 3.27, complex, $C\underline{H}_2NH$; 5.71, s, H 3; 6.5, b, NH; 7.38, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.71, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.37, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

4-(6'-Aminohexylamino)-1,5-naphthyridin-2-ol (II.21f)

4-Chloro-1,5-naphthyridin-2-ol (0.4 g), hexane-1,6-diamine (2.57 g), anhydrous sodium carbonate (0.24 g) and heptane (10.0 ml) were heated at 180° for 20 h. The crude product was extracted with ether (3 x 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, $CH_2(C\underline{H}_2)_4CH_2$; 2.71, complex, $C\underline{H}_2NH_2$; 3.29, complex, $C\underline{H}_2NH$; 5.71, s, H 3; 6.5, b, NH; 7.39, q, $J_{7,8}$ 8.5 Hz, $J_{6,7}$ 4.5 Hz, H 7; 7.72, q, $J_{7,8}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 8; 8.37, q, $J_{6,7}$ 4.5 Hz, $J_{6,8}$ 1.5 Hz, H 6.

7-Bromo-4-hydroxy-1,5-naphthyridine-3-carboxylic acid (II.27)

Ethyl 7-bromo-4-hydroxy-1,5-naphthyridine-3-carboxylate[76] (II.26) (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 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): δ 8.22, d, $J_{6,8}$ 1.0 Hz, H 8; 8.60, br, H 2,6.

7-Bromo-1,5-naphthyridin-4-ol (II.28)

7-Bromo-4-hydroxy-1,5-naphthyridine-3-carboxylic acid (II.27) (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°): δ 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 (II.29)

7-Bromo-1,5-naphthyridin-4-ol (II.28) (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 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. ($CDCl_3$): δ 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.

7-Bromo-N-(4'-diethylamino-1'-methylbutyl)-1,5-naphthyridin-4-amine (II.33a)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (II.29) (0.5 g), 5-diethylaminopentan-2-amine (3.25 g) and heptane (10.0 ml) 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. ($CDCl_3$): δ 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 (II.33b)

3-Bromo-8-chloro-1,5-naphthyridine (0.5 g), 2-diethylaminoethylamine (2.5 g) and heptane (10.0 ml) were heated at 160°, and the product was purified as for compound (II.33a) to give a yellow oil (0.6 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.08, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.63, q, J 7 Hz, $CH\underline{_2}CH_3$; 2.81, complex, $CH\underline{_2}NEt_2$; 3.33, complex, $CH\underline{_2}NH$; 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 (II.33c)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (0.5 g), 3-diethylaminopropylamine (3.0 g) and heptane (10.0 ml) was heated at 160° and the product was purified as for compound (II.33a) to give a light yellow oil (0.6 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.06, t, J 7 Hz, $C\underline{H}_3CH_2$; 1.88, complex, $CH_2C\underline{H}_2CH_2$; 2.57, q, J 7 Hz, $CH\underline{_2}CH_3$; 2.61, complex, $CH\underline{_2}NEt_2$; 3.36, complex, $CH\underline{_2}NH$; 6.48, d, $J_{2,3}$ 5.5 Hz, H 3; 7.6, br, NH; 8.35, 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.

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%).

7-Bromo-N-(4'-diethylaminobutyl)-1,5-naphthyridin-4-amine (II.33d)

3-Bromo-8-chloro-1,5-naphthyridine (0.5 g), 4-diethylaminobutylamine (1.5 g) and heptane (10.0 ml) were heated in an autoclave at 160° for 20 h and the product purified as described for compound (II.33a). 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, $C\underline{H}_3CH_2$; 1.70, complex, $CH_2(C\underline{H}_2)_2CH_2$; 2.49, q, J 7 Hz, $CH_3C\underline{H}_2$; 2.50, complex, $C\underline{H}_2NEt_2$; 3.34, complex, $NHC\underline{H}_2$; 6.50, d, $J_{2,3}$ 5.5 Hz, H 3; 8.36, d, $J_{6,8}$ 2 Hz, H 8; 8.50, d, $J_{2,3}$ 5.5 Hz, H 2; 8.65, d, $J_{6,8}$ 2 Hz, H 6. 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'-Bromo-1',5'-naphthyridin-4'-ylamino)butylamine (II.33e)

A mixture of 3-bromo-8-chloro-1,5-naphthyridine (0.5 g), butane-1,4-diamine (4.0 g) and heptane (10.0 ml) was heated at 160°, and the product was purified as described for compound (II.33a) to give a low-melting semi-solid (0.45 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.71, complex, $CH_2(C\underline{H}_2)_2CH_2$; 2.78, complex, $C\underline{H}_2NH_2$; 3.31, complex, $C\underline{H}_2NH$;

6.49, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.6, br, NH; 8.36, d, $J_{6',8'}$ 2.0 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2.0 Hz, H 6'. 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 (II.33f)

3-Bromo-8-chloro-1,5-naphthyridine (0.5 g) with pentane-1,5-diamine (4.0 g) and heptane (10.0 ml) gave a low-melting semi-solid (0.3 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.45, complex, $CH_2(\underline{CH}_2)_3CH_2$; 2.73, complex, $\underline{CH}_2NH_2$; 3.30, complex, $\underline{CH}_2NH$; 6.49, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.6, br, NH; 8.36, d, $J_{6',8'}$ 2 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2 Hz, H 6'. 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 (II.33g)

6-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)hexylamine was prepared from 3-bromo-8-chloro-1,5-naphthyridine (0.5 g) and hexane-1,6-diamine (5.0 g) in heptane (10.0 ml). The product was purified as described for compound (II.33a)

and was obtained as a low-melting semi-solid (0.45 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.60, complex, $CH_2(C\underline{H}_2)_4CH_2$; 2.70, complex, $C\underline{H}_2NH_2$; 3.29, complex, $C\underline{H}_2NH$; 6.50, d, $J_{2',3'}$ 5.5 Hz, H 3'; 8.37, d, $J_{6',8'}$ 2.0 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.66, d, $J_{6',8'}$ 2.0 Hz, H 6'. 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 (II.33h)

7-Bromo-N-(3'-dimethylaminopropyl)-1,5-naphthyridin-4-amine was prepared from 3-bromo-8-chloro-1,5-naphthyridine (0.5 g) and 3-dimethylaminopropylamine (2.0 g) in heptane (10.0 ml). The product was purified as described for compound (II.33a) and was obtained as a yellow oil (0.6 g). ^{1}H n.m.r. ($CDCl_3$): δ 1.88, complex, $CH_2C\underline{H}_2CH_2$; 2.26, s, Me_2N; 2.43, complex, $C\underline{H}_2NMe_2$; 3.36, complex, $C\underline{H}_2NH$; 6.51, d, $J_{2,3}$ 5.5 Hz, H 3; 7.1, br, NH; 8.35, d, $J_{6,8}$ 2 Hz, H 8; 8.49, d, $J_{2,3}$ 5.5 Hz, H 2; 8.65, d, $J_{6,8}$ 2 Hz, H 6.

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%).

7-Chloro-N-(2'-diethylaminoethyl)-1,5-naphthyridin-4-amine (II.34a)

4,7-Dichloro-1,5-naphthyridine[56] (II.32) (0.4 g), 2-diethylaminoethylamine (1.2 g) and heptane (10.0 ml) were heated and the product purified as for compound (II.33a) 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, $C\underline{H}_3CH_2$; 2.61, q, J 7 Hz, $CH_3C\underline{H}_2$; 2.79, t, J 6 Hz, $C\underline{H}_2NEt_2$; 3.34, complex, $C\underline{H}_2NH$; 6.48, d, $J_{2,3}$ 5.5 Hz, H 3; 7.0, b, NH; 8.17, d, $J_{6,8}$ 2 Hz, H 8; 8.51, d, $J_{2,3}$ 5.5 Hz, H 2; 8.60, d, $J_{6,8}$ 2 Hz, H 6.

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 (II.34b)

4,7-Dichloro-1,5-naphthyridine (0.4 g), 4-diethylaminobutylamine (1.5 g) and heptane (10.0 ml) were heated at 160° for 20 h and the mixture worked up as for compound (II.33a) as described above, to give 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, $C\underline{H}_3CH_2$; 1.70, complex, $CH_2(C\underline{H}_2)_2CH_2$; 2.53, q, J 7 Hz, $CH_3C\underline{H}_2$; 2.57, complex, $C\underline{H}_2NEt_2$; 3.33,

complex, $C\underline{H}_2NH$; 6.47, d, $J_{2,3}$ 5.5 Hz, H 3; 6.7, b, NH; 8.16, d, $J_{6,8}$ 2 Hz, H 8; 8.50, d, $J_{2,3}$ 5.5 Hz, H 2; 8.54, d, $J_{6,8}$ 2 Hz, H 6.

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%).

N,N-Diethyl-2-(7'-bromo-1',5'-naphthyridin-4'-ylthio)-ethylamine (II.35)

3-Bromo-8-chloro-1,5-naphthyridine (II.29) (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 thin-layer chromatography (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, $C\underline{H}_3CH_2$; 2.64, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.05, complex, $C\underline{H}_2C\underline{H}_2$; 7.37, d, $J_{2,3}$ 5 Hz, H 3'; 8.51, d, $J_{6,8}$ 2 Hz, H 8'; 8.72, d, $J_{2,3}$ 5 Hz, H 2'; 8.91, d, $J_{6,8}$ 2 Hz, H 6'.

3-Bromo-8-methoxy-1,5-naphthyridine (II.36)

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. ($CDCl_3$): δ 4.15, s, MeO; 7.00, d, $J_{6,7}$ 5.5 Hz, H 7; 8.54, d, $J_{2,4}$ 2.0 Hz, H 4; 8.82, d, $J_{6,7}$ 5.5 Hz, H 6; 8.95, d, $J_{2,4}$ 2 Hz, H 2.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)aniline (II.38), and N,N'-Bis(7"-bromo-1",5"-naphthyridin-4"-yl)benzene-1,4-diamine (II.37) 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): δ 4.69, d, $J_{2",3"}$ 6.5 Hz, H 3"; 5.17, s, H 2,3,5,6; 6.12, d, $J_{2",3"}$ 6.5 Hz, H 2"; 6.25, d, $J_{6",8"}$ 2 Hz, H 8"; 6.63, d, $J_{6",8"}$ 2 Hz, H 6".

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. ($CDCl_3$): δ 6.75, d, $J_{2,3}$ 8.5 Hz, H 2,6; 6.84, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.16, d, $J_{2,3}$ 8.5 Hz, H 3,5; 8.14, br, NH; 8.41, d, $J_{6',8'}$ 2.0 Hz, H 8'; 8.48, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.74, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (II.39)

3-Bromo-8-chloro-1,5-naphthyridine (0.3 g, 0.0013 mol), 4-amino-2-diethylaminomethylphenol 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-diethylaminomethylphenol (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. ($CDCl_3$): δ 1.14, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.67, q, J 7 Hz, $C\underline{H}_2CH_3$; 3.80, s, CH_2N; 6.86, d, $J_{2',3'}$ 5.5 Hz, H3'; 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 Hz, $J_{5,6}$ 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'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (II.40)

3-Bromo-8-chloro-1,5-naphthyridine (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, H 2,6; 6.86, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.23, d, $J_{2,3}$ 9 Hz, H 3,5; 8.44, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.48, d, $J_{6',8'}$ 2 Hz, H 8'; 8.88, d, $J_{6',8'}$ 2 Hz, H 6'; 9.2, b, NH; 9.4, b, OH.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2-dimethylaminomethylphenol (II.41a)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (II.40) (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 thin-layer chromatography (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, H 3'; 6.88, d, $J_{5,6}$ 8.5 Hz, H 6; 6.97, d, $J_{3,5}$ 3 Hz, H 3; 7.18, q, $J_{3,5}$ 3 Hz, $J_{5,6}$ 8.5

Hz, H 5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2.0 Hz, H 8'; 8.47, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.71, d, $J_{6',8'}$ 2 Hz, H 6'; 9.8, b, 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-dipropylaminomethylphenol (II.41b)

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 was worked up as described for compound (II.41a). The product was purified by thin-layer chromatography (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-dipropylaminomethylphenol (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, $C\underline{H}_3CH_2CH_2$; 1.60, complex, $CH_3C\underline{H}_2CH_2$; 2.47, complex, $CH_3CH_2C\underline{H}_2$; 3.79, s, CH_2N; 6.87, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.87, d, $J_{5,6}$ 8.5 Hz, H 6; 6.97, d, $J_{3,5}$ 2.5 Hz, H 3; 7.17, q, $J_{3,5}$ 2.5 Hz, $J_{5,6}$ 8.5 Hz, H 5; 8.2, b, NH; 8.42, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.73, d, $J_{6',8'}$ 2 Hz, H 6'; 9.4, b, OH.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2-pyrrolidin-1"-ylmethylphenol (II.41c)

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 the mixture was worked up and purified as described for compound (II.41a). The oil (0.27 g) [^{1}H n.m.r. ($CDCl_3$): δ 1.86, complex, H 3",4"; 2.66, complex, H 2",5"; 3.83, s, CH_2N; 6.84, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.86, d, $J_{5,6}$ 9 Hz, H 6; 6.96, d, $J_{3,5}$ 2.5 Hz, H 3; 7.15, q, $J_{3,5}$ 2.5 Hz, $J_{5,6}$ 9 Hz, H 5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2 Hz, H 8'; 8.47, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.70, d, $J_{6',8'}$ 2 Hz, H 6'; 9.5, b, 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 (II.41d)

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 thin-layer chromatography (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, H 3'; 7.06, s, H 3,5; 8.2, b, NH; 8.41, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.73, d, $J_{6',8'}$ 2 Hz, H 6'.

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 (II.41e)

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 and worked up, and the product purified as for compound (II.41a) 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, H 3'; 7.12, s, H 3,5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2 Hz, H 8'; 8.48, d, $J_{2',3'}$ 5 Hz, H 2'; 8.72, d, $J_{6',8'}$ 2 Hz, H 6'.

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(dipropylaminomethyl)phenol (II.41f)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (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(dipropylaminomethyl)phenol (0.5 g) was isolated as a yellow oil after thin-layer chromatography (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, $C\underline{H}_3CH_2CH_2$; 1.55, complex, $CH_3C\underline{H}_2CH_2$; 2.45, complex, $CH_3CH_2C\underline{H}_2$; 3.71, s, CH_2N; 6.90, d, $J_{2',3'}$ 5 Hz, H 3'; 7.13, s, H 3,5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2 Hz, H 8'; 8.47, d, $J_{2',3'}$ 5 Hz, H 2'; 8.73, d, $J_{6',8'}$ 2 Hz, H 6'.

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 (II.41g)

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 and worked up and the product purified as described for compound (II.41a) 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%).
^1H n.m.r. ($CDCl_3$): δ 1.83, complex, H 3",4"; 2.63, complex, H 2",5"; 3.77, s, CH_2N; 6.86, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.08, s, H 3,5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2 Hz, H 8'; 8.48, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.72, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(piperidin-1"-ylmethyl)phenol (II.41h)

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. Work up was as described above for compound (II.41a) 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%).
^1H n.m.r. ($CDCl_3$): δ 1.55, complex, H 3",4",5"; 2.51, complex, H 2",6"; 3.62, s, CH_2N; 6.89, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.08, s, H 3,5; 8.2, b, NH; 8.40, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.72, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(2"-methylpiperidin-1"-ylmethyl)phenol (II.41i)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), 2-methylpiperidine (2.0 ml) and ethanol (10.0 ml) were refluxed with stirring for 20 h. Excess amine was distilled off under vacuum. Traces of 2-methylpiperidine were removed by triturating with water

(50 ml) before the oily residue was purified by thin-layer chromatography (alumina; chloroform) to give 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(2"-methylpiperidin-1"-ylmethyl)phenol (0.2 g) as a yellow oil. (Found: C, 62.9; H, 6.9; N, 12.8. $C_{28}H_{36}BrN_5O$ requires C, 62.5; H, 6.7; N, 13.0%). ^{1}H n.m.r. ($CDCl_3$): δ 1.18, d, J 6.5 Hz, CH_3; 1.58, complex, H 3",4",5"; 2.34, complex, H 2"; 2.85, complex, H 6"; 3.36, d, J 14 Hz, 4.10, d, J 14 Hz, CH_2; 6.90, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.12, s, H 3,5; 8.19, s, NH; 8.41, d, $J_{6',8'}$ 2 Hz, H 8'; 8.48, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.73, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(3",5"-dimethylpiperidin-1"-ylmethyl)phenol (II.41j)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), 3,5-dimethylpiperidine (2.0 ml) and ethanol (10.0 ml) were refluxed with stirring for 20 h. Excess amine was distilled off under vacuum and the oily residue purified on thin-layer chromatography (alumina; chloroform then silica; methanol) to give 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(3",5"-dimethylpiperidin-1"-ylmethyl)phenol (0.12 g) as a yellow oil. (Found: C, 63.1; H, 7.2; N, 12.1. $C_{30}H_{40}BrN_5O$ requires C, 63.6; H, 7.1; N, 12.4%). ^{1}H n.m.r. ($CDCl_3$): δ 0.85, d, J 6.5 Hz, CH_3; 1.68, complex, H 3",4",5"; 2.90, complex, H 2",6"; 3.63, s, CH_2N; 6.92, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.08, s, H 3,5; 8.22, s, NH; 8.41, d, $J_{6',8'}$ 2 Hz, H 8'; 8.48, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.73, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis-(morpholin-4"-ylmethyl)phenol (II.41k)

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. Excess morpholine was distilled off under vacuum, and the product was purified by thin-layer chromatography (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, H 2",6"; 3.67, s, CH_2N; 3.76, complex, H 3",5"; 6.87, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.12, s, H 3,5; 8.2, b, NH; 8.42, d, $J_{6',8'}$ 2 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.74, d, $J_{6',8'}$ 2 Hz, H 6'.

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%).

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(4"-methylpiperazin-1"-ylmethyl)phenol (II.41l)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), N-methylpiperazine (2.0 ml) and ethanol (10.0 ml) were refluxed with stirring for 20 h and the product purified as for compound (II.41k) to give as a yellow oil 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-2,6-bis(4"-methylpiperazin-1"-ylmethyl)phenol (0.17 g) (Found: C, 54.9; H, 6.2; N, 16.8. $C_{26}H_{34}BrN_7O.1.8\ H_2O$*

*Dihydrate lost water on drying.

requires C, 54.5; H, 6.6; N, 17.1%). ^{1}H n.m.r. ($CDCl_3$): δ 2.31, s, CH_3; 2.55, complex, H 2",3",5",6"; 3.68, s, CH_2N; 6.87, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.09, s, H 3,5; 8.18, s, NH; 8.42, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.74, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-6-dimethylaminomethyl-2-pyrrolidin-1"-ylmethylphenol (II.42)

4-(7'-Bromo-1',5'-naphthyridin-4'-ylamino)-2-pyrrolidin-1"-ylmethylphenol (II.41c) (0.15 g), formalin (2.0 ml) and ethanolic dimethylamine (10 ml; 33%) were refluxed with stirring for 10 h. The reaction mixture was evaporated to dryness in vacuo to leave an oil which was purified by thin-layer chromatography (alumina; chloroform) to give 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)-6-dimethylamino-2-pyrrolidin-1"-ylmethylphenol (0.11 g) as a yellow oil.. (Found: C, 57.5; H, 5.8; N, 14.9. $C_{22}H_{26}BrN_5O$ requires C, 57.9; H, 5.7; N, 15.3%). ^{1}H n.m.r. ($CDCl_3$): δ 1.85, complex, H 3",4"; 2.33, s, CH_3; 2.67, complex, H 2",5"; 3.57, s, 6-CH_2; 3.79, s, 2-CH_2; 6.88, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.07, s, H 3,5; 8.20, s, NH; 8.41, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.72, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (II.43)

4,7-Dichloro-1,5-naphthyridine[56] (II.32) (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-diethylaminomethylphenol (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, $C\underline{H}_3CH_2$; 2.66, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.79, s, CH_2N; 6.85, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.86, d, $J_{5,6}$ 8 Hz, H 6; 6.98, d, $J_{3,5}$ 3 Hz, H 3; 7.17, q, $J_{5,6}$ 8 Hz, $J_{3,5}$ 3 Hz, H 5; 8.2, b, NH; 8.23, d, $J_{6',8'}$ 2 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)phenol (II.44)

A mixture of 4,7-dichloro-1,5-naphthyridine (0.66 g), p-aminophenol hydrochloride (0.72 g; ≃ 1:1.5), methanol (20.0 ml) and water (20.0 ml) was refluxed with stirring for 2 h. The methanol was then evaporated under reduced pressure and the aqueous solution adjusted to pH 8 with ammonium hydroxide. The yellow precipitate was collected, washed with water, and recrystallized from methanol to give 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)phenol (0.7 g), m.p. 240-241° (Found: C, 61.9; H, 3.8; N, 15.1. $C_{14}H_{10}ClN_3O$ requires C, 61.9; H, 3.7; N, 15.5%). ^{1}H n.m.r. (CD_3SOCD_3): δ 6.81, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.83, d, $J_{2,3}$ 8.5 Hz, H 2,6; 7.23, d, $J_{2,3}$ 8.5 Hz, H 3,5; 8.35, d, $J_{6',8'}$ 2 Hz, H 8'; 8.44, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.81, d, $J_{6',8'}$ 2 Hz, H 6'; 9.18, bs, NH; 9.45, bs, OH.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis-(dimethylaminomethyl)phenol (II.45a)

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)phenol (II.44) (0.2 g), formalin (2.0 ml), and ethanolic dimethylamine (20.0 ml; 33%) were refluxed with stirring for 20 h. Excess amine was distilled off under vacuum and the oily residue purified by thin-layer chromatography (alumina; chloroform) to give 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis(dimethylaminomethyl)phenol (0.22 g) as a yellow oil. (Found: C, 61.2; H, 6.4; N, 17.7. $C_{20}H_{24}ClN_5O.\frac{1}{2}H_2O$ requires C, 60.8; H, 6.4; N, 17.7%). ^{1}H n.m.r. ($CDCl_3$): δ 2.34, s, Me_2N; 3.58, s, CH_2N; 6.86, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.07, s, H 3,5; 8.18, bs, NH; 8.23, d, $J_{6',8'}$ 2 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.64, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis(diethylaminomethyl)phenol (II.45b)

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), diethylamine (2.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (II.45a) and the residue purified by thin-layer chromatography (silica; methanol) to give as a yellow oil which slowly crystallized, 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis(diethylaminomethyl)phenol (0.19 g), m.p. 106-107° (Found: C, 65.0; H, 7.5; N, 15.7. $C_{24}H_{32}ClN_5O$ requires C, 65.2; H, 7.3; N, 15.8%). ^{1}H n.m.r. ($CDCl_3$): δ 1.10, t, J 7 Hz, CH_3CH_2; 2.63, q, J 7 Hz, CH_3CH_2; 3.71, s, CH_2N; 6.88, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.11, s, H 3,5;

8.20, bs, NH; 8.23, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis(dipropylaminomethyl)phenol (II.45c)

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), dipropylamine (2.0 ml) and ethanol (10.0 ml) were refluxed with stirring for 40 h (the reaction was incomplete at 20 h). The product was purified as for compound (II.45b) to give as a yellow oil 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis-(dipropylaminomethyl)phenol (0.20 g) (Found: C, 66.4; H, 8.1; N, 13.8. $C_{28}H_{40}ClN_5O.\frac{1}{2}H_2O$ requires C, 66.3; H, 8.1; N, 13.8%). ^{1}H n.m.r. ($CDCl_3$): δ 0.89, t, J 7 Hz, $CH_3CH_2CH_2$; 1.50, complex, $CH_3CH_2CH_2$; 2.48, complex, $CH_3CH_2CH_2$; 3.70, s, CH_2N; 6.89, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.12, s, H 3,5; 8.20, bs, NH; 8.23, d, $J_{6',8'}$ 2 Hz, H 8'; 8.49, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2 Hz, H 6'.

4-(7'-Chloro-1',5'-naphthyridin-4'-ylamino)-2,6-bis(pyrrolidin-1"-ylmethyl)phenol (II.45d)

A mixture of 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), pyrrolidine (2.0 ml) and ethanol (10.0 ml) was refluxed with stirring for 20 h. Excess amine was distilled off under vacuum and traces of pyrrolidine were removed by triturating with water (50 ml) before the oily residue was purified by thin-layer chromatography (silica; methanol) to give as a yellow oil 4-(7'-chloro-1',5'-naphthyridin-4'-ylamino)-

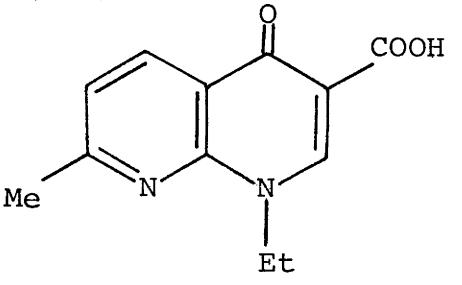
2,6-bis(pyrrolidin-1"-ylmethyl)phenol (0.21 g). (Found: C, 64.6; H, 6.6; N, 15.4. $C_{24}H_{28}ClN_5O.\frac{1}{2}H_2O$ requires C, 64.5; H, 6.5; N, 15.7%). ^{1}H n.m.r. ($CDCl_3$): δ 1.84, complex, H 3",4"; 2.64, complex, H 2",5"; 3.77, s, CH_2N; 6.87, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.09, s, H 3,5; 8.18, bs, NH; 8.23, d, $J_{6',8'}$ 2 Hz, H 8'; 8.50, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.65, d, $J_{6',8'}$ 2 Hz, H 6'.

CHAPTER III

SYNTHESIS OF 1,8-NAPHTHYRIDINES

III-1 Introduction

The literature on 1,8-naphthyridines (summarised in CHAPTER I) offered little information upon the potential of such compounds in malaria chemotherapy. However, a large number of 4-oxo derivatives of the 1,8-naphthyridine ring system have been synthesised and found to be powerful antibacterial agents.[86-88] These include 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (nalidixic acid)[89] (III.1) which is particularly effective against gram-negative bacteria found in chronic urinary tract infections.[90]

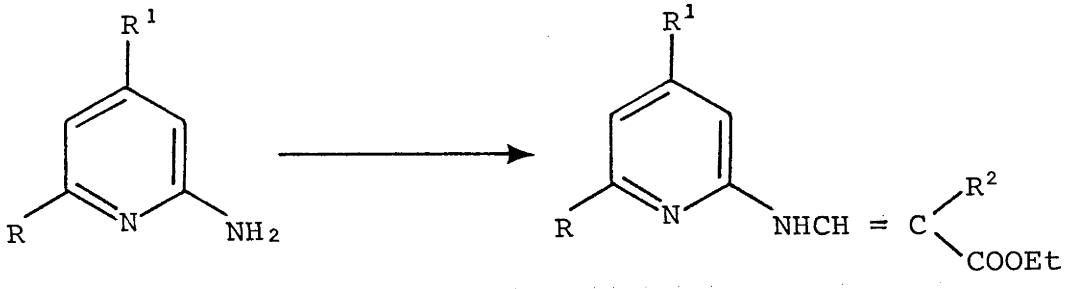


(III.1)

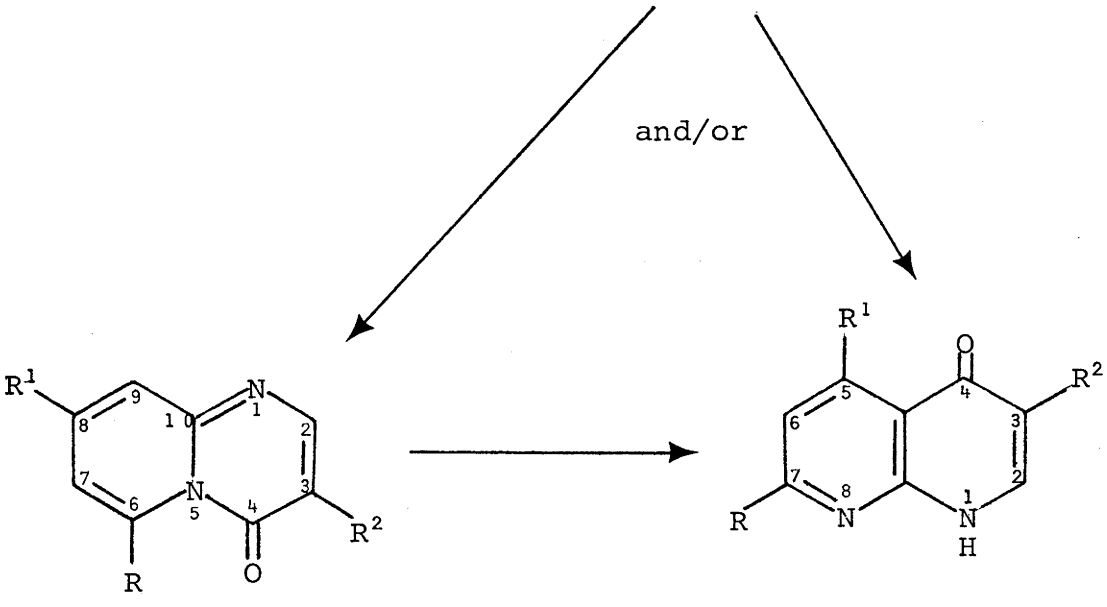
A series of 4-substituted 1,8-naphthyridines (as 8-aza analogues of chloroquine and amodiaquine) and their 2- and/or 7-methyl substituted derivatives have been prepared and these have been examined for antimalarial activity.

III-2 General Methods for Preparation of 1,8-Naphthyridines

The starting materials required for this preparative programme are 4-halogeno (or hydroxy)-1,8-naphthyridines. These can be prepared from pyridin-2-amines (III.2) with substituted acrylates to give the 2-substituted 3-(2'-pyridylamino)acrylates (III.3) which, upon ring closure, may give rise to either pyrido[1,2-a]pyrimidines (III.4) and/or 1,8-naphthyridines (III.5), depending on the conditions of cyclization.[91]



(III.2) (III.3)

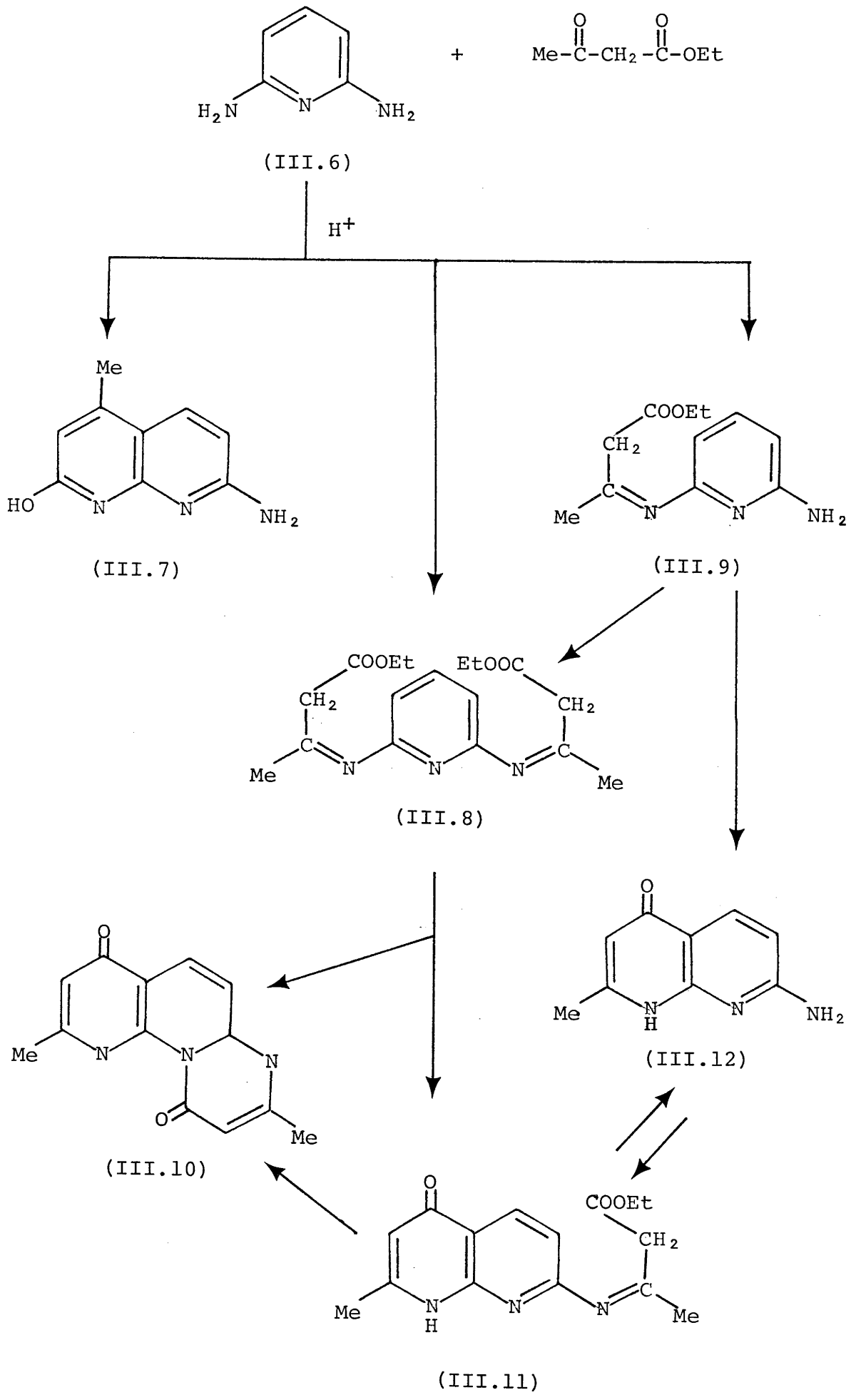


(III.4) (III.5)

The 6-substituted pyrido[1,2-a]pyrimidines (III.4) can be converted thermally into 1,8-naphthyridines (III.5) by 1 → 3N → C-acyl migration.[91] Hermecz et al.[91] reported that ring closure of (III.3) in phosphoryl chloride - polyphosphoric acid gives (III.4), but in "Dowtherm A" affords (III.4) and (III.5).

Ring transformation of the pyridopyrimidines (III.4) to the 1,8-naphthyridines (III.5) is influenced primarily by R and, to a lesser extent, by R^2. With respect to R, transformation is affected in the following order: OH < Me < NHAc, whereas for R^2 the order is: CO_2Et ~ CN ~ $COCF_3$ ~ $COCH_3$ > Ph > H > alkyl.[91]

The condensation of pyridine-2,6-diamine (III.6) with ethyl acetoacetate gives 7-amino-4-methyl-1,8-naphthyridin-2-ol (III.7), the dianil (III.8), and the monoanil (III.9).[92] Compound (III.7) corresponds to the "Knorr-type" product, whereas compounds (III.8) and (III.9) are the intermediate anils expected in a Conrad-Limpach-type condensation. Thermal cyclization of compounds (III.8) and (III.9) in refluxing "Dowtherm A" affords compounds (III.10), (III.11) and (III.12). Of these, the first two products (III.10) and (III.11) can be converted into the naphthyridine (III.12) by base hydrolysis. The structure of 7-amino-2-methyl-1,8-naphthyridin-4-ol (III.12) was determined by conversion into the corresponding dihydrazino-derivative, followed by oxidation of the latter to a tetrazole.[92]


(III.6)
H+
(III.7)
(III.9)
(III.8)
(III.12)
(III.10)
(III.11)

III-3 Preparation of Some 1,8-Naphthyridine Derivatives

The 1,8-naphthyridines required in this work were prepared from relevant pyridin-2-amines as described below. 6-Methylpyridin-2-amine (III.13) with diethyl ethoxymethylenemalonate gave diethyl (6'-methylpyridin-2'-yl)-aminomethylenemalonate[93] (III.14) which, on refluxing in diphenyl ether, gave ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate[93,94] (III.15). The latter was hydrolysed in aqueous potassium hydroxide and the unisolated acid[95] was decarboxylated in refluxing quinoline to give 7-methyl-1,8-naphthyridin-4-ol[94,95] (III.16). The last-named compound was converted as described by Brown[94] into 5-chloro-2-methyl-1,8-naphthyridine (III.17) and subsequent displacement of the chloro substituent occurred with 4-amino-2-diethylaminomethylphenol at 100° or 5-diethylaminopentan-2-amine at 160° to give (III.18a) and (III.18b), respectively (SCHEME III-1).

Ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate[93,94] (III.15) was oxidized by selenium dioxide in good yield to 6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid (III.19) which was hydrolysed in alkali and the dicarboxylic acid (III.20) lost carbon dioxide in quinoline to afford 1,8-naphthyridin-4-ol (III.21). Direct bromination of the latter with phosphoryl bromide gave 4-bromo-1,8-naphthyridine (III.22), which had previously been prepared from 2,4-dibromo-1,8-naphthyridine.[96] 4-Bromo-1,8-naphthyridine (III.22)

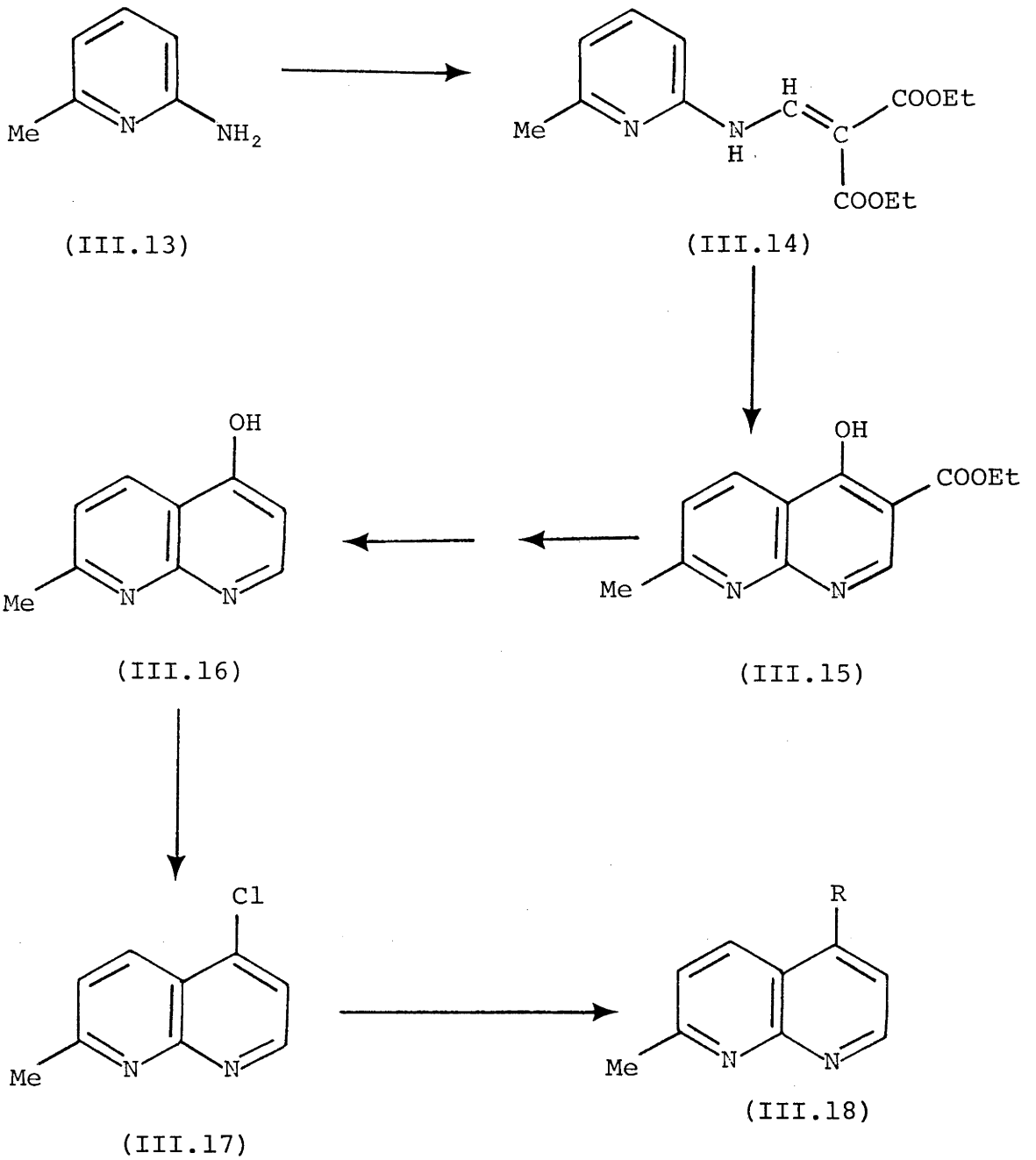
reacted with 4-amino-2-diethylaminomethylphenol or 5-diethylaminopentan-2-amine under conditions similar to those described above to give (III.23a) and (III.23b), respectively (SCHEME III-2).

4-Chloro-2,7-dimethyl-1,8-naphthyridine[97] (III.26) prepared from 6-methylpyridin-2-amine (III.13) through 2,6-dimethylpyrido[1,2-a]pyrimidin-4-one (III.24) and 2,7-dimethyl-1,8-naphthyridin-4-ol[97] (III.25) reacted with amines to give the desired compounds (III.27a) and (III.27b) (SCHEME III-3).

1,8-Naphthyridine-2,5-diol (III.32) was prepared from 6-aminopyridin-2-ol (III.28) and diethyl ethoxymethylene-malonate at 110° and subsequent ring-closure of the intermediate (III.29) in diphenyl ether followed by hydrolysis of the ester (III.30) to the acid (III.31) which was decarboxylated by refluxing in diphenyl ether for 9 h. This compound has also been prepared from 7-amino-1,8-naphthyridin-4-ol[98] and reported by Hermecz et al.[91] 2,5-Dichloro-1,8-naphthyridine (III.33), prepared from the dihydroxy compound (III.32) by chlorination with phosphoryl chloride, reacted with 4-amino-2-diethylaminomethylphenol dihydrochloride in water by replacement of the 5-chloro substituent to give 4-(7'-chloro-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.34) in which the site of substitution was established by catalytic dechlorination to the pre-prepared 2-diethylaminomethyl-4-(1',8'-naphthyridin-4'-ylamino)phenol (III.23a). 2,5-Dichloro-1,8-naphthyridine also reacted with 5-diethylamino-pentan-2-amine alone to give monosubstitution but removal

of excess 5-diethylaminopentan-2-amine was difficult (SCHEME III-4).

4,7-Dichloro-2-methyl-1,8-naphthyridine[92] (III.37), prepared from 7-amino-2-methyl-1,8-naphthyridin-4-ol[92] (III.35) through 2-methyl-1,8-naphthyridine-4,7-diol[92] (III.36) reacted with 4-amino-2-diethylaminomethylphenol-(dihydrochloride) in water at 100°, and the structure of the monosubstitution product, 4-(7'-chloro-2'-methyl-1,8-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.38), was assigned from the similar reaction of 2,5-dichloro-1,8-naphthyridine (III.33) described above (SCHEME III-5).

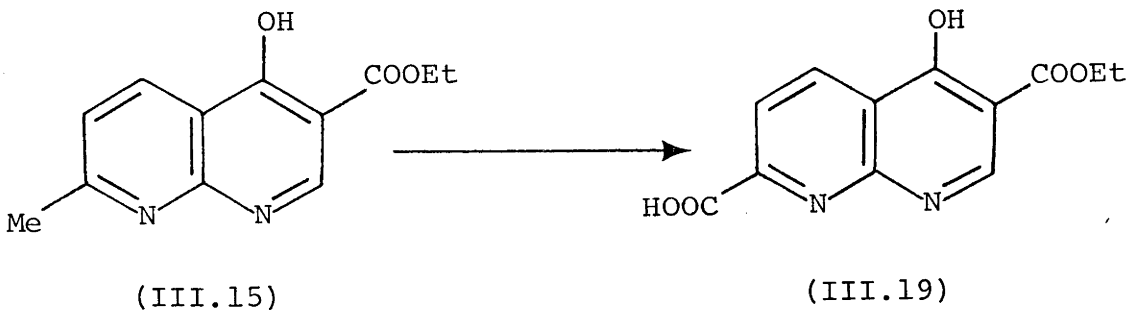


(III.13) (III.14) (III.15) (III.16) (III.17) (III.18)

(a) R = HN—⟨benzene⟩(OH, CH_2NEt_2)

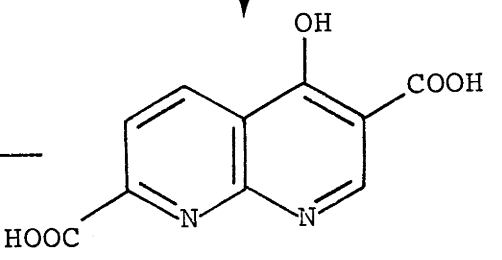
(b) R = $NHCHMe(CH_2)_3NEt_2$

SCHEME III-1

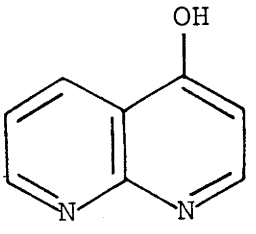


(III.15)

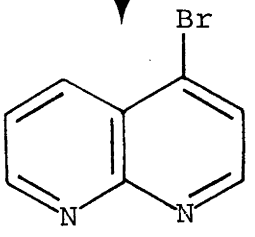
(III.19)



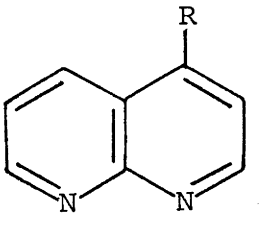
(III.20)



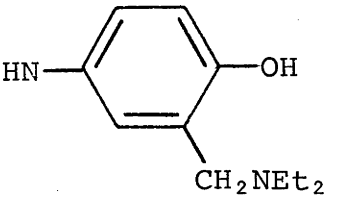
(III.21)



(III.22)

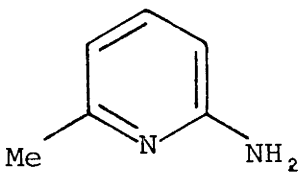


(III.23)

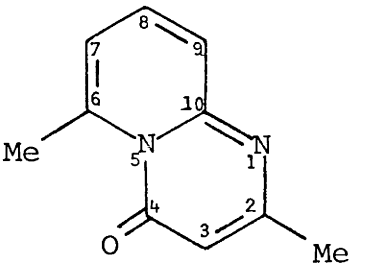
(a) R = 

(b) R = $NHCHMe(CH_2)_3NEt_2$

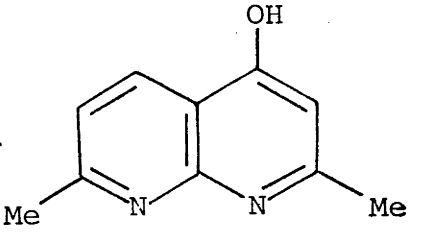
SCHEME III-2



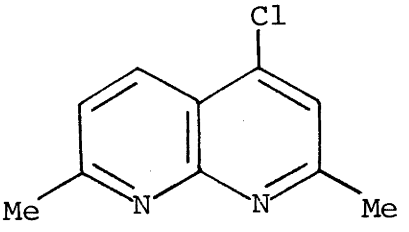
(III.13)



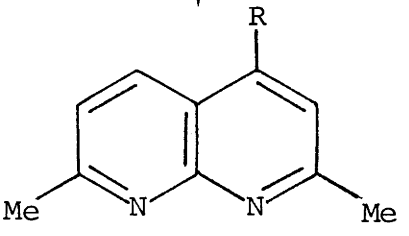
(III.24)



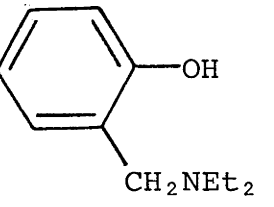
(III.25)



(III.26)

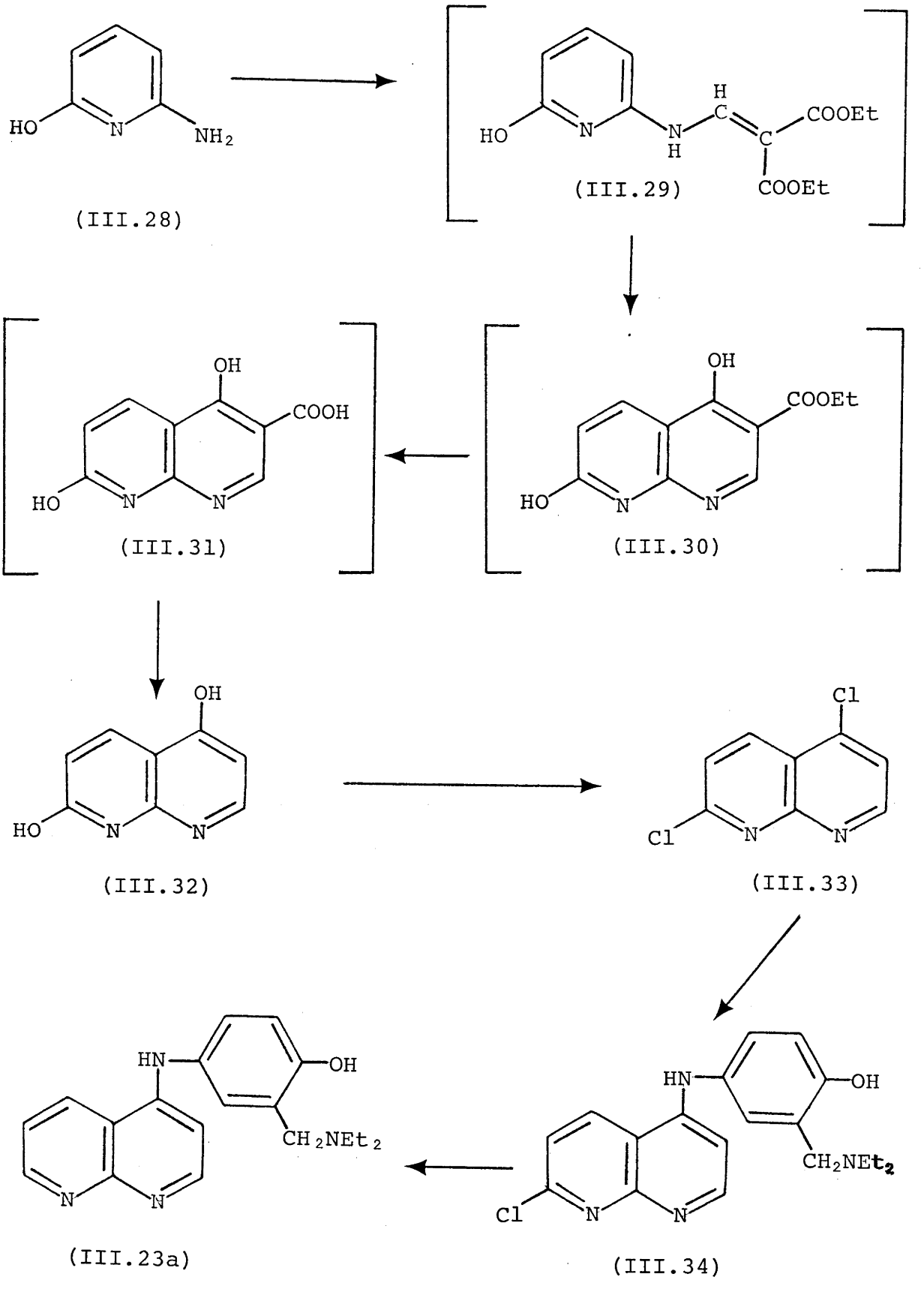


(III.27)

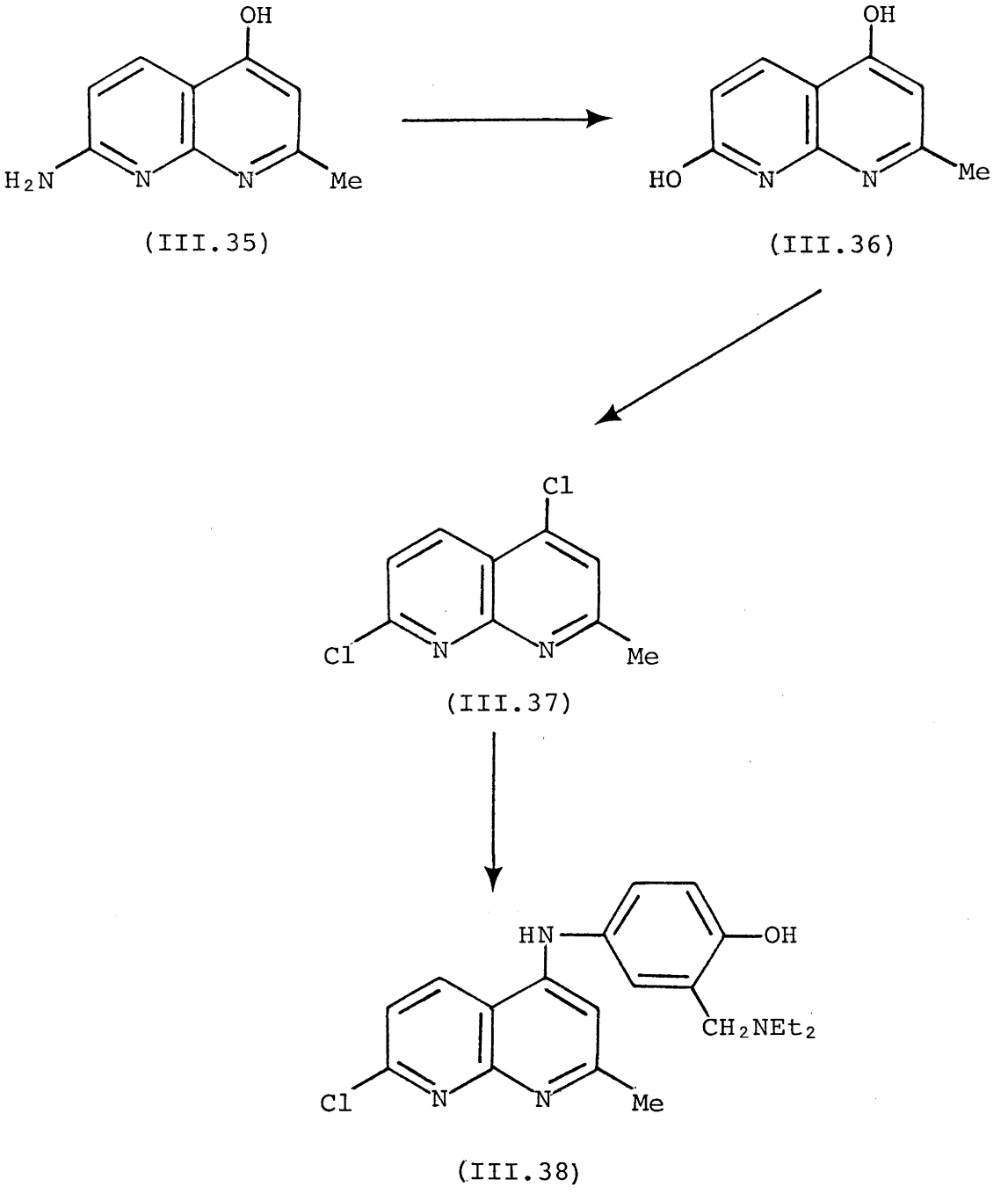
(a) R = HN—  —OH, CH_2NEt_2

(b) R = $NHCHMe(CH_2)_3NEt_2$

SCHEME III-3


HO
N
NH2
(III.28)
H
C
COOEt
HO
N
N
H
C
COOEt
(III.29)
OH
COOEt
HO
N
N
(III.30)
OH
COOH
HO
N
N
(III.31)
OH
HO
N
N
(III.32)
Cl
Cl
N
N
(III.33)
HN
OH
CH2NEt2
N
N
(III.23a)
HN
OH
CH2NEt2
Cl
N
N
(III.34)

SCHEME III-4


OH
H2N
N
N
Me
(III.35)
OH
HO
N
N
Me
(III.36)
Cl
Cl
N
N
Me
(III.37)
HN
OH
CH2NEt2
Cl
N
N
Me
(III.38)

SCHEME III-5

III-4 Experimental

General conditions and procedures for the experimental work were as described at the commencement of the Experimental Section in CHAPTER II. Compound (23b) proved difficult to analyse but ^{1}H n.m.r. data and nitrogen analyses were satisfactory.

2-Diethylaminomethyl-4-(7'-methyl-1',8'-naphthyridin-4'-ylamino)phenol (III.18a)

5-Chloro-2-methyl-1,8-naphthyridine[94] (III.17) (0.447 g, 0.0025 mol), 4-amino-2-diethylaminomethylphenol dihydrochloride (0.668 g, 0.0025 mol) and water (15 ml) were heated on a steam bath for 2 h. The cooled solution was made alkaline with aqueous ammonia and extracted four times with chloroform. The combined chloroform extracts were washed with sodium chloride solution, dried (Na_2SO_4) and evaporated to give a yellow product (1.0 g). This product was recrystallized from ethyl acetate to give 2-diethylaminomethyl-4-(7'-methyl-1',8'-naphthyridin-4'-ylamino)phenol (0.6 g) which decomposes above 186° (Found: C, 71.4; H, 7.3; N, 16.6. $C_{20}H_{24}N_4O$ requires C, 71.4; H, 7.2; N, 16.7%). ^{1}H n.m.r. ($CDCl_3$): δ 1.13, t, J 7.5 Hz, $C\underline{H}_3CH_2$; 2.65, q, J 7.5 Hz, $CH_3C\underline{H}_2$; 3.76, s, CH_2N; 6.62, d, J 5.5 Hz, H 3; 6.88, complex, ArH; 7.24, d, J 8.5 Hz, H 6; 8.23, d, J 8.5 Hz, H 5; 8.58, d, J 5.5 Hz, H 2.

N-(4'-Diethylamino-1'-methylbutyl)-7-methyl-1,8-naphthyridin-4-amine (III.18b)

5-Chloro-2-methyl-1,8-naphthyridine (1.0 g, 0.0056 mol) and 5-diethylaminopentan-2-amine (4.4 g, 0.0278 mol) were heated in an autoclave at 160° for 9 h. The reaction mixture was evaporated under reduced pressure, made alkaline with 2 M sodium hydroxide and extracted with chloroform. The product was subjected to column and thin-layer chromatography (alumina; ethyl acetate) to give N-(4'-diethylamino-1'-methylbutyl)-7-methyl-1,8-naphthyridin-4-amine (0.7 g) as a yellow oil. (Found: C, 71.6; H, 9.4; N, 18.4. $C_{18}H_{28}N_4$ requires C, 71.95; H, 9.4; N, 18.6%). ^{1}H n.m.r. ($CDCl_3$): δ 0.99, t, J 7.5 Hz, CH_3CH_2; 1.30, d, J 6.5 Hz, 1'-Me; 1.65, complex, 2.42, complex, $CH_2$2',3',4'; 2.51, q, J 7.5 Hz, CH_3CH_2; 2.71, s, 7-Me; 3.71, complex, H'; 5.45, d, J 7 Hz, NH; 6.42, d, J 5.5 Hz, H 3; 7.16, d, J 8.5 Hz, H 6; 8.09, d, J 8.5 Hz, H 5; 8.63, d, J 5.5 Hz, H 2.

6-Ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid (III.19)

Ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate[93,94] (III.15) (4.64 g, 0.02 mol), selenium dioxide (5.31 g, 0.048 mol), water (10.0 ml) and pyridine (20 ml) were refluxed with stirring for 10 h. The mixture was diluted with pyridine (50 ml), boiled to dissolve the yellow crude product, filtered and evaporated. The residue was recrystallized from pyridine and the product washed with acetone to give 6-ethoxycarbonyl-5-

hydroxy-1,8-naphthyridine-2-carboxylic acid (4.7 g), m.p. >279° (dec.) (Found: C, 54.1; H, 3.8; N, 10.5. $C_{12}H_{10}N_2O_5$ requires C, 54.9; H, 3.8; N, 10.7%). ^{1}H n.m.r. (CD_3SOCD_3): δ 1.29, t, J 7 Hz, CH_3CH_2; 4.23, q, J 7 Hz, CH_3CH_2; 8.05, d, 8.67, d, J 8 Hz, H 5,6; 8.57, b, H 2; 13.12, b, COOH.

4-Bromo-1,8-naphthyridine (III.22)

A mixture of 6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid (III.19) (9.0 g), potassium hydroxide (13.0 g) and water (90 ml) were heated on a steam bath for 1.75 h. The cooled solution was adjusted with 5 M hydrochloric acid to pH c. 2.5 and the dense light yellow precipitate of the acid (III.20) filtered off, washed with water and dried. This solid was refluxed with quinoline (120 ml) for 8 h, excess quinoline was removed under reduced pressure, and the remaining solid dissolved in the minimum volume of 1 M sodium hydroxide and extracted with chloroform to remove remaining traces of quinoline. The aqueous solution was adjusted with 1 M hydrochloric acid to pH c. 7 but the hydroxy compound (III.21) did not precipitate. The aqueous solution was evaporated to dryness to give crude hydroxy compound (III.21) (4.0 g). [^{1}H n.m.r. (CD_3OD): δ 6.35, d, J 7.5 Hz, H 3; 7.59, q, J 8.5 Hz, J 4.5 Hz, H 6; 8.05, d, J 7.5 Hz, H 2; 8.63, q, J 2 Hz, J 8.5 Hz, H 5; 8.71, q, J 2 Hz, J 4.5 Hz, H 7] which was brominated directly.

The crude hydroxy compound (III.21) (4.0 g) and phosphoryl bromide (20.0 g) were heated in an oil bath at

140-150° for 0.75 h. Ice was added carefully with stirring to the cooled mixture, and the resulting solution adjusted with sodium hydrogen carbonate solution to pH c. 6.5, and extracted with chloroform (4x). The extract was dried (Na_2SO_4) and evaporated under vacuum and the product recrystallized from light petroleum (b.p. 60-80°) to give colourless plates of 4-bromo-1,8-naphthyridine (3.3 g), m.p. 78-79° (lit.[96] 72-73°) (Found, for material dried at 20° and 20 mm Hg: C, 45.9; H, 2.4; Br, 38.3; N, 13.4. Calc. for $C_8H_5BrN_2$: C, 46.0; H, 2.4; Br, 38.2; N, 13.4%). ^{1}H n.m.r. ($CDCl_3$): δ 7.59, q, J 4 Hz, J 8.5 Hz, H 6; 7.78, d, J 5 Hz, H 3; 8.56, q, J 2 Hz, J 8.5 Hz, H 5; 8.92, d, J 5 Hz, H 2; 9.17, q, J 4 Hz, J 2 Hz, H 7.

2-Diethylaminomethyl-4-(1',8'-naphthyridin-4'-ylamino)phenol (III.23a)

4-Bromo-1,8-naphthyridine (III.22) (0.42 g, 0.002 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0.534 g, 0.002 mol) in water (15 ml) were heated on a steam bath for 2 h. The reaction mixture was worked up as described above for the reaction of 5-chloro-2-methyl-1,8-naphthyridine (III.17). The chloroform extract gave a crude product (0.84 g) which recrystallized from toluene to give yellow crystals of 2-diethylaminomethyl-4-(1',8'-naphthyridin-4'-ylamino)phenol (0.5 g), m.p. 174° (dec.) (Found: C, 71.2; H, 6.9; N, 17.4. $C_{19}H_{22}N_4O$ requires C, 70.8; H, 6.9; N, 17.4%). ^{1}H n.m.r. (CD_3OD): δ 1.14, t, J 7.5 Hz, CH_3CH_2; 2.69, q, J 7.5 Hz, CH_3CH_2; 3.83, s, CH_2N; 6.67, d, J 6 Hz, H 3; 7.08, complex, ArH; 7.50, q, J 4 Hz,

J 8 Hz, H 6; 8.46, d, J 6 Hz, H 2; 8.75, q, J 8 Hz, J 2 Hz, H 5; 8.93, q, J 2 Hz, J 4 Hz, H 7.

N-(4'-Diethylamino-1'-methylbutyl)-1,8-naphthyridin-4-amine (III.23b)

4-Bromo-1,8-naphthyridine (III.22) (1.05 g, 0.005 mol) and 5-diethylaminopentan-2-amine (3.95 g, 0.025 mol) were heated in an autoclave at 160° for 9 h. The reaction mixture was worked up as described above for the reaction of 5-chloro-2-methyl-1,8-naphthyridine (III.17) with 5-diethylaminopentan-2-amine. The dried chloroform extracts (Na_2SO_4) were evaporated to a viscous brown oil which was subjected to column chromatography (alumina; methanol). The product was washed by decantation with light petroleum (b.p. 60-80°) to remove remaining traces of 5-diethylamino-pentan-2-amine, and dried at 20° and 20 mm Hg to give N-(4'-diethylamino-1'-methylbutyl)-1,8-naphthyridin-4-amine (1.1 g) (Found: N, 19.4. $C_{17}H_{26}N_4$ requires N, 19.6%). ^{1}H n.m.r. ($CDCl_3$): δ 0.99, t, J 7 Hz, CH_3CH_2; 1.31, d, J 6 Hz, 1'-Me; 1.67, complex, 2.44, complex, $CH_2$2',3',4'; 2.52, q, J 7 Hz, CH_3CH_2; 3.73, complex, H 1'; 5.68, d, J 7 Hz, NH; 6.48, d, J 5.5 Hz, H 3; 7.28, q, J 8.5 Hz, J 5 Hz, H 6; 8.27, q, J 2 Hz, J 8.5 Hz, H 5; 8.69, d, J 5.5 Hz, H 2; 9.97, q, J 2 Hz, J 5 Hz, H 7.

2-Diethylaminomethyl-4-(2',7'-dimethyl-1',8'-naphthyridin-4'-ylamino)phenol (III.27a)

4-Chloro-2,7-dimethyl-1,8-naphthyridine[97] (III.26) (0.1 g, 0.0005 mol) and 4-amino-2-diethylaminomethylphenol

dihydrochloride (0.134 g, 0.0005 mol) in water (3.0 ml) were heated on a steam bath for 2 h. The reaction mixture was worked up as described above. The product was subjected to thin-layer chromatography (alumina; ethyl acetate), treated with 20% ethanolic hydrogen chloride, the mixture evaporated to dryness and the solid recrystallized from t-butyl alcohol to give yellow crystals of 2-diethylaminomethyl-4-(2',7'-dimethyl-1',8'-naphthyridin-4'-ylamino)phenol dihydrochloride (0.12 g), which sublimed at temperatures greater than 175° (Found: C, 54.6; H, 7.2; Cl, 15.3; N, 11.7. $C_{21}H_{26}N_4O.2HCl.2H_2O$: C, 54.9; H, 7.0; Cl, 15.4; N, 12.2%). ^{1}H n.m.r. (D_2O): δ 1.36, t, J 7.5 Hz, $C\underline{H}_3CH_2$; 2.58, s, 2-Me; 2.76, s, 7-Me; 3.26, q, J 7.5 Hz, $CH_3C\underline{H}_2$; 6.61, s, H 3; 7.41, complex, ArH; 7.64, d, 8.66, d, J 9 Hz, H 5,6.

N-(4'-Diethylamino-1'-methylbutyl)-2,7-dimethyl-1,8-naphthyridin-4-amine (III.27b)

4-Chloro-2,7-dimethyl-1,8-naphthyridine (1.0 g) and 5-diethylaminopentan-2-amine (4.11 g) were heated in an autoclave at 160° for 9 h. The mixture was worked up as described above for compound (III.18b). The chloroform extract gave a viscous brown oil which was purified by column chromatography and thin-layer chromatography (alumina; ethyl acetate) to give oily N-(4'-diethylamino-1'-methylbutyl)-2,7-dimethyl-1,8-naphthyridin-4-amine (0.64 g) (Found, for material dried at 20° and 20 mm Hg: C, 72.4; H, 9.9; N, 17.8. $C_{19}H_{30}N_4$ requires C, 72.6; H, 9.6; N, 17.8%). ^{1}H n.m.r. ($CDCl_3$): δ 0.99, t, J 7 Hz,

CH_3CH_2; 1.29, d, J 6.5 Hz, 1'-Me; 1.63, complex, 2.40, complex, $CH_2$2',3',4'; 2.51, q, J 7 Hz, CH_3CH_2; 2.61, s, 2-Me; 2.68, s, 7-Me; 3.70, complex, H 1'; 5.23, d, J 7 Hz, NH; 6.32, s, H 3; 7.11, d, 7.98, d, J 8.5 Hz, H 5,6.

1,8-Naphthyridine-2,5-diol (III.32)

6-Aminopyridin-2-ol (III.28) (4.0 g, 0.036 mol) and diethyl ethoxymethylenemalonate (7.86 g, 0.036 mol) were heated in an oil bath at 110° for 1.5 h. The cooled reaction mixture was dissolved in ethanol (c. 100 ml), filtered, and the filtrate evaporated to give a dark yellow oil which was refluxed in diphenyl ether (200 ml) for 9 h. The resultant solid was heated on a steam bath with sodium hydroxide (3.0 g) in water (100 ml) for 1.75 h, adjusted to pH 2.5 and the solid filtered off. The solid was added to diphenyl ether (200 ml) and this mixture refluxed for a further 9 h, cooled as rapidly as possible, diluted with light petroleum (b.p. 60-80°) (1000 ml). The yellow precipitate (2.5 g) was filtered off, washed with light petroleum (b.p. 60-80°) and dried. A sample of this material was recrystallized from a large volume of methanol to give 1,8-naphthyridine-2,5-diol m.p. 355-357° (lit.[91,98] >320°, >360°) (Found: C, 59.2; H, 3.2; N, 17.9. Calc. for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3%). ^{1}H n.m.r. (1 M NaOD): δ 6.30, d, J 6 Hz, H 3; 6.50, d, 8.18, d, J 9 Hz, H 5,6; 8.07, d, J 6 Hz, H 2.

2,5-Dichloro-1,8-naphthyridine (III.33)

Crude 1,8-naphthyridine-2,5-diol (III.32) (1.0 g) and phosphoryl chloride (10.0 ml) were heated in an oil bath at 120° for 0.75 h. The cooled reaction mixture was cautiously poured onto ice, and adjusted with aqueous sodium hydrogen carbonate to pH c. 5.5. This mixture was extracted with chloroform, the extract dried (Na_2SO_4), solvent evaporated and the product recrystallized from light petroleum (b.p. 60-80°) to give 2,5-dichloro-1,8-naphthyridine (0.8 g), m.p. 131-132° (Found: C, 48.1; H, 2.1; N, 14.1. $C_8H_4Cl_2N_2$ requires C, 48.3; H, 2.0; N, 14.1%). ^{1}H n.m.r. ($CDCl_3$): δ 7.58, d, J 9 Hz, H 3; 7.59, d, 9.00, d, J 5 Hz, H 5,6; 8.54, d, J 9 Hz, H 2.

4-(7'-Chloro-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.34)

A mixture of 2,5-dichloro-1,8-naphthyridine (III.33) (0.12 g, 0.0006 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0.16 g, 0.0006 mol) in water (10 ml) were heated on a steam bath for 2 h. After cooling, the reaction mixture was made alkaline with 14 M ammonium hydroxide, and gave a dense yellow precipitate. This product was collected and recrystallized from toluene to give 4-(7'-chloro-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (0.15 g), m.p. >360° (Found: C, 63.3; H, 6.1; Cl, 9.95; N, 15.4. $C_{19}H_{21}ClN_4O$ requires C, 63.9; H, 5.9; Cl, 9.9; N, 15.7%). ^{1}H n.m.r. (CD_3OD): δ 1.14, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.67, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.83, s, CH_2N; 6.67, d, J 6 Hz, H 3; 7.07, complex, ArH; 7.47, d, 8.69, d, J 8 Hz, H 5,6; 8.42, d, J 6 Hz, H 2.

Dechlorination of 4-(7'-chloro-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.34) to 2-Diethylaminomethyl-4-(1',8'-naphthyridin-4'-ylamino)phenol (III.23a)

A mixture of 4-(7'-chloro-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.34) (0.036 g), magnesium oxide (0.5 g), ethanol (30 ml) and 10% palladium - charcoal (0.05 g) was hydrogenated at room temperature and pressure until hydrogen uptake ceased. The reaction mixture was filtered through Celite, the filtrate evaporated to dryness, and the solid subjected to thin-layer chromatography (silica; methanol). The product was dissolved in methanol, the solution diluted with light petroleum (b.p. 80-100°), and the mixture concentrated to give a yellow precipitate of 2-diethylaminomethyl-4-(1',8'-naphthyridin-4'-ylamino)phenol, m.p. 174° (dec.), undepressed on admixture with authentic material prepared above. The ^{1}H n.m.r. and i.r. spectra were also identical with those of the authentic compound.

4-(7'-Chloro-2'-methyl-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethylphenol (III.38)

4,7-Dichloro-2-methyl-1,8-naphthyridine[92] (III.37) (0.213 g, 0.001 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0.267 g, 0.001 mol) in water (15 ml) were heated on a steam bath for 2 h. The mixture was worked up as described above and the yellow precipitate was recrystallized from cyclohexane to give 4-(7'-chloro-2'-methyl-1',8'-naphthyridin-4'-ylamino)-2-diethylaminomethyl-

phenol (0.3 g), m.p. 174-176° (Found: C, 65.1; H, 6.4; Cl, 9.55; N, 14.9. $C_{20}H_{23}ClN_4O$ requires C, 64.8; H, 6.3; Cl, 9.6; N, 15.1%). ^{1}H n.m.r. ($CDCl_3$): δ 1.14, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.54, s, 2-Me; 2.66, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.78, s, CH_2N; 6.55, s, H 3; 6.91, complex, ArH; 7.31, d, 8.15, d, J 8.5 Hz, H 5,6.

CHAPTER IV

SYNTHESIS OF 4-(7'-TRIFLUOROMETHYLQUINOLIN-4'-YLAMINO)PHENOLS, 4-[2',7'- AND 2',8'-BIS-(TRIFLUOROMETHYL)QUINOLIN-4'-YLAMINO]PHENOLS AND N^4-SUBSTITUTED 2,7- (AND 2,8-) BIS(TRIFLUOROMETHYL)QUINOLIN-4-AMINES

IV-1 Introduction

The value of substituting a fluoro or fluorine-containing groups for halogens, hydrogen, hydroxyl or amino in prototype medicinals has been demonstrated in the past.[99] Such an effect is shown by mono and bis(trifluoromethyl) substituents in the quinoline nucleus of antimalarials described in CHAPTER I. This effect and the observation by Schmidt *et al.*[16] that the cross-resistance between chloroquine and amodiaquine (a Mannich base) in resistant strains of *P. falciparum* was not absolute, prompted us to examine various mono and bis(trifluoromethyl)quinolin-4'-ylaminophenols carrying mono- and di-Mannich bases for antimalarial activity.

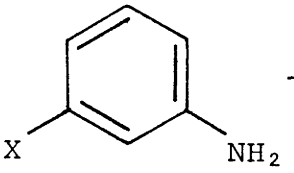
IV-2 Methods of Preparation of Some Quinolin-4-ols

The 4-chloro-7-trifluoromethylquinoline required in this study is commercially available but methods for synthesis of its precursor, the quinolinol, are briefly reviewed below for completeness.

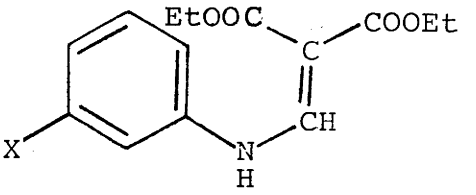
IV-2-A 7-(Halogeno or Trihalogenomethyl) Substituted- quinolin-4-ols

Probably the most generally useful method for the preparation of quinolin-4-ols is that due originally to Gould and Jacobs,[100] and later developed by Price and Roberts.[70] In this, the aromatic amine (IV.1) is condensed with ethoxymethylenemalonic ester, and the resulting acrylate (IV.2) is cyclized by heating in diphenyl ether to give ethyl 7-substituted-4-hydroxy-quinoline-3-carboxylates (IV.3) as the major products and little or practically undetectable amounts of the isomeric 5-substituted compounds (IV.4).[70,101] Saponification and subsequent decarboxylation of compounds (IV.3) afforded the 7-(halogeno or trihalogenomethyl) substituted-quinolin-4-ols (IV.5).

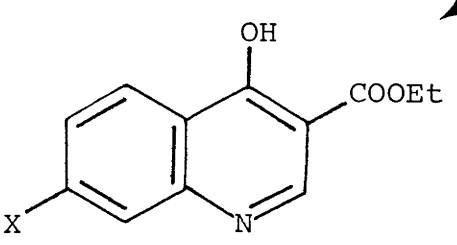
In this way, 7-trifluoromethylquinolin-4-ol can be prepared from 3-trifluoromethylaniline[101] and 7-chloro (and fluoro)-quinolin-4-ols from 3-chloro-[70] and 3-fluoroaniline,[101] respectively.



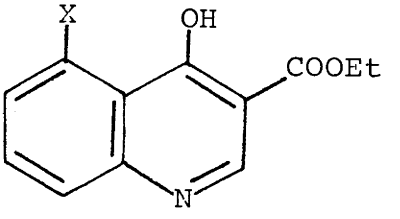
(IV.1)



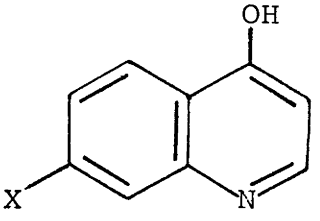
(IV.2)



(IV.3)



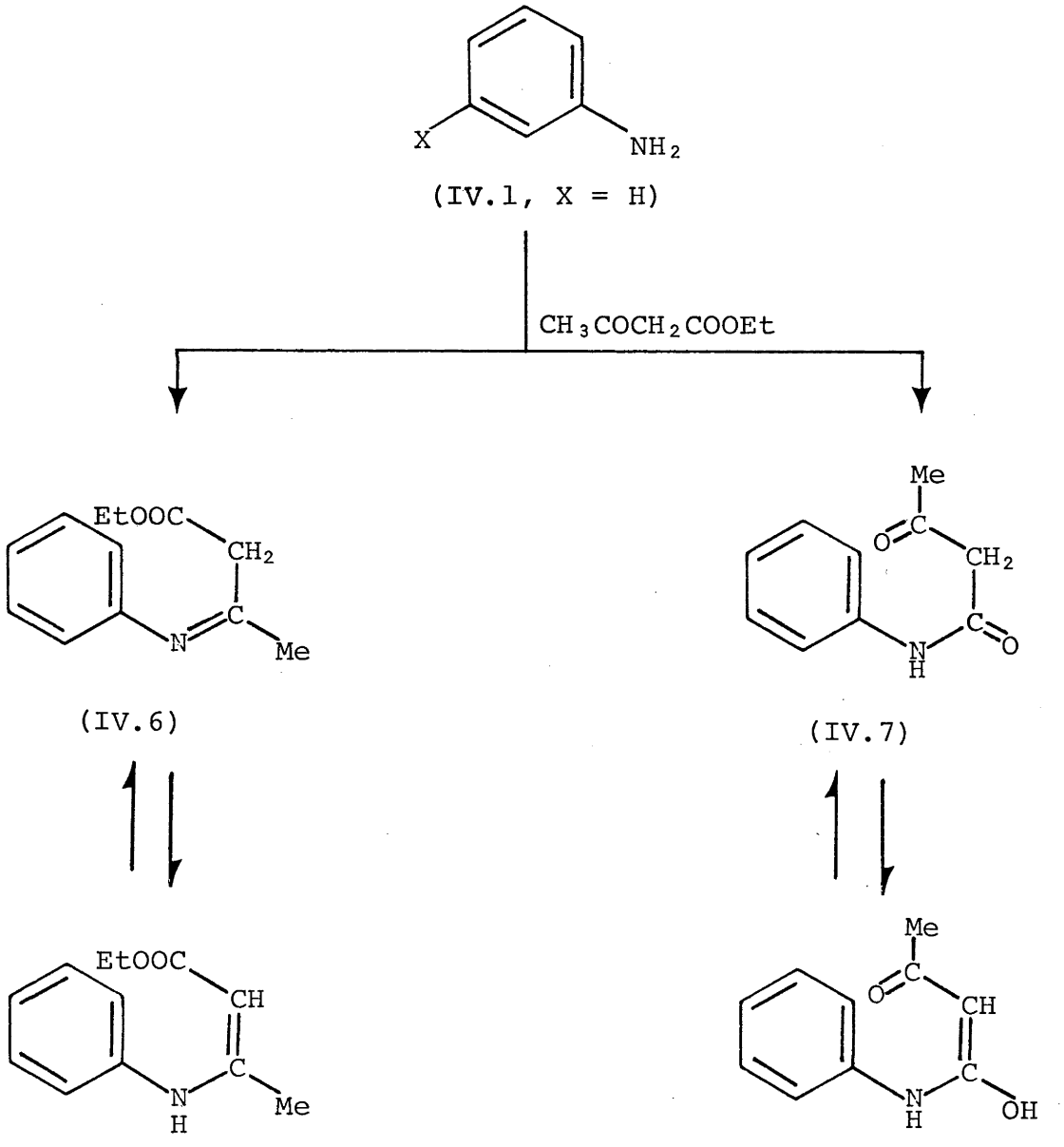
(IV.4)



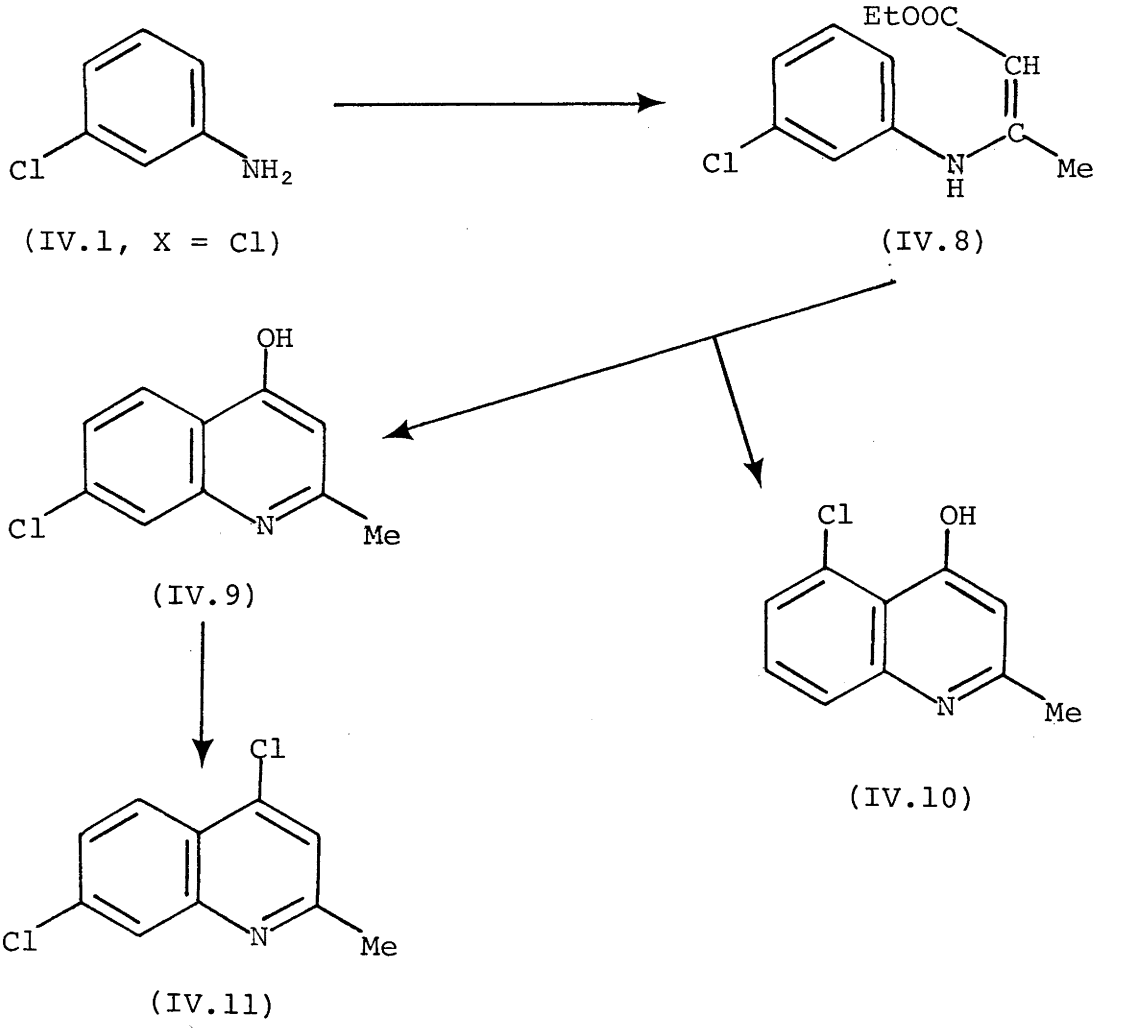
(IV.5)

IV-2-B 2,7-Disubstituted-quinolin-4-ols

β-Keto esters, such as ethyl acetoacetate, can react with an aromatic amine in either of two ways: (1) by reaction of the amine with the carbonyl group to give ethyl β-anilinocrotonate or the anil (IV.6); (2) by reaction of the amine with the ester to give the anilide (IV.7). The factors governing the manner in which the condensation takes place have been greatly clarified by Hauser and Reynolds.[102]



However, Coffey et al.[103] observed in Conrad-Limpach syntheses that β-m-chloroanilinocrotonate (IV.8) was obtained in good yield by use of hydrochloric acid as a catalyst. Cyclization of the crotonate (IV.8) was achieved in refluxing diphenyl to give 7-chloro-2-methylquinolin-4-ol (IV.9) as the major product and the isomeric 5-chloro-2-methylquinolin-4-ol (IV.10) in small quantity.[104] The structure of 7-chloro-2-methylquinolin-4-ol (IV.9) was established by conversion into 4,7-dichloro-2-methylquinoline (IV.11) and subsequent comparison with an authentic specimen prepared unambiguously[104] from 7-chloro-2-methylquinoline through 7-chloro-2-methylquinoline N-oxide and treatment of the N-oxide with phosphoryl chloride to give the dichloromethylquinoline (IV.11).



(IV.1, X = Cl)

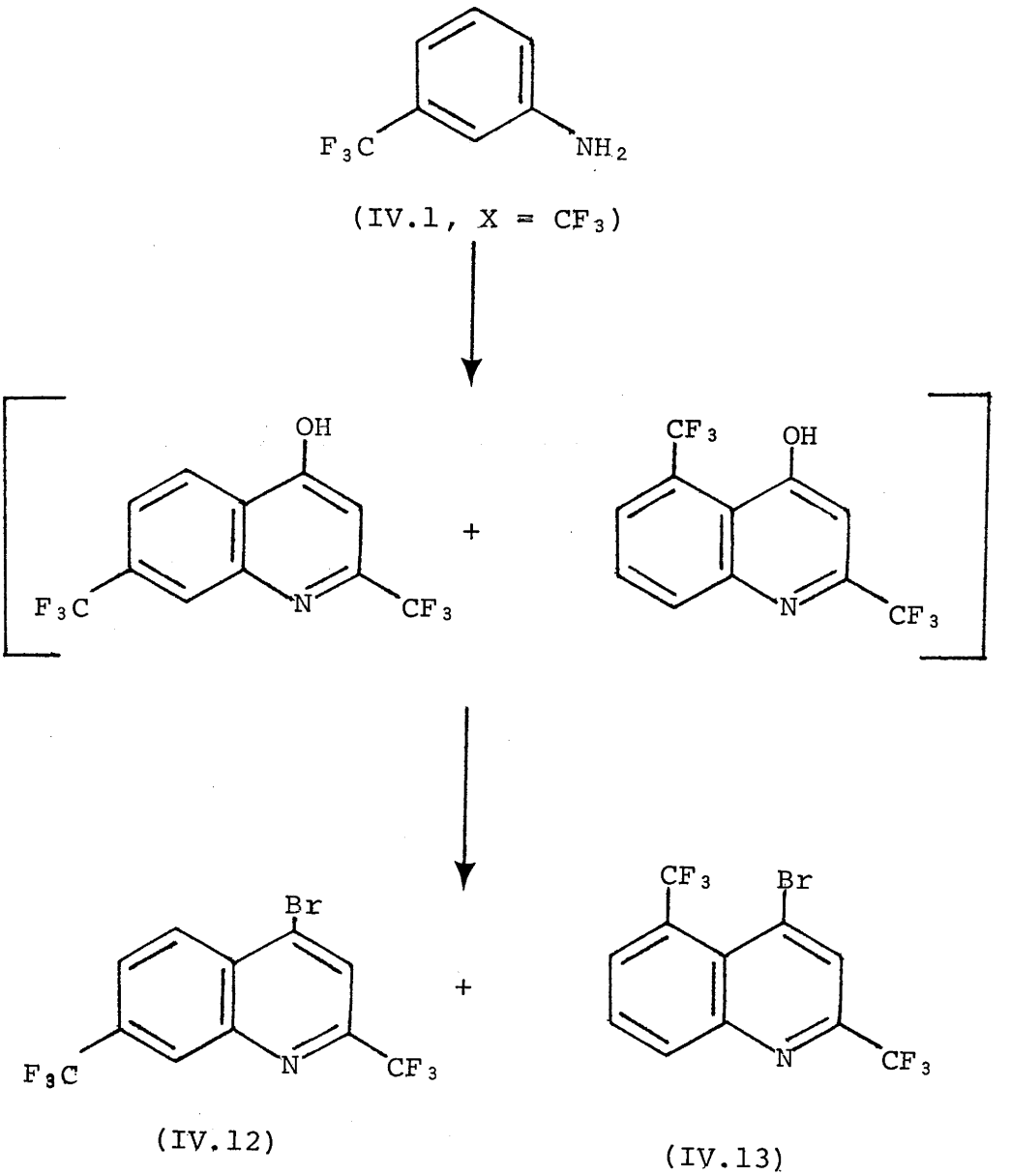
(IV.8)

(IV.9)

(IV.10)

(IV.11)

In the presence of polyphosphoric acid, condensation of 3-trifluoromethylaniline (IV.1, X = CF_3) with ethyl 4,4,4-trifluoroacetoacetate gave a mixture of 2,7- and 2,5-bis(trifluoromethyl)quinolinones which could be converted directly to a mixture of 4-bromo derivatives, at which point it was separated into (IV.12) and (IV.13) respectively.[65] Compound (IV.12) predominated in the mixture.[65]



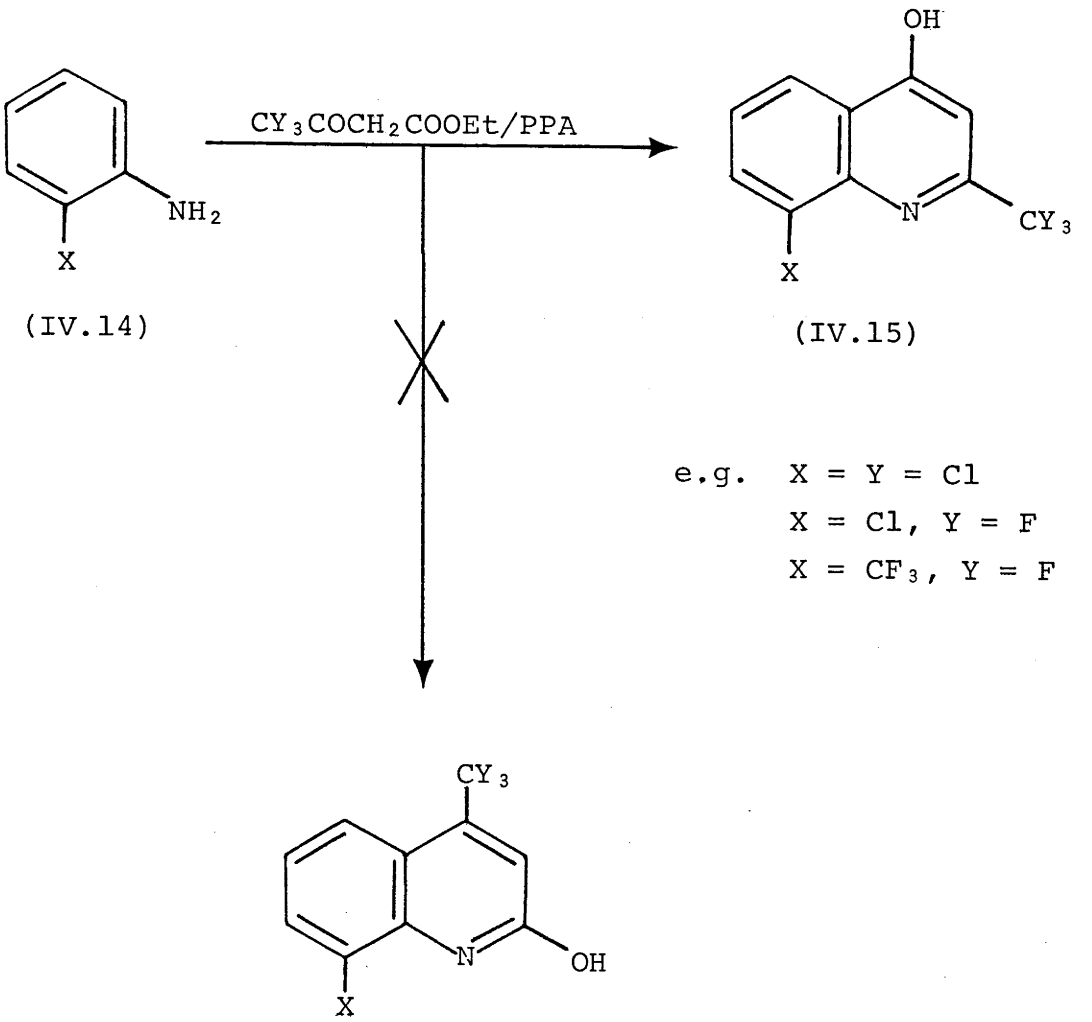
(IV.1, X = CF_3)

(IV.12)

(IV.13)

IV-2-C 2,8-Disubstituted-quinolin-4-ols

The condensation of substituted anilines (IV.14) with ethyl 4,4,4-trifluoroacetoacetate in the presence of polyphosphoric acid gives only the quinolin-4-ols[64,65,105] (IV.15), whereas this reaction with ethyl acetoacetate gives a mixture of quinolin-2(and 4)ols, depending upon whether the amine reacts with the ester or the β-keto group.[106] Apparently the electron-withdrawing power of the trifluoromethyl group leads to exclusive reaction of the (now) electron-deficient β-keto group with the amine.[107]



(IV.14) (IV.15)

e.g. X = Y = Cl
X = Cl, Y = F
X = CF_3, Y = F

IV-3 Preparation of 4-(7'-Trifluoromethylquinolin-4'-ylamino)phenols

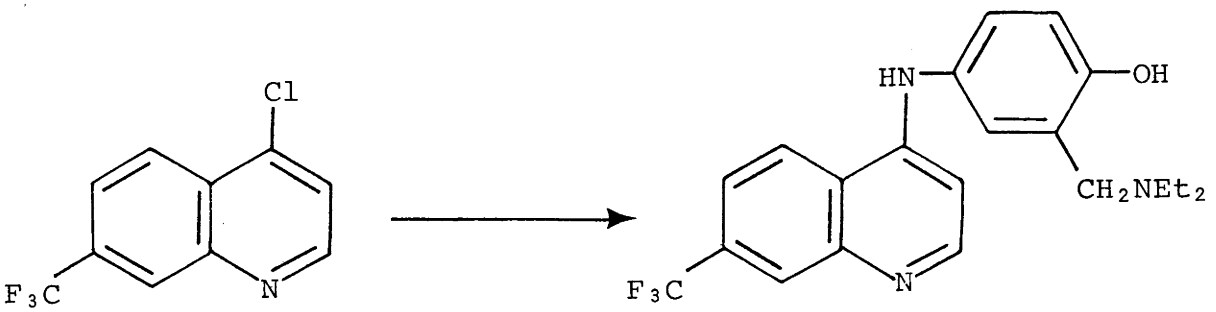
4-Chloro-7-trifluoromethylquinoline[101] (IV.16) when refluxed with 4-amino-2-diethylaminomethylphenol dihydrochloride or p-aminophenol hydrochloride in water gave 2-diethylaminomethyl-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.17) and 4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.18), respectively. Compound (IV.18) with formalin, ethanol and a large excess of dimethylamine, diethylamine, dipropylamine, pyrrolidine, piperidine, 2-methylpiperidine, 3,5-dimethylpiperidine, morpholine or N-methylpiperazine at reflux for 20 h gave the di-Mannich bases (IV.19a-i) (SCHEME IV-1).

IV-4 Preparation of 4-[2',7'- and 2',8'-Bis-(trifluoromethyl)quinolin-4'-ylamino]phenols and N^4-Substituted-2,7-(and 2,8-)bis-(trifluoromethyl)quinolin-4-amines

The 2,7-bis(trifluoromethyl)quinolines (IV.21, IV.23b-g) were prepared similarly from 4-bromo-2,7-bis-(trifluoromethyl)quinoline[65] (IV.20) or through 4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.22), as appropriate. However, compound (IV.22) with formalin, ethanol and a large excess of diisobutylamine at reflux for 72 h gave only the mono-Mannich base (IV.23a) (SCHEME IV-2).

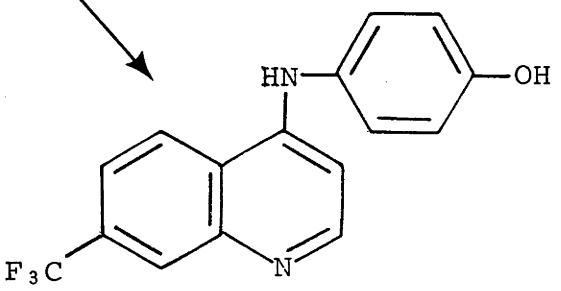
The 2,8-bis(trifluoromethyl)quinoline (IV.26) was similarly prepared through the bromo-compound (IV.24) and

the quinolinylaminophenol precursor (IV.25). 4-Bromo-2,7- and 4-bromo-2,8-bis(trifluoromethyl)quinoline[65] (IV.20, IV.24) with 2-diethylaminoethylamine and 5-diethylamino-pentan-2-amine at 160° gave the quinolin-4-amines (IV.28a-b, IV.27a-b) respectively (SCHEME IV-3).

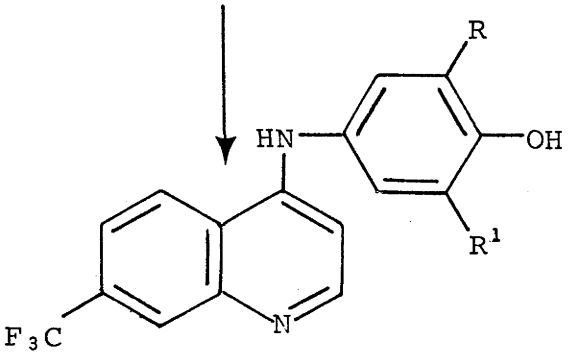


(IV.16)

(IV.17)



(IV.18)

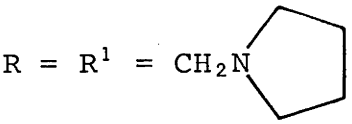


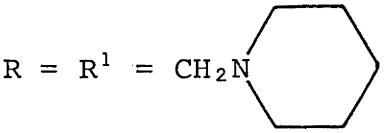
(IV.19)

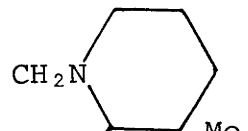
(a) $R = R^1 = CH_2NMe_2$

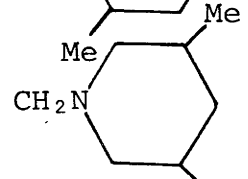
(b) $R = R^1 = CH_2NEt_2$

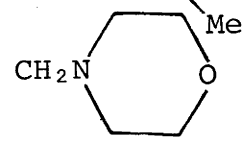
(c) $R = R^1 = CH_2NPr_2$

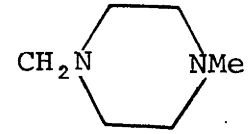
(d) $R = R^1 =$ 

(e) $R = R^1 =$ 

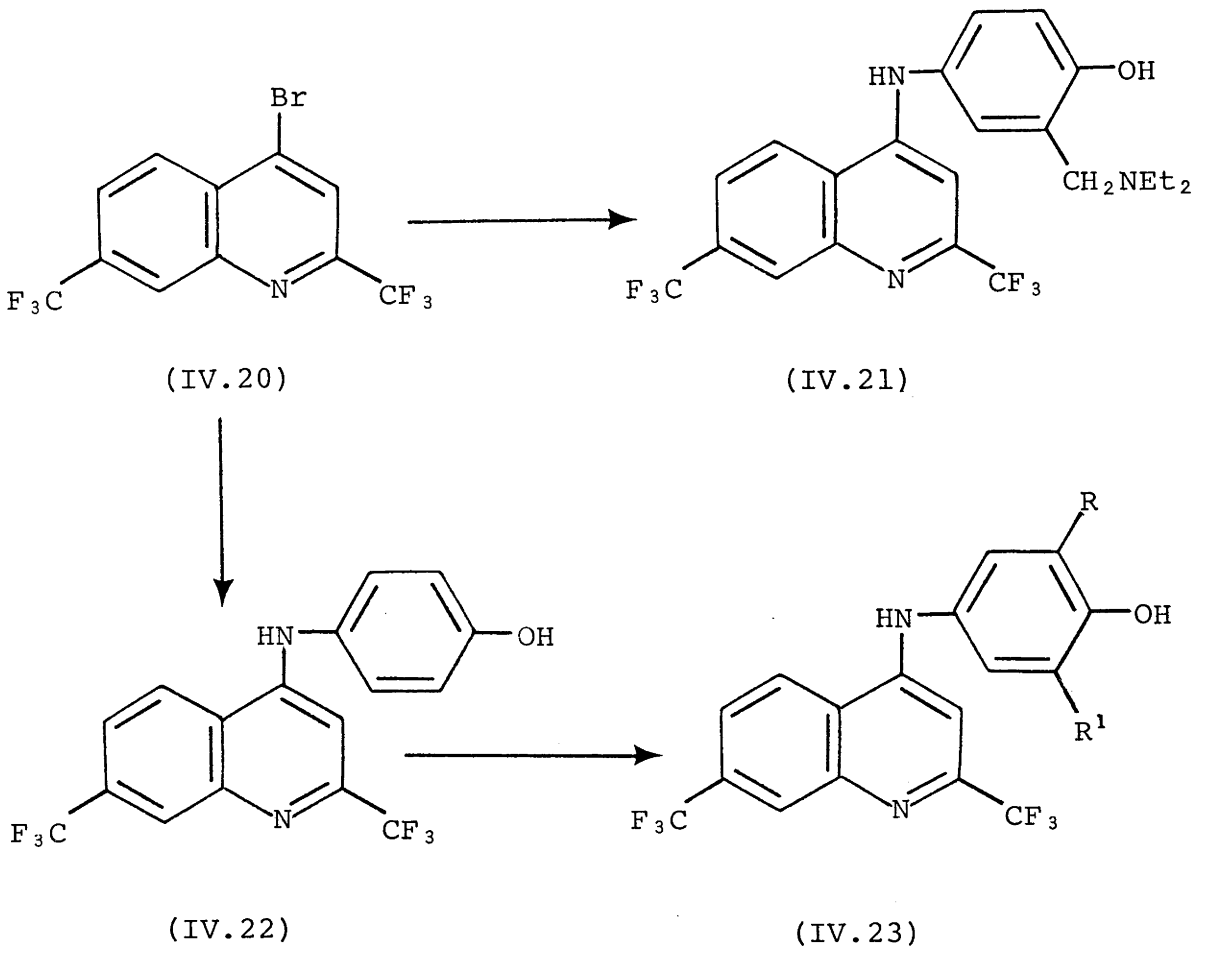
(f) $R = R^1 =$ 

(g) $R = R^1 =$ 

(h) $R = R^1 =$ 

(i) $R = R^1 =$ 

SCHEME IV-1

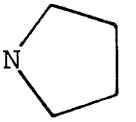


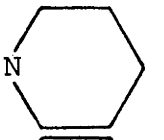
(a) R = H, $R^1 = CH_2N^iBu_2$

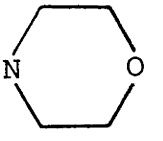
(b) $R = R^1 = CH_2NMe_2$

(c) $R = R^1 = CH_2NEt_2$

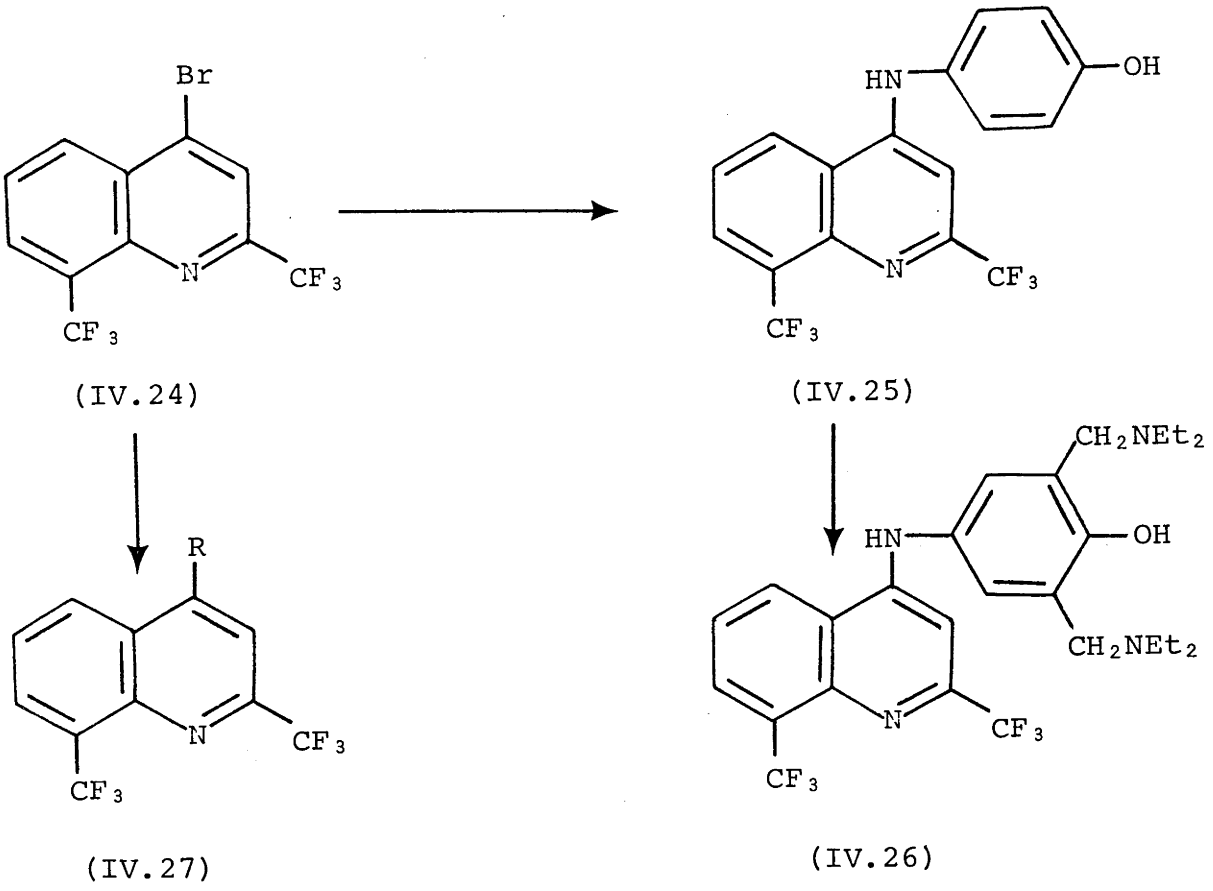
(d) $R = R^1 = CH_2NPr_2$

(e) $R = R^1 =$ 

(f) $R = R^1 =$ 

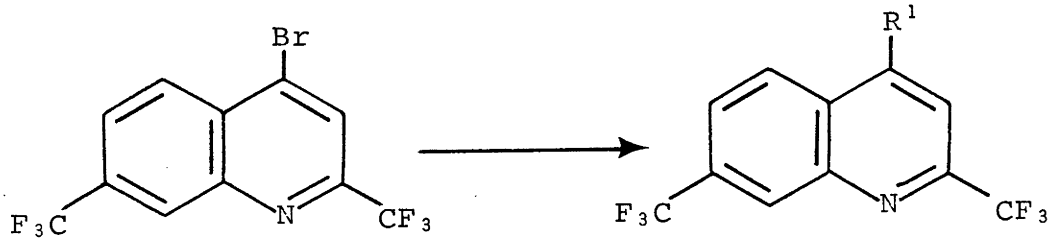
(g) $R = R^1 =$ 

SCHEME IV-2



(a) R = $NH(CH_2)_2NEt_2$

(b) R = $NHCHMe(CH_2)_3NEt_2$



(a) R^1 = $NH(CH_2)_2NEt_2$

(b) R^1 = $NHCHMe(CH_2)_3NEt_2$

SCHEME IV-3

IV-5 Experimental

General conditions relating to experimental procedures were as outlined at the commencement of the Experimental Section in CHAPTER II.

2-Diethylaminomethyl-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.17)

4-Chloro-7-trifluoromethylquinoline (0.5 g) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0.75 g) in a mixture of methanol (15.0 ml) and water (5.0 ml) were refluxed with stirring for 2 h, and the methanol evaporated under reduced pressure. After chilling, the yellow precipitate was collected, washed well with water and recrystallized from aqueous ethanol to give 2-diethylaminomethyl-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.5 g), m.p. 210-212° (Found: C, 64.3; H, 5.7; N, 10.7. $C_{21}H_{22}F_3N_3O$ requires C, 64.8; H, 5.7; N, 10.8%). ^{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_2; 6.73, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.87, d, $J_{5,6}$ 8.5 Hz, H 6; 6.93, d, $J_{3,5}$ 3 Hz, H 3; 7.11, q, $J_{3,5}$ 3 Hz, $J_{5,6}$ 8.5 Hz, H 5; 7.64, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.03, d, $J_{5',6'}$ 9 Hz, H 5'; 8.31, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (IV.18)

4-Chloro-7-trifluoromethylquinoline (IV.16) (0.5 g), p-aminophenol hydrochloride (0.41 g), methanol (15 ml) and water (5.0 ml) were refluxed with stirring for 2 h as above. The yellow precipitate was collected, suspended in water (30 ml), and adjusted with ammonium hydroxide to

pH 7-8, and then recrystallized from aqueous ethanol to give 4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.6 g), m.p. 253-254° (Found: C, 61.3; H, 3.9; N, 8.9. $C_{16}H_{11}F_3N_2O.\frac{1}{2}H_2O$ requires C, 61.3; H, 3.9; N, 8.9%). ^{1}H n.m.r. (CD_3SOCD_3): δ 6.66, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.85, d, $J_{2,3}$ 9 Hz, H 2,6; 7.17, d, $J_{2,3}$ 9 Hz, H 3,5; 7.74, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.13, bs, NH; 8.47, d, $J_{2',3'}$ 5.5 Hz, H 2'; 8.61, d, $J_{5',6'}$ 9 Hz, H 5'; 8.99, s, H 8'; 9.46, s, OH.

2,6-Bis(dimethylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19a)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (IV.18) (0.3 g), formalin (5.0 ml) and ethanolic dimethylamine (15.0 ml; 33%) were refluxed with stirring for 20 h. The solution was evaporated to dryness and the oily residue was subjected to thin-layer chromatography (alumina; ether) to give an oil which slowly crystallized and was recrystallized from aqueous ethanol to give yellow crystals of 2,6-bis(dimethylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.32 g) m.p. 86-88° (Found, for a sample dried at 40° and 0.2 mm Hg: C, 63.5; H, 6.2; N, 13.5. $C_{22}H_{25}F_3N_4O$ requires C, 63.2; H, 6.0; N, 13.4%). ^{1}H n.m.r. ($CDCl_3$): δ 2.32, s, CH_3; 3.57, s, 2 x CH_2; 6.71, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.8, b, NH; 7.01, s, H 3,5; 7.60, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.03, d, $J_{5',6'}$ 9 Hz, H 5'; 8.28, s, H 8'; 8.54, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(diethylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19b)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.3 g), diethylamine (5.0 ml) and formalin (5.0 ml) in ethanol (10.0 ml) were refluxed as in the preparation of compound (IV.19a). The crude product was subjected to thin-layer chromatography (alumina; chloroform) and recrystallized from a mixture of methanol and light petroleum (b.p. 60-80° to give yellow crystals of 2,6-bis(diethylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.31 g), m.p. 169-170° (Found: C, 65.8; H, 7.1; N, 12.0. $C_{26}H_{33}F_3N_4O$ requires C, 65.8; H, 7.0; N, 11.8%). ^{1}H n.m.r. ($CDCl_3$): δ 1.10, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.64, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.72, s, CH_2; 6.6, bs, NH; 6.75, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.07, s, H 3,5; 7.63, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.00, d, $J_{5',6'}$ 9 Hz, H 5'; 8.30, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(dipropylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19c)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.3 g), dipropylamine (5.0 ml), formalin (5.0 ml) and ethanol (10.0 ml) were refluxed as in the preparation of compound (IV.19a). The crude product was subjected to thin-layer chromatography (alumina; chloroform then silica; ether) and the yellow oil crystallized on standing to give 2,6-bis-(dipropylaminomethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.20 g), m.p. 113-114° (Found, for sample dried at 80° and 0.2 mm Hg: C, 67.9; H, 7.8; N, 10.5%.

$C_{30}H_{41}F_3N_4O$ requires C, 67.9; H, 7.8; N, 10.6%).
^{1}H n.m.r. ($CDCl_3$): δ 0.88, t, J 7 Hz, CH_3; 1.50, complex, $CH_3\underline{CH}_2$; 2.49, complex, $\underline{CH}_2CH_2CH_3$; 3.70, s, CH_2; 6.7, b, NH; 6.76, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.08, s, H 3,5; 7.62, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.04, d, $J_{5',6'}$ 9 Hz, H 5'; 8.30, s, H 8'; 8.54, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(pyrrolidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19d)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.3 g), pyrrolidine (5.0 ml), formalin (5.0 ml) and ethanol (10.0 ml) were refluxed as in the preparation of compound (IV.19a), and excess pyrrolidine removed by distillation in a vacuum. The residue was triturated with water (50 ml) and the crude product subjected to thin-layer chromatography (alumina; methanol then alumina; ether) to give as a yellow oil 2,6-bis(pyrrolidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.23 g) (Found: C, 64.1; H, 6.4; N, 10.9. $C_{26}H_{29}F_3N_4O$ 1.1 H_2O requires C, 63.7; H, 6.4; N, 11.4%). ^{1}H n.m.r. ($CDCl_3$): δ 1.86, complex, H 3",4"; 2.69, complex, H 2",5"; 3.80, s, CH_2; 6.45, s, NH; 6.73, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.06, s, H 3,5; 7.62, q, $J_{6',8'}$ 1.5 Hz, $J_{5',6'}$ 9 Hz, H 6'; 8.02, d, $J_{5',6'}$ 9 Hz, H 5'; 8.29, s, H 8'; 8.55, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(piperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19e)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.3 g), piperidine (5.0 ml), formalin (5.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (IV.19d). The crude product was purified by thin-layer chromatography (alumina; chloroform) and recrystallized from cyclohexane to give 2,6-bis(piperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)-phenol (0.31 g), m.p. 170-171° (Found: C, 67.5; H, 6.95; N, 11.3. $C_{28}H_{33}F_3N_4O$ requires C, 67.5; H, 6.7; N, 11.2%). ^{1}H n.m.r. ($CDCl_3$): δ 1.55, complex, H 3",4",5"; 2.51, complex, H 2",6"; 3.62, s, CH_2; 6.7, s, NH; 6.74, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.04, s, H 3,5; 7.63, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.01, $J_{5',6'}$ 9 Hz, H 5'; 8.30, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(2"-methylpiperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19f)

A mixture of 4-(7'-trifluoromethylquinolin-4'-ylamino)-phenol (0.2 g), formalin (2.0 ml), 2-methylpiperidine (2.0 ml) and ethanol (10.0 ml) was treated and the product purified as in the preparation of compound (IV.19e) to give a solid which was recrystallized from aqueous ethanol affording yellow crystals of 2,6-bis(2"-methyl-piperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.18 g), m.p. 102-104° (Found: C, 68.5; H, 7.3; N, 10.4. $C_{30}H_{37}F_3N_4O$ requires C, 68.4; H, 7.1; N, 10.6%). ^{1}H n.m.r. ($CDCl_3$): δ 1.18, d, J 6.5 Hz, CH_3; 1.58,

complex, H 3",4",5"; 2.32, complex, H 2"; 2.90, complex, H 6"; 3.36, d, J 14 Hz, 4.10, d, J 14 Hz, CH_2N; 6.68, bs, NH; 6.76, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.07, s, H 3,5; 7.64, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.02, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.30, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(3",5"-dimethylpiperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19g)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), 3,5-dimethylpiperidine (2.0 ml) and ethanol (10.0 ml) were treated and the product purified as in the preparation of compound (IV.19b) to give, as a yellow oil, 2,6-bis(3",5"-dimethylpiperidin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.19 g) (Found: C, 67.0; H, 7.5; N, 9.7. $C_{32}H_{41}F_3N_4O.1H_2O$ requires C, 67.1; H, 7.6; N, 9.8%). ^{1}H n.m.r. ($CDCl_3$): δ 0.86, d, J 6.5 Hz, CH_3; 1.65, complex, H 3",4",5"; 2.90, complex, H 2",6"; 3.64, s, CH_2N; 6.78, bs, NH; 6.79, d, $J_{2',3'}$ 5.5 Hz, H 3'; 7.04, s, H 3,5; 7.63, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.02, bs, OH; 8.03, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.30, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(morpholin-1"-ylmethyl)-4-(7'-trifluoromethyl-quinolin-4'-ylamino)phenol (IV.19h)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.3 g), morpholine (5.0 ml), formalin (5.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (IV.19d) to give after thin-layer chromatography (alumina; chloroform) and recrystallization from aqueous

ethanol, yellow needles of 2,6-bis(morpholin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (0.29 g), m.p. 198-200° (Found: C, 62.45; H, 5.9; N, 11.4. $C_{26}H_{29}F_3N_4O_3$ requires C, 62.1; H, 5.8; N, 11.15%). ^{1}H n.m.r. ($CDCl_3$): δ 2.56, complex, H 2",6"; 3.66, s, CH_2N; 3.75, complex, H 3",5"; 6.72, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.81, s, NH; 7.07, s, H 3,5; 7.62, q, $J_{5',6'}$ 9 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.04, d, $J_{5',6'}$ 9 Hz, H 5'; 8.29, s, H 8'; 8.56, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2,6-Bis(4"-methylpiperazin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol (IV.19i)

4-(7'-Trifluoromethylquinolin-4'-ylamino)phenol (0.2 g), formalin (2.0 ml), N-methylpiperazine (2.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (IV.19d). The oily residue was purified by column (alumina; chloroform) and thin-layer chromatography (silica; methanol) to give, as a yellow oil which crystallized, 2,6-bis(4"-methylpiperazin-1"-ylmethyl)-4-(7'-trifluoromethylquinolin-4'-ylamino)phenol, m.p. 163-164° (Found: C, 62.9; H, 7.2; N, 15.7. $C_{28}H_{35}F_3N_6O.\frac{1}{2}H_2O$ requires C, 62.6; H, 6.8; N, 15.6%). ^{1}H n.m.r. ($CDCl_3$): δ 2.30, s, CH_3; 2.53, complex, H 2",3",5",6"; 3.67, s, CH_2N; 6.73, d, $J_{2',3'}$ 5.5 Hz, H 3'; 6.86, bs, NH; 7.04, s, H 3,5; 7.63, d, $J_{5',6'}$ 8.5 Hz, H 6'; 8.85, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.30, s, H 8'; 8.55, d, $J_{2',3'}$ 5.5 Hz, H 2'.

2-Diethylaminomethyl-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (IV.21)

4-Bromo-2,7-bis(trifluoromethyl)quinoline[65] (IV.20) (0.2 g), 4-amino-2-diethylaminomethylphenol dihydrochloride (0.2 g), methanol (10.0 ml), and water (3.0 ml) were refluxed as in the preparation of compound (IV.18) but for 72 h. The product was recrystallized from water with a little hydrochloric acid to give 2-diethylaminomethyl-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol hydrochloride (0.21 g), m.p. 150° (Found: C, 53.4; H, 4.5; N, 8.2. $C_{22}H_{21}F_6N_3O.HCl$ requires: C, 53.5; H, 4.5; N, 8.5%). ^1H n.m.r. (free base in CD_3SOCD_3): δ 1.12, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.76, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.93, s, CH_2; 6.83, s, H 3'; 6.93, d, $J_{5',6'}$ 8.5 Hz, H 6; 7.22, d, $J_{5',6'}$ 8.5 Hz, H 5; 7.28, bs, H 3; 7.91, q, $J_{6',8'}$ 1.5 Hz, H 6'; 8.29, bs, H 8';1.73, d, $J_{5',6'}$ 8.5 Hz, H 5'; 9.62, s, OH.

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.22)

4-Bromo-2,7-bis(trifluoromethyl)quinoline (0.4 g), p-aminophenol hydrochloride (0.26 g), methanol (15.0 ml) and water (5.0 ml) were refluxed with stirring as in the preparation of compound (IV.18) but for 48 h. The yellow precipitate was collected and recrystallized from aqueous methanol to give 4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.23 g), m.p. 245-246° (Found: C, 54.4; H, 2.65; N, 7.5. $C_{17}H_{10}F_6N_2O$ requires C, 54.85; H, 2.7; N, 7.5%). ^1H n.m.r. (CD_3OD): δ 6.88, s, H 3'; 6.94, d, $J_{2,3}$ 9 Hz, H 2,6; 7.22, d, $J_{2,3}$ 9 Hz, H 3,5; 7.80, q,

$J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.28, bs, H 8'; 8.53, d, $J_{5',6'}$ 8.5 Hz, H 5'.

2-Diisobutylaminomethyl-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (IV.23a)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]-phenol (IV.22) (0.2 g), diisobutylamine (3.0 ml), formalin (3.0 ml) and ethanol (10.0 ml) were refluxed with stirring for 72 h and worked up as in the preparation of compound (IV.19d). The product was subjected to column and thin-layer chromatography (alumina; chloroform) to give, as a yellow oil, the mono-Mannich base, 2-diisobutylaminomethyl-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.15 g) (Found: C, 60.5; H, 5.8; N, 8.15. $C_{26}H_{29}F_6N_3O$ requires C, 60.8; H, 5.7; N, 8.2%). ^{1}H n.m.r. ($CDCl_3$): δ 0.95, d, J 6 Hz, CH_3; 1.96, complex, CH; 2.25, d, J 6 Hz, CH_2CH; 3.71, s, CH_2N; 6.91, d, $J_{5,6}$ 7.5 Hz, H 6; 6.95, s, H 3'; 6.97, bs, H 3; 7.13, q, $J_{5,6}$ 7.5 Hz, $J_{3,5}$ 2.5 Hz, H 5; 7.71, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.06, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.40, bs, H 8'.

2,6-Bis(dimethylaminomethyl)-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (IV.23b)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.2 g), ethanolic dimethylamine (15 ml; 33%) and formalin (5 ml; 36%) were treated as in the preparation of compound (IV.19a). The crude product was purified by thin-layer chromatography (alumina; chloroform) and recrystallization from cyclohexane to give yellow crystals of 2,6-bis-

(dimethylaminomethyl)-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (0.2 g), m.p. 199-200° (Found: C, 57.1; H, 5.2; N, 11.4. $C_{23}H_{24}F_6N_4O$ requires C, 56.8; H, 5.0; N, 11.5%). ^{1}H n.m.r. ($CDCl_3$): δ 2.32, s, CH_3; 3.58, s, CH_2; 6.98, s, H 3'; 7.03, s, H 3,5; 7.25, b, NH; 7.67, d, $J_{5',6'}$ 8.5 Hz, H 6'; 8.07, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.40, s, H 8'; 9.25, b, OH.

2,6-Bis(diethylaminomethyl)-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (IV.23c)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]-phenol (0.15 g), diethylamine (3.0 ml), formalin (3.0 ml), and ethanol (10.0 ml) were allowed to react and the product purified as in the preparation of compound (IV.23b) to give 2,6-bis(diethylaminomethyl)-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol as a yellow oil which slowly solidified. (Found: C, 59.9; H, 6.2; N, 10.5. $C_{27}H_{32}F_6N_4O$ requires C, 59.8; H, 5.95; N, 10.3%). ^{1}H n.m.r. ($CDCl_3$): δ 1.09, t, J 7 Hz, CH_3CH_2; 2.63, q, J 7 Hz, CH_3CH_2; 3.72, s, CH_2; 7.0, b, NH; 7.03, s, H 3'; 7.08, s, H 3,5; 7.71, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.05, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.42, s, H 8'.

The hydrobromide, recrystallized from propan-2-ol, had m.p. 220° (Found: C, 42.5; H, 4.9; N, 7.4. $C_{27}H_{32}F_6N_4O.2HBr.3H_2O$ requires C, 42.75; H, 5.3; N, 7.4%).

2,6-Bis(dipropylaminomethyl)-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.23d)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.2 g), dipropylamine (3.0 ml), formalin (3.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (IV.23b). The oily residue was subjected to column (alumina; chloroform) and thin-layer chromatography (silica; chloroform) to give 2,6-bis(dipropylaminomethyl-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol as a yellow oil (Found: C, 62.2; H, 6.9; N, 9.3. $C_{31}H_{40}F_6N_4O$ requires C, 62.2; H, 6.7; N, 9.4%). ^{1}H n.m.r. ($CDCl_3$): δ 0.87, t, J 7 Hz, CH_3; 1.49, complex, $CH_3\underline{CH}_2$; 2.48, complex, $\underline{CH}_2CH_2CH_3$; 3.70, s, $\underline{CH}_2N$; 6.94, bs, NH; 6.98, s, H 3'; 7.09, s, H 3,5; 7.71, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.05, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.43, s, H 8'.

2,6-Bis(pyrrolidin-1"-ylmethyl)-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.23e)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.2 g), pyrrolidine (3.0 ml), formalin (3.0 ml) and ethanol (10.0 ml) were treated as in the preparation of compound (IV.19d) except that trituration was with water (2 x 20 ml). The crude product was purified by thin-layer chromatography (alumina; chloroform) to give 2,6-bis-(pyrrolidin-1"-ylmethyl)-4-[2',7'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (0.2 g) as a yellow oil. (Found: C, 60.4; H, 5.7; N, 10.5. $C_{27}H_{28}F_6N_4O$ requires C, 60.2; H, 5.2; N, 10.4%). ^{1}H n.m.r. ($CDCl_3$): δ 1.82, complex, H 3",4"; 2.63, complex, H 2",5"; 3.76, s, CH_2;

7.01, s, H 3'; 7.04, s, H 3,5; 7.25, bs, NH; 7.68, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.09, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.40, s, H 8'.

It did not give crystalline salts with ethanolic hydrogen bromide or picric acid.

2,6-Bis(piperidin-1"-ylmethyl)-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.23f)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.2 g), piperidine (3.0 ml), formalin (3.0 ml) and ethanol (10.0 ml) were treated and the product purified as in the preparation of compound (IV.23e). The oil solidified on standing and was recrystallized from aqueous ethanol to give yellow crystals of 2,6-bis(piperidin-1"-ylmethyl-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.22 g), m.p. 123-124° (Found: C, 57.6; H, 5.5; N, 9.3. $C_{29}H_{32}F_6N_4O.2H_2O$ requires C, 57.8; H, 6.0; N, 9.3%). ^1H n.m.r. ($CDCl_3$): δ 1.55, complex, H 3",4",5"; 2.51, complex, H2",6"; 3.62, s, CH_2; 7.04, s, H 3,5; 7.15, s, H 3'; 7.4, bs, NH; 7.69, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.05, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.42, s, H 8'.

2,6-Bis(morpholin-1"-ylmethyl)-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.23g)

4-[2',7'-Bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.2 g), morpholine (3.0 ml), formalin (3.0 ml) and ethanol (10.0 ml) were treated and the product purified as in the preparation of compound (IV.23e). The oil solidified on standing and was recrystallized from aqueous ethanol to give

yellow crystals of 2,6-bis(morpholin-1"-ylmethyl)-4-[2',7'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (0.25 g), m.p. 194-195° (Found: C, 57.2; H, 5.1; N, 10.0. $C_{27}H_{28}F_6N_4O_3$ requires C, 56.8; H, 4.9; N, 9.8%). ^{1}H n.m.r. ($CDCl_3$): δ 2.57, complex, H 2",6"; 3.68, s, CH_2; 3.75, complex, H 3",5"; 6.99, s, H 3'; 7.10, s, H 3,5; 7.70, q, $J_{5',6'}$ 8.5 Hz, $J_{6',8'}$ 1.5 Hz, H 6'; 8.06, d, $J_{5',6'}$ 8.5 Hz, H 5'; 8.42, s, H 8'.

2,6-Bis(diethylaminomethyl)-4-[2',8'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.26)

4-Bromo-2,8-bis(trifluoromethyl)quinoline[65] (IV.24) (0.4 g), p-aminophenol hydrochloride (0.26 g), ethanol (15.0 ml) and water (5.0 ml) were heated in an autoclave at 160° for 48 h. The reaction mixture was washed out with methanol and the crude product subjected to thin-layer chromatography (alumina; ethanol) to give presumably 4-[2',8'-bis(trifluoromethyl)quinolin-4'-ylamino]phenol (IV.25) (0.1 g) to which was added diethylamine (2.0 ml), formalin (2.0 ml) and ethanol (5.0 ml) and this solution refluxed for 20 h. This mixture was evaporated to dryness and the product after thin-layer chromatography (alumina; chloroform and silica; methanol) gave, as a yellow oil, 2,6-bis(diethylaminomethyl)-4-[2',8'-bis(trifluoromethyl)-quinolin-4'-ylamino]phenol (0.06 g) (Found: C, 59.55; H, 5.9; N, 10.1. $C_{27}H_{32}F_6N_4O$ requires C, 59.8; H, 5.9; N, 10.3%). ^{1}H n.m.r. ($CDCl_3$): δ 1.09, t, J 7 Hz, CH_3CH_2; 2.63, q, J 7 Hz, CH_3CH_2; 3.71, s, CH_2; 6.3, b, NH; 7.02, s, H 3'; 7.06, s, H 3,5; 7.49 - 8.15, multiplet, H 5',6',7'.

N-(2'-Diethylaminoethyl)-2,7-bis(trifluoromethyl)-quinolin-4-amine (IV.28a)

4-Bromo-2,7-bis(trifluoromethyl)quinoline (IV.20) (0.2 g) and 2-diethylaminoethylamine (0.7 g) in heptane (10.0 ml) were heated in an autoclave at 160° for 20 h. The reaction mixture was washed out with methanol, the solvents evaporated and excess amine removed at c. 100°/0.5 mm Hg. The product was subjected to thin-layer chromatography (alumina; chloroform) and recrystallized from aqueous methanol to give N-(2'-diethylaminoethyl-2,7-bis(trifluoromethyl)quinolin-4-amine (0.15 g), m.p. 98-99°. (Found, for sample dried at 70° and 0.2 mm Hg: C, 54.1; H, 5.3; N, 10.8. $C_{17}H_{19}F_6N_3$ requires C, 53.8; H, 5.05; N, 11.1%). ^{1}H n.m.r. ($CDCl_3$): δ 1.10, t, J 7 Hz, CH_3CH_2; 2.65, q, J 7 Hz, CH_2CH_3; 2.87, complex, CH_2N; 3.31, complex, CH_2NH; 6.6, b, NH; 6.74, s, H 3; 7.68, q, $J_{5,6}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 6; 7.89, d, $J_{5,6}$ 8.5 Hz, H 5; 8.37, bs, H 8.

N-(4'-Diethylamino-1'-methylbutyl)-2,7-bis(trifluoromethyl)quinolin-4-amine (IV.28b)

4-Bromo-2,7-bis(trifluoromethyl)quinoline (0.2 g) with 5-diethylaminopentan-2-amine (1.0 g) in heptane as in the preparation of compound (IV.28a) gave, after thin-layer chromatography (alumina; chloroform), N-(4'-diethylamino-1'-methylbutyl)-2,7-bis(trifluoromethyl)quinolin-4-amine (0.2 g) as a yellow oil. (Found: C, 57.0; H, 6.2; N, 10.0. $C_{20}H_{25}F_6N_3$ requires C, 57.0; H, 6.0; N, 10.0%). ^{1}H n.m.r. ($CDCl_3$): δ 1.02, t, J 7 Hz, CH_3CH_2; 1.35, d, J 6 Hz, CH_3CH; 1.74, complex, CH_2CH_2CH; 2.45, complex, CH_2N; 2.54,

q, J 7 Hz, $C\underline{H}_2CH_3$; 3.80, complex, CH; 6.10, bd, J 6 Hz, NH; 6.80, s, H 3; 7.62, q, $J_{5,6}$ 8.5 Hz, $J_{6,8}$ 1.5 Hz, H 6; 7.94, d, $J_{5,6}$ 8.5 Hz, H 5; 8.37, bs, H 8.

N-(2'-Diethylaminoethyl)-2,8-bis(trifluoromethyl)-quinolin-4-amine (IV.27a)

4-Bromo-2,8-bis(trifluoromethyl)quinoline (IV.24) (0.2 g), 2-diethylaminoethylamine (0.7 g) and heptane (10.0 ml) were heated and the product purified as in the preparation of (IV.28a) to give white crystals of N-(2'-diethylaminoethyl)-2,8-bis(trifluoromethyl)quinolin-4-amine (0.18 g), m.p. 55-56° (Found, for sample dried at 30° and 0.2 mm Hg: C, 53.9; H, 5.3; N, 11.0. $C_{17}H_{19}F_6N_3$ requires C, 53.8; H, 5.05; N, 11.1%). ^{1}H n.m.r. ($CDCl_3$): δ 1.09, t, J 7 Hz, $C\underline{H}_3CH_2$; 2.63, q, J 7 Hz, $CH_3C\underline{H}_2$; 2.85, complex, CH_2N; 3.26, complex, CH_2NH; 6.5, b, NH; 6.72, s, H 3; 7.43 - 8.06, multiplet, H 5,6,7.

N-(4'-Diethylamino-1'-methylbutyl)-2,8-bis(trifluoromethyl)quinolin-4-amine (IV.27b)

4-Bromo-2,8-bis(trifluoromethyl)quinoline (0.2 g), 5-diethylaminopentan-2-amine (1.0 g) and heptane (10.0 ml) were heated and the product purified as in the preparation of compound (IV.27a) to give N-(4'-diethylamino-1'-methylbutyl)-2,8-bis(trifluoromethyl)quinolin-4-amine (0.22 g) as a yellow oil. (Found: C, 56.7; H, 6.3; N, 9.8. $C_{20}H_{25}F_6N_3$ requires C, 57.0; H, 6.0; N, 10.0%). ^{1}H n.m.r. ($CDCl_3$):

δ 1.01, t, J 7 Hz, $C\underline{H}_3CH_2$; 1.33, d, J 6.5 Hz, $C\underline{H}_3CH$; 1.71, complex, CH $C\underline{H}_2C\underline{H}_2$; 2.45, complex, CH_2N: 2.53, q, J 7 Hz, $CH_3C\underline{H}_2$; 3.77, complex, CH; 5.92, d, J 7 Hz, NH; 6.78, s, H 3; 7.39 - 8.04, multiplet, H 5,6,7.

CHAPTER V

BIOLOGICAL EVALUATION OF ANTIMALARIAL ACTIVITY

V-1 Introduction to Antimalarial Testing

Adequate measures for the evaluation of candidate compounds in malaria chemotherapy are of paramount importance. Moreover, the choice of laboratory methods or screening procedures can be critical. The history of malaria chemotherapy shows many discrepancies between promising laboratory results and clinical utility although, occasionally, gratifying agreement is apparent. Several major problems may arise in an antimalarial drug evaluation programme. These include the variations in drug susceptibility among life cycle stages of parasites and the diversity of objectives. The latter encompasses treatment of the acute attack, radical cure, suppression, prophylaxis and interrupting transmission.

Nevertheless various experimental models are now available to assess the activity of established and potential new antimalarial compounds. These include the use of avian, rodent and simian malarias and, more recently, the development of techniques for the continuous *in vitro* cultivation[108] of *Plasmodium falciparum* which has provided unprecedented opportunities for advancing the search for new antimalarial drugs and for elucidating the mechanisms of action of existing drugs.

However, two of these screening procedures only, namely the *in vivo* blood schizontocide screen in rodent

malaria and the *in vitro* method involving a semi-automated microdilution technique, will be discussed below.

V-1-A In Vivo *Blood Schizontocide Screen in Rodent Malaria*

The numerous isolated species and subspecies of rodent malarias can be divided into two main series, the *bergei* group and the *vinckei* group. The former, consisting of *P. bergei*, *P. yoelii*, *P. y. nigeriensis* and other subspecies is used in the majority of chemotherapy research projects. The *vinckei* group, containing *P. vinckei*, *P. chabaudi*, and several subspecies is less used.

The rodent malaria models are often used as a primary and secondary screen before monkey malaria screens. Moreover, the correlation of data on compounds tested in rodent malaria systems with monkey malaria system is usually in agreement.[109-111] Blood schizontocide screens in rodent malaria are usually performed in one or other of the following two ways:-

V-1-Ai *Single-Dose Regimens*

These comprise the Rane's test[112] and Fink and Kretschmar's test.[113] The former test system is based on the use of mice, inoculated intraperitoneally with asexual blood parasites, and treated 3 days later with one subcutaneous injection of the test compound. Antimalarial activity is assessed by comparing survival times of treated

mice with those of infected, but untreated controls. The Fink and Kretschmar's test system assesses antimalarial activity by determining the prolongation of survival of mice by 20% ($\ddot{U}D_{20}$). This procedure was developed as a simple test to save time (no blood films required) and to use a smaller amount of test compound.

Since the development of the Rane's test system, over 250,000 compounds have been tested with approximately 8,000 exhibiting some antimalarial activity.[114] It is interesting to note that all compounds currently used in humans infected with malaria are active in the Rane's test.

V-1-Aii Multiple-Dose Regimens

A great many multi-dose test systems for evaluating potential antimalarial agents have been designed and described in the past. These include the Early Test Procedures, Four-Day Test, Drug-Diet Methods and the Six-Day Test as summarized by Ager.[114]

Chemotherapy studies using rodent malaria are, however, diversified and the proper standardisation of a test system involves the close scrutiny of a large number of variables. For example, rodent strains vary tremendously in their susceptibility to malaria.[115-117] Overall, the rodent malaria models have proven to be extremely valuable in assessing the activity of established and potential new antimalarial compounds.

V-1-B In Vitro Evaluation of Potential Antimalarial Drugs

The discovery of an efficient method of cultivating the blood stages of P. falciparum by Trager and Jensen[108] in 1976 was an event of major importance. Soon after, Desjardins et al.[118] described a rapid semiautomated technique for assessment of antimalarial drug activity using continuous cultures as a source of known resistant and susceptible isolates of P. falciparum. This technique, which employs standard microtitration equipment and radioisotope uptake as an indicator of parasite growth and multiplication, was designed with maximum efficiency and precision for use in an experimental antimalarial drug development programme. Analyses of the resulting data required application of non-linear curve fitting techniques. The data for each active compound were fitted to a generalised logistic-logarithmic function which included the ID_{50} (concentration of a drug causing 50% inhibition of the incorporation of radiolabelled nucleic acid precursor, ^{3}H-hypoxanthine) as one of its parameters. The output from the computer programme included a graph such as those in Figs. V.1 and V.2, which show the activity of chloroquine against a sensitive (African-Uganda I) and resistant (Vietnam-Smith) isolate of P. falciparum, respectively. Also included in the output were the respective estimates of the ID_{50} and slope of the curve with corresponding 95% confidence limits. These estimates for chloroquine, amodiaquine, quinine, pyrimethamine, and mefloquine against two isolates of the parasite are shown in Table V.1 (data from ref.119).

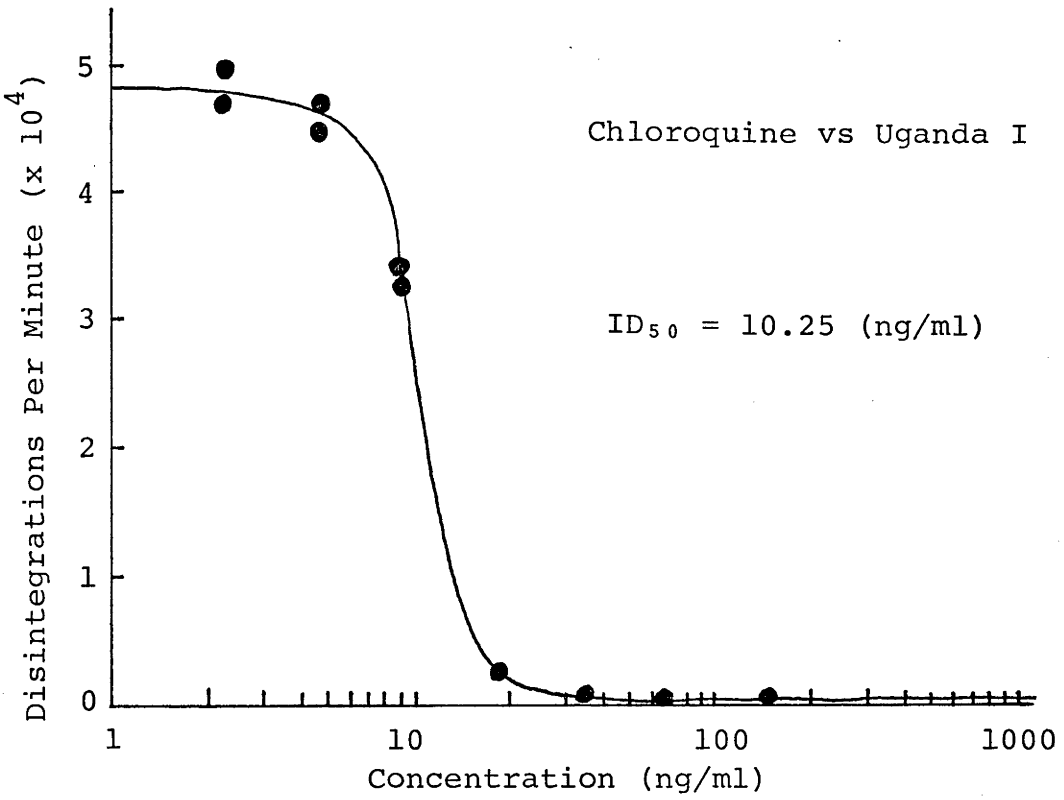


Fig. V.1. A logistic-logarithmic analysis of the effect of chloroquine at various concentrations on the uptake of ^{3}H-hypoxanthine *in vitro* by erythrocytes parasitised with a chloroquine-sensitive isolate (African-Uganda I) of *P. falciparum*. After Desjardins *et al.* (ref. 118).

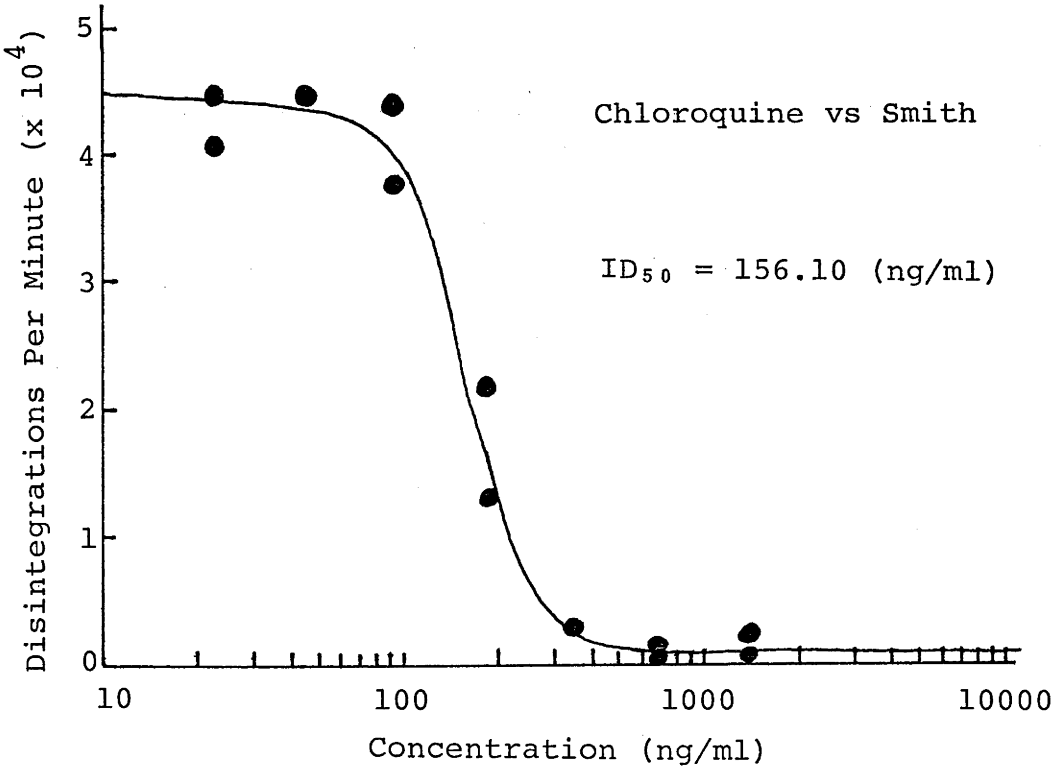


Fig. V.2. A logistic-logarithmic analysis of the effect of chloroquine at various concentrations on the uptake of ^{3}H-hypoxanthine *in vitro* by erythrocytes parasitized with a chloroquine-resistant isolate (Vietnam-Smith) of *P.falciparum*. After Desjardins *et al.* (ref. 118).

Table V.1 The *in vitro* antimalarial activity of chloroquine, amodiaquine, quinine, mefloquine (WR 142490) and pyrimethamine expressed as the concentration (ng/ml) causing 50% inhibition (ID_{50}) of the uptake of ^{3}H-hypoxanthine by *Plasmodium falciparum*.

Drug	Parasite strain	
	African (Uganda I)	Vietnam (Smith)
Chloroquine	9.5 ± 0.78[a] (n=12)	182 ± 23.4 (n=12)
Amodiaquine	9.8 ± 0.45 (n=2)	23.7 ± 5.15 (n=2)
Quinine	26.1 ± 5.57 (n=12)	109 ± 8.5 (n=12)
Mefloquine (WR 142490)	6.7 ± 1.00 (n=12)	7.8 ± 1.41 (n=12)
Pyrimethamine	4.7 ± 0.40 (n=2)	>1500 (n=2)

[a] All values are the mean ± 1 SE of n separate determinations of the ID_{50}

V-2 Determination of Antimalarial Activity of Compounds Synthesised during this Work

Compounds synthesised in this work were screened for antimalarial activity by the following sequence of tests. Firstly each chemical was examined for toxicity in mice prior to the preliminary antimalarial screen. In this, mice were injected intraperitoneally with appropriate doses of the test chemical to establish dosages which would not cause acute toxic death among the test mice. Secondly, each chemical was evaluated in a preliminary screen for antimalarial activity in an *in vivo* test in mice infected with *P. vinckei vinckei*. Then potential antimalarial candidates from the preliminary screen were forwarded to the Army Malarial Research Unit, Ingleburn, N.S.W., Australia, for further *in vitro* evaluation against both chloroquine-sensitive (FCQ-27) and chloroquine-resistant (K-1) strains of *P. falciparum*.

V-2-A Toxicity Testing

Each chemical 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 between 100 to 200 mg/kg of body weight. Appropriate adjustment of the dosage was necessary in some cases until no detection of acute toxic death among the test mice.

V-2-B Preliminary Antimalarial Screen

Mice were injected intraperitoneally with 10^6 erythrocytes infected with P. vinckei vinckei which were obtained from an infected donor mouse. After 5 days (and daily thereafter) each mouse was examined for suitable parasitaemia levels (generally 10-20%). In this, thin blood smears were taken, slides were fixed with methanol, 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 50, 100 or 200 mg/kg of body weight 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 time intervals indicated in Tables (V.2-8) 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 primaquine and/or chloroquine (as diphosphates).

V-2-C In Vitro Screen against two Isolates of Chloroquine-sensitive and Chloroquine-resistant Plasmodium falciparum

The semiautomated microdilution technique as described by Desjardins et al.[118] with slight modification[120] was employed for measuring the activity of potential anti-malarial agents [previously showing promise in the P. vinckei - mouse model (V-2-B)] against cultured intraerythrocytic asexual forms of Plasmodium falciparum. The two isolates of P. falciparum used in the in vitro screen were maintained routinely by the culture technique of Trager and Jensen[108] and are from the following sources:

FCQ-27 isolate from Dr G. Butcher (Royal Newcastle Hospital, Newcastle, Australia).

K-1 isolate from Dr A. Saul (Queensland Institute of Medical Research).

These in vitro tests were carried out by Mr Haydn V. Scott of the Army Malaria Research Unit, Milpo, Ingleburn, New South Wales, Australia, and the results were recorded in Tables (V.9-11).

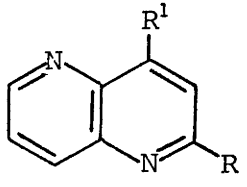
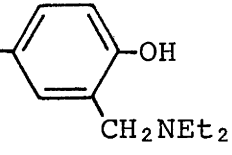
Peters et al.[121] have derived chloroquine resistance indices of 1.4 and 6.9 for the FCQ-27 and K-1 isolates respectively, from data reported earlier.[122,123] Our results[120] give an index of 0.4 for FCQ-27 and 10.7 for K-1; but would not be expected to yield the same numerical values as the earlier studies since different experimental procedures[120] were employed. Knowles et al.,[124] from an examination of 18 isolates of P. falciparum ranked FCQ-27 as the second most chloroquine sensitive and K-1 the second most chloroquine resistant.

V-3 Results of Antimalarial Tests

The compounds described in CHAPTER II, III and IV were screened for antimalarial activity in the preliminary *in vivo* tests against *P. vinckei vinckei* in mice and promising compounds were further evaluated in the *in vitro* tests against *P. falciparum* as described above. The *in vivo* results are recorded in Tables (V.2-8) and the *in vitro* results are in Tables (V.9-11).

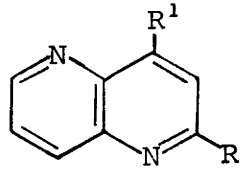
V-3-A In Vivo Tests against Plasmodium vinckei vinckei in Mice

Table V.2 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; 0h denotes pretreatment.

Compound		Solvent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	6h	24h	48h
II.19	R = OMe, R^1 = 	PO	100	16	25	41	73
II.20a[B]	R = OMe, R^1 = $NH(CH_2)_2NEt_2$	NS	100	13	25	44	80
II.20b	R = OMe, R^1 = $NH(CH_2)_3NEt_2$	PO	100	30	42	72	80
II.20c[B]	R = OMe, R^1 = $NH(CH_2)_3NH_2$	NS	100	35	60	76	80
II.20d[B]	R = OMe, R^1 = $NH(CH_2)_4NH_2$	NS	100	20	38	61	87
II.20e[B]	R = OMe, R^1 = $NH(CH_2)_5NH_2$	NS	100	15	37	62	85
II.20f[B]	R = OMe, R^1 = $NH(CH_2)_6NH_2$	NS	100	23	41	66	88
II.21a	R = OH, R^1 = $NH(CH_2)_2NEt_2$	PO	100	18	27	60	84
II.21b	R = OH, R^1 = $NH(CH_2)_3NEt_2$	PO	100	18	27	56	85

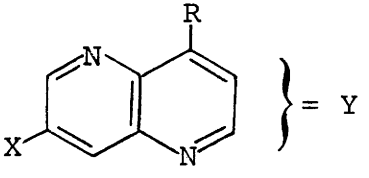
Cont...

Table V.2 Cont. Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; 0h denotes pretreatment.

Compound		Sol-A vent	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	6h	24h	48h
II.21c	R = OH, R^1 = $NH(CH_2)_3NH_2$	NS	100	10	13	27	71
II.21d	R = OH, R^1 = $NH(CH_2)_4NH_2$	NS	100	16	19	42	77
II.21e	R = OH, R^1 = $NH(CH_2)_5NH_2$	NS	100	7	11	30	72
II.21f	R = OH, R^1 = $NH(CH_2)_6NH_2$	NS	100	10	14	28	67
NS	-	-	-	14	19	47	80
PO	-	-	-	24	33	63	77
Primaquine[C]	-	NS	30	9	8	4	2
Chloroquine[C]	-	NS	20	16	18	8	1

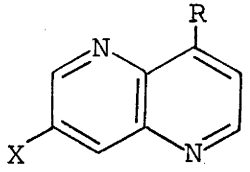
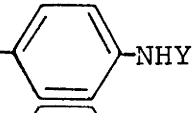
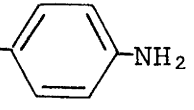
[A] PO, peanut oil; NS, normal saline.
[B] 2HBr.
[C] Diphosphate.

Table V.3 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells.												
				0h	9h	24h	48h	3d	6d	8d	9d	10d	13d	14d	19d	4w	14w
II.33a	X = Br, R = $NHCHMe(CH_2)_3NEt_2$	PO	200	4	2	1	<1	<1	<1			<1	<1				H
II.33b[B]	X = Br, R = $NH(CH_2)_2NEt_2$	NS	200	10	9	<1	<1	<1	<1			0	0				H
II.33c[B]	X = Br, R = $NH(CH_2)_3NEt_2$	NS	100	11	12	6	22	48									
II.33d[B]	X = Br, R = $NH(CH_2)_4NEt_2$	NS	100	13	17	4	7	12	35	9	5			<1	<1	<1	
II.33e[B]	X = Br, R = $NH(CH_2)_4NH_2$	NS	200	6	3	<1	<1	22									
II.33f[B]	X = Br, R = $NH(CH_2)_5NH_2$	NS	200	6	7	12	36	59									
II.33g[B]	X = Br, R = $NH(CH_2)_6NH_2$	NS	200	6	7	25	55	85									
II.33h[B]	X = Br, R = $NH(CH_2)_3NMe_2$	NS	200	12	13	1	5	18									
II.34a[B]	X = Cl, R = $NH(CH_2)_2NEt_2$	NS	200	17	20	5	<1	4	34	19	7			<1	<1	<1	
II.34b[B]	X = Cl, R = $NH(CH_2)_4NEt_2$	NS	100	13	17	5	2	4	56	22	10			<1	<1	<1	

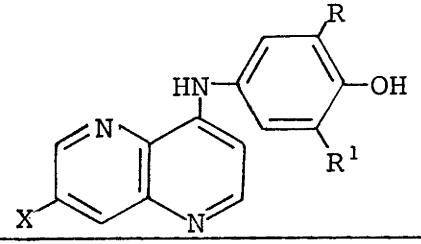
Cont...

Table V.3 Cont. Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound	 = Y	Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	6d	8d	9d	10d	13d	14d	19d	4w	14w
II.35	X = Br, R = $S(CH_2)_2NEt_2$	PO	200	9	14	29	65	83	C								
II.37[D]	X = Br, R = 	PO	200	8	20	29	59	65									
II.38	X = Br, R = 	NS	200	3	13	34	76	80									
NS	-	-	-	27	45	63	88	E									
PO	-	-	-	19	42	66	85	E									
Chloroquine[F]	-	NS	40	28	30	4	<1	<1	10	71	82[G]						

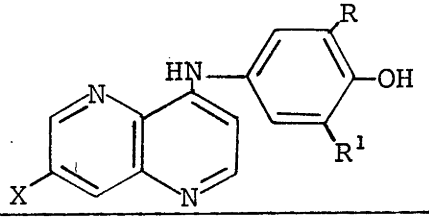
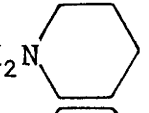
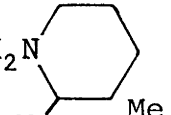
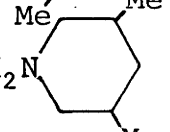
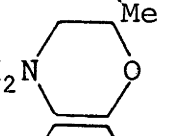
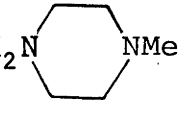
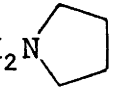
[A] PO, peanut oil; NS, normal saline.
[B] Dihydrobromide.
[C] All three mice dead.
[D] Hydrochloride.
[E] Two of the three mice dead at 3 days.
[F] Diphosphate.
[G] All mice dead at 10 days.
[H] Mice alive after 14 weeks.

Table V.4 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound		Solvent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	6d	8d	9d	10d	11d	14d	19d	4w
II.40	X = Br, R = R^1 = H	PO	200	16	34	62	88	B								
II.41a[C]	X = Br, R = H, R^1 = CH_2NMe_2	NS	200	27	30	9	<1	<1	11	8	4			<1	<1	<1
II.39	X = Br, R = H, R^1 = CH_2NEt_2	PO	200	11	10	1	<1	<1	<1			<1[D]				
II.41b	X = Br, R = H, R^1 = CH_2NPr_2	PO	200	16	27	16	3	5	26	14	5			<1	<1	<1
II.41c[C]	X = Br, R = H, R^1 = CH_2N⬠	NS	200	19	26	3	<1	<1	25	28	18			<1	<1	<1
II.41d	X = Br, R = R^1 = CH_2NMe_2	PO	200	18	24	5	<1	<1	<1	<1	<1			<1	<1	<1
II.41e	X = Br, R = R^1 = CH_2NEt_2	NS	100	10	9	<1	<1	<1	<1	<1	<1			16	<1	<1
II.41f	X = Br, R = R^1 = CH_2NPr_2	PO	200	22	32	7	<1	<1	<1	<1	<1			<1	<1	<1
II.41g	X = Br, R = R^1 = CH_2N⬠	PO	100	11	11	1	<1	<1	<1	<1	<1			<1	<1	<1

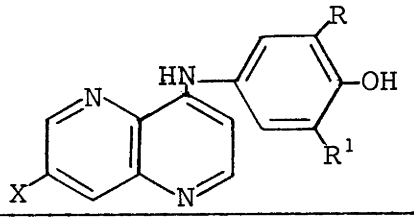
Cont...

Table V.4 Cont. Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	6d	8d	9d	10d	11d	14d	19d	4w
II.41h	X = Br, R = R^1 = CH_2N 	PO	200	17	13	1	<1	<1	<1	<1	<1			63	E	
II.41i	X = Br, R = R^1 = CH_2N 	PO	100	9	3	<1	<1	<1	<1	<1	1	14	28	F		
II.41j	X = Br, R = R^1 = CH_2N 	PO	100	14	20	13	<1	<1	<1	<1	<1	<1	<1	<1	<1	
II.41k	X = Br, R = R^1 = CH_2N 	PO	200	15	15	<1	<1	<1	<1	<1	<1			16	G	
II.41l	X = Br, R = R^1 = CH_2N 	PO	100	10	4	1	<1	<1	<1	<1	<1	<1	<1	3[H]		
II.42	X = Br, R = CH_2NMe_2, R^1 = CH_2N 	PO	100	9	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	

Cont...

Table V.4 Cont. Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

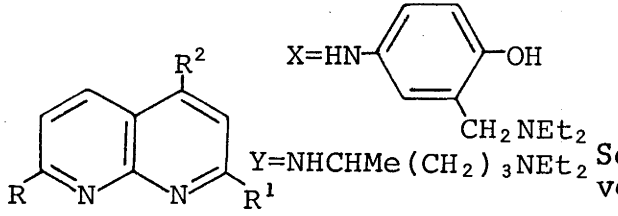
Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	6d	8d	9d	10d	11d	14d	19d	4w
II.43	X = Cl, R = H, R^1 = CH_2NEt_2	PO	200	14	12	1	<1	<1	3	15	21			<1	<1	<1
II.45a	X = Cl, R = R^1 = CH_2NMe_2	PO	100	13	11	1	<1	<1	<1	<1	<1	3	5	I		
II.45b	X = Cl, R = R^1 = CH_2NEt_2	PO	100	4	1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
II.45c	X = Cl, R = R^1 = CH_2NPr_2	PO	100	10	7	2	1	<1	2	17	21	27	7	2	<1[J]	
II.45d	X = Cl, R = R^1 = CH_2N	PO	100	9	5	<1	<1	<1	<1	<1	<1	<1	<1	<1	K	
NS	-	-	-	27	45	63	88	L								
PO	-	-	-	19	42	66	85	L								
Chloroquine[M]	-	NS	40	24	18	3	<1	<1	2	2	<1	<1	<1	<1	<1	

Cont...

Footnotes to Table V.4:

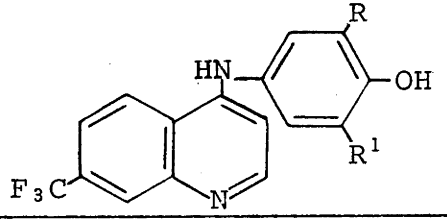
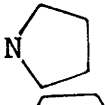
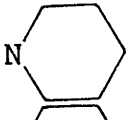
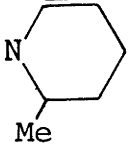
[A] PO, peanut oil; NS, normal saline.
[B] All three mice dead.
[C] Dihydrobromide.
[D] Mice alive after 14 weeks.
[E] Two mice dead, parasitaemia of third mouse <1%.
[F] Two mice dead at 14 days, parasitaemia of third mouse 8% at 14 days and <1% at 19 days.
[G] One mouse dead, parasitaemia of remaining two mice <1%.
[H] Parasitaemia of one mouse 12% at 14 days. This mouse dead at 19 days, parasitaemia of other two mice <1%.
[I] One mouse dead at 14 days, parasitaemia of other two average 11%.
[J] Parasitaemia rose in one mouse only, to 80%, then declined.
[K] One mouse dead at 19 days, parasitaemia of other two mice <1%.
[L] Two of the three mice dead at 3 days.
[M] Diphosphate.

Table V.5 Preliminary antimalarial screening results against *Plasmodium vinckei vinckei* in mice. Times given are those after injection of the chemical under test. Time: h, hours; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	6h	24h	48h
III.23a	R = R^1 = H, R^2 = X	PO	100	14	27	53	87
III.23b	R = R^1 = H, R^2 = Y	PO	50	19	33	53	85
III.18a	R = Me, R^1 = H, R^2 = X	PO	100	11	18	31	68
III.18b	R = Me, R^1 = H, R^2 = Y	PO	100	7	15	42	72
III.27a[B]	R = R^1 = Me, R^2 = X	NS	100	20	33	58	85
III.27b	R = R^1 = Me, R^2 = Y	PO	100	9	18	47	81
III.34	R = Cl, R^1 = H, R^2 = X	PO	100	12	16	42	76
III.38	R = Cl, R^1 = Me, R^2 = X	PO	100	6	13	34	71
NS	-	-	-	9	13	38	79
PO	-	-	-	8	14	38	80
Primaquine[C]	-	NS	30	9	8	4	2
Chloroquine[C]	-	NS	20	16	18	8	1

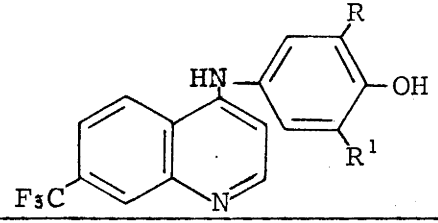
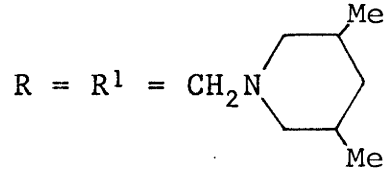
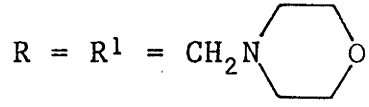
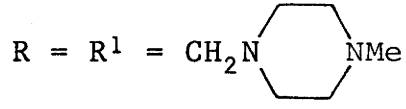
[A] PO, peanut oil; NS, normal saline. [B] 2HCl.2H_2O. [C] Diphosphate.

Table V.6 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells.												
				0h	9h	24h	48h	3d	6d	8d	9d	10d	11d	12d	14d	15d	4w
IV.18	R = R[1] = H	PO	100	7	10	14	51	80[B]									
IV.17	R = H, R[1] = CH_2NEt_2	PO	100	11	5	2	<1	<1	C	D	27	52	67	83	11	7	<1
IV.19a	R = R[1] = CH_2NMe_2	PO	100	6	3	1	<1[E]	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19b	R = R[1] = CH_2NEt_2	PO	100	6	14	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19c	R = R[1] = CH_2NPr_2	PO	100	11	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19d	R = R[1] = 	PO	100	8	4	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19e	R = R[1] = 	PO	100	5	2	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19f	R = R[1] = 	PO	100	18	18	4	<1	<1	<1	<1	<1	<1	<1	3	26[F]		

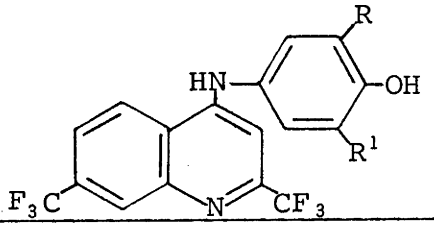
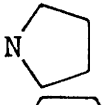
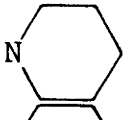
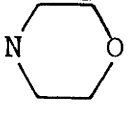
Cont...

Table V.6 Cont. Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	6d	8d	9d	10d	11d	12d	14d	15d	4w
IV.19g		PO	100	12	12	6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
IV.19h		PO	100	18	12	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
IV.19i		PO	50	7	4	2	<1	<1	<1	5	14	33	40	G			
NS	-	-	-	11	19	28	57	H									
PO	-	-	-	8	13	31	63	H									
Chloroquine[I]	-	NS	40	24	18	3	<1	<1	2	<1	<1	<1	<1	<1	<1	<1	

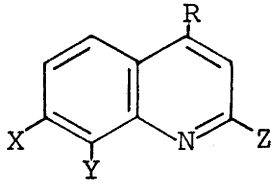
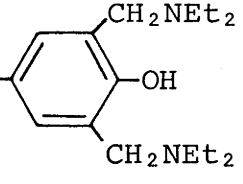
A PO, peanut oil; NS, normal saline.
B All mice dead at 4 days.
C Parasitaemia of one mouse 75%, other two mice <1%.
D One mouse dead, parasitaemia of other two 15%.
E One mouse dead.
F All mice dead at 19 days.
G Two mice dead at 12 days, parasitaemia of other mouse <1% at 19 days.
H One mouse dead at 3 days, all mice dead at 4 days.
I Diphosphate.

Table V.7 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d
IV.22	R = R^1 = H	PO	100	20	16	53	86	
IV.21[B]	R = H, R^1 = CH_2NEt_2	NS	100	6	4	10	28	45
IV.23a	R = H, R^1 = $CH_2N^iBu_2$	PO	100	6	8	25	71	83
IV.23b	R = R^1 = CH_2NMe_2	PO	100	11	13	44	82	86
IV.23c	R = R^1 = CH_2NEt_2	PO	100	20	24	30	49	56
IV.23d	R = R^1 = CH_2NPr_2	PO	100	10	13	38	71	91
IV.23e	R = R^1 = 	PO	100	12	16	32	68	85
IV.23f	R = R^1 = 	PO	100	12	17	45	78	82
IV.23g	R = R^1 = 	PO	100	15	17	35	75	83
NS	-	-	-	7	9	31	75	85
PO	-	-	-	15	17	44	81	89
Chloroquine[C]	-	NS	40	13	20	1	<1	<1

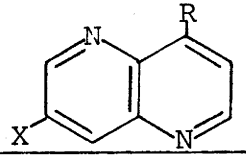
A PO, peanut oil; NS, normal saline. B Hydrochloride. C Diphosphate.

Table V.8 Preliminary antimalarial screening results against Plasmodium vinckei vinckei in mice. Times given are those after injection of the chemical under test. Time: h, hours; d, days; 0h denotes pretreatment.

Compound		Sol-vent[A]	Dose (mg/kg)	Mean (%) of parasite-infected red cells. 0h	9h	24h	48h	3d	4d
IV.28a	X=Z=CF_3, Y=H, R=$NH(CH_2)_2NEt_2$	PO	100	11	13	41	75	82	
IV.28b	X=Z=CF_3, Y=H, R=$NHCHMe(CH_2)_3NEt_2$	PO	100	6	10	28	62	82	
IV.27a	X=H, Y=Z=CF_3, R=$NH(CH_2)_2NEt_2$	PO	100	15	21	57	84	88	
IV.27b	X=H, Y=Z=CF_3, R=$NHCHMe(CH_2)_3NEt_2$	PO	100	6	9	27	63	84	
IV.26	X=H, Y=Z=CF_3, 	PO	100	12	15	9	8	27	55
NS	-	-	-	7	9	31	73	85	
PO	-	-	-	15	17	44	81	89	
Chloroquine[B]	-	NS	40	13	20	1	<1	<1	<1

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

Table V.9 In vitro antimalaria activity of a series of N^4-substituted 7-bromo (and chloro)-1,5-naphthyridin-4-amines, chloroquine, amodiaquine and mefloquine against two isolates of P. falciparum.

Compound		50% inhibitory concentration (nmol/l)*	
		P. falciparum strain	
		FCQ-27	K-1
II.33b[A]	X = Br, R = $NH(CH_2)_2NEt_2$	4.2	>256
II.33d[A]	X = Br, R = $NH(CH_2)_4NEt_2$	>64	>64
II.33a	X = Br, R = $NHCHMe(CH_2)_3NEt_2$	6.2	>64
II.34a[A]	X = Cl, R = $NH(CH_2)_2NEt_2$	>512	>512
II.34b[A]	X = Cl, R = $NH(CH_2)_4NEt_2$	>128	>128
Chloroquine	-	13.5 ± 4.2**	343.0 ± 114**
Amodiaquine	-	3.0 ± 0.1***	13.9 ± 3.4***
Mefloquine	-	10.1 ± 5.4***	4.9 ± 3.3***

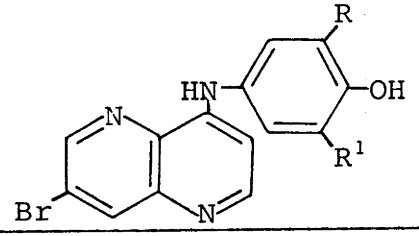
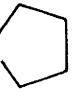
[A] Dihydrobromide.

* Results are obtained in one test only, unless otherwise indicated.

** Results are the mean of seven tests.

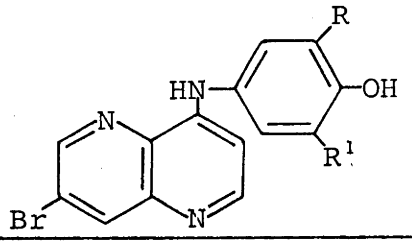
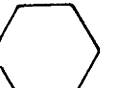
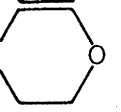
*** Results are the mean (± standard error) of three tests calculated after logarithmic transformation of data (ref. 120).

Table V.10 *In vitro* antimalaria activity of a series of 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)phenols, chloroquine, amodiaquine and mefloquine against two isolates of *P. falciparum*.

Compound		50% inhibitory concentration (nmol/l)*	
		P. falciparum strain	
		FCQ-27	K-1
II.41a[A]	R = H, R^1 = CH_2NMe_2	28.8 ± 4.8	>64
II.39	R = H, R^1 = CH_2NEt_2	34.7 ± 11.0	>64
II.41b	R = H, R^1 = CH_2NPr_2	>64	>64
II.41c[A]	R = H, R^1 = CH_2N 	34.7 ± 7.6	>64
II.41d	R = R^1 = CH_2NMe_2	2.9 ± 1.1	6.6 ± 2.2
II.41e	R = R^1 = CH_2NEt_2	4.6 ± 2.0	20.8 ± 8.9
II.41f	R = R^1 = CH_2NPr_2	2.5 ± 1.6	8.5 ± 4.0
II.41g	R = R^1 = CH_2N 	3.0 ± 0.9	9.3 ± 4.3

Cont...

Table V.10 Cont. *In vitro* antimalaria activity of a series of 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)phenols, chloroquine, amodiaquine and mefloquine against two isolates of *P. falciparum*.

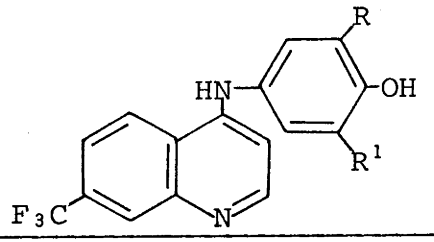
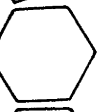
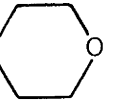
Compound		50% inhibitory concentration (nmol/l)*	
		P. falciparum strain	
		FCQ-27	K-1
II.41h	$R = R^1 =$ 	34.8 ± 9.2	>64
II.41k	$R = R^1 =$ 	24.1 ± 0.3	>64
Chloroquine	-	13.5 ± 4.2**	343.0 ± 114**
Amodiaquine	-	3.0 ± 0.1	13.9 ± 3.4
Mefloquine	-	10.1 ± 5.4	4.9 ± 3.3

A Dihydrobromide.

* Results are the mean (± standard error) of three tests (unless otherwise indicated) calculated after logarithmic transformation of data (ref.120).

** Results are the mean of seven tests.

Table V.11 *In vitro* antimalaria activity of a series of 4-(7'-trifluoromethylquinolin-4'-ylamino)phenols and chloroquine against two isolates of *P. falciparum*.

Compound		50% inhibitory concentration (nmol/l)*	
		P. falciparum strain	
		FCQ-27	K-1
IV.17	R = H, R^1 = CH_2NEt_2	2.1 ± 0.4	5.5 ± 2.7
IV.19a	R = R^1 = CH_2NMe_2	4.3 ± 1.8	7.0 ± 2.3
IV.19b	R = R^1 = CH_2NEt_2	1.0 ± 0.5	2.6 ± 0.3
IV.19c	R = R^1 = CH_2NPr_2	1.7 ± 1.6	2.0 ± 0.7
IV.19d	R = R^1 = 	0.8 ± 0.4	2.1 ± 0.7
IV.19e	R = R^1 = 	0.5 ± 0.3	0.8 ± 0.4
IV.19h	R = R^1 = 	4.5 ± 0.4	6.8 ± 2.2
Chloroquine	-	13.0 ± 6.4**	325 ± 200**

* Results are the mean (± standard error) of five tests (unless otherwise indicated) calculated after logarithmic transformation of data (ref.120).

** Results are the mean of ten tests.

V-4 Discussion of Results

Although preliminary *in vivo* rodent screening results were obtained in full for all target chemicals synthesised in this work, only some of the candidate compounds selected for further *in vitro* tests against *P. falciparum* were evaluated in time to be included in this thesis. Discussion of the results obtained is dealt with separately under two headings.

V-4-A In Vivo *Screen against* P. vinckei vinckei

It is clear from Table V.2 that none of the $\underline{N}^4$-substituted-2-methoxy (and 2-hydroxy)-1,5-naphthyridin-4-amines showed any significant antimalarial activity (as blood schizontocides) at a dosage of 100 mg/kg, as compared to the controls, chloroquine and primaquine. These observations are in contrast to the report of McCaustland and Cheng[56] that "5-azapamaquine" (I.21b) and its chloro-analogue (I.21d) were active against *P. bergei*. The role of this series of 2,4-disubstituted 1,5-naphthyridin-4-amines (also considered as derivatives of 8-aminoquinolines) as potential prophylactic agents is yet to be evaluated in either the *P. cynomolgi* - rhesus monkey test system[125,126] or other appropriate avian, or rodent malaria models.

The $\underline{N}^4$-substituted-7-bromo (and chloro)-1,5-naphthyridin-4-amines (Table V.3) all showed blood schizontocidal activity in varying degree. Apparent cures were effected in the case of "5-azabromoquine" (II.33a) and compound (II.33b). Relative to "bromoquine"[127] which has

an LD_{50} of 72 mg/kg in mice[127] for a single intraperitoneal (i.p.) dose, "5-azabromoquine" is significantly less toxic, with no apparent ill effects at a dosage of 200 mg/kg. It appears therefore that aza-substitution also decreases toxicity. Of the naphthyridines with terminal primary amino groups, the highest activity was shown by compound (II.33c) which decreased to no significant activity in (II.33g) at the test concentration of 200 mg/kg. The sulfide (II.35), unlike its nitrogen analogue (II.33b), showed no antimalarial activity which is consistent with Schönhöfer's hypothesis[128,129] that a quinonoid system between the ring nitrogen and the amine side chain in 4-, 6-, or 8-aminoquinoline derivatives is required for antimalarial activity. N,N'-Bis(7"-bromo-1",5"-naphthyridin-4"-yl)benzene-1,4-diamine (II.37) and 4-(7'-bromo-1',5'-napthyridin-4'-ylamino)aniline (II.38) were also devoid of any activity against P. vinckei vinckei in mice.

All the mono- and di-Mannich bases (Table V.4) derived from 4-[7'-bromo (and chloro)-1',5'-naphthyridin-4'-ylamino]-phenols, were extremely effective as blood schizontocides. Parasitaemia in most cases was reduced to less than 1% within 24 to 48 h following a single i.p. dose of 100 to 200 mg/kg of the test chemicals. This low level of parasitaemia was maintained in many instances, to and beyond 19 days of the test period. The pattern of an initial knockdown of parasite level by a test compound and then an upsurge followed by a decrease in parasitaemia again is the classical example of the involvement of host-immune response. The "unsymmetrical" di-Mannich base

(II.42) also appeared to be an effective blood schizontocide in this P. vinckei vinckei - mouse model.

All of the 1,8-naphthyridine derivatives (Table V.5) including the 8 aza-analogue (III.34) of amodiaquine (I.5a) were found to be inactive as antimalarials. It appeared that 8 aza-substitution in the quinoline ring of amodiaquine destroys the antimalarial activity.

The mono- and di-Mannich bases (Table V.6) of 4-(7'-trifluoromethylquinolin-4'-ylamino)phenols all showed very significant antimalarial activity in a single i.p. dose of 100 mg/kg [except for compound (IV.19i) which was toxic at 100 mg/kg and was tested at 50 mg/kg]. Parasitaemia of test mice was reduced to less than 1% in all cases between 24 to 48 h following treatment.

These observations were not repeated in the 4-[2',7'- and 2',8'-bis(trifluoromethyl)quinolin-4'-ylamino]phenols and $\underline{N}^4$-substituted 2,7- (and 2,8-)bis(trifluoromethyl)-quinolin-4-amines reported in Tables V.7 and V.8. It appeared that insertion of the 2-trifluoromethyl substituent into compound (IV.19b) to give (IV.23c) eliminated the antimalarial activity shown by the former; and a shift of the trifluoromethyl substituents to the 2,8-positions gave (IV.26) which also reduced the antiplasmodial activity. Nevertheless, 2,7- and 2,8-bis(trifluoromethyl) substituents have been shown[65] to be structural requirements for potent blood schizontocides in various quinolinemethanols including mefloquine.

V-4-B In Vitro Screen against P. falciparum

Among the few 7-bromo (and chloro)-1,5-naphthyridin-4-amines (Table V.9) selected for in vitro P. falciparum test, only compounds (II.33a) and (II.33b) approached the potency of chloroquine and mefloquine against the FCQ-27 isolate, but seemed to show cross-resistance with chloroquine in the test against the K-1 strain of P. falciparum.

However, when the 4-(7'-bromo-1',5'-naphthyridin-4'-ylamino)phenols (Table V.10) were examined for activity against P. falciparum, all except compound (II.41b) were highly active against the chloroquine-sensitive FCQ-27 strain; and of these, compounds (II.41d-g) showed little or no cross-resistance with chloroquine against the K-1 isolate. Moreover, the potency of the latter four compounds (as measured by their ID_{50} values) approached, and was not significatly different from, those of either mefloquine or amodiaquine.

The series of Mannich bases (Table V.11) derived from 4-(7'-trifluoromethylquinolin-4'-ylamino)phenols appeared to be extremely active with ID_{50} values all well below 10 nmol/l with both isolates of P. falciparum. Compound (IV.19e) in particular, is far superior to either chloroquine, amodiaquine or mefloquine and the ID_{50} of the former compound is essentially the same for the two strains of P. falciparum.

The in vitro results obtained in Tables V.10 and V.11 suggest that the Mannich bases (II.41d-g), (IV.17) and (IV.19a-h) are a series of antimalarial compounds worthy

of further study, especially when earlier toxicity trials are taken into account[130,131] (cf. the LD_{50} for a single i.p. dose of chloroquine, 68-78 mg/kg[132]). These compounds will be investigated further in in vivo studies by testing against chloroquine-sensitive and resistant lines of P. bergei produced in mice as well as by examining their antimalarial activity against P. falciparum in owl monkeys (Aotus trivirgatus).

Nevertheless, the work covered in this thesis is far from complete. Further work is envisaged to involve the synthesis of similar Mannich bases with quinazoline or pyrido[3,2-d]pyrimidine as the heterocyclic nucleus carrying suitable halogeno or trihalogenomethyl substituents, because the present work and various literature evidence suggest aza-substitution in the quinoline nucleus of antimalarial agents reduces their intrinsic toxicity. It is therefore hoped that this further work will lead to an emergence of a new class of antimalarials in an attempt to overcome or alleviate the existing problem of drug resistance.

INDEX TO NEW COMPOUNDS

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"Potential Antimalarials. I. 1,8-Naphthyridines"
Aust. J. Chem., 1984, 37, 1065-1073.

2. Barlin, G. B., and Tan, W.-L.
"Potential Antimalarials. II. N^4-Substituted 2-Methoxy (and 2-Hydroxy)-1,5-naphthyridin-4-amines"
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5. Barlin, G. B., and Tan, W.-L.
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Aust. J. Chem., Paper No. VB28/557.

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Potential Antimalarials. I 1,8-Naphthyridines

Gordon B. Barlin and Weng-Lai Tan

Medical Chemistry Group, John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.

Abstract

A number of 1,8-naphthyridines including 8-aza analogues of chloroquine and amodiaquine, and similar 1,8-naphthyridines with 2- and 7-methyl substituents have been prepared. These compounds showed minimal antimalarial activity in a preliminary *in vivo* screen against *Plasmodium vinckei vinckei*.

Introduction

The acquired resistance of strains of malaria parasites to many of the known antimalarials[1–4] has prompted the preparation of new structure types which incorporate other heterocyclic rings or variations to substituents in presently used heterocyclic nuclei to give compounds which may be more effective antimalarial agents.

McCaustland and Cheng[5] synthesized several 1,5-naphthyridine congeners of chloroquine (1; X = CH) and found that 7-chloro-*N*-(4′-diethylamino-1′-methylbutyl)-1,5-naphthyridin-4-amine (1; X = N), '5-azachloroquine', 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. Other potential antimalarial 1,5(and 1,8)-naphthyridines have been synthesized by Adams *et al.*,[6] and Goldberg *et al.*[7]

Chien and Cheng[8] have also prepared a number of 1,7-naphthyridines in which the electron-withdrawing chloro substituent of chloroquine and amodiaquine was

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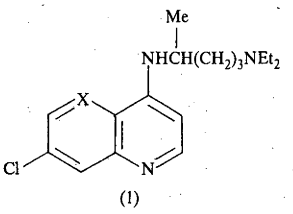
replaced by a doubly bound ring nitrogen atom. *N*-(4′-Diethylamino-1′-methylbutyl)-1,7-naphthyridin-4-amine (2) and 2-diethylaminomethyl-4-(1′,7′-naphthyridin-4′-ylamino)phenol produced only a slight extension in survival time of mice infected with *P. berghei* compared to untreated controls. Neither of these compounds approached the potency of chloroquine.



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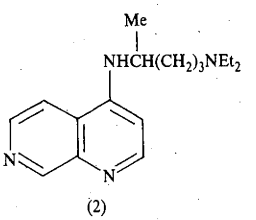

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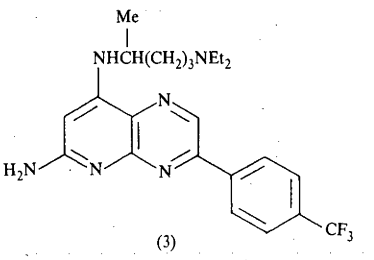

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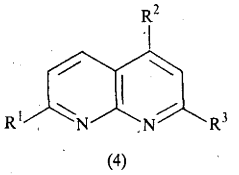

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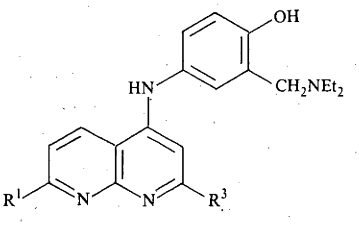

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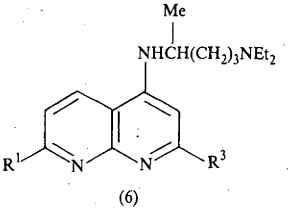

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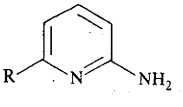

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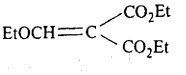

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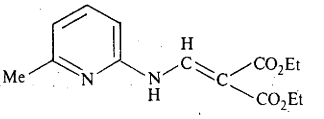

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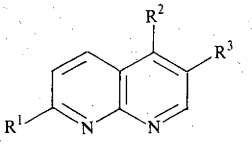

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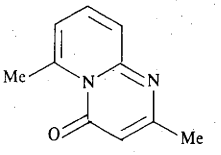

(11)

The effect on antimalarial activity when the chloroquine molecule was modified by the addition of (A) ring nitrogens, (B) exocyclic groups containing electron-rich centres, and (C) groups capable of hydrophobic bonding to the quinoline ring has been examined by Temple, Rose, Elliott and Montgomery.[9,10] They synthesized a large series of substituted pyrido[2,3-*b*]pyrazines and found the most potent, when screened in the *P. berghei*/mouse model for blood schizontocidal activity, to be 8-(4′-diethylamino-1′-methylbutyl)amino-3-*p*-(trifluoromethyl)phenylpyrido[2,3-*b*]pyrazin-6-amine (3). It gave 100% cures at a dose of 640 mg/kg, and was less acutely toxic and much superior to chloroquine in this model.

[9] Temple, C., Rose, J. D., Elliott, R. D., and Montgomery, J. A., *J. Med. Chem.*, 1968, **11**, 1216.
[10] Temple, C., Rose, J. D., Elliott, R. D., and Montgomery, J. A., *J. Med. Chem.*, 1970, **13**, 853.

We have commenced a study of potential antimalarial substances, and in this paper report on the synthesis and testing of a series of 1,8-naphthyridines (8-azaquinolines) (4)–(6).

Synthesis

The synthesis of the 1,8-naphthyridines in this work commenced from pyridin-2-amines. 6-Methylpyridin-2-amine (7; R = Me) with diethyl ethoxymethylenemalonate (8) gave diethyl (6′-methylpyridin-2′-yl)aminomethylenemalonate[11] (9) which refluxed in diphenyl ether gave ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate[11,12] (10; R^1 = Me, R^2 = OH, R^3 = COOEt). The latter, hydrolysed in aqueous potassium hydroxide, and the acid[13] (not isolated) decarboxylated in refluxing quinoline to 7-methyl-1,8-naphthyridin-4-ol[12,13] (10; R^1 = Me, R^2 = OH, R^3 = H). The last-named compound was converted as described by Brown[12] into 5-chloro-2-methyl-1,8-naphthyridine and displacement of the chloro substituent occurred with 4-amino-2-diethylaminomethylphenol at 100° and 5-diethylaminopentan-2-amine at 160° to give (5) and (6) (R^1 = Me, R^3 = H) respectively.

Ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (10; R^1 = Me, R^2 = OH, R^3 = COOEt) was oxidized by selenium dioxide in good yield to 6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid (10; R^1 = COOH, R^2 = OH, R^3 = COOEt) which hydrolysed in alkali and the diacid decarboxylated in quinoline to 1,8-naphthyridin-4-ol (10; R^1 = R^3 = H, R^2 = OH). Direct bromination of the latter with phosphoryl bromide gave 4-bromo-1,8-naphthyridine which had previously been prepared from 2,4-dibromo-1,8-naphthyridine.[14] 4-Bromo-1,8-naphthyridine reacted with 4-amino-2-diethylaminomethylphenol and 5-diethylaminopentan-2-amine under similar conditions to those described above to give (5) and (6) (R^1 = R^2 = H) respectively.

4-Chloro-2,7-dimethyl-1,8-naphthyridine[15] (4; R^1 = R^3 = Me, R^2 = Cl) was prepared from 6-methylpyridin-2-amine (7; R = Me) through 2,6-dimethylpyrido-[1,2-*a*]pyrimidin-4-one (11) and 2,7-dimethyl-1,8-naphthyridin-4-ol[15] (4; R^1 = R^3 = Me, R^2 = OH), and it reacted with amines to give the desired potential antimalarials.

1,8-Naphthyridine-2,5-diol was prepared from 6-aminopyridin-2-ol (7; R = OH) and diethyl ethoxymethylenemalonate at 100° followed by hydrolysis of the ester (10; R^1 = R^2 = OH, R^3 = COOEt) to the acid which was decarboxylated by refluxing in diphenyl ether for 9 h. This compound has also been prepared from 7-amino-1,8-naphthyridin-4-ol[16] and reported by Hermecz *et al.*[17] 2,5-Dichloro-1,8-naphthyridine, prepared from the dihydroxy compound by chlorination with phosphoryl chloride, reacted with 4-amino-2-diethylaminomethylphenol dihydrochloride in water by replacement of the 5-chloro substituent to give 4-(7′-chloro-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol in which the site of sub-

[11] Lappin, G. L., *J. Am. Chem Soc.*, 1948, **70**, 3348.
[12] Brown, E. V., *J. Org. Chem.*, 1965, **30**, 1607.
[13] Möller, K., and Süs, O., *Justus Liebigs Ann. Chem.*, 1957, **612**, 153.
[14] Czuba, W., and Wozniak, M., *Synthesis*, 1974, 809.
[15] Chandler, C. J., Deady, L. W., Reiss, J. A., and Tzimos, V., *J. Heterocycl. Chem.*, 1982, **19**, 1017.
[16] Carboni, S., Da Settimo, A., Bertini, D., Ferrarini, P. L., Livi, O., Mori, C., and Tonetti, I., *Gazz. Chim. Ital.*, 1972, **102**, 253.
[17] Hermecz, I., Mészáros, Z., Vasvári-Debreczy, L., Horváth, A., Horváth, G., and Pongor-Csákvári, M., *J. Chem. Soc., Perkin Trans. 1*, 1977, 789.

stitution was established by catalytic dechlorination to the pre-prepared 2-diethylaminomethyl-4-(1′,8′-naphthyridin-4′-ylamino)phenol. 2,5-Dichloro-1,8-naphthyridine also reacted with 5-diethylaminopentan-2-amine alone to give monosubstitution but removal of excess 5-diethylaminopentan-2-amine was difficult. The absence of disubstitution is probably associated with relative deactivation of the chloro substituent in the monoamino monochloro product.

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

Compound	Dose (mg/kg)	Mean (%) of parasite infected red cells						
		Pre-treatment	Time from administration of dose					
			3 h	6 h	12 h	20 h	22 h	24 h
(5; $R^1 = R^3 = H$)	10	24	45			[A]		
	20	25	32	34				[A]
	50	40	40				[A]	
(6; $R^1 = R^3 = H$)	10	24	26			[A]		
	20	28	[A]					
	50	35	[A]					
(5; $R^1 = Me$, $R^3 = H$)	10	31	41			38		
	20	25	35	35	31			[A]
	50	43	43				[A]	
(6; $R^1 = Me$, $R^3 = H$)	10	34	44			[A]		
	20	43	63	65	68			[A]
	50	50	[A]					
(5; $R^1 = R^3 = Me$)[B]	50	40	40				55	
(6; $R^1 = R^3 = Me$)	10	28	29			40		
	20	36	36			46		
	30	23	29	30	34			60
	50	40	[A]					
(5; $R^1 = Cl$, $R^3 = H$)	10	29	39	45	41			[A]
(5; $R^1 = Cl$, $R^3 = Me$)	10	19	27	29	[A]			
Control		28	40	38	52			58

[A] Toxic death.
[B] $2HCl.2H_2O$.

7-Amino-2-methyl-1,8-naphthyridin-4-ol (4; $R^1 = NH_2$, $R^2 = OH$, $R^3 = Me$) was prepared by condensation of pyridine-2,6-diamine (7; $R = NH_2$) with ethyl acetoacetate in diphenyl ether. The desired product was separated from the mixture containing the isomeric 2-hydroxy-4-methyl compound by the preferential solubility of the former in ethanol. Carboni *et al.*[16] have reported the preparation of 7-amino-2-methyl-1,8-naphthyridin-4-ol from pyridine-2,6-diamine and ethyl acetoacetate through a series of intermediates, but the preparation reported by Hauser and Weiss[18] is in error.[16]

4,7-Dichloro-2-methyl-1,8-naphthyridine[19] (4; $R^1 = R^2 = Cl$, $R^3 = Me$) (prepared from 7-amino-2-methyl-1,8-naphthyridin-4-ol[19] through 2-methyl-1,8-naphthyridine-4,7-diol)[19] reacted with 4-amino-2-diethylaminomethylphenol (dihydrochloride) in water at 100°, and the structure of the monosubstitution product, 4-(7′-chloro-2′-methyl-1,8-naphthyridin-4′ylamino)-2-diethylaminomethylphenol, was assigned from the similar reaction of 2,5-dichloro-1,8-naphthyridine described above.

[18] Hauser, C. R., and Weiss, M. J., *J. Org. Chem.*, 1949, **14**, 453.
[19] Carboni, S., Da Settimo, A., Pirisino, G., and Segnini, D., *Gazz. Chim. Ital.*, 1966, **96**, 103.

Biological Activities

In vivo evaluation for antimalarial activity against *Plasmodium vinckei vinckei* in preliminary screening in rodents was examined, and the results are summarized in Table 1. Minimal antimalarial activity was detected in the compounds examined when compared to the progressive increase in mean percentage of parasite infected red cells of the control sample.

More refined test results will be presented in a forthcoming publication.

Experimental

Solids for analysis were dried 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 FX90Q Fourier transform spectrometer with tetramethylsilane (in $CDCl_3$ and CD_3SOCD_3) and sodium 3-trimethylsilylpropanesulfonate (in D_2O) as internal standards.

Ethyl 4-Hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (*10*; $R^1 = Me$, $R^2 = OH$, $R^3 = COOEt$)

This compound was prepared from 6-methylpyridine-2-amine by reaction with diethyl ethoxymethylenemalonate at 110° to give diethyl (6′-methylpyridin-2′-yl)aminomethylenemalonate[11] followed by ring closure by repeated refluxing in diphenyl ether[11,12] for 10 min. The product,[11] recrystallized from ethanol, had m.p. 271–272° (lit.[11] 278–280°). ^{1}H n.m.r. CD_3SOCD_3: δ 1·28, t, J 7 Hz, CH_3CH_2; 2·60, s, 7-Me; 4·21, q, J 7 Hz, CH_3CH_2; 7·70, d, 8·40, d, J 10·5 Hz, H5,6; 8·48, s, H2.

7-Methyl-1,8-naphthyridin-4-ol (*10*; $R^1 = Me$, $R^2 = OH$, $R^3 = H$)

A mixture of ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (2·0 g) and potassium hydroxide (3·0 g) in water (20 ml) was heated on a steam bath for 1·75 h, cooled and adjusted with 5 M hydrochloric acid to pH *c.* 3·5. The free acid separated as a dense yellowish precipitate (1·2 g) which was filtered off, washed with water and dried. This product was refluxed in quinoline (40 ml) for 2·5 h, excess solvent removed under reduced pressure, the residue dissolved in 1 M sodium hydroxide and extracted with a small volume of ether to remove the last traces of quinoline. The aqueous solution was neutralized with 1 M hydrochloric acid, and the dense precipitate filtered off and recrystallized from water to give 7-methyl-1,8-naphthyridin-4-ol (0·83 g), m.p. 231–232° (lit.[12,13,20] 236–237°, 238–240°) (Found: C, 66·5; H, 4·9; N, 17·1. Calc. for $C_9H_8N_2O$: C, 66·7; H, 5·1; N, 17·3%). ^{1}H n.m.r. ($CDCl_3$): δ 2·66, s, 7-Me; 6·36, d, J 8 Hz, H3; 7·17, d, 8·61, d, J 11 Hz, H5,6; 7·71, m, H2.

5-Chloro-2-methyl-1,8-naphthyridine (*10*; $R^1 = Me$, $R^2 = Cl$, $R^3 = H$)

7-Methyl-1,8-naphthyridin-4-ol (1·5 g) was chlorinated with phosphoryl chloride (10·0 ml) as described by Brown.[12] The product recrystallized from light petroleum (b.p. 60–80°) with charcoal filtration gave pink needles of 5-chloro-2-methyl-1,8-naphthyridine (1·45 g), m.p. 116–118° (lit.[12] 121–122°) (Found, for sample dried at 20° and 20 mmHg: C, 60·6; H, 4·0; Cl, 19·6; N, 15·9. Calc. for $C_9H_7ClN_2$: C, 60·5; H, 3·95; Cl, 19·8; N, 15·7%). ^{1}H n.m.r. ($CDCl_3$): δ 2·83, s, 7-Me; 7·46, d, J 8 Hz, H2; 7·50, d, 8·95, d, J 4·5 Hz, H5,6; 8·46, d, J 8 Hz, H3.

2-Diethylaminomethyl-4-(7′-methyl-1′,8′-naphthyridin-4′-ylamino)phenol (*5*; $R^1 = Me$, $R^3 = H$)

5-Chloro-2-methyl-1,8-naphthyridine (0·447 g, 0·0025 mol), 4-amino-2-diethylaminomethylphenol dihydrochloride (0·668 g, 0·0025 mol) and water (15 ml) were heated on a steam bath for 2 h. The cooled solution was made alkaline with aqueous ammonia and extracted with chloroform (4×). The chloroform extract was washed with sodium chloride solution, dried (Na_2SO_4) and evaporated to give a yellow product (1·0 g). This product was recrystallized from ethyl acetate to

[20] Bowie, R. A., Mullan, M. J. C., and Unsworth, J. F., *J. Chem. Soc., Perkin Trans. 1*, 1972, 1106.

give 2-diethylaminomethyl-4-(7′-methyl-1′,8′-naphthyridin-4′-ylamino)phenol (0·6 g), which decomposes above 186° (Found: C, 71·4; H, 7·3; N, 16·6. $C_{20}H_{24}N_4O$ requires C, 71·4; H, 7·2; N, 16·7%). ^{1}H n.m.r. ($CDCl_3$): δ 1·13, t, J 7·5 Hz, CH_3CH_2; 2·65, q, J 7·5 Hz, CH_3CH_2; 3·76, s, CH_2N; 6·62, d, J 5·5 Hz, H3; 6·88, complex, HAr; 7·24, d, J 8·5 Hz, H6; 8·23, d, J 8·5 Hz, H5; 8·58, d, J 5·5 Hz, H2.

N-(4′-Diethylamino-1′-methylbutyl)-7-methyl-1,8-naphthyridin-4-amine (*6*; $R^1 = Me$, $R^3 = H$)

5-Chloro-2-methyl-1,8-naphthyridine (1·0 g, 0·0056 mol) and 5-diethylaminopentan-2-amine (4·4 g, 0·0278 mol) were heated in an autoclave at 160° for 9 h. The reaction mixture was evaporated under reduced pressure, made alkaline with 2 M sodium hydroxide and extracted with chloroform. The product was subjected to column and thin-layer chromatography (alumina; ethyl acetate) to give *N-(4′-diethylamino-1′-methylbutyl)-7-methyl-1,8-naphthyridin-4-amine* (0·7 g) as a yellow oil (Found: C, 71·6; H, 9·4; N, 18·4. $C_{18}H_{28}N_4$ requires C, 71·95; H, 9·4; N, 18·6%). ^{1}H n.m.r. ($CDCl_3$): δ 0·99, t, J 7·5 Hz, CH_3CH_2; 1·30, d, J 6·5 Hz, 1′-Me; 1·65, complex, 2·42, complex, CH_2 2′,3′,4′; 2·51, q, J 7·5 Hz, CH_3CH_2; 2·71, s, 7-Me; 3·71, complex, H1′; 5·45, d, J 7 Hz, NH; 6·42, d, J 5·5 Hz, H3; 7·16, d, J 8·5 Hz, H6; 8·09, d, J 8·5 Hz, H5; 8·63, d, J 5·5 Hz, H2.

6-Ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic Acid (*10*; $R^1 = COOH$, $R^2 = OH$, $R^3 = COOEt$)

Ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (4·64 g, 0·02 mol), selenium dioxide (5·31 g, 0·048 mol), water (10·0 ml) and pyridine (20 ml) were refluxed with stirring for 10 h. The mixture was diluted with pyridine (50 ml), boiled to dissolve the yellow crude product, filtered and evaporated. The residue was recrystallized from pyridine and the product washed with acetone to give *6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid* (4·7 g), m.p. >279° (dec.) (Found: C, 54·1; H, 3·8; N, 10·5. $C_{12}H_{10}N_2O_5$ requires C, 54·9; H, 3·8; N, 10·7%). ^{1}H n.m.r. (CD_3SOCD_3): δ 1·29, t, J 7 Hz, CH_3CH_2; 4·23, q, J 7 Hz, CH_3CH_2; 8·05, d, 8·67, d, J 8 Hz, H5,6; 8·57, b, H2; 13·12, b, COOH.

4-Bromo-1,8-naphthyridine (*10*; $R^1 = R^3 = H$, $R^2 = Br$)

A mixture of 6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid (9·0 g), potassium hydroxide (13·0 g) and water (90 ml) were heated on a steam bath for 1·75 h. The cooled solution was adjusted with 5 M hydrochloric acid to pH *c.* 2·5, and the dense light yellow precipitate of the acid filtered off, washed with water and dried. This solid was refluxed with quinoline (120 ml) for 8 h, excess quinoline removed under reduced pressure, and the solid remaining dissolved in the minimum volume of 1 M sodium hydroxide and extracted with chloroform to remove remaining traces of quinoline. The aqueous solution was adjusted with 1 M hydrochloric acid to pH *c.* 7 but the hydroxy compound did not precipitate. The aqueous solution was evaporated to dryness to give crude hydroxy compound (4·0 g) [^{1}H n.m.r. (CD_3OD): δ 6·35, d, J 7·5 Hz, H3; 7·59, q, J 8·5 Hz, J 4·5 Hz, H6; 8·05, d, J 7·5 Hz, H2; 8·63, q, J 2 Hz, J 8·5 Hz, H5; 8·71, q, J 2 Hz, J 4·5 Hz, H7] which was brominated directly.

The crude hydroxy compound (4·0 g) and phosphoryl bromide (20·0 g) were heated in an oil bath at 140–150° for 0·75 h. Ice was added carefully with stirring to the cooled mixture, and the resulting solution adjusted with sodium hydrogen carbonate solution to pH *c.* 6·5, and extracted with chloroform (4×). The extract was dried (Na_2SO_4) and evaporated under vacuum and the product recrystallized from light petroleum (b.p. 60–80°) to give colourless plates of 4-bromo-1,8-naphthyridine (3·3 g), m.p. 78–79°(lit.,[14] 72–73°) (Found, for material dried at 20° and 20 mmHg: C, 45·9; H, 2·4; Br, 38·3; N, 13·4. Calc. for $C_8H_5BrN_2$: C, 46·0; H, 2·4; Br, 38·2; N, 13·4%). ^{1}H n.m.r. ($CDCl_3$): δ 7·59, q, J 4 Hz, J 8·5 Hz, H6; 7·78, d, J 5 Hz, H3; 8·56, q, J 2 Hz, J 8·5 Hz, H5; 8·92, d, J 5 Hz, H2; 9·17, q, J 4 Hz, J 2 Hz, H7.

2-Diethylaminomethyl-4-(1′,8′-naphthyridin-4′-ylamino)phenol (*5*; $R^1 = R^3 = H$)

4-Bromo-1,8-naphthyridine (0·42 g, 0·002 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0·534 g, 0·002 mol) in water (15 ml) were heated on a steam bath for 2 h. The reaction mixture was worked up as described above for the reaction of 4-chloro-7-methyl-1,8-naphthyridine with the same amine. The chloroform extract gave a crude product (0·84 g) which recrystallized

from toluene to give yellow crystals of *2-diethylaminomethyl-4-(1′,8′-naphthyridin-4′-ylamino)phenol* (0·5 g), m.p. 174° (dec.) (Found: C, 71·2; H, 6·9; N, 17·4. $C_{19}H_{22}N_4O$ requires C, 70·8; H, 6·9; N, 17·4%). ^{1}H n.m.r. (CD_3OD): δ 1·14, t, J 7·5 Hz, CH_3CH_2; 2·69, q, J 7·5 Hz, CH_3CH_2; 3·83, s, CH_2N; 6·67, d, J 6 Hz, H3; 7·08, complex, ArH; 7·50, q, J 4 Hz, J 8 Hz, H6; 8·46, d, J 6 Hz, H2; 8·75, q, J 8 Hz, J 2 Hz, H5; 8·93, q, J 2 Hz, J 4 Hz, H7.

N-*(4′-Diethylamino-1′-methylbutyl)-1,8-naphthyridin-4-amine* (*6*; $R^1 = R^3 = H$)

4-Bromo-1,8-naphthyridine (1·05 g, 0·005 mol) and 5-diethylaminopentan-2-amine (3·95 g, 0·025 mol) were heated in an autoclave at 160° for 9 h. The reaction mixture was worked up as described above for the reaction of 4-chloro-7-methyl-1,8-naphthyridine with 5-diethylaminopentan-2-amine. The dried chloroform extracts (Na_2SO_4) were evaporated to a viscous brown oil which was subjected to column chromatography (alumina; methanol). The product was washed by decantation with light petroleum (b.p. 60–80°) to remove remaining traces of 5-diethylaminopentan-2-amine, and dried at 20° and 20 mmHg to give N-*(4′-diethylamino-1′-methylbutyl)-1,8-naphthyridin-4-amine* (1·1 g) (Found: N, 19·4. $C_{17}H_{26}N_4$ requires N, 19·6%). ^{1}H n.m.r. ($CDCl_3$): δ 0·99, t, J 7 Hz, CH_3CH_2; 1·31, d, J 6 Hz, 1′-Me; 1·67, complex, 2·44, complex, CH_2 2′,3′,4′; 2·52, q, J 7 Hz, CH_3CH_2; 3·73, complex, H1′; 5·68, d, J 7 Hz, NH; 6·48, d, J 5·5 Hz, H3; 7·28, q, J 8·5 Hz, J 5 Hz, H6; 8·27, q, J 2 Hz, J 8·5 Hz, H5; 8·69, d, J 5·5 Hz, H2; 9·97, q, J 2 Hz, J 5 Hz, H7.

4-Chloro-2,7-dimethyl-1,8-naphthyridine (*4*; $R^1 = R^3 = Me$, $R^2 = Cl$)

This compound was prepared from 6-methylpyridin-2-amine and ethyl acetoacetate through 2,6-dimethylpyrido[1,2-*a*]pyrimidin-4-one[15] and 2,7-dimethyl-1,8-naphthyridin-4(1*H*)-one[15] [^{1}H n.m.r. ($CDCl_3$): δ 2·41, s, 2-Me; 2·61, s, 7-Me; 6·14, s, H3; 7·15, d, 8·50, d, J 8 Hz, H5,6] followed by chlorination with phosphoryl chloride.[15] The 4-chloro-2,7-dimethyl-1,8-naphthyridine had m.p. 84–86° (lit.[15] 83).

2-Diethylaminomethyl-4-(2′,7′-dimethyl-1′,8′-naphthyridin-4′-ylamino)phenol (*5*; $R^1 = R^3 = Me$)

4-Chloro-2,7-dimethyl-1,8-naphthyridine (0·1 g, 0·0005 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0·134 g, 0·0005 mol) in water (3·0 ml) were heated on a steam bath for 2 h. The reaction mixture was worked up as described above. The product was subjected to t.l.c. (alumina; ethyl acetate), treated with 20% ethanolic hydrogen chloride, the mixture evaporated to dryness and the solid recrystallized from t-butyl alcohol to give yellow crystals of *2-diethylaminomethyl-4-(2′,7′-dimethyl-1′,8′-naphthyridin-4′-ylamino)phenol dihydrochloride* (0·12 g), which sublimed at temperatures greater than 175° (Found: C, 54·6; H, 7·2; Cl, 15·3; N, 11·7. $C_{21}H_{26}N_4O.2HCl.2H_2O$: C, 54·9; H, 7·0; Cl, 15·4; N, 12·2%). ^{1}H n.m.r. (D_2O): δ 1·36, t, J 7·5 Hz, CH_3CH_2; 2·58, s, 2-Me; 2·76, s, 7-Me; 3·26, q, J 7·5 Hz, CH_3CH_2; 6·61, s, H3; 7·41, complex, ArH; 7·64, d, 8·66, d, J 9 Hz, H5,6.

N-*(4′-Diethylamino-1′-methylbutyl)-2,7-dimethyl-1,8-naphthyridin-4-amine* (*6*; $R^1 = R^3 = Me$)

4-Chloro-2,7-dimethyl-1,8-naphthyridine (1·0 g) and 5-diethylaminopentan-2-amine (4·11 g) were heated in an autoclave at 160° for 9 h. The mixture was worked up as described above. The chloroform extract gave a viscous brown oil which was purified by column chromatography and t.l.c. (alumina; ethyl acetate) to give oily N-*(4′-diethylamino-1′-methylbutyl)-2,7-dimethyl-1,8-naphthyridin-4-amine* (0·64 g) (Found, for material dried at 20° and 20 mmHg: C, 72·4; H, 9·9; N, 17·8. $C_{19}H_{30}N_4$ requires C, 72·6; H, 9·6; N, 17·8%). ^{1}H n.m.r. ($CDCl_3$): δ 0·99, t, J 7 Hz, CH_3CH_2; 1·29, d, J 6·5 Hz, 1′-Me; 1·63, complex, 2·40, complex, CH_2 2′,3′,4′; 2·51, q, J 7 Hz, CH_3CH_2; 2·61, s, 2-Me; 2·68, s, 7-Me; 3·70, complex, H1′; 5·23, d, J 7 Hz, NH; 6·32, s, H3; 7·11, d, 7·98, d, J 8·5 Hz, H5,6.

1,8-Naphthyridine-2,5-diol (*10*; $R^1 = R^2 = OH$, $R^3 = H$)

6-Aminopyridin-2-ol (4·0 g, 0·036 mol) and diethyl ethoxymethylenemalonate (7·86 g, 0·036 mol) were heated in an oil bath at 110° for 1·5 h. The cooled reaction mixture was dissolved in ethanol (*c.* 100 ml), filtered, and the filtrate evaporated to give a dark yellow oil. This oil was heated on a steam bath with sodium hydroxide (3·0 g) in water (100 ml) for 1·75 h, adjusted to pH 2·5

and the solid filtered off. This solid was added to diphenyl ether (200 ml) and the mixture refluxed for 9 h, cooled as rapidly as possible, and diluted with light petroleum (b.p. 60–80°) (1000 ml). The yellow precipitate (2·5 g) was filtered off, washed with light petroleum (b.p. 60–80°) and dried. A sample of this material was recrystallized from a large volume of methanol to give 1,8-naphthyridine-2,5-diol, m.p. 355–357° (lit.[16,17] >320°, >360°) (Found: C, 59·2; H, 3·2; N, 17·9. Calc. for $C_8H_6N_2O_2$: C, 59·3; H, 3·7; N, 17·3%). ^{1}H n.m.r. (1 M NaOD): δ 6·30, d, J 6 Hz, H3; 6·50, d, 8·18, d, J 9 Hz, H5,6; 8·07, d, J 6 Hz, H2.

2,5-Dichloro-1,8-naphthyridine (*10*; $R^1 = R^2 = Cl$, $R^3 = H$)

Crude 1,8-naphthyridine-2,5-diol (1·0 g) and phosphoryl chloride (10·0 ml) were heated in an oil bath at 120° for 0·75 h. The cooled reaction mixture was cautiously poured onto ice, and adjusted with aqueous sodium hydrogen carbonate to pH *c.* 5·5. This mixture was extracted with chloroform, the extract dried (Na_2SO_4), solvent evaporated, and the product recrystallized from light petroleum (b.p. 60–80°) to give *2,5-dichloro-1,8-naphthyridine* (0·8 g), m.p. 131–132° (Found: C, 48·1; H, 2·1; N, 14·1. $C_8H_4Cl_2N_2$ requires C, 48·3; H, 2·0; N, 14·1%). ^{1}H n.m.r. ($CDCl_3$): δ 7·58, d, J 9 Hz, H3; 7·59, d, 9·00, d, J 5 Hz, H5,6; 8·54, d, J 9 Hz, H2.

4-(7′-Chloro-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol (*5*; $R^1 = Cl$, $R^3 = H$)

A mixture of 2,5-dichloro-1,8-naphthyridine (0·12 g, 0·0006 mol) and 4-amino-2-diethylaminomethylphenol dihydrochloride (0·16 g, 0·0006 mol) in water (10 ml) were heated on a steam bath for 2 h. After cooling, the reaction mixture was made alkaline with 14 M ammonium hydroxide, and gave a dense yellow precipitate. This product was collected and recrystallized from toluene to give *4-(7′-chloro-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol* (0·15 g), m.p. >360° (Found: C, 63·3; H, 6·1; Cl, 9·95; N, 15·4. $C_{19}H_{21}ClN_4O$ requires C, 63·9; H, 5·9; Cl, 9·9; N, 15·7%). ^{1}H n.m.r. (CD_3OD): δ 1·14, t, J 7 Hz, CH_3CH_2; 2·67, q, J 7 Hz, CH_3CH_2; 3·83, s, CH_2N; 6·67, d, J 6 Hz, H3; 7·07 complex, ArH; 7·47, d, 8·69, d, J 8 Hz, H5,6; 8·42, d, J 6 Hz, H2.

Dechlorination of 4-(7′-Chloro-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol to 2-Diethylaminomethyl-4-(1′,8′-naphthyridin-4′-ylamino)phenol (*5*; $R^1 = R^3 = H$)

A mixture of 4-(7′-chloro-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol (0·036 g), magnesium oxide (0·5 g), ethanol (30 ml) and 10% palladium-charcoal (0·05 g) were hydrogenated at room temperature and pressure until hydrogen uptake ceased. This mixture was filtered through Celite, the filtrate evaporated to dryness, and the solid subjected to t.l.c. (silica; methanol). The product was dissolved in methanol, the solution diluted with light petroleum (b.p. 80–100°), and the mixture concentrated to give a yellow precipitate of 2-diethylaminomethyl-4-(1′,8′-naphthyridin-4′-ylamino)phenol, m.p. 174° (dec.), not depressed on admixture with authentic material prepared above. The ^{1}H n.m.r. and i.r. spectra were also identical with authentic compound.

Reaction of 2,5-Dichloro-1,8-naphthyridine with 5-Diethylaminopentan-2-amine

2,5-Dichloro-1,8-naphthyridine (0·4 g, 0·002 mol) and 5-diethylaminopentan-2-amine (1·58 g, 0·01 mol) were heated in an autoclave at 160° for 9 h. The mixture was dissolved in methanol, the solvent evaporated, and the residue treated with water (20 ml) and 2 M sodium hydroxide (1·0 ml) and extracted with chloroform (4×). The chloroform extracts were dried (Na_2SO_4), evaporated and the product subjected to t.l.c. (alumina and silica; chloroform), extracted with light petroleum (b.p. 60–80°) to remove excess amine reactant and dried at 130° and 1 mmHg (Found: N, 17·7. $C_{17}H_{25}ClN_4$ requires N, 17·5%). The ^{1}H n.m.r. ($CDCl_3$) [δ 0·99, t, J 7 Hz, CH_3CH_2; 1·28, d, J 6·5 Hz, 1′-Me; 1·56, complex, 2·40, complex, CH_2 2′,3′,4′; 2·50, q, J 7 Hz, CH_3CH_2; 3·67, complex, H1′; 5·16, d, J 8 Hz, NH; 6·24, d, J 6 Hz, H3; 6·48, d, 7·84, d, J 9 Hz, H5,6; 8·41, d, J 6 Hz, H2] also showed traces of 5-diethylaminopentan-2-amine.

7-Amino-2-methyl-1,8-naphthyridin-4-ol (*4*; $R^1 = NH_2$, $R^2 = OH$, $R^3 = Me$)

A mixture of pyridine-2,6-diamine (22 g, 0·2 mol; commercial), ethyl acetoacetate (39 g, 0·3 mol) and diphenyl ether (500 ml) was stirred and heated in an oil bath at 130° for 0·5 h, then refluxed

for 2 h. After cooling, the yellow precipitate was filtered off, washed with light petroleum (b.p. 80–100°) and dried. It was recrystallized from ethanol, and the product washed with ethyl acetate to give 7-amino-2-methyl-1,8-naphthyridin-4-ol (8·0 g), m.p. 268–270° (lit.[19] 282–284°) (Found: C, 61·8; H, 5·4; N, 34·4. Calc. for $C_9H_9N_3O$: C, 61·7; H, 5·2; N, 34·0%). ^{1}H n.m.r. (CD_3SOCD_3): δ 2·23, s, 2-Me; 5·72, s, H3; 6·42, d, 7·95, d, J 8·5 Hz, H5,6; 6·67, bs, NH_2; 11·21, bs, OH (?). This product was clearly different (m.p., ^{1}H n.m.r. and i.r.) from the isomeric 7-amino-4-methyl-1,8-naphthyridin-2-ol, prepared as described by Brown[12] (Method D) and purified according to Seide,[21] which had m.p. >360° (lit.[21] darkening from 340° and decomposing about 405°) and ^{1}H n.m.r. (CD_3SOCD_3): δ 2·67, s, 4-Me; 5·99, bs, H3; 6·34, d, 7·69, d, J 9 Hz, H5,6; 6·58, bs, NH_2. The i.r. spectra of both isomers are consistent with those obtained by Carboni and co-workers.[19,22]

4,7-Dichloro-2-methyl-1,8-naphthyridine (*4*; $R^1 = R^2 = Cl$, $R^3 = Me$)

This compound was prepared from 7-amino-2-methyl-1,8-naphthyridin-4-ol through 2-methyl-1,8-naphthyridin-4,7-diol [^{1}H n.m.r. (1 M NaOD): δ 2·35, s, 2-Me; 6·19, s, H3; 6·45, d, 8·11, d, J 9 Hz, H5,6] by chlorination with phosphoryl chloride as described by Carboni *et al.*[19] It was recrystallized from light petroleum (b.p. 60–80°) and had m.p. 178–180° (lit.[19] 180°). ^{1}H n.m.r. ($CDCl_3$): δ 2·77, s, 2-Me; 7·46, s, H3; 7·50, d, 8·44, d, J 9 Hz, H5,6.

4-(7′-Chloro-2′-methyl-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethylphenol (*5*; $R^1 = Cl$, $R^3 = Me$)

4,7-Dichloro-2-methyl-1,8-naphthyridine (0·213 g, 0·001 mol) and 4-amino-2-diethylamino-methylphenol dihydrochloride (0·267 g, 0·001 mol) in water (15 ml) were heated on a steam bath for 2 h. The mixture was worked up as described above and the yellow precipitate was recrystallized from cyclohexane to give *4-(7′-chloro-2′-methyl-1′,8′-naphthyridin-4′-ylamino)-2-diethylaminomethyl-phenol* (0·3 g), m.p. 174–176° (Found: C, 65·1; H, 6·4; Cl, 9·55; N, 14·9. $C_{20}H_{23}ClN_4O$ requires C, 64·8; H, 6·3; Cl, 9·6; N, 15·1%). ^{1}H n.m.r. ($CDCl_3$): δ 1·14, t, J 7 Hz, CH_3CH_2; 2·54, s, 2-Me; 2·66, q, J 7 Hz, CH_3CH_2; 3·78, s, CH_2N; 6·55, s, H3; 6·91, complex, ArH; 7·31, d, 8·15, d, J 8·5 Hz, H5,6.

Preliminary Antimalarial Screen

Mice were injected intraperitoneally with 10^6 erythrocytes infected with *Plasmodium vinckei vinckei* 6 days prior to administration of the chemical. Each dosage of the chemical (in 0·2 ml of 50% dimethylformamide with normal saline) was given intraperitoneally at concentrations of 10, 20, 30, and 50 mg/kg of body weight to three mice at each test concentration. Thin blood smears were taken at various time intervals while a minimum of two mice survived from each test group. Slides were fixed, stained (Giemsa's stain) and the mean percentage of parasite-infected red cells determined. The results for each chemical at the various dose levels are recorded in Table 1 and were discontinued (Table entry as toxic death) at the death of the second mouse of each test group due either to the toxicity of the chemical or the malarial infection.

Acknowledgments

We thank Dr D. J. Brown for helpful discussions, Dr I. Clarke for the supervision of the preliminary antimalarial screening and Mr S. Ireland and Mr S. Sullivan for technical assistance with this operation, and Dr M. D. Fenn for the ^{1}H n.m.r. spectra. One of us (W.L.T.) thanks this University for support as a scholar.

Manuscript received 24 November 1983

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[22] Carboni, S., and Pirisino, G., *Ann. Chim.* (*Rome*), 1962, **52**, 340.

Aust. J. Chem., 1984, **37**, 2469–77

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

Gordon B. Barlin and Weng-Lai Tan

Medical Chemistry Group, John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.

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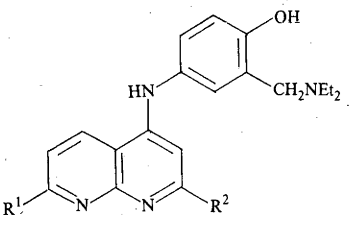
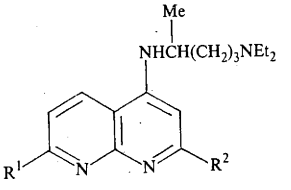
derivatives of 1,5-naphthyridin-4-amines for testing for antimalarial activity. The various amine side chains incorporated in these new compounds were selected from those present in substances which had previously shown activity[5,7] in animal screening experiments and also in clinical use, for example,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



(1)



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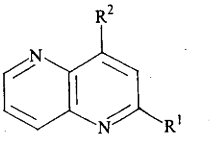

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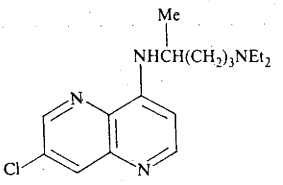
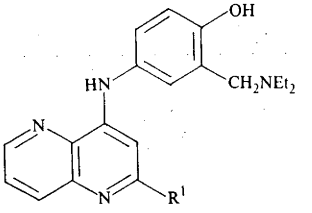


(4)



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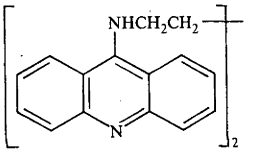

(6)

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 ^{1}H 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 ^{1}H 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).

Acknowledgments

We thank Dr D. J. Brown for helpful discussions, Professor A. W. Pound and Dr I. A. Clark for advice on the antimalarial screening and Mr S. Ireland for assistance with this operation, Dr M. D. Fenn for the ^{1}H and ^{13}C n.m.r. spectra, and Dr J. K. MacLeod and his staff for the mass spectra. One of us (W.-L.T.) thanks this University for support as a Scholar.

Manuscript received 14 May 1984

Aust. J. Chem., 1985, **38**, 459–65

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

Gordon B. Barlin and Weng-Lai Tan

Medical Chemistry Group, John Curtin School of Medical Research,
Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.

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.

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0004-9425/85/030459$02.00

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.

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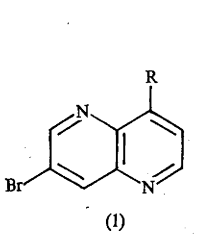
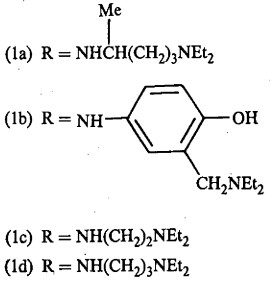
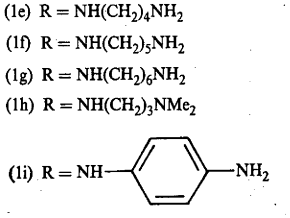
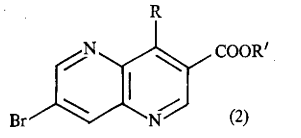


(1)







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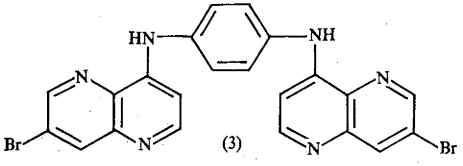

(3)

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

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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): δ 8·22, d, $J_{6,8}$ 1·0 Hz, H8; 8·60, br, H2,6.

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°): δ 6·64, d, $J_{2,3}$ 6 Hz, H3; 8·29, d, $J_{2,3}$ 6·0 Hz, H2; 8·33, d, $J_{6,8}$ 2 Hz, H8; 8·65, d, $J_{6,8}$ 2 Hz, H6.

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. ($CDCl_3$): δ 7·77, d, $J_{6,7}$ 5·0 Hz, H7; 8·62, d, $J_{2,4}$ 2·0 Hz, H4; 8·85, d, $J_{6,7}$ 5·0 Hz, H6; 9·07, d, $J_{2,4}$ 2 Hz, H2.

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. ($CDCl_3$): δ 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, H3′; 6·87, d, $J_{5,6}$ 8 Hz, H6; 6·99, d, $J_{3,5}$ 2·5 Hz, H3; 7·17, q, $J_{3,5}$ 2·5, $J_{5,6}$ 8 Hz, H5; 8·2, br, NH; 8·44, d, $J_{6',8'}$ 2 Hz, H8′; 8·48, d, $J_{2',3'}$ 5·5 Hz, H2′; 8·74, d, $J_{6',8'}$ 2 Hz, H6′.

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. ($CDCl_3$): δ 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, H3; 8·36, 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.

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. ($CDCl_3$): δ 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, H2; 7·0, br, NH; 8·37, d, $J_{6,8}$ 2 Hz, H8; 8·51, d, $J_{2,3}$ 5·5 Hz, H3; 8·69, d, $J_{6,8}$ 2·0 Hz, H6.

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. ($CDCl_3$): δ 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. ($CDCl_3$): δ 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. ($CDCl_3$): δ 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. ($CDCl_3$): δ 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. ($CDCl_3$): δ 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): δ 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. ($CDCl_3$): δ 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. ($CDCl_3$): δ 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.

Acknowledgments

We thank Dr D. J. Brown for helpful discussions, Professor A. W. Pound and Dr I. A. Clark for advice on the antimalarial screening and Mr S. Ireland for assistance with this operation, Dr M. D. Fenn for the ^{1}H n.m.r. spectra, and Dr J. K. McLeod and his staff for the mass spectra. One of us (W.-L.T.) thanks this University for support as a Scholar.

Manuscript received 8 October 1984

Aust. J. Chem., 1985, **38**, 905–11

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

Gordon B. Barlin and Weng-Lai Tan

Medical Chemistry Group, John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.

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.

[1] Barlin, G. B., and Tan, W.-L., *Aust. J. Chem.*, 1984, **37**, 1065.
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0004-9425/85/060905$02.00

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]).

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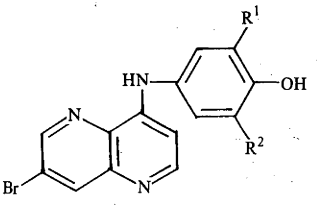
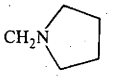
Table 1. Preliminary antimalarial screening results against *Plasmodium vinckei vinckei* in mice

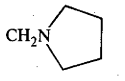
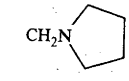
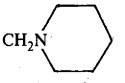
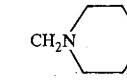
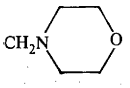
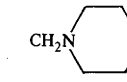
For details of test procedures see Experimental section. Times given are those after injection of the chemical under test. Time: h, hours; d, days; w, weeks; 0 h denotes pretreatment

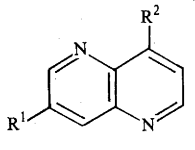
Compound	Solvent[A]	Dose (mg/kg)	Mean percentage of parasite-infected red cells 0 h	9 h	24 h	48 h	3 d	6 d	8 d	9 d	14 d	19 d	4 w
(1a)	PO	200	16	34	62	88	[B]						
(1b)[C]	NS	200	27	30	9	<1	<1	11	8	4	<1	<1	<1
(1c)	PO	200	16	27	16	3	5	26	14	5	<1	<1	<1
(1d)[C]	NS	200	19	26	3	<1	<1	25	28	18	<1	<1	<1
(1e)	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]			

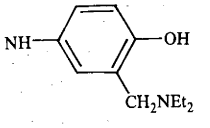
[A] PO, peanut oil; NS, normal saline.
[B] All three mice dead.
[C] Dihydrobromide.
[D] Two mice dead, parasitaemia of third mouse <1%.
[E] One mouse dead, parasitaemia of remaining two mice <1%.
[F] Two of the three mice dead at 3 days.
[G] Diphosphate.
[H] All mice dead at 10 days.



	R^1	R^2
(1a)	H	H
(1b)	H	CH_2NMe_2
(1c)	H	CH_2NPr_2
(1d)	H	
(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)		
(1i)		
(1j)		



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

	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).

Acknowledgments

We thank Dr D. J. Brown for helpful discussions, Professor A. W. Pound and Dr I. A. Clark for advice on the antimalarial screening and Mr S. Ireland for assistance with this operation, and Dr M. D. Fenn for the ^{1}H n.m.r. spectra. One of us (W.-L.T.) thanks this University for support as a Scholar.

Manuscript received 28 November 1984