TRICYCLIC SYSTEMS DERIVED FROM 2-AMINO-1,8-NAPHTHYRIDINES

SUMMARY OF THESIS

Methods available for the synthesis of 2-amino-1,8-naphthyridines are described. A brief summary of their physical properties is followed by a survey of the substitution reactions which these compounds undergo, and which can lead to the formation of various tricyclic systems. The angular systems formed are tetrazolo[1,5-a][1,8]naphthyridines, imidazo[1,2-a][1,8]naphthyridines, and pyrimido[1,2-a][1,8]naphthyridines; cyclisation in a linear fashion produces anthyridines.

The antibacterial properties of some 1,8-naphthyridine derivatives are discussed, in particular those of the established antibacterial agent nalidixic acid (1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one-3-carboxylic acid).

The practical work described in this thesis concerned the preparation of some new 2-amino-1,8-naphthyridines from 2,6-diamino-4-ethoxypyridine, as well as known examples prepared from 2,6-diaminopyridine.

The product of the reaction between 2,6-diaminopyridine and benzoylacetone has been assigned the structure 7-amino-4-methyl-2-phenyl-1,8-naphthyridine and not 7-amino-2-methyl-4-phenyl-1,8-naphthyridine as given in the literature. This assignment has been made on the results of spectroscopic studies.

Several new 2-vinylamino-1,8-naphthyridines were prepared from the aminonaphthyridines; the three reagents employed were diethyl ethoxymethylenemalonate, ethyl ethoxymethylene-acetoacetate and ethyl ethoxymethylenecyanoacetate.

Several new examples of the pyrimido [1,2-a] [1,8] naphthyridine system have been prepared by the intramolecular electrophilic cyclisation of 2-vinylamino-1,8-naphthyridines. Two new anthyridines have been prepared; one of these was prepared from a 2-vinylaminonaphthyridinone, and since all the anthyridines in the literature which have been prepared have been derived from 2-vinylaminonaphthyridinones, the significance of this is discussed, and an explanation put forward regarding the difficulties of preparing anthyridines from vinylamino-naphthyridines bearing only alkyl or aryl substituents.

The other example of the anthyridine system formed, 3,7-dicarbethoxy-5-ethoxyanthyridin-4,6(1H,9H)-dione, was made by a direct reaction with 2,6-diamino-4-ethoxypyridine, the first recorded one-step synthesis of an anthyridine from a pyridine.

Five new examples of the imidazo [1,2-a] [1,8] naphthyridine system have been prepared, by reaction of 2-amino-1,8-naphthyridines with α-halocarbonyl compounds. Three of these compounds contained one substituent in the imidazole ring, and this substituent has been assigned to the position furthest from the bridgehead nitrogen atom, on the basis of n.m.r. studies on these and other imidazonaphthyridines.

Three new 2-acetamido-1,8-naphthyridine-3-carboxamides have been prepared, and the cyclisation of these compounds has given three examples of a hitherto unreported heterocylcic system, the pyrimido [4,5-b] [1,8] naphthyridines. N.m.r. and mass spectroscopic data has been presented in support of the structural assignments.

A selection of compounds prepared in the course of this work has been submitted for inclusion in a screening programme for new antimicrobial compounds. Three compounds were also tested for anticonvulsant activity in rats. The results of these tests are presented; these show that none of the compounds submitted displayed any useful antimicrobial or anticonvulsant properties.

THESIS

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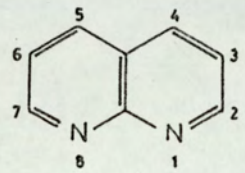
INTRODUCTION

SYNTHESES OF 2-AMINO-1,8-NAPHTHYRIDINES

1,8-Naphthyridine or 1,8-diazanaphthalene (1) is a bicyclic system formed by the fusion of two pyridine rings. Reviews of the synthesis and properties of 1,8-naphthyridines have been published by Allen in 1950, by Weiss and Hauser in 1961, and by Paudler and Kress in 1970. Most syntheses of 2-amino-1,8-naphthyridines (2) are adaptations of quinoline syntheses. They



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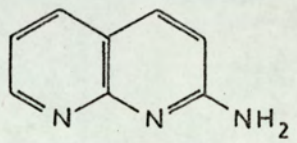

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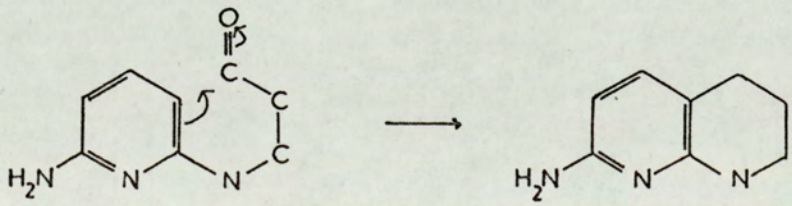
may be classified into three types: A, those that involve cyclisation into a pyridine ring, employing 2,6-diaminopyridine as starting material; B, those that employ 3-substituted-2-aminopyridines as starting materials; and C, the direct amination of 1,8-naphthyridine.

(A) Syntheses from 2,6-diaminopyridine.

These reactions involve an intramolecular electrophilic substitution of a side chain derivative of the 2-amino group into the 3-position of the pyridine ring (3 → 4). Factors controlling the synthesis are the electron availability at the 3-position and the nature of the side chain substituent.



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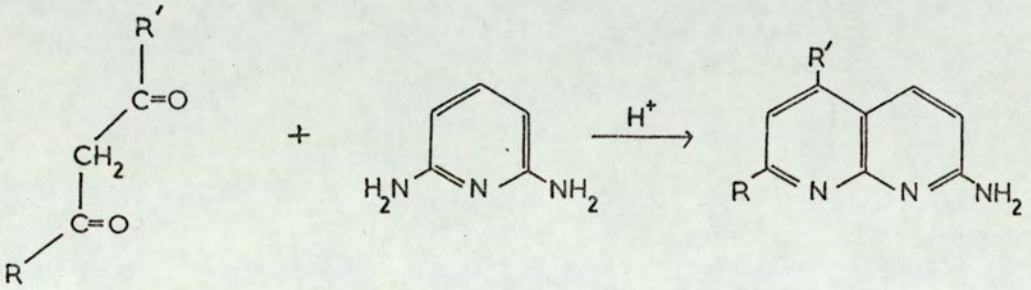
(1) Syntheses with β-diketones. Combes method.

7-Amino-2,4-dimethyl-1,8-naphthyridine (5) was prepared by the reaction of 2,6-diaminopyridine with acetylacetone. (Mangini and Colonna, 1943a). 2-Amino-7-methyl-1,8-naphthyridine (5a) was prepared by employing the dimethylacetal of acetylacetaldehyde. (Brown, 1965). Benzoylacetone gave a product to which has been assigned the structure 7-amino-2-methyl-4-phenyl-1,8-naphthyridine (6; Mangini and Colonna, 1943b).

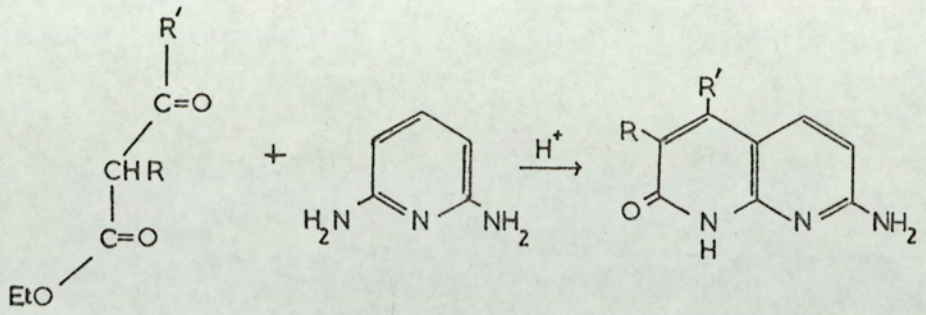


(5) R = R' = Me; (5a) R = Me, R' = H

(6) R = Me, R' = Ph

(2) Syntheses with β-keto esters. The Knorr synthesis.

The reaction of 2,6-diaminopyridine with ethyl acetoacetate gave 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7; Brown, 1965). The same compound was prepared by Hauser and Weiss in 1949 who incorrectly assigned to it the structure 7-amino-2-methyl-1,8-naphthyridin-4(1H)-one. Ethyl benzoylacetate has been shown to give 7-amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8; Mangini and Colonna, 1941); similarly, ethyl phenylformylacetate gave 7-amino-3-phenyl-1,8-naphthyridin-2(1H)-one (9; Carboni et al., 1969a). 7-Amino-4-ethoxycarbonyl-1,8-naphthyridin-2(1H)-one (10) was prepared from 2,6-diaminopyridine and ethyl oxalacetate (Carboni and Pirisino, 1962a); the same workers later prepared 7-amino-4-ethoxycarbonyl-3-methyl-1,8-naphthyridin-2(1H)-one (11) using ethyl 2-oxalylpropionate. (Carboni and Pirisino, 1962b).



(7) R = H, R' = Me

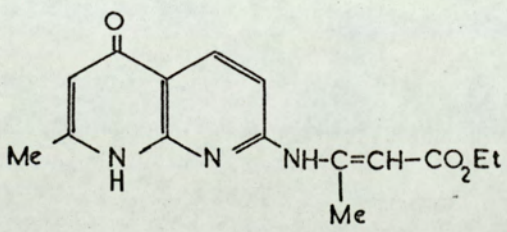
(8) R = H, R' = Ph

(9) R = Ph, R' = H

(10) R = H, R' = CO_2Et

(11) R = Me, R' = CO_2Et

Carboni and his co-workers (1966a) showed that treatment of 2,6-diaminopyridine with ethyl acetoacetate at room temperature for a prolonged period of time gives a mixture of products. 7-Amino-4-methyl-1,8-naphthyridin-2(1H)-one (7) can be isolated in fair yield; working up the mother liquors yields the vinylamino derivative (12) which can be degraded thermally to 7-amino-2-methyl-1,8-naphthyridin-4(1H)-one (13).



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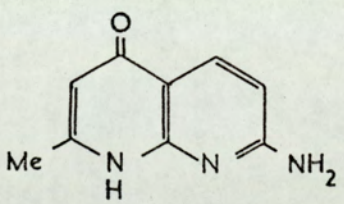

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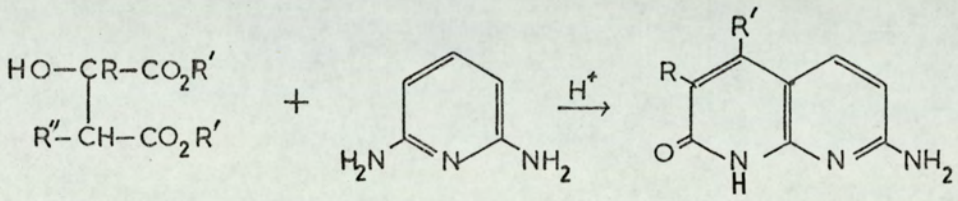
(3) Syntheses from α-hydroxyacids and esters.

The reaction of 2,6-diaminopyridine with malic acid (14) produced 7-amino-1,8-naphthyridin-2(1H)-one (15). Similarly, ethyl 3-methylmalate (16) gave 7-amino-3-methyl-1,8-naphthyridin-2(1H)-one (17), and citric acid (18) led to 7-amino-1,8-naphthyridin-2(1H)-one-4-acetic acid (19). (Carboni et al., 1964b).



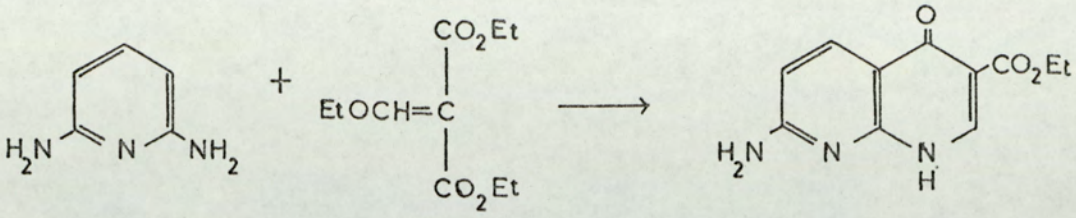
(14) R = R' = R'' = H (15) R = R' = H

(16) R = H, R' = Et, R'' = Me (17) R = Me, R' = H

(18) R = CH_2CO_2H, R' = R'' = H (19) R = H, R' = CH_2CO_2H

(4) Synthesis with diethyl ethoxymethylenemalonate.

A good yield of ethyl-7-amino-1,8-naphthyridin-4(1H)-one-3-carboxylate (20) was obtained by condensation of 2,6-diaminopyridine with diethyl ethoxymethylenemalonate (EMME). This ester was easily hydrolysed to the corresponding acid which was decarboxylated to form 7-amino-1,8-naphthyridin-4(1H)-one (21). (Adams et al., 1946).



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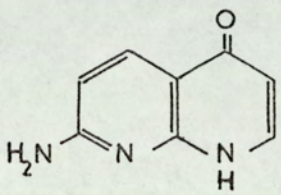

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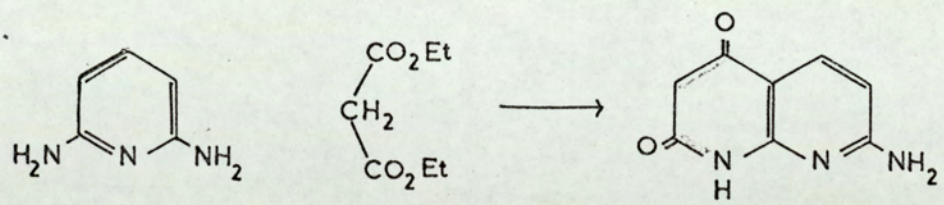
(5) Synthesis with diethyl malonate.

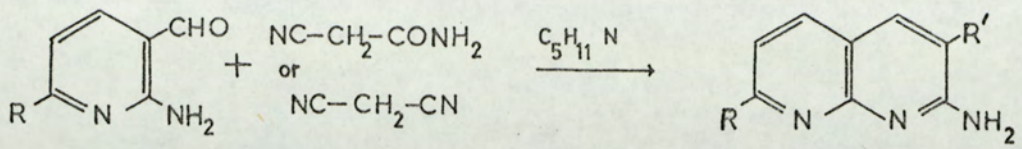
7-Amino-1,8-naphthyridin-2,4(1H,3H)-dione (22) was prepared by Lappin et al (1950) by reaction of diethyl malonate with 2,6-diaminopyridine. No catalyst was required, and the yield was quantitative.



(22)

(B) Syntheses from 3-substituted-2-aminopyridines. The Friedländer synthesis.

These syntheses employ condensations of activated methylene compounds with 2-aminonicotinaldehydes. The reactions are carried out under mild conditions in the presence of a base catalyst.



(23) R = H

(24) R = H, R' = CN

(25) R = H, R' = $CONH_2$

(26) R = Ph

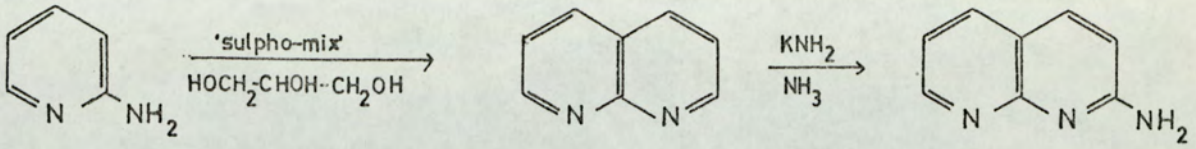
(27) R = Ph, R' = CN

(28) R = Ph, R' = $CONH_2$

Excellent yields of 2-amino-3-cyano-1,8-naphthyridine (24) and 2-amino-1,8-naphthyridine-3-carboxamide (25) were obtained by the reaction of 2-aminonicotinaldehyde (23) with malononitrile and cyanoacetamide respectively. (Hawes and Wibberley, 1966). The 7-phenyl analogues (27 and 28) were similarly prepared from 2-amino-6-phenylnicotinaldehyde (26). The same workers prepared 2-amino-1,8-naphthyridine (2) from 2-amino-3-cyano-1,8-naphthyridine (24) by hydrolysis followed by decarboxylation. Similarly, 2-amino-7-phenyl-1,8-naphthyridine was obtained from 2-amino-3-cyano-7-phenyl-1,8-naphthyridine (27). (Hawes and Wibberley, 1967).

(C) Direct amination of 1,8-naphthyridine. The Chichibabin synthesis.

1,8-Naphthyridine (1) was prepared via a Skraup reaction on 2-aminopyridine by Paudler and Kress (1968); amination of this compound gave 2-amino-1,8-naphthyridine (2). Confirmation of the structure was provided by n.m.r. spectroscopy.



(1) (2)

PROPERTIES AND REACTIONS OF 2-AMINO-1,8-NAPHTHYRIDINES

Physical Properties

All the known 2-amino-1,8-naphthyridines are stable crystalline solids, having fairly high melting points (above 200°). The 2-amino-1,8-naphthyridinones are all insoluble in most common organic solvents and have melting points in excess of 350°. Spectroscopic properties of these compounds, including ultra-violet, infra-red, nuclear magnetic resonance and mass spectra have been reported though such data for all the known 2-amino-1,8-naphthyridines is incomplete.

A knowledge of the π-electron density distribution in the 1,8-naphthyridine system enables one to suggest that electrophilic substitution will occur at the 3-position in 2-amino-1,8-naphthyridines. The calculated total π-electron densities for 1,8-naphthyridine are shown in Figure 1; this indicates that the carbon atom in the 3-position is relatively electron rich. (Paudler and Kress, 1968). In 2-amino-1,8-naphthyridines, the amino group should further enhance this property by virtue of the electron donating capacity of the amino group, and the n.m.r. data for 2-amino-1,8-naphthyridine itself (Figure 2; τ values in trifluoroacetic acid) gives an indication of the

electron density at the 3-position. The protons in the 3- and 6-positions are shielded relative to those in the 4-, 5- and 7-positions. (Paudler and Kress, 1968).

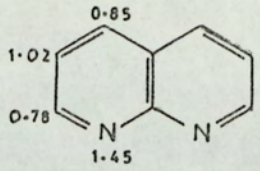


Figure 1
Calculated total π-electron densities.

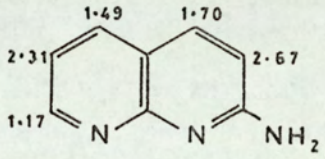


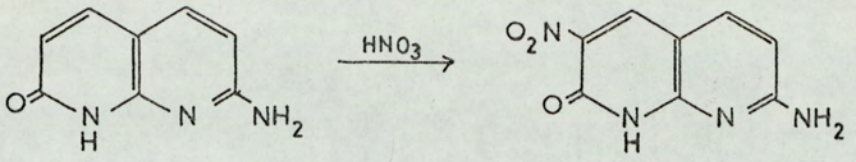
Figure 2
Chemical shifts shown as τ values (CF_3CO_2D).

Electrophilic substitutions.

Chlorination of 7-amino-2,4-dimethyl-1,8-naphthyridine (5) has been reported to give a high yield of the 6-chloro compound. (Cilag Limited, 1949).

The nitration of 7-amino-1,8-naphthyridin-2(1H)-one (15) has been studied by Carboni et al (1969b). Nitration at room temperature gave 7-amino-3-nitro-1,8-naphthyridin-2(1H)-one (29). The isomeric compound, 7-amino-6-nitro-1,8-naphthyridin-2(1H)-one (30) was obtained by condensation between 2,6-diamino-3-nitropyridine and malic acid. Both these mono-nitro compounds gave 7-amino-3,6-dinitro-1,8-

naphthyridin-2(1H)-one (31) by nitration under more vigorous conditions.



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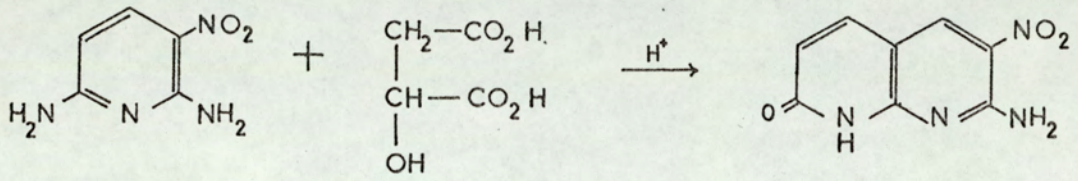

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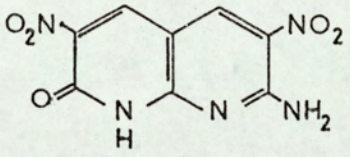
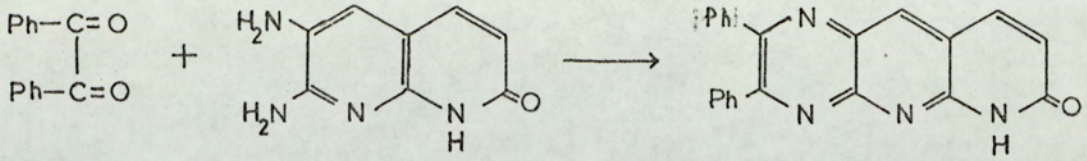


(31)

Treatment of the mono-nitro compound (30) with tin and hydrochloric acid gave 6,7-diamino-1,8-naphthyridin-2(1H)-one (32) which in turn gave 2,3-diphenylpyrazino [2,3-b] [1,8] naphthyridin-8(9H)-one (33) when treated with benzil. This is the first reported preparation of this ring system.



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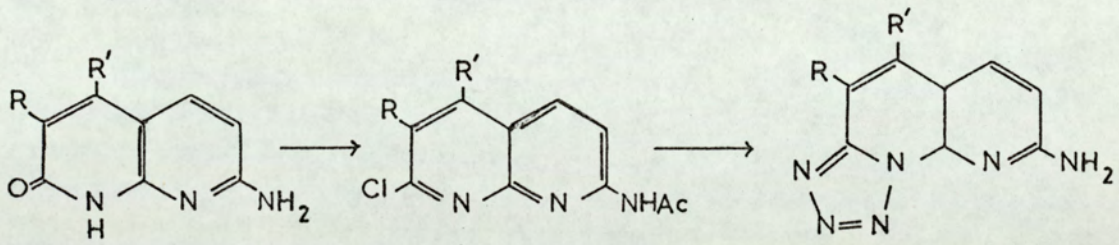
Formation of tetrazolo [1,5-a] [1,8] naphthyridines

Intramolecular electrophilic substitutions at the heterocyclic nitrogen atom are involved in the formation of tetrazolo-derivatives of 1,8-naphthyridines.

Reaction of 7-amino-1,8-naphthyridin-2(1H)-one (15) with acetic anhydride followed by treatment of the product with phosphoryl chloride gave 2-acetamido-7-chloro-1,8-naphthyridine (34) which on treatment with sodium azide followed by alkali produced 8-aminotetrazolo[1,5-a] [1,8]naphthyridine (35). (Carboni et al., 1966a)



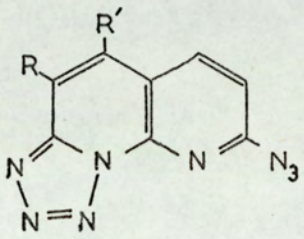
(34) R = R' = H (35) R = R' = H

(36) R = H, R' = Me

(37) R = H, R' = Ph

(38) R = Me, R' = H

Analogous compounds (36, 37 and 38) were prepared from 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7; Carboni et al., 1967a), 7-amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8; Carboni et al., 1968) and 7-amino-3-methyl-1,8-naphthyridin-2(1H)-one (17; Carboni et al., 1967b). The authors were not able to decide whether the azidotetrazolo-derivatives of these three naphthyridines exist in form (39) or the isomeric structure (40).



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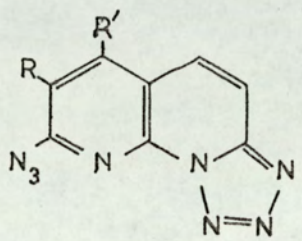

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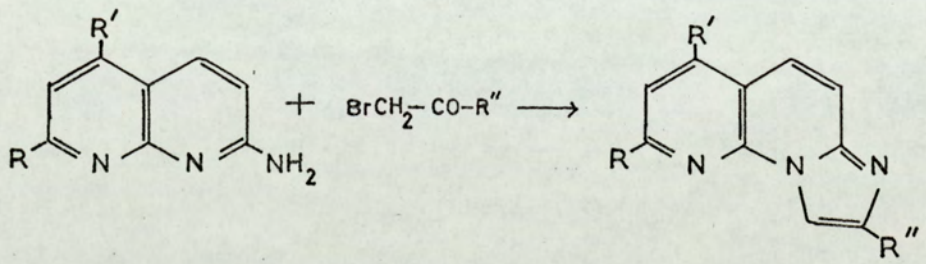
Formation of imidazo[1,2-a][1,8]naphthyridines.

Two examples of the imidazo[1,2-a][1,8]naphthyridine system have been reported in the literature. (Schmid and Gründig, 1958). Both were prepared by reaction of 7-amino-2,4-dimethyl-1,8-naphthyridine (5) with α-halocarbonyl compounds. Bromoacetone gave 2,4,8-trimethylimidazo[1,2-a][1,8]naphthyridine (41) and



(5)

(41) R = R' = R'' = Me

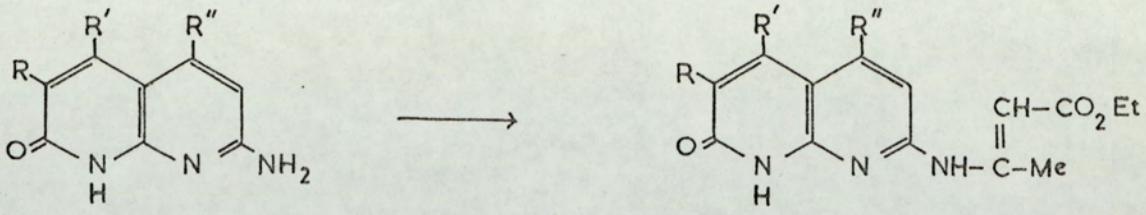
(42) R = R' = Me, R'' = Ph

phenacyl bromide gave 2,4-dimethyl-8-phenylimidazo[1,2-a][1,8] naphthyridine (42). The assignment of the substituent in the imidazole ring to the 8-position has not been supported by any further studies.

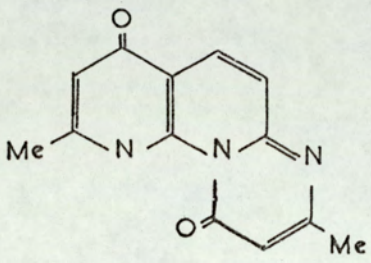
Formation of pyrimido[1,2-a][1,8]naphthyridines.

2-Amino-1,8-naphthyridines react readily with ethyl acetoacetate and with diethyl ethoxymethylenemalonate (EMME) to form vinylamino derivatives; the latter may be induced to undergo intramolecular electrophilic cyclisation, in which the heterocyclic nitrogen atom acts as the electron donor, to produce angular tricyclic compounds, the pyrimido[1,2-a][1,8] naphthyridines.

Carboni and his colleagues (1966b, 1967c) prepared the vinylamino compounds (43 a-h) from eight different 7-amino-1,8-naphthyridin-2(1H)-ones; thermal cyclisation in an inert medium at 250° gave the pyrimido[1,2-a][1,8] naphthyridin-2,10(1H,10H)-diones (44 a-h). 2,8-Dimethylpyrimido[1,2-a][1,8]naphthyridin-4,10(1H,10H)-dione (45) was prepared from the vinylamino compound (12) derived from 7-amino-2-methyl-1,8-naphthyridin-4(1H)-one (13).



(43) a - h



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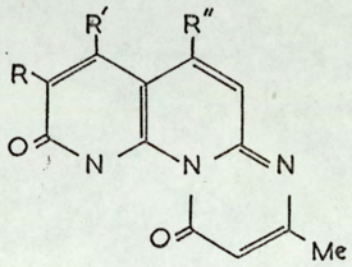
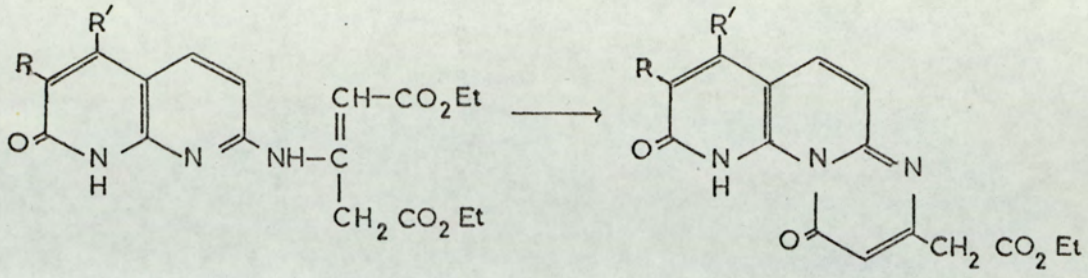


(44) a - h

	R	R'	R''
a	H	Me	H
b	H	H	H
c	Me	H	H
d	H	Ph	H
e	H	H	Ph
f	H	CO_2Et	H
g	H	CO_2H	H
h	Ph	H	H

Vinylamino compounds derived from 2-amino-1,8-naphthyridines and diethyl acetonedicarboxylate were also reported by Carboni et al (1969a). The five vinylamino compounds (46 a-e) were cyclised thermally to the pyrimido[1,2-a] [1,8] naphthyridines (47 a-e).



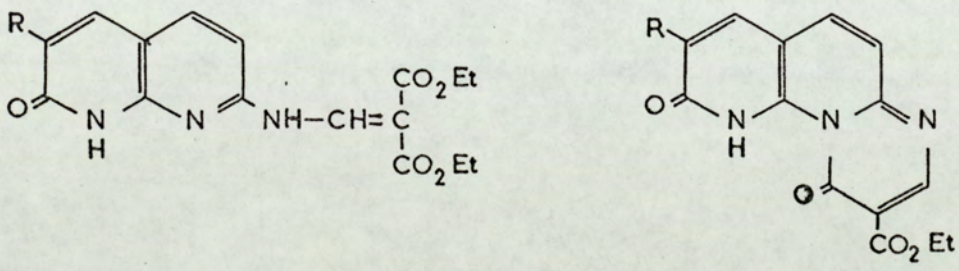
(46) a - e (47) a - e

(a) R = R' = H (d) R = H, R' = Me

(b) R = Me, R' = H (e) R = H, R' = Ph

(c) R = Ph, R' = H

Ethoxymethylenemalonic ester was used by Carboni et al., (1967d) to prepare two further pyrimido[1,2-a][1,8]naphthyridines via the intermediate vinylamino derivatives. Ethyl 3-methylpyrimido[1,2-a][1,8]naphthyridin-2,10(1H,10H)-dione-9-carboxylate (49) was prepared from 7-amino-3-methyl-1,8-naphthyridin-2(1H)-one (17) via the vinylamino derivative (48). The 3-phenyl analogue (50) was similarly formed from 7-amino-3-phenyl-1,8-naphthyridin-2(1H)-one (9).



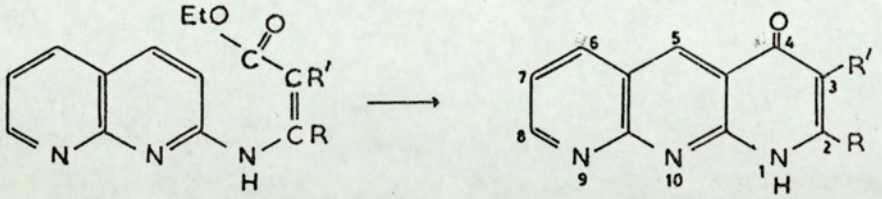
(48) R = Me (49) R = Me

(50) R = Ph

All the pyrimido [1,2-a] [1,8] naphthyridines reported were solids which could be recrystallised from ethanol or methanol, with melting points in the range 160-310°. Analyses, ultra-violet and infra-red spectra were presented as evidence for the structural assignments; no n.m.r. data was given. It is reported that all could be transformed to the parent amino-naphthyridines by treatment in aqueous alkaline solution.

Formation of anthyridines.

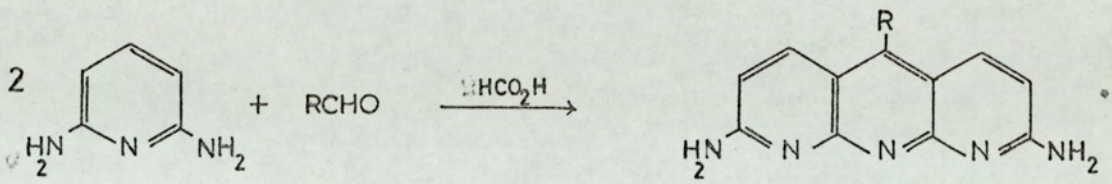
When vinylamino derivatives of 1,8-naphthyridines are cyclised thermally they may be expected to cyclise either onto the heterocyclic nitrogen, to produce the angular pyrimido [1,2-a] [1,8] naphthyridines already described, or into the pyridine ring to produce linear tricyclic compounds, the anthyridines. Anthyridine is the accepted trivial name for 1,9,10-triazaänthracene or pyrido [2,3-b] [1,8] naphthyridine and the numbering shown (51) is that given in the Ring Index. (Patterson, Capell and Walker, 1960).



(51)

Schoeller and von Schickh (1935) reported the preparation of anthyridines by the reaction of 2,6-diaminopyridine or one of its acylated substitution products with an aldehyde and formic acid. For example, a mixture of formic acid and formaldehyde gave the product formulated as 2,8-diaminoanthyridine (52). All the

compounds prepared by this method were bright yellow water-soluble solids possessing bactericidal properties. No analytical data or other evidence was given in support of the structural assignments. No evidence was given by Takahashi et al., (1947)



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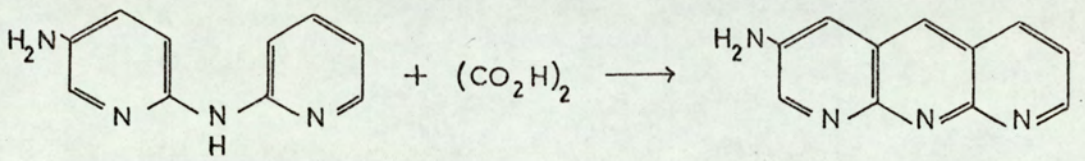
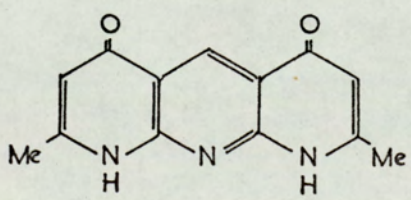


(53)

who claimed the preparation of 3-aminoanthyridine (53) from 5-amino-2,2'-dipyridylamine by treatment with oxalic acid in glycerin at 130°. The product had a melting point of 128°.

The anthyridine (54) which Hauser and Weiss (1949) claimed to have isolated by treatment of the divinylamino compound (55) derived from 2,6-diaminopyridine and ethyl acetoacetate was



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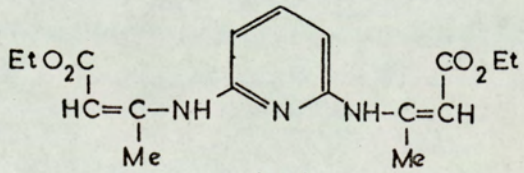
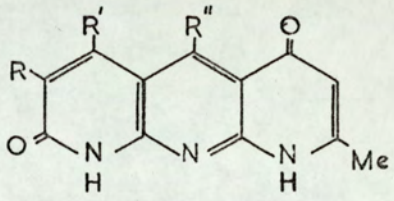


(55)

shown by Carboni et al (1966a) to be the pyrimido[1,2-a][1,8] naphthyridine (45).

Treatment of the vinylamino compounds (43) at higher temperatures than those used to produce the pyrimido[1,2-a][1,8] naphthyridines (44) led to a series of anthyridines (56; Carboni et al., 1966b, 1967c), and the anthyridine (54) was similarly prepared from the vinylamino compound (12).

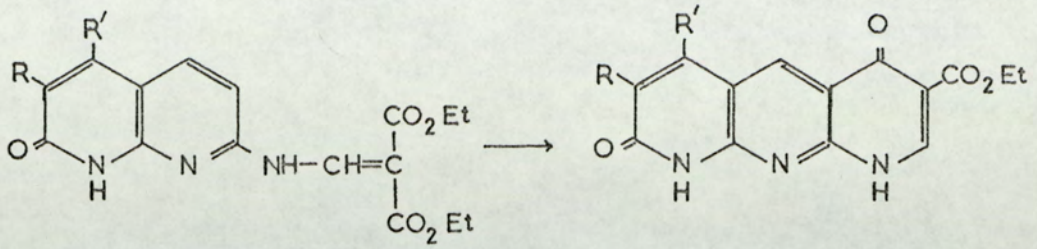
	R	R'	R''
a	H	Me	H
b	H	H	H
c	Me	H	H
d	H	Ph	H
e	H	H	Ph
f	H	CO_2Et	H
g	H	CO_2H	H
h	Ph	H	H



(56) a - h

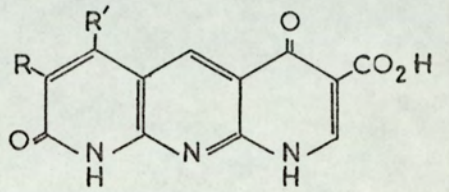
The five anthyridines (56 a, b, c, d and h) could also be prepared by high temperature cyclisation of the vinylamino compounds (46 a-e). (Carboni et al 1969a). All the anthyridines (56 a-h) could also be prepared by treating the pyrimido[1,2-a][1,8]naphthyridines (44 a-h) at high temperatures. (Carboni et al 1966b, 1967c).

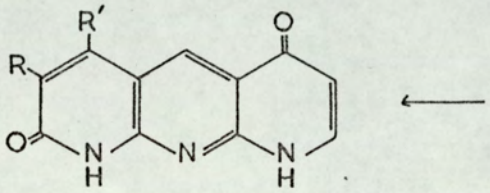
The anthyridine carboxylic esters (58 a-e) were also prepared by Carboni et al (1967d) by treatment of the vinylamino compounds (57 a-e) at 250°. Alkaline hydrolysis of these anthyridines led to the carboxylic acids (59 a-e) and decarboxylation of these acids to the anthyridine-diones (60 a-e).



(57) a - e

(58) a - e





(60) a - e

(59) a - e

(a) R = R' = H

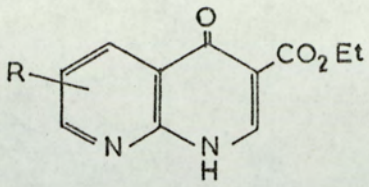
(b) R = Me, R' = H

(c) R = H, R' = Me

(d) R = Ph, R' = H

(e) R = H, R' = Ph

The fact that the compounds (58) can be hydrolysed is supporting evidence for the assignment of the linear tricyclic structure to these compounds, rather than the angular tricyclic structures of type (49). This stability of the anthyridine ring system compared with pyrimidonaphthyridines (which break down to the parent aminonaphthyridines) is analogous to that of the naphthyridine carboxylic esters (61) compared with pyridopyrimidines (62). (Lappin, 1948). In the angular structures, the $-N-\overset{R}{\underset{|}{C}}=O$ group is susceptible to acid-catalysed cleavage of the acyl function.



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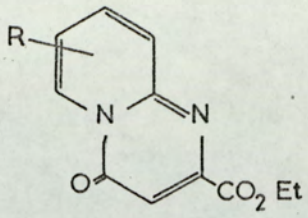
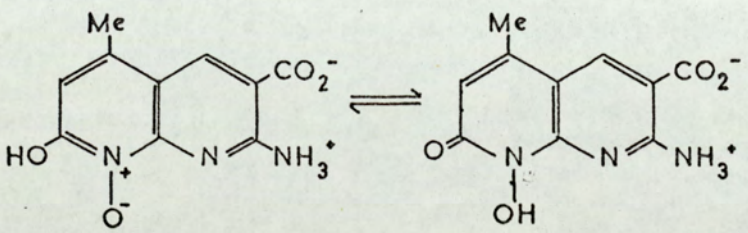


(62)

Further evidence for the structure of the anthyridines was provided by analyses, UV and IR data. All the compounds were high melting-point solids (above 320°) which were insoluble in water and common organic solvents.

The anthyridines were stable to treatment with nitric acid or potassium permanganate. Peroxyacetic acid however, produced the N-oxides of 2-amino-1,8-naphthyridine-3-carboxylic acids. For example, the anthyridine (56a) gave the N-oxide (63) which on treatment with $TiCl_3$ gave the naphthyridine (64). (Carboni et al 1966b). The structure of the degradation products provided further evidence for the structure of the anthyridines.



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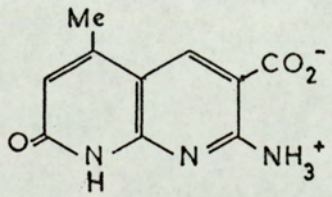
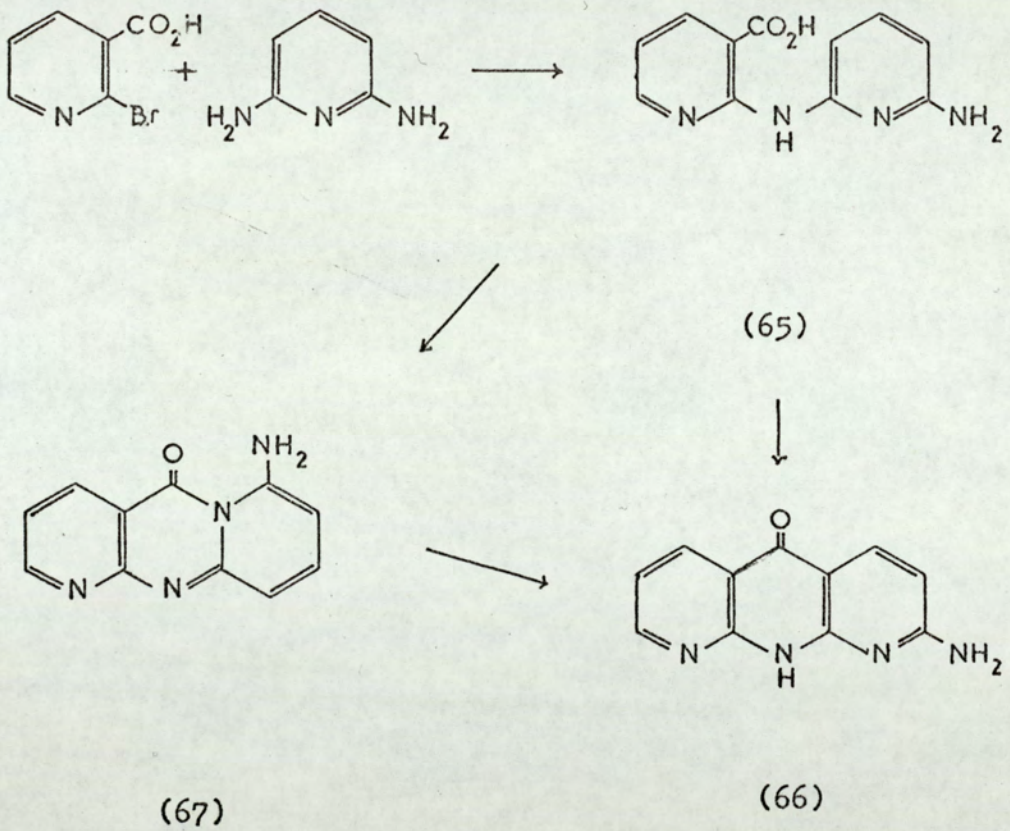


(64)

An alternative synthesis of anthyridines was reported by Carboni et al (1969c). An Ullmann reaction between 2-bromonicotinic acid and 2,6-diaminopyridine gave the dipyridylaminocarboxylic acid (65) which was converted to the anthyridine (66) by treatment in sulphuric acid at 200°; treatment of the same acid in polyphosphoric acid at 170° gave the dipyrido [1,2-a:2',3'-d] pyrimidinone (67) which itself could be converted to the isomeric anthyridine (66) by treatment with sulphuric acid at 200°.



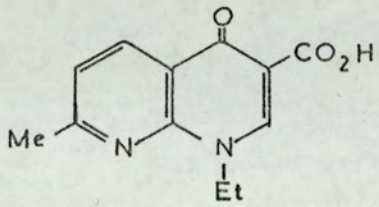
(65)

(67)

(66)

Antibacterial properties of some 1,8-naphthyridine derivatives.

Nalidixic acid (Negram; 1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one-3-carboxylic acid (68) is an antibacterial drug in current clinical use. It was prepared by Lesher et al (1962) from 2-amino-6-methylpyridine.



(68)

Nalidixic acid belongs to the class of agents which act by inhibiting nucleic acid synthesis. (Russell, 1969). In stationary phase cultures of Escherichia coli, nalidixic acid has no effect, but morphological changes were induced during the growing phase.

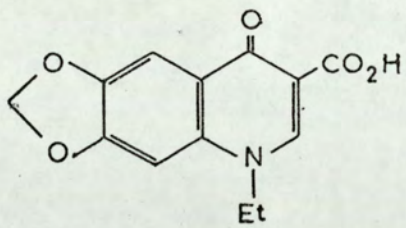
The drug is unusual as it is active in vitro and in vivo against many gram-negative organisms including Proteus, Aerobacter, Klebsiella, Shigella, Brucella, Pseudomonas, and Salmonella, whilst it is practically without effect against gram-positive bacteria. It is administered orally, easily absorbed through the gastro-intestinal tract and excreted in the urine where it is in sufficient concentration to be effective against the causative organisms of urinary tract infections, especially those due to Proteus species. In clinical practice, its high activity and relative freedom from side effects makes nalidixic acid a useful alternative to the sulphonamides, antibiotics and nitrofurazones, particularly for cystitis and pyelonephritis. (Swinney, 1964).

The discovery of nalidixic acid stimulated a search for other

active compounds in the 1,8-naphthyridine series. Hawes (1967) has reported the results of pharmacological screening tests on several 2-amino-1,8-naphthyridines. Diuretic effects in rats were found in 2-amino-3-phenyl-1,8-naphthyridine, 2-amino-3(2-pyridyl)-1,8-naphthyridine and 2-amino-7-phenyl-1,8-naphthyridine-3-carboxamide as well as in other 1,8-naphthyridines not bearing an amino substituent. Both 2-amino-1,8-naphthyridine-3-carboxamide and its 7-phenyl derivative showed anti-inflammatory activity in rats.

Antibacterial activity against selected micro-organisms in vitro was lacking in the above-mentioned compounds.

It has been found that some aspects of the nalidixic acid molecule can be varied quite markedly without loss of activity. The quinoline derivative, oxolinic acid (69) is one example which has been clinically tested; it is highly active against gram-negative organisms. (Doub, 1967).



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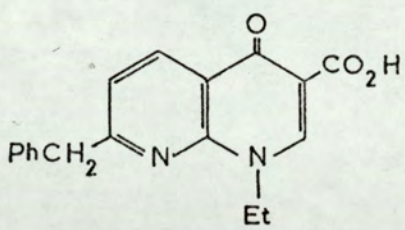
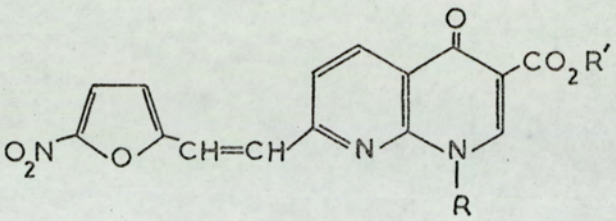


(70)

Amfonelic acid, 7-benzyl-1-ethyl-1,8-naphthyridin-4(1H)-one-3-carboxylic acid (70) has been found to be a potent C.N.S. stimulant. (Lesher, 1969).

Antibacterial properties have been found in furylvinyl-1,8-naphthyridines (71) prepared by condensation of the appropriate furfuraldehyde with methyl-1,8-naphthyridines. (Daiichi Seiyaki Co., 1969).



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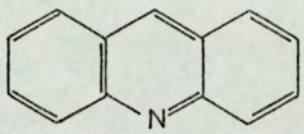


(72)

Anthyridines may be regarded as 8diaza-analogues of acridine (72); derivatives of the latter have long been important in the pharmaceutical field as antiseptic compounds for topical application, and the synthesis of anthyridines has been pursued with a view to testing the antimicrobial properties of these compounds. (Carboni et al., 1969c).

DISCUSSION

The aim of the work described in this thesis was to investigate the conversion of 2-amino-1,8-naphthyridines into tricyclic compounds for an evaluation of their microbiological and pharmacological properties. Four tricyclic systems have been investigated:-

(1) pyrimido [1,2-a][1,8] naphthyridines;

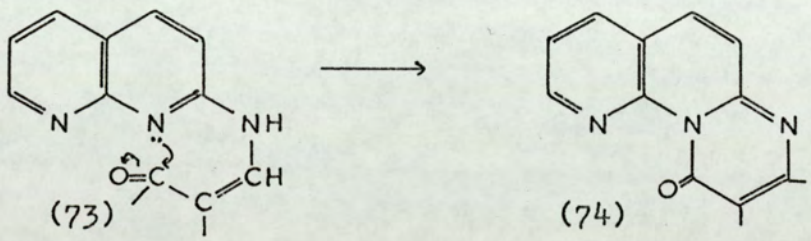
(2) anthyridines;

(3) imidazo [1,2-a][1,8] naphthyridines;

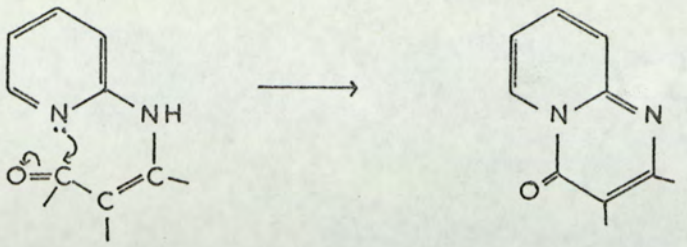
(4) a hitherto unreported system, the pyrimido [4,5-b] [1,8] naphthyridines.

THE SYNTHESIS OF PYRIMIDO[1,2-a][1,8]NAPHTHYRIDINES.

The synthesis of these angular tricyclic compounds was based on the method already used successfully by Carboni and his colleagues (1966b, 1967c, 1967d, 1969a), which involves the thermal cyclisation of suitably substituted 2-vinylamino-naphthyridines (73⟶74).



Their formation is similar to that of pyridopyrimidines (75⟶76) and is more favourable than formation of linear compounds because the electron density at the nitrogen atom of the pyridine ring is higher than elsewhere in the ring.



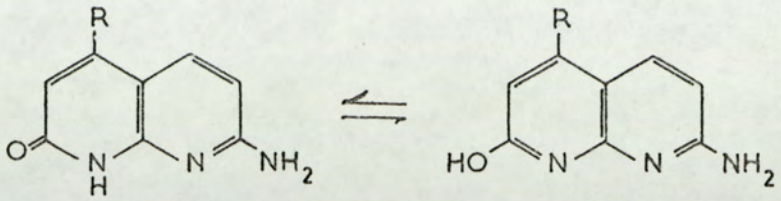
(75) (76)

The syntheses of pyrimido[1,2-a][1,8]naphthyridines achieved during this work involved the preparation of 2-amino-1,8-naphthyridines, including some new examples, the formation of 2-vinylaminonaphthyridines of four types, and the cyclisation of the latter compounds. The formation of pyrimidonaphthyridines from 2,6-divinylaminopyridines was also attempted.

(a) The synthesis of 2-amino-1,8-naphthyridines.

7-Amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8) was prepared by the literature method (Carboni et al 1968) from 2,6-diaminopyridine and ethyl benzoylacetate. The reaction of 2,6-diaminopyridine with ethyl acetoacetate gave 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7; Brown, 1965). 7-Amino-2,4-dimethyl-1,8-naphthyridine (5) was prepared by heating 2,6-diaminopyridine and acetylacetone in orthophosphoric acid as described by Bernstein et al (1947). Attempts to prepare 7-amino-2,4-diphenyl-1,8-naphthyridine by reaction of 2,6-diaminopyridine with dibenzoylmethane in orthophosphoric acid resulted in the recovery of starting materials only. Beyer (1887) reported that dibenzoylmethane failed to react with aniline in the presence of sulphuric acid.

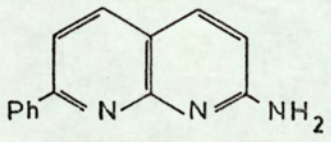
The infra-red spectra for the naphthyridinones (7) and (8) indicate that these compounds exist predominantly in the



(77) (78)

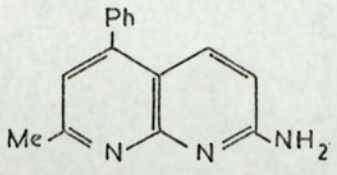
amide form (77) rather than the tautomeric hyroxy form (78). Both compounds show a strong band at 1670 $cm.^{-1}$ due to the C=O stretching vibration, whereas broad -OH vibration bands at c. 3400 $cm.^{-1}$ are absent. Both the compounds are referred to in the literature as hydroxynaphthyridines.

Benzoylacetaldehyde with 2,6-diaminopyridine in orthophosphoric acid gave 2-amino-7-phenyl-1,8-naphthyridine (79). This compound had been prepared by Hawes and Wibberley (1967) by the hydrolysis followed by decarboxylation of 2-amino-7-phenyl-1,8-naphthyridine-3-carboxamide (28)

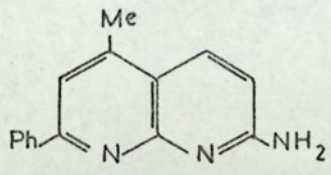


(79)

The reaction of 2,6-diaminopyridine with benzoylacetone in orthophosphoric acid gave a slightly better yield of product of equal melting point to that reported by Mangini and Colonna (1943b), and the spectroscopic evidence, summarised below, and given detail in the Experimental section, indicates that the product is 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) and not the isomeric compound, 7-amino-2-methyl-4-phenyl-1,8-naphthyridine (6).

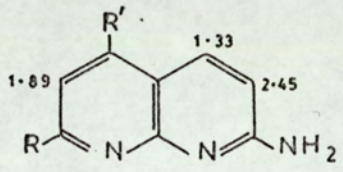


(6)



(80)

The n.m.r. assignments for the ring protons of the methylphenylnaphthyridine (6) or (80) are shown in figure 3.



(Me group resonance (R or R') = τ6.96)

Figure 3

Chemical shifts in τ values (CF_3CO_2H)

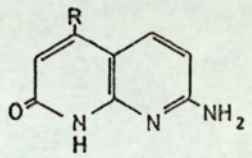
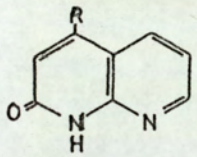
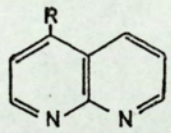
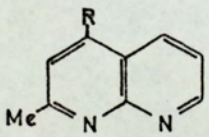
N.m.r. assignments for 2-amino-7-phenyl-1,8-naphthyridine (79), 2-amino-7-methyl-1,8-naphthyridine (5a) and 7-amino-2,4-dimethyl-1,8-naphthyridine (5) have been made and are recorded in the Experimental section. The methyl groups in the latter compound are isochronous, and the resonance position is very close to that of the methyl group in the methylphenylnaphthyridine (figure 3) thus it is not possible to assign the methyl group in the latter compound to the 4-position on the basis of its chemical shift.

Chemical shifts for the ring protons in the two possible methylphenylnaphthyridines (6) and (80) depends on a knowledge of the effects of methyl and phenyl groups on the

ortho position (this data is available in tables such as those compiled by Elvidge (1967)) and on the effects of methyl and phenyl groups on the peri position. Data on the latter effects is not given in published tables, thus the results for various compounds have been collected together in Table 1, and illustrates that protons are deshielded more by a peri-methyl than by a peri-phenyl or peri-hydrogen.

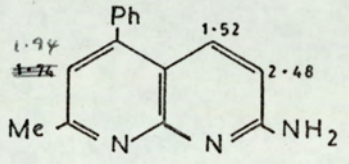
Table 1

Chemical shifts (5-H) in τ values.

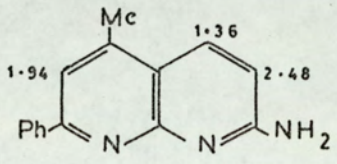
Compound	R = H	R = Ph	R = Me
		1.70	1.53
Solvent = CF_3CO_2H			
	1.96	1.95	1.84
Solvent = CF_3CO_2H			
	1.78	-	1.62
Solvent = $CDCl_3$*			
	1.99	-	1.74
Solvent = $CDCl_3$*			

*Data from Paudler and Kress (1967a)

From the available data, one may forecast n.m.r. shift values for the two isomers, 7-amino-2-methyl-4-phenyl-1,8-naphthyridine (6) and 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) and these are shown in figure 4. When these forecast values are compared with the found values (figure 3) it may be seen that the product of the reaction must be 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) and not the isomer (6) as suggested by Mangini and Colonna (1943b).



(6)



(80)

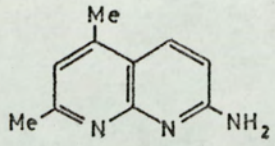
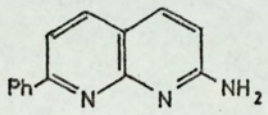
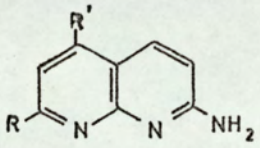
Figure 4

Predicted chemical shifts in τ values (CF_3CO_2H).

Further evidence for the structure of the aminomethylphenylnaphthyridine (6) or (80) is provided by the mass spectrum of this compound, 7-amino-2,4-dimethyl-1,8-naphthyridine (5), and 2-amino-7-phenyl-1,8-naphthyridine (79). The full data is recorded for each compound in the Experimental section. Table 2 shows some of the more important assignments.

Table 2

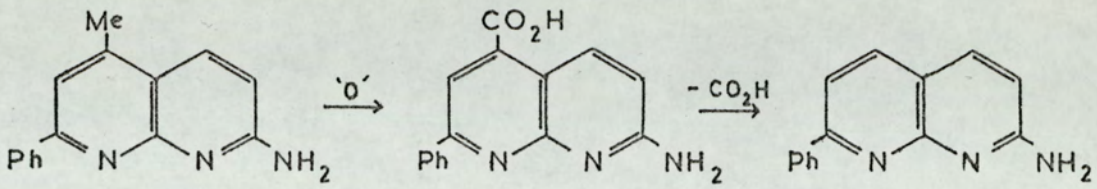
Mass spectral data - %relative abundance of peaks

Compound	M	M-H	M-Me	M-HCN	M-Me-PhCN
 (5)	100	18	1	22	-
 (79)	100	38	-	10	-
 (6) or (80)	100	24	15	13	4

The loss of a PhCN fragment (m/e 103) occurs from the (M-1) ion in 2-amino-7-phenyl-1,8-naphthyridine (79). The loss of a PhCN fragment (in the sequence M→M-Me→M-Me-PhCN) from the methylphenylnaphthyridine (6 or 80) indicates the 2-phenyl isomer (80).

However the absence of a MeCN fragment (m/e 41) in the spectrum of the methylphenylnaphthyridine (6 or 80) cannot be taken as evidence for the structure being the 4-methyl isomer. Paudler and Kress (1967b) reported no cases of MeCN fragments being expelled in one step from parent ions in the spectra of various methyl-1,8-naphthyridines, and Draper and Maclean (1968) reported similar findings on examination of various monomethylquinolines.

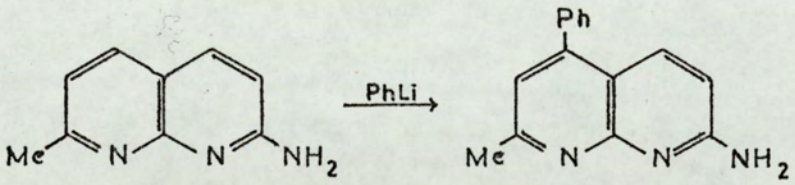
Attempts to oxidise compound (80) or its acetylated derivative, 7-acetamido-4-methyl-2-phenyl-1,8-naphthyridine, were not successful. It had been hoped to decarboxylate the oxidation product (81) to produce the known 2-amino-7-phenyl-1,8-naphthyridine (79).



(80) (81) (79)

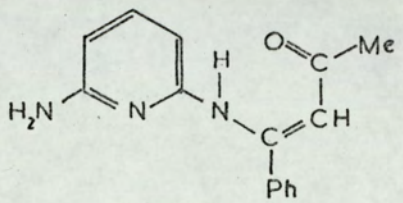
Unchanged starting material was obtained when oxidations with the usual inorganic reagents were attempted. Attempts to prepare the styryl derivative of the methylphenylnaphthyridine (80) were also unsuccessful. Some methylquinolines have been oxidised *via* their styryl derivatives. (Royer, 1949).

A theoretically attractive method for the unequivocal synthesis of 7-amino-2-methyl-4-phenyl-1,8-naphthyridine (6) involves the reaction of phenyl lithium on the known 2-amino-7-methyl-1,8-naphthyridine (5a). The latter compound failed to undergo reaction with phenyl lithium, however.

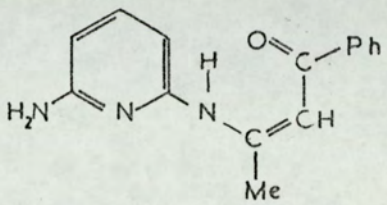


(5a) (6)

A small yield of 2-amino-6(2-acetyl-1-phenylvinylamino)pyridine (82) was isolated from the reaction mixture when the Combes reaction between 2,6-diaminopyridine and benzoylacetone was carried out in boiling xylene, in the absence of acid. This compound gave 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) in good yield when treated with orthophosphoric acid.

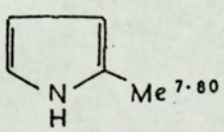


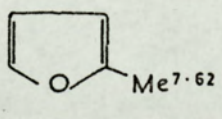
(82)



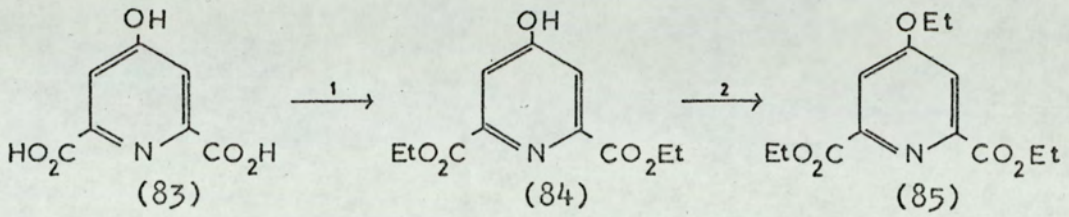
(82a)

The vinylaminopyridine (82) was examined by n.m.r. spectroscopy ($CDCl_3$ spectrum detailed in Experimental section); the methyl group resonates at τ7.46, a position which is consistent with the structure shown rather than the alternative 2-amino-6(2-benzoyl-1-methylvinylamino)pyridine (82a). A methyl group attached to a $-\overset{|}{C}=N$ group is shielded with respect to one attached to a $-\overset{|}{C}=O$ group; Elvidge (1967) has published tables of collected data which show that $Me-\overset{|}{C}=O$ resonates at τ7.83, compared with $Me-\overset{|}{C}=N$ at 8.00. Similarly, the methyl group in 2-methylpyrrole is shielded compared with the methyl group in 2-methylfuran; see the chemical shifts ($CDCl_3$) shown below.

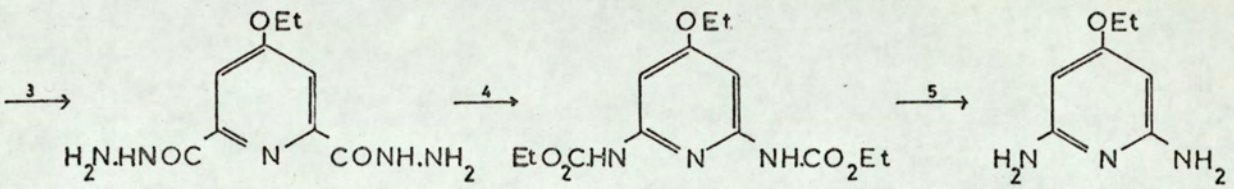




2,6-Diamino-4-ethoxypyridine (88) was used as the starting material for the preparation of two new 2-amino-1,8-naphthyridines. This compound was prepared from chelidamic acid (83) by the route outlined below (83→88) which was devised by Markees and Kidder (1956, 1968). The overall yield of product, based on chelidamic acid, was poor.



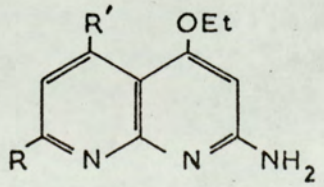
(83) (84) (85)



(86) (87) (88)

Reagents: (1) EtOH/HCl (2) NaOEt/EtI (3) $NH_2NH_2.H_2O$
(4) $HCl/NaNO_2$; EtOH (5) KOH/EtOH

The reaction of 2,6-diamino-4-ethoxypyridine (88) with acetylacetone in orthophosphoric acid gave an excellent yield of 7-amino-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (89). Reaction with benzoylacetone in orthophosphoric acid gave a product to which the structure 7-amino-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (90) has been assigned.

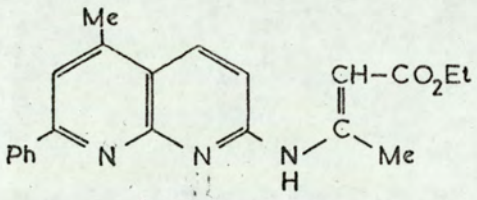


(89) R = R' = Me
(90) R = Ph, R' = Me

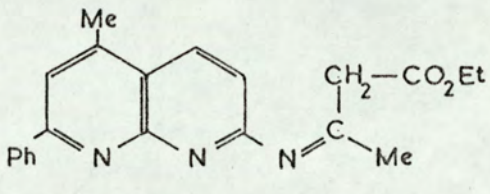
The n.m.r. spectrum of 7-amino-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (89) shows the effect of the 5-ethoxy group in enhancing the electron density at the 6-position, compared with the corresponding dimethylnaphthyridine (5) prepared from 2,6-diaminopyridine. In compound (89) 6-H resonates at τ 3.31, compared with 2.50 for the compound (5). (CF_3CO_2H spectra).

(b) The synthesis of 2-vinylaminonaphthyridines.

Ethyl acetoacetate has already been used extensively to prepare 2-vinylaminonaphthyridines. In this work, one new example was prepared. 7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (80) gave the vinylamino derivative (91) when heated under reflux in acetoacetic ester. Attempts to prepare the analogous



(91)



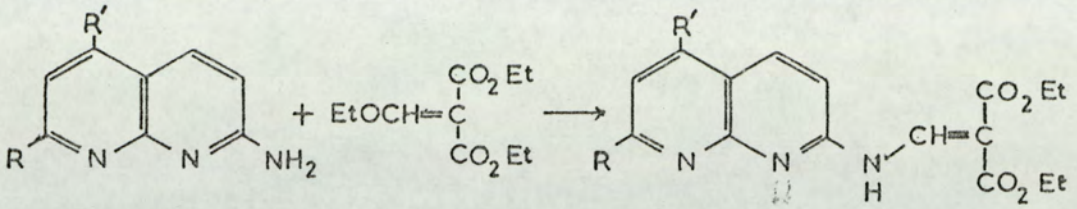
(92)

compound from 7-amino-2,4-dimethyl-1,8-naphthyridine (5) resulted in the production of a yellow compound which failed to give a correct analysis after sublimation and recrystallisation.

The n.m.r. spectrum of compound (91) clearly indicates the enamine structure rather than the alternative anil (92). The spectrum (in $CDCl_3$) shows the -NH proton resonating as a broad singlet at τ -1.30 (removed on deuteration of the sample) and the vinyl =CH- protom at 5.10 (singlet). The low position of the -NH proton indicates that it is a hydrogen-bonded group.

Three new vinylamino derivatives were prepared by the use of diethyl ethoxymethylenemalonate (93). 7-Amino-2,4-dimethyl-1,8-naphthyridine (5) gave the dimethylnaphthyridine derivative

(94) and 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) produced the methylphenyl compound (95). In both cases the reactions

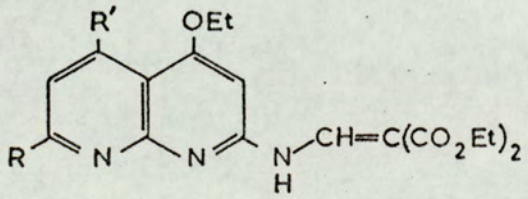


(94) R = R' = Me
(95) R = Ph, R' = Me

proceeded smoothly when the naphthyridines were refluxed in ethanol solution containing an excess of diethyl ethoxymethylene-malonate (EMME).

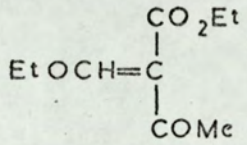
The n.m.r. spectra provided confirmation of the structure of the derivatives. For both the compounds (94 and 95) the vinyl proton resonated as a doublet at τ 0.50 (J = 13 Hz.); the large coupling constant is typical of the system -NH-CH= and similar values were found by Bottomley et al (1967) in studies on aminoacrylic esters.

The 5-ethoxynaphthyridine (90) also reacted with EMME to produce the 5-ethoxy-2-vinylaminonaphthyridine (96). Spectral data provided evidence for the structure of this compound and for the ethoxyvinylaminonaphthyridine (97) which was derived from the dimethylethoxynaphthyridine (89). The n.m.r. spectrum of the ethoxyvinylaminonaphthyridine (97) was determined in deuterochloroform; the -NH proton resonated at τ -1.23 (doublet, J = 12.5 Hz.).

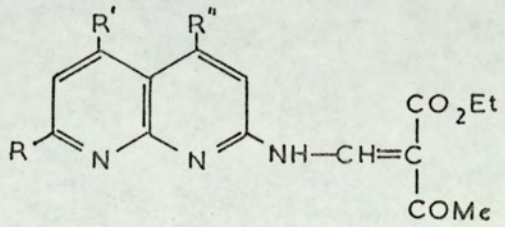


(96) R = Ph, R'= Me
(97) R = R' = Me

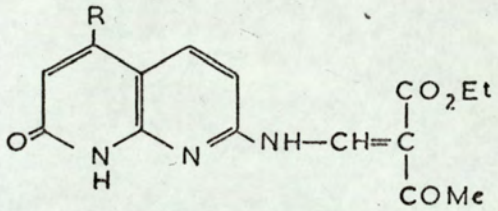
Ethyl ethoxymethyleneacetoacetate (98) was prepared by the method of Yasuda (1959) from ethyl acetoacetate and triethyl orthoformate. When reacted with 2-aminonaphthyridines, by stirring under reflux in ethanolic solutions, several new vinylamino compounds were formed. The dimethylvinylamino-naphthyridine (99) was prepared from 7-amino-2,4-dimethyl-1,8-naphthyridine (5) and the methylphenylvinylaminonaphthyridine (100) from 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80).



(98)



(99) R = R' = Me, R'' = H
(100) R = Ph, R' = Me, R'' = H
(101) R = Ph, R' = Me, R'' = OEt



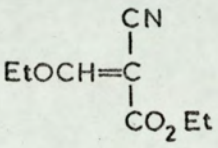
(102) R = Me
(103) R = Ph

The ethoxymethylphenylnaphthyridine (90) also produced a derivative (101) with ethyl ethoxymethyleneacetoacetate. Attempts were made to prepare the corresponding derivative from the ethoxydimethylnaphthyridine (89), but only very small yields of impure material resulted.

The 4-methyl-7-vinylaminonaphthyridinone (102) was prepared from the 4-methylnaphthyridinone (7), and the 4-phenyl-7-vinyl-aminonaphthyridinone (103) from the 4-phenylnaphthyridinone (8). Since the starting materials (7) and (8) are both insoluble in hot ethanol, these compounds were made by heating the naphthyridinones in a large excess of the ethoxymethylene

compound; the temperature was controlled so that charring of the reaction mixture was not allowed to occur.

Ethyl ethoxymethylenecyanoacetate (104) gave a good yield of the vinylaminonaphthyridine (105) when an ethanolic solution of the reagent and 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80) was stirred under reflux. The dimethylnaphthyridine (5) however gave a reaction product which could not be purified sufficiently for product identification.



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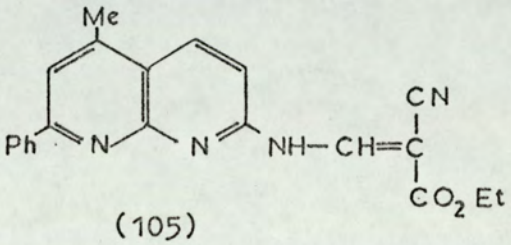
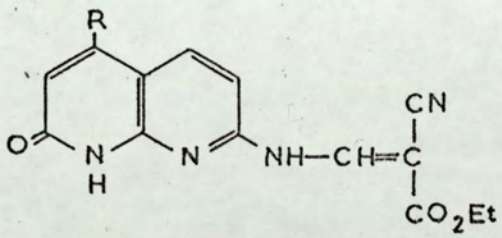
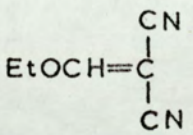


(105)

When a mixture of 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7) and excess ethyl ethoxymethylenecyanoacetate (104) was added to boiling Dowtherm-A, the cooled solution produced a good yield of the vinylaminonaphthyridinone (106). The analogous 4-phenyl compound (107) was prepared from 7-amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8) in the same manner, and a quantitative yield of crude product obtained.



(106) R = Me
(107) R = Ph



(108)

The fourth ethoxymethylene compound used in this work was ethoxymethylenemalononitrile (108), prepared by the method of Jones (1952). No new vinylamino compounds were prepared using this reagent however. When 7-amino-2,4-dimethyl-1,8-naphthyridine

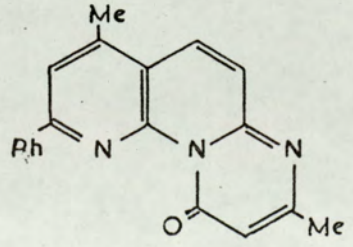
(5) was stirred under reflux in ethanolic solution with an excess of the reagent, a crude product was obtained from which no identifiable compound could be obtained.

Apart from ethoxymethylenemalonitrile (108), the ethoxymethylene compounds proved to be useful reagents for the preparation of new derivatives. The reaction mixtures always assumed a deep red (or purple) colour when these compounds were employed, and most of the crude products were red or purple; the recrystallised compounds were colourless.

(c) The cyclisation of 2-vinylaminonaphthyridines to pyrimido[1,2-a][1,8]naphthyridines.

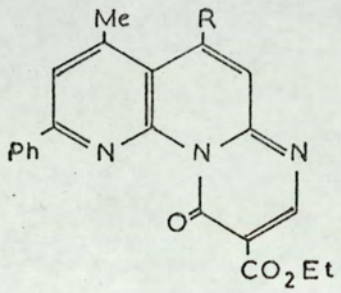
The procedure used to prepare pyrimido[1,2-a][1,8]naphthyridines from 2-vinylaminonaphthyridines was the same in all cases; the vinylamino compound was added to a boiling solution of Dowtherm-A, and boiling continued under reflux for a period of 5-20 minutes. Addition of petroleum ether to the cooled solution usually precipitated the cyclised products. It was found important to use boiling Dowtherm-A as good yields of products were not obtained when the solution was below boiling point; it was also important to use dilute solutions, and to stop heating the mixture when charring began to occur.

4,8-Dimethyl-2-phenyl-10H-pyrimido[1,2-a][1,8]naphthyridin-10-one (109) was obtained in good yield through the cyclisation of the vinylamino compound (91). The IR spectrum of the product shows



(109)

no bands assigned to N-H stretching vibrations. The band at 1690 $cm.^{-1}$ is assigned to the ring C=O stretching vibration. The n.m.r. spectrum ($CDCl_3$) displays a pair of doublets at τ 2.23 and 2.88, both having J = 9 Hz. These are assigned to the adjacent ring protons, 5-H and 6-H respectively. Similar features are displayed in the n.m.r. spectrum of 4,8-dimethylpyrimido [1,2-a] [1,8] naphthyridin-2,10(1H,10H)-dione (44a) which was prepared by the method of Carboni et al (1966b).



(110) R = H
(111) R = OEt

The two 9-ethoxycarbonylpyrimidonaphthyridines (110) and (111) were prepared by treatment of the vinylamino compounds (95) and (96) in Dowtherm-A. Yields were good in both cases.

The methylphenylpyrimidonaphthyridine (110) shows two C=O stretching vibrations in the infra-red spectrum, one at 1730 $cm.^{-1}$ assigned to ester C=O, the other at 1690 $cm.^{-1}$ assigned to the cyclic amide C=O group. The ultra-violet spectrum of this compound shows two main absorption bands, one at 229 nm., the other just within the visible region at 415 nm.; both bands are assigned to π-π^* transitions associated with an extended conjugated system bearing auxochromic groups. The precursor vinylaminonaphthyridine (95) also showed intense bands in the UV spectrum, but none higher than 383 nanometres.

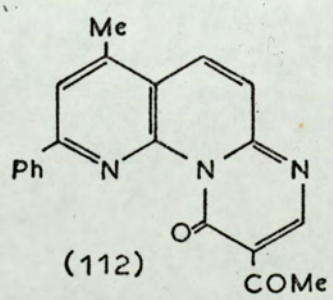
The n.m.r. spectrum ($CDCl_3$) of compound (110) supports the assigned structure, with the adjacent ring protons 5-H and 6-H resonating as doublets at τ 2.01 and 2-75, J = 9 Hz. The most

deshielded proton in the spectrum, apart from -NH, was 8-H, resonating at τ1.28 (singlet). The n.m.r. spectrum of the 5-ethoxypyrimidonaphthyridine (111) also shows 8-H at a low field, τ 1.32. The most interesting feature in the spectrum of this compound, however, was the relatively high position of 6-H. This proton resonates at τ 3.47 (singlet), a position normally regarded as being outside the 'aromatic' region. This shielding is due to the electron-donating properties of the adjacent 5-ethoxy group.

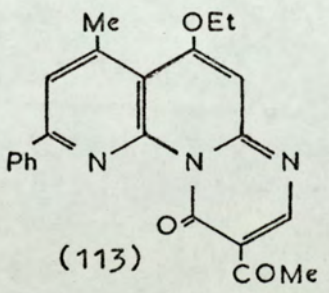
Treatment of the methylphenylpyrimidonaphthyridine (110) in boiling aqueous alkaline solution produced the parent naphthyridine, 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80).

The dimethylnaphthyridine derivatives, (94) and (97), failed to cyclise in Dowtherm-A. Starting material, along with some tar, was recovered in both cases.

Two new pyrimidonaphthyridines were prepared from ethyl ethoxymethyleneacetoacetate derivatives of naphthyridines. The 9-acetylpyrimidonaphthyridine (112) was prepared from the methylphenylvinylaminonaphthyridine (100), and the 9-acetyl-5-ethoxypyrimidonaphthyridine (113) from the ethoxymethylphenylvinylaminonaphthyridine (101).



(112)



(113)

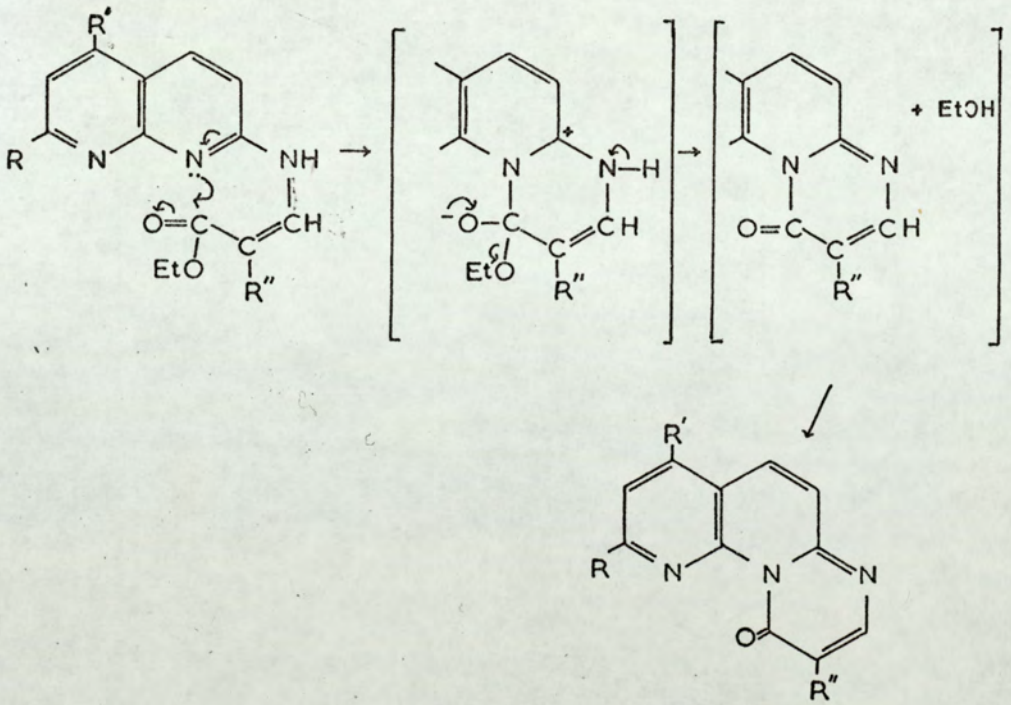
Spectroscopic data supports the structural assignments. The n.m.r. spectra confirm the presence in both compounds of acetyl groups.

The dimethylvinylaminonaphthyridine (99) failed to undergo cyclisation when treated in boiling Dowtherm-A.

No other pyrimido [1,2-a] [1,8] naphthyridines were prepared from 2-vinylamino compounds. Both the phenylvinylaminonaphthyridinone (103) and the methylphenylvinylaminonaphthyridine (105) gave unchanged starting materials when treated in Dowtherm-A, and the methylvinylaminonaphthyridinone (102) gave an anthyridine (discussed later).

All the pyrimido [1,2-a] [1,8] naphthyridines prepared in this work had melting points below 300°, and were soluble in common organic solvents such as ethanol and chloroform. The recrystallisation of these compounds was effected in ethanol or 2-ethoxyethanol.

A suggested mechanism for the formation of pyrimido [1,2-a] [1,8] naphthyridines from vinylaminonaphthyridines is outlined below:-



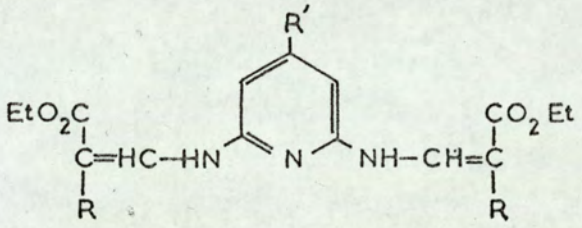
It is perhaps surprising that ring closure of the vinylamino compounds derived from ethyl ethoxymethyleneacetoacetate (100 and

101) proceeded through the carbonyl of the ester group rather than through the more reactive carbonyl of the acetyl group.

(d) The preparation of vinylaminonaphthyridines and divinylaminopyridines from diaminopyridines.

Both 2,6-diaminopyridine and 2,6-diamino-4-ethoxypyridine (88) react readily with ethoxymethylene compounds to produce 2,6-divinylaminopyridines.

2,6-Diaminopyridine produced the divinylpyridine (114) when heated under reflux with an excess of neat diethyl ethoxymethylenemalonate. Similar conditions were used to produce the divinylpyridine (115) from ethyl ethoxymethyleneacetoacetate (98); the yields in both cases were good. Analogous compounds (116) and



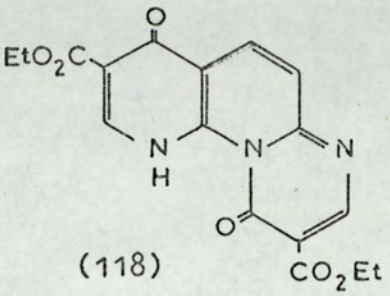
(114) R = CO_2Et, R' = H
(115) R = COMe, R' = H
(116) R = CO_2Et, R' = OEt
(117) R = COMe, R' = OEt

(117) were produced when 2,6-diamino-4-ethoxypyridine was refluxed in ethanolic solution with EMME and ethyl ethoxymethyleneacetoacetate, respectively.

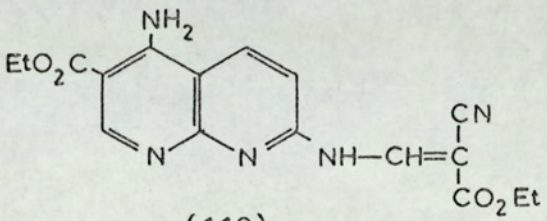
Confirmation of the structures was provided by n.m.r. spectroscopy. The shielding effect of the 4-ethoxy group is shown by a comparison of the shift positions (in $CDCl_3$) of the β-protons in the divinylaminopyridine (115) with the divinylaminoethoxypyridine (117). The respective values are τ 3.29 and 3.80.

Attempts were made to prepare pyrimidonaphthyridines from the above four compounds by treatment in boiling Dowtherm-A. Only in one case was a pure compound isolated. The EMME

derivative (114) gave the pyrimidonaphthyridine (118); the yield of crude material was fair, and purification by chromatography through an alumina column gave a very small yield of pure product. The other divinylaminopyridines (115,116,117) all gave insufficient yields of crude, impure materials to permit isolation of identifiable products.



(118)



(119)

Treatment of 2,6-diaminopyridine in ethanol under reflux with ethyl ethoxymethylenecyanoacetate (104) gave a good yield of product which after purification was identified as the vinylaminonaphthyridine (119). The latter compound showed four bands in the IR spectrum (3450, 3350, 3300 and 3250 $cm.^{-1}$) assigned to N-H stretching modes; cyclisation of the intermediate divinylamino compound had thus taken place onto the carbon of the nitrile group rather than through the ester group carbonyl carbon.

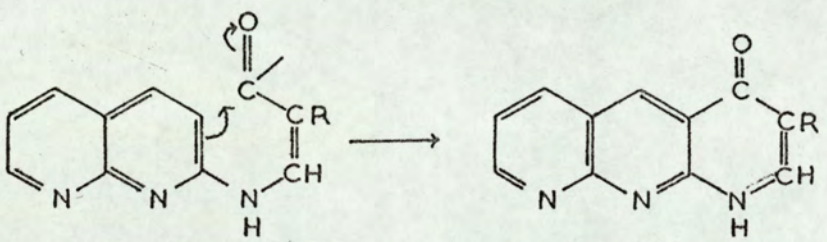
Attempts to cyclise the vinylaminonaphthyridine (119) further by treatment in Dowtherm-A gave unchanged starting material.

THE SYNTHESIS OF ANTHYRIDINES.

Three main approaches were used in attempts to prepare new examples of this linear tricyclic system. The first method involved the cyclisation of 2-vinylaminonaphthyridines. The second method involved the use of 2,6-diaminopyridines as starting materials, and the final method employed a 3-substituted-2-aminonaphthyridine.

(a) Synthesis of anthyridines from 2-vinylaminonaphthyridines.

This approach was based on the method already used successfully by Carboni and co-workers (1966b, 1967c, 1967d, 1969a) and involves the thermal cyclisation of 2-vinylamino-naphthyridines. Anthyridine formation follows intramolecular electrophilic cyclisation into the ring (120→121); it



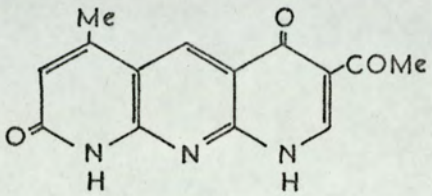
(120) (121)

requires that the electron density at the 3-position in the aminonaphthyridine should be sufficiently high to allow an intramolecular electrophilic attack by the electron-deficient carbonyl carbon to proceed.

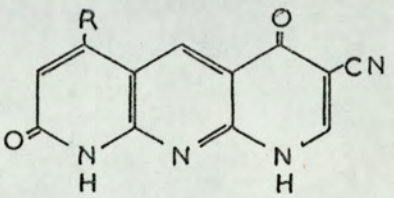
The 2-vinylaminonaphthyridines prepared in the course of this work and reported in the foregoing pages were all subjected to thermal treatment at temperatures up to 340^{0} in attempts to prepare anthyridines. The method recommended by Carboni and his colleagues was used; compounds were added to liquid paraffin preheated to 320^{0} and the temperature maintained at this level for 10 minutes. The formation of anthyridines would be indicated

by precipitation in the mixture (anthyridines are insoluble in most organic solvents, especially non-polar compounds).

However the only new anthyridine prepared from a vinylaminonaphthyridine was 7-acetyl-4-methylanthyridin-2,6(1H,9H)-dione (122) derived from the vinylaminonaphthyridinone (102) by treatment of the latter in boiling Dowtherm-A. The 4-phenyl analogue of (102) failed to undergo cyclisation when treated in Dowtherm-A or in liquid paraffin at 340°.



(122)



(123) R = Me
(124) R = Ph

The anthyridine (122) was a high melting solid (>330°), insoluble in common organic solvents. The n.m.r. spectrum provided confirmation of the structural assignment. The lowest peak in the spectrum (CF_3CO_2H) at τ 0.02 is assigned to 5-H; the other two aromatic protons resonate at τ 0.40 (8-H) and 2.87 (3-H). The low position of the 5-H is consistent with its central position in a deshielding environment.

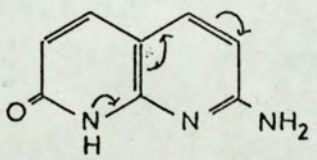
The two vinylaminonaphthyridinones derived from ethyl ethoxymethylenecyanoacetate (106 and 107) failed to give pure tricyclic compounds when treated in liquid paraffin at 340°. In each case a poor yield of a high melting (>330°) solid was obtained, probably the anthyridinones formulated as (123) and (124), but analytically pure samples could not be obtained. The IR spectra of the crude products showed bands at 2250 $cm.^{-1}$ assigned to the C≡N stretching vibration.

No other anthyridines were obtained by thermal treatment of vinylaminonaphthyridines. No anthyridines could be made by

the treatment in liquid paraffin of any of the pyrimido [1,2-a] [1,8] naphthyridines prepared in this work. The rearrangement of angular tricyclic compounds to the linear isomers was reported extensively by Carboni and co-workers.

From the results obtained it would seem that anthyridines cannot be prepared from vinylaminonaphthyridines or pyrimidonaphthyridines which bear only alkyl or aryl substituents in the first ring. All the anthyridines reported in the literature by Carboni and his colleagues were prepared from naphthyridinones. It is necessary to consider the formation of these compounds before discussion of the results.

Pyrimido [1,2-a] [1,8] naphthyridine formation may be inherently easier than anthyridine formation, because the nitrogen atom in the central ring has a greater electron density than the β-carbon atom (see figure 1). Their ease of formation is reflected in the milder conditions often employed in their production. Anthyridine formation may be promoted by any factors which increase the electron density at the β-carbon atom. An amide function in the first ring may do this. The nitrogen atom in such structures as the naphthyridinone (125) is in the sp_3 form and electrons less tightly bound to this atom.



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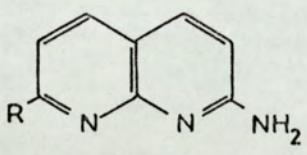
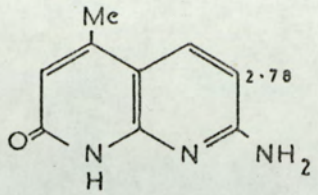


(126)

In naphthyridines such as (126) bearing only alkyl or aryl substituents, there is less tendency for electron drift to the second ring. The effect is reflected in the n.m.r. spectra of the naphthyridines (figure 5) where it may be seen that

the relative electron density at the β-position (6-H) is higher in the naphthyridinones.



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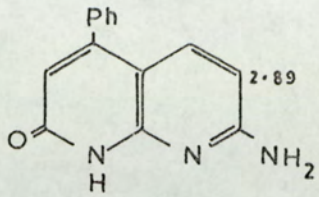

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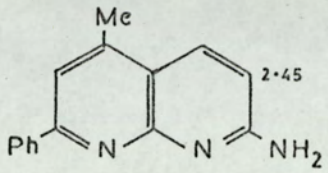

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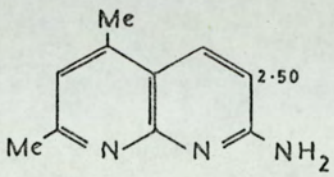
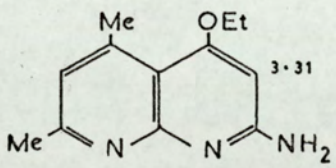


(5)

Figure 5

Chemical shifts in τ values (CF_3CO_2H)

The failure of the 5-ethoxy-2-vinylaminonaphthyridines such as (96), (97) and (101) to undergo conversion to anthyridines is difficult to rationalise. The electron density at the β-carbon atom in 5-ethoxynaphthyridines is much enhanced by the adjacent electron-donating function, as indicated by the n.m.r. shift values (CF_3CO_2H) for the ethoxynaphthyridine (89). Of course



(89)

the donor properties of the ethoxy group would be expected to strengthen the basicity of the ring nitrogen atom as well, thus promoting pyrimidonaphthyridine formation.

A suggested mechanism for the formation of anthyridines from vinylaminonaphthyridines is shown in figure 6.

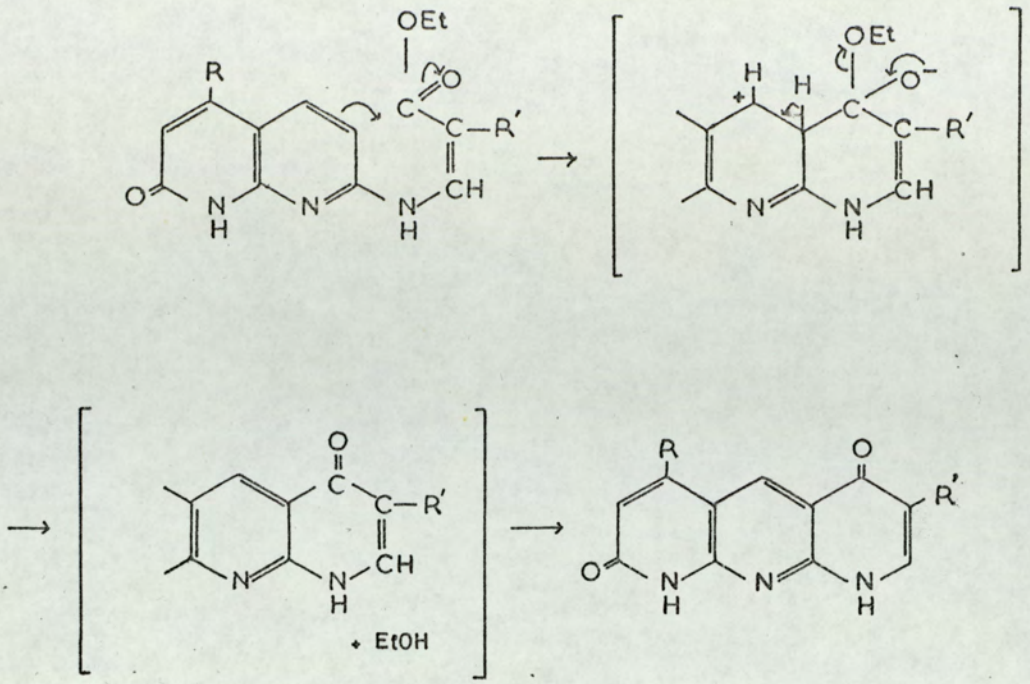


Figure 6

Suggested mechanism for formation of anthyridines.

The rearrangement of pyrimido [1,2-a][1,8] naphthyridines to anthyridines may be envisaged as following the mechanistic pathway outlined in figure 7. Breakage of the bridgehead C-N bond is followed by cyclisation into the ring through the newly created electron-deficient carbonyl carbon atom.

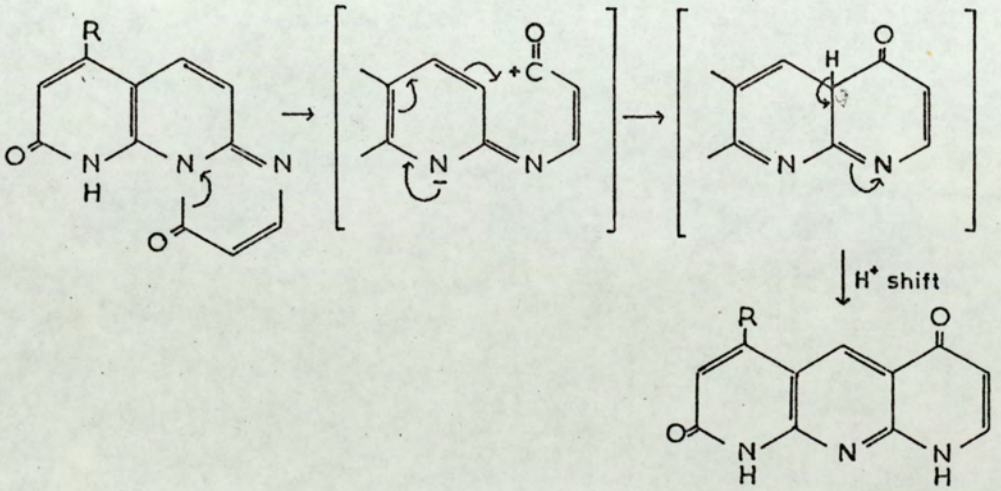


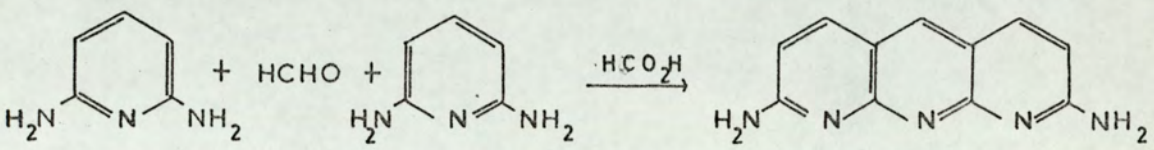
Figure 7

Suggested mechanism for the rearrangement of angular pyrimidonaphthyridines to anthyridines.

(b) The synthesis of anthyridines from 2,6-diaminopyridines.

(1) Schoeller and von Schickh's method.

Schoeller and von Schickh (1935) claimed the preparation of anthyridines from 2,6-diaminopyridine by the reaction of the latter with aldehydes in the presence of formic acid. The tricyclic compound is constructed from two pyridine rings, no naphthyridine intermediate being involved. An attempt was made to repeat one of their preparations, 2,8-diaminoanthyridine (52).



(52)

A mixture of 2,6-diaminopyridine with formic acid and formalin was refluxed on a steam bath. Steam distillation of the reaction mixture was followed by evaporation and addition of acid to the cooled concentrate; the orange solid which precipitated was recrystallised from ethanol. The yield was poor.

The water-soluble solid gave microanalytical data which did not correspond to the structure (52). Nitrogen was present in the compound. Mass spectroscopic examination showed no clear molecular ion peak. Infra-red examination showed no bands assigned to N-H stretching vibrations. The n.m.r. spectrum showed a series of peaks in the region τ 4.5 - 6.5, but no peaks in the aromatic region. UV examination showed strong absorption bands extending well into the visible region of the spectrum, with an intense band at 455 nm. The compound showed only one spot on TLC examination.

No definite structure could be assigned to the product, which on the evidence seems unlikely to be an anthyridine.

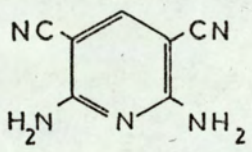
A mixture of formaldehyde and formic acid, known as the Eschweiler-Clarke reagent, is used for the methylation of primary and secondary amines, (Eschweiler, 1905):-

$$RNH_2 + 2\ HCHO + 2\ HCO_2H \longrightarrow RNMe_2 + 2\ CO_2 + 2\ H_2O$$

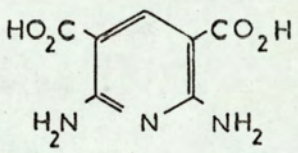
The product obtained from 2,6-diaminopyridine is apparently more complex than a simple tertiary amine.

(2) Proposed synthesis from 2,6-diamino-3,5-dicyanopyridine.

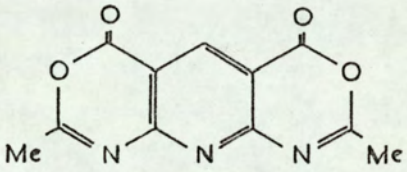
2,6-Diamino-3,5-dicyanopyridine (127) is a good potential precursor of the anthyridine system. The hydrolysis product 2,6-diaminopyridine-3,5-dicarboxylic acid (128) has been prepared and used by Cottis (1962) to produce the tricyclic system (129) by reaction with acetic anhydride.



(127)

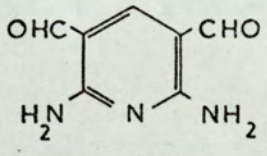


(128)

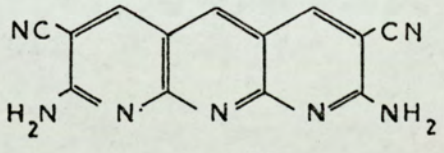


(129)

It was hoped to be able to prepare 2,6-diaminopyridine-3,5-dialdehyde (130) and to use this compound to prepare anthyridines of the type (131) by reaction with active methylene



(130)



(131)

compounds. This is an extension of the Friedländer synthesis, already used successfully for the preparation of naphthyridines

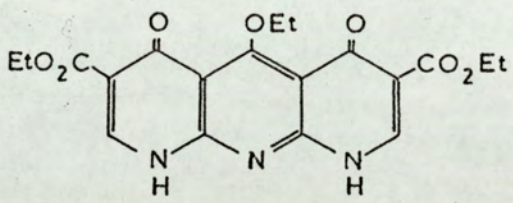
by Hawes and Wibberley (1966).

The method of Little et al (1958) was used to prepare 2,6-diamino-3,5-dicyanopyridine (127), for which 1,1,3,3-tetracyanopropene (Cottis and Tieckelmann, 1961) was the starting material. The preparation of the dicyanopyridine (127) was successful; an attempted Stephen reduction on the compound, using anhydrous stannous chloride, gave unchanged starting material.

Cottis (1962) reported that hydrolysis of the dicyanopyridine (127) to 2,6-diaminopyridine-3,5-dicarboxylic acid (128) could be effected by boiling the compound in aqueous alkaline solution. Several attempts were made to repeat this preparation, using the same and more vigorous conditions, but hydrolysis was never effected, and the route was abandoned.

(3) Synthesis from 2,6-diamino-4-ethoxypyridine.

When 2,6-diamino-4-ethoxypyridine (88) was heated under reflux in diethyl ethoxymethylenemalonate a precipitate appeared in the solution after 6 - 7 minutes; this product, insoluble in organic solvents and of melting point above 340° showed an n.m.r. spectrum consistent with the anthyridine structure (132).



(132)

This is the first anthyridine known to have been prepared directly from a pyridine derivative. Similar treatment of 2,6-diamino-4-ethoxypyridine in ethyl ethoxymethyleneacetoacetate gave only intractable tars.

No suitable solvent could be found for the recrystallisation of the anthyridine (132) and analysis of the acid-washed material gave incorrect figures. The mass spectrum of the compound shows a molecular ion peak at the calculated value (m/e 401) and a base peak at m/e 255, which is consistent with the loss from the molecular ion of a $-CO_2Et$ fragment.

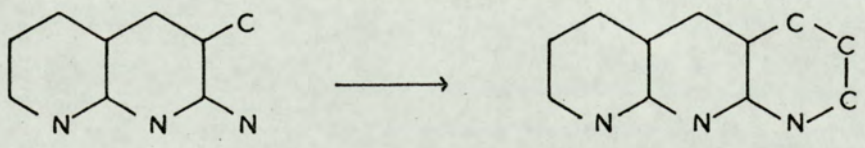
The yield of the compound was 11%, and since 2,6-diamino-4-ethoxypyridine is only made by a five stage synthesis from chelidamic acid in an overall yield of 10%, this route for the preparation of anthyridines is of limited use.

Treatment of 2,6-diaminopyridine in neat EMME has already been stated to give the divinylaminopyridine (114) and this compound gave the pyrimido [1,2-a] [1,8] naphthyridine (118) on thermal cyclisation. No anthyridine was obtained from (114).

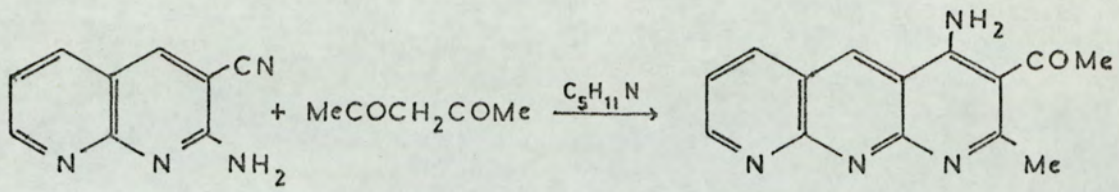
The electron density at the β-positions in 2,6-diamino-4-ethoxypyridine is evidently sufficiently enhanced by the 4-ethoxy group to permit electrophilic cyclisation into the ring to occur.

(c) Synthesis of anthyridines from 3-substituted-2-aminonaphthyridines.

Consideration was given to the preparation of anthyridines by an application of the Friedländer synthesis to 3-substituted 2-aminonaphthyridines. A linear system is envisaged as being constructed by reaction of the naphthyridine with a suitable activated methylene compound:-



2-Amino-3-cyano-1,8-naphthyridine (24) was stirred under reflux in ethanolic solution with an excess of acetylacetone, using piperidine as catalyst. It was hoped to form the anthyridine (133). A complete recovery of starting material

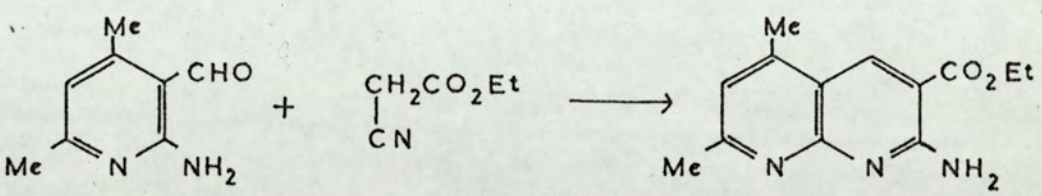


(24) (133)

was obtained in this instance.

Naphthyridine-3-aldehydes would be the starting materials of choice in these reactions; the reactivity of substituent groups in these condensations lies in the order -CHO> $-CO_2Et$> -C≡N. The conversion of compounds such as the nitrile (24) to the corresponding aldehyde is impracticable on account of the number of stages involved.

A possibly more reactive precursor than the cyanonaphthyridine (24) is ethyl 2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (135) and an attempt was made to synthesise this compound from 2-amino-4,6-dimethylnicotinaldehyde (134). The latter was

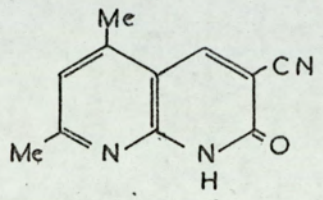


(134) (135)

prepared by a method based on the route described for 2-amino-6-phenylnicotinaldehyde (26) by Hawes and Wibberley (1966); the initial starting material for the synthesis was ethyl 2-amino-4,6-dimethylnicotinate, made by the method of Dornow and Karlson (1940).

The reaction yielded two products, ethyl-2-amino-5,7-dimethyl-

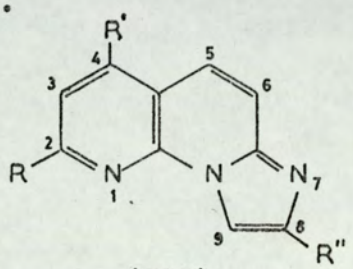
1,8-naphthyridine-3-carboxylate (135) and 3-cyano-5,7-dimethyl-1,8-naphthyridin-2(1H)-one (136), of which the nitrile (136) was the major one. The ester (135) could not be prepared free from all traces of the nitrile (136) and the method was abandoned as unsuitable. Hawes and Wibberley (1966) found that 2-amino-6-phenylnicotinaldehyde gave the corresponding 3-cyanonaphthyridinone under the same conditions.



(136)

THE SYNTHESIS OF IMIDAZO [1,2-a] [1,8]NAPHTHYRIDINES.

Some new imidazonaphthyridines were prepared to see how readily the reaction could be applied to aminonaphthyridines using other α-halocarbonyl compounds besides bromoacetone and phenacyl bromide. The two examples of this ring system reported in the literature (41, 42) have been formulated as 8-substituted imidazonaphthyridines (137) but no evidence has been put forward for this assignment.

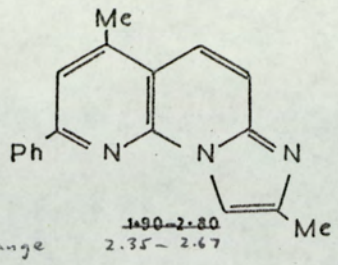


(137)

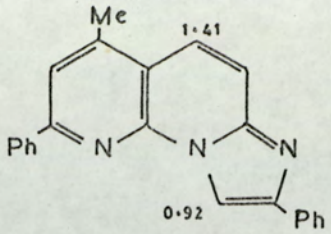
7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (80) was used in the preparation of three new imidazonaphthyridines. Reaction of this naphthyridine with bromoacetone gave 4,8-dimethyl-2-phenyl-imidazo [1,2-a] [1,8] naphthyridine (138). Phenacyl bromide was used to prepare 2,8-diphenyl-4-methylimidazo [1,2-a][1,8] naphthyridine (139) and ethyl bromopyruvate for the preparation of 8-carbethoxy-4-methyl-2-phenylimidazo [1,2-a][1,8] naphthyridine (140).

The n.m.r. spectra of these three compounds were studied in order to make accurate structural assignments. In order to help the assignments, two imidazonaphthyridines which bear no substituents in the imidazole ring were prepared; these were 2,4-dimethylimidazo [1,2-a][1,8]naphthyridine (141), prepared from 7-amino-2,4-dimethyl-1,8-naphthyridine (5) and bromoacetal, and 4-methyl-2-phenylimidazo [1,2-a][1,8]naphthyridine (142) prepared from the methylphenylaminonaphthyridine (80) and bromoacetal. The conditions described by Roe (1963) for the

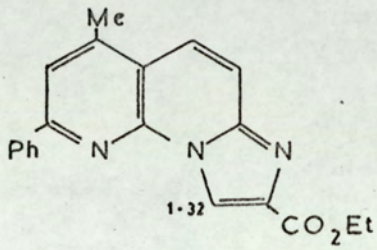
preparation of imidazo[1,2-a]pyridines from 2-aminopyridines were used in the preparation of the imidazonaphthyridines (141) and (142).



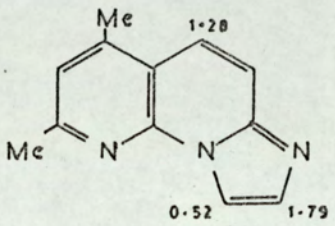
(138)



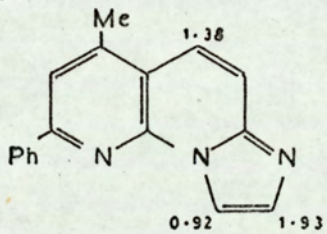
(139)



(140)*



(141)



(142)

*($CDCl_3$)

Figure 8

Chemical shifts in τ values (CF_3CO_2H).

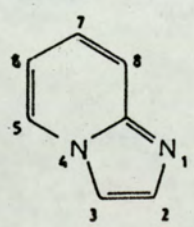
The n.m.r. data for the five new imidazonaphthyridines is shown in figure 8. For the two imidazonaphthyridines (141) and (142) which bear no substituent in the imidazole ring it is reasonable to predict that the most deshielded proton is the one on the carbon adjacent to the bridgehead nitrogen; this proton (9-H) is subjected to deshielding not only by the

adjacent nitrogen but by the overall environment, including the first ring of the tricyclic system. Hence the assignments given in figure 8. The coupling constants for the imidazole ring protons were 2.5 Hz (compound 141) and 2.0 Hz (compound 142).

The extremely low position of the 9-H in the dimethyl-imidazonaphthyridine (141) compared with the methylphenylimidazo-naphthyridine (142) is explained as a solvent effect. In the strong acid solvent, protonation of the nitrogen atoms occurs and this aids deshielding of 9-H in both compounds. But in the methylphenyl compound (142) the 2-phenyl group shields 9-H by partially blocking the protonation of the 1-nitrogen atom. The spectra of the two compounds in a non-protonating solvent, dimethyl sulphoxide, show a reversal of the position. In this solvent, 9-H for the methylphenyl compound (142) resonates at τ1.15, while 9-H in the dimethyl compound (141) is at the more upfield position, τ 1.22.

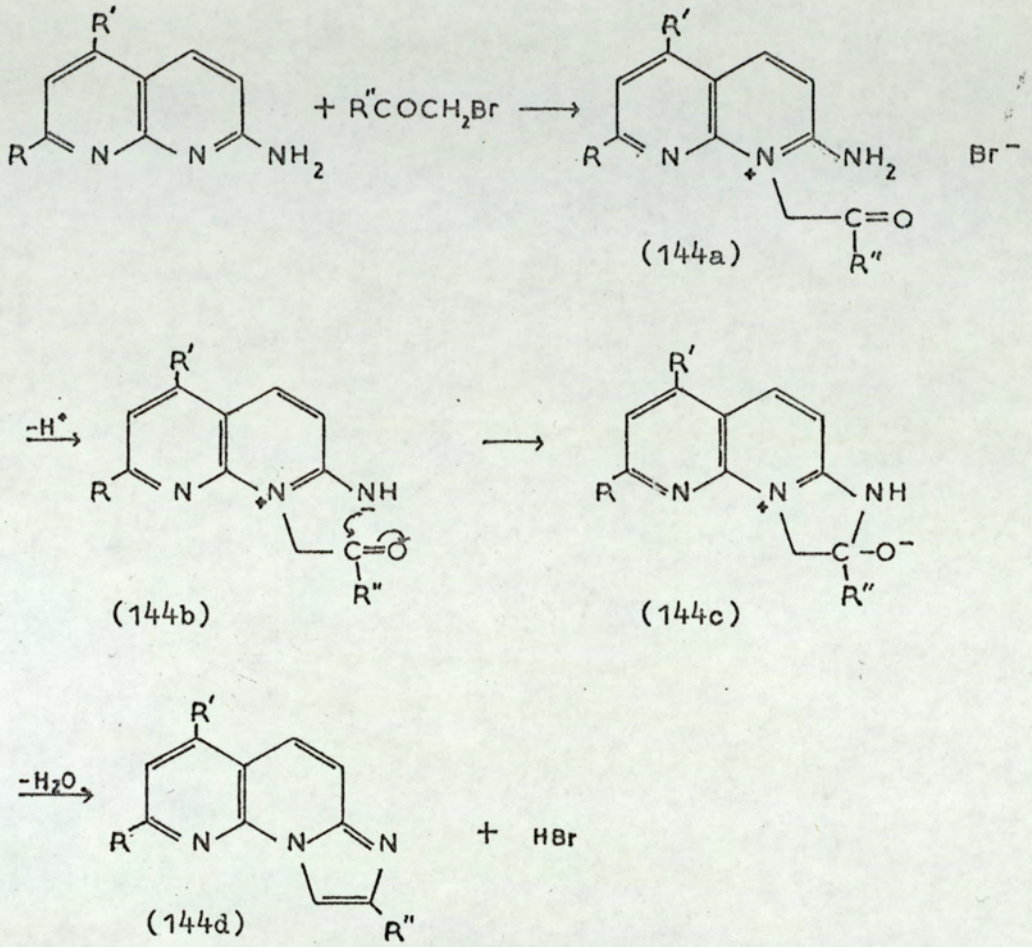
The low field position of the imidazole ring proton in the methylphenylimidazonaphthyridines (138, 139 and 140) enables this to be assigned to 9-H, and the substituent is thus carried in the 8-position, as shown in figure 8.

A similar system to the imidazo [1,2-a] [1,8] naphthyridines has been studied by Paudler and Blewitt (1965). In the spectrum of imidazo [1,2-a] pyridine (143) the proton adjacent to the bridgehead nitrogen (3-H) resonated at a higher field than 2-H. That these assignments were correct was established by a comparison of the spectrum of the parent ring with those of several substituted derivatives.



(143)

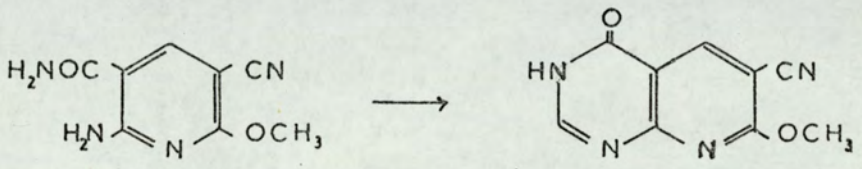
A possible mechanism for the formation of imidazo [1,2-a] [1,8] naphthyridines is outlined below. This mechanism envisages the formation of the quaternized product (144a) as the initial stage, which is followed by an internal nucleophilic attack leading to (144c), which presumably loses a proton and the elements of one



molecule of water before aromatization to the imidazonaphthyridine (144d). The initial stage determines the position of substitution in the imidazole ring.

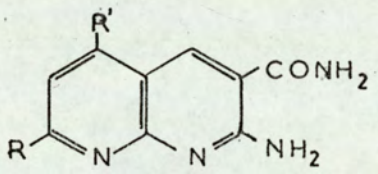
THE SYNTHESIS OF PYRIMIDO[4,5-b][1,8]NAPHTHYRIDINES.

Mulvey, Cottis and Tieckelmann (1964) reported the preparation of 2,4,6-trisubstituted pyrido[2,3-d]pyrimidines; a typical procedure was the conversion of 2-amino-5-cyano-6-methoxy-3-pyridinecarboxamide (146) to 6-cyano-7-methoxypyrido[2,3-d]-pyrimidin-4(3H)-one (147) by reaction with triethyl orthoformate in acetic anhydride.

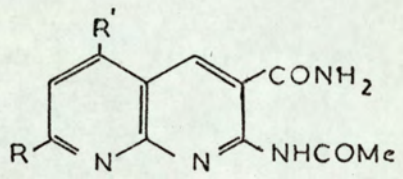


(146) (147)

When this reaction was applied to 2-amino-1,8-naphthyridine-3-carboxamide (25), analysis of the product showed it to be the acetylated amine, 2-acetamido-1,8-naphthyridine-3-carboxamide (148).



(25) R = R' = H
(28) R = Ph, R' = H
(28a) R = R' = Me



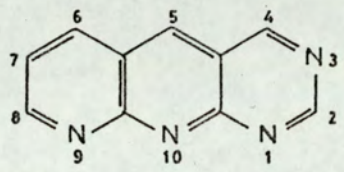
(148) R = R' = H
(149) R = Ph, R' = H
(150) R = R' = Me

The infra-red spectrum of the acetamidonaphthyridine (148) showed bands assigned to amide I carbonyl at 1700 and 1680 $cm.^{-1}$, and amide II carbonyl vibrations at 1640 and 1570 $cm.^{-1}$. These bands are consistent with the structural assignment.

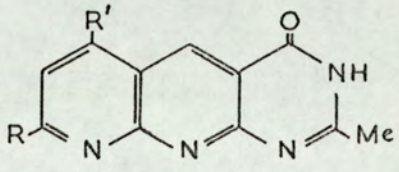
When 2-amino-7-phenyl-1,8-naphthyridine-3-carboxamide (28) was stirred in warm acetic anhydride, a good yield of 2-acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide (149) was

obtained. 2-Acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (150) was similarly obtained from 2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (28a).

When 2-acetamido-1,8-naphthyridine-3-carboxamide (148) was treated in warm aqueous ammonia solution the tricyclic compound 2-methylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (152) was obtained in nearly quantitative yield. The structural assignment was made on the basis of analytical, n.m.r. and mass spectral data. The product was the first example of the pyrimido[4,5-b][1,8]naphthyridines (151) known to have been prepared.



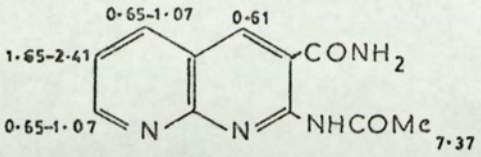
(151)



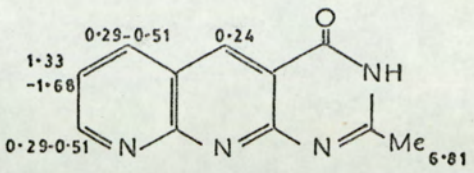
(152) R = R' = H
(153) R = Ph, R' = H
(154) R = R' = Me

2-Methyl-8-phenylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (153) was similarly prepared from 2-acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide (149), and 2,6,8-trimethylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (154) from 2-acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (150). Yields were excellent in both cases.

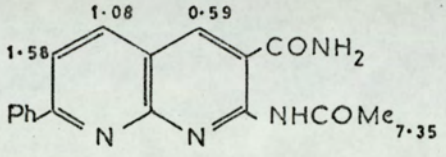
The n.m.r. spectral assignments for the three pyrimido[4,5-b][1,8]naphthyridines and their precursors are shown in figure 9. In each case the lowest peak in the spectrum arose from 5-H. This proton is more deshielded than in the precursors, and this is due to the influence of the carbonyl group which is rigid in the tricyclic compounds and thus causes greater deshielding. The low position of 5-H in the trimethylpyrimidonaphthyridine (154) is also ascribed to peri-deshielding by 6-methyl in that compound.



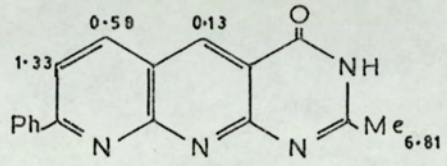
(148)



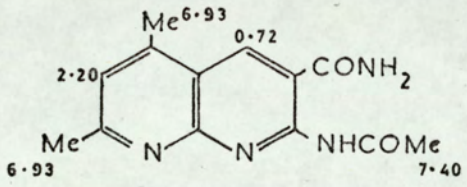
(152)



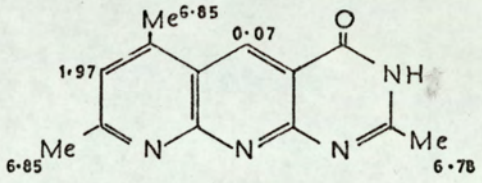
(149)



(153)



(150)



(154)

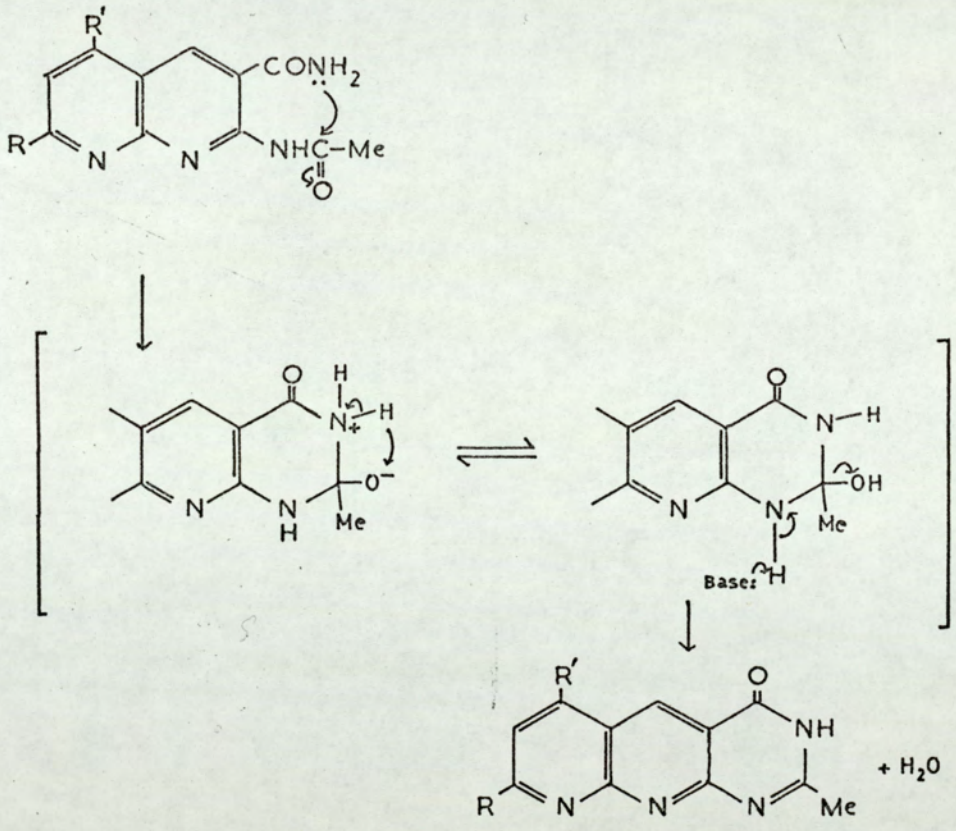
Figure 9

Chemical shifts in τ values (CF_3CO_2H)

The mass spectra of all three pyrimido[4,5-b][1,8]naphthyridines have been measured. A characteristic feature in all three spectra is that the base peak is formed by the loss of a hydrogen atom from the molecular ion. An [M-2] ion is also seen in the spectra of the 2-methylpyrimidonaphthyridine (152) and the methylphenylpyrimidonaphthyridine (153). The [M-1] and [M-2] ions are apparently fairly stable, and carry a high proportion of the total ion current. An [M-2] ion, due to the loss of a second hydrogen atom from the molecular ion, is an unusual feature.

The other outstanding feature in the spectra is the loss from the molecular ion $[M]^+$ or from $[M-1]^+$ of a MeCN fragment. Evidently the expulsion of this fragment is easier from pyrimidine rings than it is from pyridine rings; as has been noted earlier, there is no evidence that MeCN is lost in one step from methylnaphthyridines.

A plausible mechanism for the cyclisation of 2-acetamido-1,8-naphthyridine-3-carboxamides is shown below. The initial step is the nucleophilic attack of the nitrogen of the naphthyridinamido-group on the carbonyl carbon of the acetamido-group.



MICROBIOLOGICAL AND PHARMACOLOGICAL RESULTS.

A selection of compounds prepared during the course of this work was submitted for inclusion in a general antimicrobial screening programme. Compounds were tested for *in vitro* activity against the selected microorganisms listed in Table 3. Test levels employed in the programme were 200, 50, 12.5 and 3.125 µg./ml.

The compounds submitted were 7-amino-2,4-dimethyl-1,8-naphthyridine (5), 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80), 7-amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8), 7-(2-carbethoxy-1-methylvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (91), 7-(2-dicarbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (95), 7-(2-dicarbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine (94), 7-(2-acetyl-2-carbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine (99), 7-(2-acetyl-2-carbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (100), 7-(2-acetyl-2-carbethoxyvinylamino)-4-phenyl-1,8-naphthyridin-2(1H)-one (103), 7-(2-carbethoxy-2-cyanovinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (105), 2,6-bis(2-acetyl-2-carbethoxyvinylamino)pyridine (115), ethyl 4-methyl-2-phenyl-10H-pyrimido[1,2-a][1,8]naphthyridin-10-one-9-carboxylate (110), ethyl 4-methyl-2-phenylimidazo[1,2-a][1,8]naphthyridine-8-carboxylate (140), and 2,8-diphenyl-4-methylimidazo[1,2-a][1,8]naphthyridine (139).

Apart from the dimethylvinylaminonaphthyridine (94), which showed weak activity (at 200 µg./ml.) against Trichophyton mentagrophytes, Mycobacterium smegmatis and Streptococcus pyogenes, none of the compounds showed activity against amy of the microorganisms.

Table 3

Organisms used for testing *in vitro* antimicrobial or antifungal activity.

Streptococcus faecalis

Staphylococcus aureus (resistant strain)

Staphylococcus aureus (sensitive strain)

Klebsiella pneumoniae

Pseudomonas aeruginosa

Escherichia coli

Salmonella typhimurium

Trichophyton mentagrophytes (fungus)

Candida albicans (fungus)

Mycobacterium smegmatis

Bacillus subtilis

Fusarium oxysporum (fungus)

Penicillium citrinum (fungus)

Aspergillus niger (fungus)

Cyptococcus neoformans (yeast)

Blastomyces dermatitidis (yeast)

Xanthomonas vesicatoria

Streptococcus pyogenes

Sarcina lutea

Three compounds were also tested for anticonvulsant activity in rats. These were 7-(2-dicarbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine (94), 7-(2-dicarbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (95), and 2,8-diphenyl-4-methyl-imidazo [1,2-a] [1,8] naphthyridine (139). Each compound was administered orally (200 mgm./kgm.) but all failed to antagonise Metrazol-induced convulsions. The test was part of a screening programme for new drugs with tranquillizing activity.

(All the testing was carried out in the Pharmacology laboratories of Smith, Kline and French Limited, Philadelphia, U.S.A.)

EXPERIMENTAL

Infra-red spectra were determined for liquid paraffin mulls on a Unicam SP 200 spectrophotometer, unless otherwise stated.

Ultra-violet spectra were recorded on a Unicam SP 800 spectrophotometer.

Nuclear magnetic resonance spectra were determined at 60 MHz using tetramethylsilane as internal standard on a Varian A60-A spectrometer. Abbreviations used in the interpretation of n.m.r. spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad singlet; J = coupling constant.

Mass spectra were determined with an A.E.I. MS9 spectrometer operating at 50 μa and 70 eV. Mass spectral data is presented as m/e readings, with the figures in parentheses representing the percentage abundance of each peak. M^+ signifies the molecular ion peak; m* denotes metastable peaks.

Melting points are uncorrected; sublimation and reaction temperatures are those of an external silicone fluid bath.

Petroleum ether refers to the fraction of boiling range 60-80°. Dowtherm-A refers to the mixture having the composition: diphenyl ether 76%, diphenyl 24%.

Microanalyses were determined by Dr F.B. Strauss, Oxford, England, or by Dr A. Bernhardt, Max-Planck Institut für Kohlenforschung, Mülheim, West Germany.

SYNTHESES OF 2-AMINO-1,8-NAPHTHYRIDINES.

7-Amino-4-methyl-1,8-naphthyridin-2(1H)-one (7).

2,6-Diaminopyridine (10.9 g), ethyl acetoacetate (13 g) and orthophosphoric acid (40 ml) were heated together under reflux on a steam bath for 1 hr. The cooled solution was diluted with ice-water and basified with ammonia solution to yield the naphthyridinone (11.7 g, 67%), m.p. above 350°.

$\nu_{max.}$ 3350, 3150 (N-H); 1670 (C=O), 1630 (C=N), 1060, 940, 890, 850, 720, and 680 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 1.53 (1H, d, J 10 Hz, 5-H), 2.78 (1H, d, J 10 Hz, 6-H), 3.00 (1H, s, 3-H) and 7.27 (3H, s, 4-Me).

7-Amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8).

This compound was prepared from 2,6-diaminopyridine and ethyl benzoylacetate by the method of Carboni et al (1968). Yield of the crude naphthyridinone was 38%, m.p. above 350°.

$\nu_{max.}$ 3350, 3150 (N-H); 1670 (C=O), 1610 (C=N), 1550, 1530, 1430, 1380, 890, 840, 780, and 710 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 1.70 (1H, d, J 9 Hz, 5-H), 2.20-2.58 (5H, m, phenyl protons), 2.89 (1H, d, J 9 Hz, 6-H), 2.95 (1H, s, 3-H).

7-Amino-2,4-dimethyl-1,8-naphthyridine (5).

2,6-Diaminopyridine (2.18 g), acetylacetone (2.0 g) and orthophosphoric acid (15 ml) were heated together under reflux on a steam bath for 2 hr. The cooled solution was diluted with ice-water, basified with ammonia solution to precipitate the naphthyridine (2.1 g, 60%), m.p. 214-215° (from water). (Bernstein et al (1947) obtained 85%, m.p. 216-218°).

$\lambda_{max.}$(EtOH) 236 nm (log ε 4.59) and 339 (4.02).

$\nu_{max.}$ (KBr) 3300, 3100 (N-H); 1640 (C=N), 1620, 1600, 1520, 1340, 800, 740 and 700 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 1.41 (1H, d, J 9 Hz, 5-H), 2.31 (1H, s, 3-H), 2.50 (1H, d, J 9 Hz, 6-H), 7.04 (6H, s, 2-Me and 4-Me).

m/e 175(1), 174(15), 173(100), 172(18), 158(2), 147(11), 146(22), 145(5), 141(2), 131(5), 130(3), 104(4), 103(3), 86(3), 77(6), 65(3), 63(4), 52(3), 51(4), 41(3), 39(4), 28(4).

m* 144.3 (173→158).

Attempted preparation of 7-amino-2,4-diphenyl-1,8-naphthyridine. (Page 25).

A stirred mixture of 2,6-diaminopyridine (1.09 g), dibenzoylmethane (2.4 g) and orthophosphoric acid (20 ml) was heated at 140° for 3 hr. Addition of ammonia solution to the cooled reaction mixture precipitated dibenzoylmethane (2.15 g), identified by undepressed mixed m.p. determination.

Repetition of the reaction, with extension of the heating period to 15 hr, always gave a quantitative recovery of unchanged dibenzoylmethane.

2-Amino-7-phenyl-1,8-naphthyridine (79).

A stirred mixture of 2,6-diaminopyridine (4.4 g), benzoylacetaldehyde (11 g) and orthophosphoric acid (40 ml) was heated at 100° for 1 hr. The cooled mixture was filtered, and the filtrate treated with dilute ammonia solution. The gummy solid which precipitated was boiled with ethyl acetate, then washed with ether till the washings were colourless. The crude product (3 g) had m.p. 225° (decomp.). (Hawes and Wibberley (1967) found m.p. 229-230°). The infra-red

spectrum agreed with the published spectrum.

τ (CF_3CO_2H) 1.04 (1H, d, J 8.5 Hz, 5-H), 1.46 (1H, d, J 9 Hz, 4-H), 1.74 (1H, d, J 8.5 Hz, 6-H), 1.83-2.60 (6H, m, 3-H and phenyl protons).

2-Amino-7-methyl-1,8-naphthyridine (5a).

A mixture of 2,6-diaminopyridine (5.5 g), acetylacetaldehyde dimethylacetal (7.25 g) and orthosphosphoric acid (100 ml) was stirred and heated at 80-85° for 3 hr. The ice-cooled solution was neutralised with sodium hydroxide solution, and filtered. The filtrate was made alkaline (pH 11) and extracted with chloroform. The dried ($MgSO_4$) extracts were evaporated to yield 2 g brown powder, m.p. 150-170°.

This crude material was dissolved in the minimum quantity of chloroform and applied to an alumina column. After elution with $CHCl_3$ till the eluate was colourless, the naphthyridine was removed from the column by elution with $CHCl_3$:MeOH 80:20. A yield of crude product of 1.3 g was obtained, m.p. 160-175°. (Brown (1965) gives 175-185° for the crude material. No details of the chromatographic purification were given.)

$\nu_{max.}$ 3400, 3200 (N-H); 1660, 1640, 1600, 1560, 1520, 1400, 1360, 1320, 1140, 850, 820, 810, 800 and 790 $cm.^{-1}$

τ (CF_3CO_2H) 1.17 (1H, d, J 9 Hz, 5-H), 1.52 (1H, d, J 9.5 Hz, 4-H), 2.12 (1H, d, J 9 Hz, 6-H), 2.48 (1H, d, J 9.5 Hz, 3-H), 6.94 (3H, s, 7-Me).

7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (80).

2,6-Diaminopyridine (2.72 g), benzoylacetone (4.05 g) and orthophosphoric acid (35 ml) were stirred and heated under reflux at 140° for 2 hr. Water was added to the cooled mixture, and the precipitate collected. Treatment of the solid with boiling dilute ammonia solution, followed by thorough washing with water gave the naphthyridine (4.4 g, 80%) m.p. 247-248° (from 50% ethanol). (Mangini and Colonna, (1943b) obtained 75%, m.p. 247-248°).

$\lambda_{max.}$ (EtOH) 242 nm (log ε 4.69) and 355 nm (4.16).

$\nu_{max.}$ 3300, 3200 (N-H); 1620 (C=N), 1600, 1520, 1420, 1350, 810, 770 and 680 $cm.^{-1}$

τ (CF_3CO_2H) 1.33 (1H, d, J 10 Hz, 5-H), 1.89 (1H, s, 3-H), 1.96-2.30 (5H, m, phenyl protons), 2.45 (1H, d, J 10 Hz, 6-H), 6.97 (3H, s, 4-Me).

m/e 237(1), 236(17), 235(100), 234(24), 220(15), 209(5), 208(13), 192(3), 190(2), 165(1), 118(7), 117(4), 116(4), 110(2), 105(3), 103(4), 96(1), 90(2), 77(4), 76(2), 63(2), 51(2), 39(2), 31(4), 28(2).

m* 184.1 (235→208), 206 (235→220).

7-Acetamido-4-methyl-2-phenyl-1,8-naphthyridine was obtained in 90% yield by treatment of the above naphthyridine in acetic anhydride. M.p. 206-206° (Mangini and Colonna (1943b) give m.p. 208°).

$\nu_{max.}$ 3250 (N-H), 1710 (C=O), 1620 (C=N), 1600, 1530, 1330, 1290, 790 and 700 $cm.^{-1}$

Attempted oxidation of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine. (Page 31)

7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 1 g) was suspended in water (40 ml) containing sodium dichromate (2 g); sulphuric acid (3 ml) was added to the mixture which was then boiled under reflux for 1 hr. The cooled mixture was filtered and the residue treated with warm aqueous ammonia solution. The treated solid was washed with water and dried; IR examination of the product showed it to be unchanged aminonaphthyridine. Recovery was 1 g.

This procedure was repeated using a reflux period of 24 hr. The yield of unchanged aminonaphthyridine was again quantitative.

When neutral or alkaline potassium permanganate were employed as oxidising agents, unchanged aminonaphthyridine was obtained quantitatively. Large excesses of the agents were employed, using reflux times up to 24 hr.

Attempted oxidation of 7-acetamido-4-methyl-2-phenyl-1,8-naphthyridine using potassium permanganate or sodium dichromate-sulphuric acid gave only unchanged acetamidonaphthyridine.

Attempted preparation of 7-acetamido-4-methyl-2-styryl-1,8-naphthyridine. (Page 31)

7-Acetamido-4-methyl-2-phenyl-1,8-naphthyridine (1.2 g) was mixed with benzaldehyde (2 g) and acetic anhydride (3 ml). The mixture was heated under reflux for 24 hr. The cooled mixture separated into an aqueous and an oily layer. The latter was separated and stirred with petroleum ether, to produce a viscous tarry liquid. After drying the latter in a desiccator, it was stirred with diethyl ether to precipitate a brown powder (0.7 g). This powder was treated in boiling petroleum ether, the suspension filtered, and a cream powder obtained from the cooled filtrate. This product (0.5 g) had m.p. 170-180°, and was shown by TLC to consist of two components, one of which was unchanged acetamidonaphthyridine. (Kodak silica gel 'chromagram'; chloroform 9: methanol 1. UV visualisation). Repeated attempts to purify the material by treatment with petroleum ether were unsuccessful. N.m.r. examination of the crude material indicated that it was mostly unchanged acetamidonaphthyridine.

Reaction of phenyl lithium with 2-amino-7-methyl-1,8-naphthyridine. (Page 31)

Lithium metal (0.035 g) in small strips was stirred under reflux in sodium-dried ether (15 ml) and dry bromobenzene (1.1 g) added slowly (30 min). The mixture was refluxed for a further 30 min, then a solution of 2-amino-7-methyl-1,8-naphthyridine (5a; 0.79 g) in 2-ethoxyethanol (50 ml) was added slowly (30 min). Ether was removed from the mixture by distillation, and the residual mixture refluxed for 2 hr. Finally ether (50 ml) was added to the cooled solution, and the mixture refluxed 1 hr,

then filtered. The residue (0.7 g) was shown by IR examination to be unchanged starting material.

2-Amino-6-(2-acetyl-1-phenylvinylamino)pyridine (82).

A mixture of 2,6-diaminopyridine (11 g), benzoylacetone (16 g) and xylene (400 ml) was refluxed for 72 hr in a flask attached to a Dean and Stark apparatus. A total of 0.8 ml of water was collected in the apparatus. The mixture was cooled to 40° then filtered to remove unchanged 2,6-diaminopyridine which had precipitated. The filtrate was allowed to stand at room temperature for 24 hr, then filtered to collect the vinylaminopyridine (1.5 g), yellow powder, m.p. 138-140°. This product was twice recrystallised from ethanol to yield pale yellow needles, m.p. 144-146°.

(Found: C, 71.2; H, 6.0; N, 16.5. $C_{15}H_{15}N_3O$ requires C, 71.4; H, 6.1; N, 16.4%).

$\nu_{max.}$ 3450, 3350, 3200 (N-H); 1640 (C=O), 1610 (C=N), 1590, 1530, 1480, 1330, 1310, 1230, 1160, 1070, 860, 770, 750, 730, 700 and 690 $cm.^{-1}$

$\tau(CDCl_3)$ -2.50 (2H, br, 2-NH_2), 1.94-2.16 (2H, m, 2 x phenyl protons), 2.44-2.83 (4H, m, 4-H and 3 x phenyl protons), 3.55 (1H, d, J 8 Hz, 3-H), 3.83 (1H, d, J 8 Hz, 5-H), 4.12 (1H, s, -CH=), 5.60 (1H, br, -NH-, signal removed on deuteration of sample), 7.46 (3H, s, -COMe).

2,6-Diamino-4-ethoxypyridine (88).

Diethyl 4-ethoxypyridine-2,6-dicarboxylate (85) was prepared from chelidamic acid by the method of Markees et al (1968). This ester was converted to 2,6-diamino-4-ethoxypyridine by the method published earlier by Markees and Kidder (1956). The overall yield of product (from chelidamic acid) was 10%. The crude product (m.p. 129-131°) was used in the following syntheses.

7-Amino-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (89).

A stirred mixture of 2,6-diamino-4-ethoxypyridine (0.6 g), acetylacetone (2 g) and orthophosphoric acid (25 ml) was heated under reflux at 130° for 1 hr. The cooled solution was diluted with water (30 ml) and basified with ammonia solution. The resulting suspension was centrifuged and the product washed with ammonia soltn. followed by water, to yield the naphthyridine (0.8 g, 94%), pale orange needles, m.p. 228-230° (from water).

(Found: C, 65.4; H, 6.8; N, 18.7. $C_{12}H_{15}N_3O$ requires C, 66.3; H, 6.9; N, 19.3%)

$\nu_{max.}$ 3350, 3150 (N-H); 1640 (C=N), 1610, 1580, 1330, 1230, 1200, 1110 (C-O), and 820 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 2.41 (1H, s, 3-H), 3.31 (1H, s, 6-H), 5.49 (2H, q, J 7 Hz, $-OCH_2Me$), 6.91 (3H, s, 2-Me), 7.10 (3H, s, 4-Me), 8.32 (3H, t, J 7 Hz, $-OCH_2\underline{Me}$).

7-Amino-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (90).

2,6-Diamino-4-ethoxypyridine (0.3 g), benzoylacetone (0.8 g) and orthophosphoric acid (10 ml) were stirred and heated under reflux at 130-140° for 2 hr. Addition of water (15 ml) to the cooled solution gave at first an oil; after stirring the suspension for 30 min, a pale yellow solid precipitated. Treatment of this solid with boiling aqueous ammonia solution followed by water gave the naphthyridine (0.32 g, 57%) colourless prisms, m.p. 227-228° (from ethanol-water).

(Found: C, 73.3; H, 6.2; N, 14.8. $C_{17}H_{17}N_3O$ requires C, 73.1; H, 6.1; N, 15.0%).

$\nu_{max.}$ 3400, 3250 (N-H); 1670, 1620, 1580, 1230; 1110 (C-O), 830, 780 and 700 $cm.^{-1}$

SYNTHESES OF 2-VINYLAMINO-1,8-NAPHTHYRIDINES.

Product derived from ethyl acetoacetate.

7-(2-Carbethoxy-1-methylvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (91).

A stirred mixture of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 2 g), ethyl acetoacetate (50 ml) and conc. hydrochloric acid (0.4 ml) was heated under reflux at 210° for 24 hr. The cooled mixture was filtered, and the filtrate evaporated under reduced pressure to yield a solid which was washed thoroughly with ether before drying. The yield of vinylaminonaphthyridine was 0.7 g (25%), pale yellow needles, m.p. 149-151° (from ethanol).

(Found: C, 72.3; H, 5.9; N, 12.3. $C_{21}H_{21}N_3O_2$ requires C, 72.6; H, 6.1; N, 12.1%).

$\nu_{max.}$ 3200 (N-H), 1660 (C=O), 1640 (C=N), 1620, 1600, 1350, 1300, 1270, 1240, 1160, 1150, 1010, 800, 780 and 700 $cm.^{-1}$

$\tau(CDCl_3)$ -1.30 (1H, br, removed on deuteration, -NH), 1.72-2.18 (3H, m, 5-H and phenyl protons), 2.40-2.67 (4H, m, 3-H and phenyl protons), 3.11 (1H, d, J 9 Hz, 6-H), 5.10 (1H, s, =C<u>H</u>-CO_2Et), 5.82 (2H, q, J 7 Hz, -$CO_2C\underline{H}_2$Me), 7.21 (3-H, s, -CH=C(-<u>Me</u>)-), 7.37 (3H, s, 4-Me), 8.73 (3H, t, J 7 Hz, -$CO_2CH_2\underline{Me}$).

Products derived from ethyl ethoxymethylenemalonate (EMME).

7-(2,2-diethoxycarbonylvinylamino)-2,4-dimethyl-1,8-naphthyridine (94).

A mixture of 7-amino-2,4-dimethyl-1,8-naphthyridine (5; 1.73 g), EMME (2.2 g) and ethanol (25 ml) was heated under reflux for 2 hr. Addition of water (20 ml) to the cooled reaction mixture precipitated the vinylaminonaphthyridine (2.2 g, 64%), colourless prisms, m.p. 154° (from ethanol).

(Found: C, 62.8; H, 6.1; N, 12.1%; M^+ 343. $C_{18}N_{21}N_3O_4$ requires C, 62.9; H, 6.2; N, 12.2%; M^+ 343).

$\lambda_{max.}$ (EtOH) 287 nm (log ε 4.24) and 366 (4.61).

$\nu_{max.}$ 3200 (N-H), 1680 (C=O), 1600, 1580, 1510, 1460, 1400, 1370, 1330, 1290, 1240 (C-O), 1100, 1030, 800 and 740 $cm.^{-1}$

τ(CF_3CO_2H) 0.50 (1H, d, J 13 Hz, -NH-CH=), 1.27 (1H, d, J 9 Hz, 5-H), 2.21 (1H, d, J 9 Hz, 6-H), 2.30 (1H, s, 3-H), 5.47 (4H, q, J 7 Hz, 2 x $-CO_2CH_2Me$), 6.97 (3H, s, 2-Me), 7.00 (3H, s, 4-Me), 8.50 (6H, t, J 7 Hz, 2 x $-CO_2CH_2Me$).

m/e 344(1), 343(6), 299(8), 298(5), 271 (24), 270 (100), 252(6), 224(6), 223(4), 198(4), 197(4), 196(4), 195(4), 158(16), 157(54), 156(4), 155(4), 142(88), 130(8), 116(3), 104(4), 89(3), 78(4), 77(12), 65(5), 53(8), 51(4), 45(7), 39(8), 31(37), 29(77), 27(25).

7-(2,2-Dicarbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (95).

A stirred mixture of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (1.18 g), EMME (1.2 g) and ethanol (24 ml) was heated under reflux for 2 hr. The solution was cooled, filtered, and the residue washed thoroughly with ethanol to

yield the vinylaminonaphthyridine (1.4 g, 70%), colourless prisms, m.p. 168-171° (from ethanol).

(Found: C, 68.3; H, 5.6; N, 10.5%; M^+ 405. $C_{23}H_{23}N_3O_4$ requires C, 68.2; H, 5.7; N, 10.4%; M^+ 405).

$\lambda_{max.}$ ($CHCl_3$) 258 nm (log ε 4.4), 292 (4.4) and 383(4.64)

$\nu_{max.}$ 3200 (N-H), 1710 (C=O), 1650, 1620, 1600, 1580, 1520, 1400, 1340, 1300, 1280, 1230, 1150, 1100, 1070, 1040, 1000, 860, 840, 800, 780 and 690 $cm.^{-1}$

τ(CF_3CO_2H) 0.50 (1H, d, J 13 Hz, -NH-CH=), 1.28 (1H, d, J 9 Hz, 5-H), 1.83-2.33 (7H, m, 3-H, 6-H, and phenyl protons), 5.50 (4H, q, J 7 Hz, 2 x $-CO_2CH_2Me$), 6.96 (3H, s, 4-Me), 8.53 (6H, t, J 7 Hz, 2 x $-CO_2CH_2Me$).

m/e 406(1), 405(5), 360(6), 335(3), 334(23), 332(100), 314(3), 287(4), 285(19), 262(5), 260(28), 259(29), 258(3), 220(8), 219(27), 217(3), 190(8), 165(3), 144(3), 130(6), 110(3), 109(8), 102(3), 96(3), 77(13), 53(4), 51(4), 46(5), 45(5), 31(26), 29(36), 27(16).

m* 272.0 (405→332), 202.0 (332→259).

7-(2,2-Dicarbethoxyvinylamino)-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (96).

7-Amino-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (90; 0.15 g) was dissoved in a mixture of EMME (0.7 g) and ethanol (10 ml), and the mixture stirred and heated under reflux for 1 hr. The reaction mixture was cooled, and the material which precipitated was collected, washed with ethanol and dried to yield the vinylaminonaphthyridine (0.20 g, 86%), colourless prisms, m.p. 197-199° (from ethanol).

(Found: C, 66.9; H, 6.2 ; N, 9.4. $C_{25}H_{27}N_3O_5$ requires C, 66.8; H, 6.1 ; N, 9.4%).

$\nu_{max.}$ (KBr) 3300 (N-H), 3100 (C=C), 1730 (C=O), 1660 (C=N), 1600, 1580, 1390, 1350, 1300, 1240, 1180, 1110, 1070, 830, 810, 780 and 700 $cm.^{-1}$

7-(2,2-Dicarbethoxyvinylamino)-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (97).

A stirred mixture of 7-amino-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (89; 0.4 g), EMME (1.6 g) and ethanol (20 ml) was heated under reflux for 2 hr. Water (60 ml) and ether (20 ml) were added to the cooled solution. The mixture was shaken, allowed to separate, and the ether layer washed with water before drying over $MgSO_4$. Evaporation of the solvent yielded the vinylaminonaphthyridine (0.4 g, 56%), colourless prisms, m.p. 151-153° (from petroleum ether of b.p. 100-120°).

$\nu_{max.}$ 3150 (N-H), 1710 (C=O), 1650, 1600, 1580, 1560, 1310, 1290, 1230, 1170, 1100, 1070, 1040; 820, 810 $cm.^{-1}$

$\tau(CDCl_3)$ -1.23 (1H, br, -N<u>H</u>-CH=), 0.65 (1H, d, J 12.5 Hz, -NH-C<u>H</u>=), 3.03 (1H, s, 3-H), 3.80 (1H, s, 6-H), 5.45-6.06 (6H, m, 2 x $-CO_2C\underline{H}_2Me$ and $-OC\underline{H}_2Me$), 7.27 (3H, s, 2-Me), 7.35 (3H, s, 4-Me), 8.29-8.83 (9H, m, 2 x $-CO_2CH_2\underline{Me}$ and $-OCH_2\underline{Me}$).

Products derived from ethyl ethoxymethyleneacetoacetate

Ethyl ethoxymethyleneacetoacetate (98) was prepared from ethyl acetoacetate and triethyl orthoformate by the method of Yasuda (1959). The product was a colourless liquid of characteristic odour, b.p. 120-126°(5 mm) or 132-137°(10 mm). (Yasuda quotes b.p. 149-151° (16 mm).

7-(2-Acetyl-2-carbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine (99).

A mixture of 7-amino-2,4-dimethyl-1,8-naphthyridine (0.86 g), ethyl ethoxymethyleneacetoacetate (1.8 g) and ethanol (20 ml) was stirred and heated under reflux for 2 hr. Addition of water (20 ml) to the cooled solution caused the precipitation of a red oil; the mixture was stirred for 1 hr, and the oil solidified. The solid was collected, washed thoroughly with ethanol and dried to yield the vinylaminonaphthyridine (0.7 g, 45%). The product crystallised as the monohydrate from ethanol, colourless prisms, m.p. 174-175°.

(Found: C, 60.9; H, 6.3; N, 12.6. $C_{17}H_{19}N_3O_3.H_2O$ requires C, 61.6; H, 6.4; N, 12.9%).

$\lambda_{max.}$(EtOH) 289 nm (log ε 4.05) and 375 (4.64).

$\nu_{max.}$(KBr) 3380, 3200 (N-H); 3080, 2980, 1715 (ester C=O), 1695 (keto C=O), 1640 (C=N), 1610, 1570, 1515, 1300, 1235, 1195, 1085, 1060, 800 and 760 $cm.^{-1}$

(Spectrum recorded on Perkin-Elmer 237 grating spectrometer).

τ(CF_3CO_2H) 0.40 (1H, d, J 11 Hz, -NH-CH=), 1.22 (1H, d, J 9 Hz, 5-H), 2.15 (1H, d, J Hz, 6-H), 2.25 (1H, s, 3-H), 5.42 (2H, q, J 8 Hz, $-CO_2CH_2Me$), 6.96 (3H, s, 2-Me), 7.00 (3H, s, 4-Me), 7.21 (3H, s, -COMe), 8.48 (3H, t, J 8 Hz, $-CO_2CH_2Me$).

7-(2-Acetyl-2-carbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (100).

A stirred mixture of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 3.54 g), ethyl ethoxymethyleneacetoacetate (4 g) and ethanol (40 ml) was heated under reflux for 40 min. The solution was cooled and the vinylaminonaphthyridine collected, washed with ethanol and dried. The yield was 5 g (89%), pale yellow needles, m.p. 174-176° (from ethanol). (Found: C, 70.2; H, 5.8; N, 11.0. $C_{22}H_{21}N_3O_3$ requires C, 70.4; H, 5.6; N, 11.2%).

$\lambda_{max.}$ ($CHCl_3$) 258 nm (log ε 4.41), 294 (4.21) and 389 (4.68).

$\nu_{max.}$ 1720 (ester C=O), 1660 (ketone C=O), 1620 (C=N), 1600, 1540, 1360, 1300, 1250, 1160, 1080, 1030, 880, 840, 810, 780, 770 and 710 $cm.^{-1}$

τ(CF_3CO_2H) 0.33 (1H, d, J 11 Hz, -NH-CH=), 1.19 (1H, d, J 9 Hz, 5-H), 1.76-2.33 (7-H, m, 3-H, 6-H and phenyl protons), 5.43 (2H, q, J 7 Hz, $-CO_2CH_2Me$), 6.92 (3H, s, 4-Me), 7.22 (3H, s, -COMe), 8.50 (3H, t, J 7 Hz, $-CO_2CH_2Me$).

7-(2-Acetyl-2-carbethoxyvinylamino)-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (101).

A solution of 7-amino-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (90; 0.3 g) and ethyl ethoxymethyleneacetoacetate (0.9 g) in ethanol (20 ml) was refluxed on a steam-bath for 1 hr. Water (2 ml) was added to the cooled solution to precipitate the vinylaminonaphthyridine which was washed with 50% aqueous ethanol before drying. The yield was 0.4 g (89%), small buff needles, m.p. 167-169° (from ethanol).

(Found: C, 68.6; H, 6.2; N, 10.2. $C_{24}H_{25}N_3O_4$ requires C, 68.7; H, 6.0; N, 10.0%).

$\nu_{max.}$ (KBr) 1700 (ester C=O), 1690 (ketone C=O), 1640 (C=N), 1610, 1600, 1570, 1390, 1310, 1290, 1240, 1100, 1070, 820, 780 and 700 $cm.^{-1}$

$\tau(CDCl_3)$ 2.85 (1H, br, -NH-CH=), 0.58 (1H, d, J 12 Hz, -NH-CH=), 1.67-2.58 (6H, m, 3-H and phenyl protons), 3.67 (1H, s, 6-H), 5.67 (4H, q, J 7 Hz, $-CO_2CH_2Me$ and $-OCH_2Me$), 7.10 (3H, s, 4-Me), 7.40 (3H, s, -COMe), 8.62 (3H, t, J 7 Hz, $-CO_2CH_2Me$), 8.42 (3H, t, J 7 Hz, $-OCH_2Me$).

7-(2-acetyl-2-carbethoxyvinylamino)-4-methyl-1,8-naphthyridin-2(1H)-one (102).

A solution of 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7; 1.5 g) in ethyl ethoxymethyleneacetoacetate (6 g) was stirred and heated at 170-180° for 1 hr. The cooled solution was filtered, and the residue washed with ethanol. The dried solid was extracted with chloroform in a Soxhlet apparatus for 4 hr, and evaporation of the solvent yielded 0.5 g of the vinylaminonaphthyridine (21%), cream needles, m.p. 274-276° (from 2-ethoxyethanol).

(Found: C, 61.1; H, 5.6; N, 13.2. $C_{16}H_{17}N_3O_4$ requires C, 61.0; H, 5.4; N, 13.3%).

$\nu_{max.}$ 3350, 3150 (N-H); 1700 (ester C=O), 1660 (ketone C=O), 1640 (amide C=O), 1600, 1590, 1300, 1230, 1070, 820, and 800 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.43 (1H, br, -NH-CH=), 1.49 (1H, d, J 9 Hz, 5-H), 2.47 (1H, d, J 9 Hz, 6-H), 2.90 (1H, s, 3-H), 5.38 (2H, q, J 7 Hz, $-CO_2CH_2Me$), 7.18 (3H, s, 4-Me),

7.22 (3H, s, -COMe), 8.47 (3H, t, J 7 Hz, $-CO_2CH_2\underline{Me}$).

7-(2-Acetyl-2-carbethoxyvinylamino)-4-phenyl-1,8-naphthyridin-2(1H)-one (103).

7-Amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8; 2 g) and ethyl ethoxymethyleneacetoacetate (7 g) were mixed and heated together at 130° for 30 min. The mixture was cooled and ethanol (15 ml) added to precipitate the vinylaminonaphthyridine (2.3 g, 74%), colourless prisms, m.p. 240-242° (from 2-ethoxyethanol).

(Found: C, 66.4; H, 5.0; N, 10.9. $C_{21}H_{19}N_3O_4$ requires C, 66.9; H, 5.1; N, 11.1%).

$\nu_{max.}$ 1690 (ester C=O), 1650 (ketone C=O), 1600, 1590, 1570, 1390, 1290, 1250, 1230, 1120, 1070, 830, 800, 790 and 700 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.34 (1H, d, J 12 Hz, -NH-CH=), 1.59 (1H, d, J 9 Hz, 5-H), 2.40 (5-H, s, phenyl protons), 2.50 (1H, d, J 9 Hz, 6-H), 2.81 (1H, s, 3-H), 5.37 (2H, q, J 7 Hz, $-CO_2CH_2Me$), 7.18 (3H, s, -COMe), 8.44 (3H, t, J 7 Hz, $-CO_2CH_2Me$).

Products derived from ethyl ethoxymethylenecyanoacetate.

7-(2-carbethoxy-2-cyanovinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (105).

A solution of ethyl ethoxymethylenecyanoacetate (104; 1.6 g) in ethanol (30 ml) was added to a boiling solution of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 1.2 g) in ethanol (20 ml). The mixture was boiled under reflux for 10 min, then cooled and filtered. The residual solid was washed with ethanol and dried to yield the vinylaminonaphthyridine (81%), colourless prisms, m.p. 208-210° (from 2-ethoxyethanol).

(Found: C, 70.2; H, 5.0; N, 15.7. $C_{21}H_{18}N_4O_2$ requires C, 70.4; H, 5.0; N, 15.6%).

$\nu_{max.}$ 2250 (C≡N), 1680 (C=O), 1630 (C=N), 1600, 1580, 1340, 1300, 1240, 1200, 820, 800 and 770 $cm.^{-1}$

τ(CF_3CO_2H) 0.86 (1H, d, J 13 Hz, -NH-C<u>H</u>=), 1.10 (1H, d, J 9 Hz, 5-H), 1.80-2.33 (7-H, m, 3-H, 6-H and phenyl protons), 5.46 (2H, q, J 7 Hz, $-CO_2C\underline{H}_2Me$), 6.87 (3H, s, 4-Me), 8.50 (3H, t, J 7 Hz, $-CO_2CH_2\underline{Me}$).

7-(2-Carbethoxy-2-cyanovinylamino)-4-methyl-1,8-naphthyridin-2(1H)-one (106).

7-Amino-4-methyl-1,8-naphthyridin-2(1H)-one (7; 1.75 g) was mixed with ethyl ethoxymethylenecyanoacetate (104; 2 g) and the mixture added to boiling Dowtherm-A (36 g). The mixture was boiled gently for 10 min. After cooling, the suspension was poured into a basin (charred material was separated and discarded) and petroleum ether (20 ml) added to precipitate the vinylaminonaphthyridine (2 g, 66%), colourless prisms, m.p.

290-292° (decomp.) (from 2-ethoxyethanol).

(Found: C, 60.2; H, 4.7; N, 18.6. $C_{15}H_{14}N_4O_3$ requires C, 60.4; H, 4.7; N, 18.8%).

$\nu_{max.}$ 3250 (N-H), 2250 (C≡N), 1690 (ester C=O), 1660 (amide C=O), 1640 (C=N), 1600, 1570, 1530, 1410, 1350, 1300, 1240 (C-O), 790 and 740 $cm.^{-1}$

τ(CF_3CO_2H) 0.98 (1H, d, J 13 Hz, -NH-CH=), 1.42 (1H,d, J 9 Hz, 5-H), 2.40 (1H, d, J 9 Hz, 6-H), 2.79 (1H, s, 3-H), 5.49 (2H, q, J 7 Hz, $-CO_2CH_2Me$), 7.15 (3H, s, 4-Me), 8.51 (3H, t, J 7 Hz, $-CO_2CH_2Me$).

7-(2-Carbethoxy-2-cyanovinylamino)-4-phenyl-1,8-naphthyridin-2(1H)-one (107).

A mixture of 7-amino-4-phenyl-1,8-naphthyridin-2(1H)-one (8; 0.6 g) and ethyl ethoxymethylenecyanoacetate (0.85 g) was added to boiling Dowtherm-A (20 g), and the solution boiled for 5 min. The hot mixture was filtered to remove charred material, and the filtrate cooled to yield the vinylaminonaphthyridinone (0.9 g, 100%), colourless prisms, m.p. 282-285° (from 2-ethoxyethanol).

(Found: C, 66.3; H, 4.6; N, 15.3. $C_{20}H_{16}N_4O_3$ requires C, 66.7; H, 4.5; N, 15.6%).

$\nu_{max.}$ 3250 (N-H), 2250 (C≡N), 1690 (ester C=O), 1660 (amide C=O), 1640 (C=N), 1600, 1560, 1520, 1350, 1300, 1230 (C-O), 1180, 1130, 780, 750, 710 and 690 $cm.^{-1}$

τ(CF_3CO_2H) 0.96 (1H, d, J 13 Hz, -NH-CH=), 1.57 (1H, d, J 9 Hz, 5-H), 2.20-2.60 (6H, m, 5-H and phenyl protons), 2.75 (1H, s, 3-H), 5.51 (2H, q, J 7 Hz, $-CO_2CH_2Me$), 8.50 (3H, t, J 7 Hz, $-CO_2CH_2Me$).

SYNTHESES OF PYRIMIDO[1,2-a][1,8]NAPHTHYRIDINES.

4,8-Dimethylpyrimido[1,2-a][1,8]naphthyridin-2,10(1H,10H)-dione (44a).

This compound was prepared by the method of Carboni et al (1966b) from 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7). The n.m.r. spectrum of the compound was determined and the assignments are recorded here.

τ(CF_3CO_2H) 1.47 (1H, d, J 9 Hz, 5-H), 2.38 (1H, d, J 9 Hz, 6-H), 3.07 (1H, s, 3-H), 3.68 (1H, s, 9-H), 7.33 (3H, s, 8-Me), 7.43 (3H, s, 4-Me).

4,8-Dimethyl-2-phenylpyrimido[1,2-a][1,8]naphthyridin-10(10H)-one (109).

7-(2-Carbethoxy-1-methylvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (91; 0.5 g) was added to boiling Dowtherm-A (20 g) and the solution boiled for 10 min. The solution was cooled and petroleum ether (20 ml) added to precipitate the pyrimidonaphthyridinone (0.3 g), yellow needles, m.p. 193-195° (from ethanol). (Yield: 69%).

(Found: C, 75.9; H, 5.1; N, 13.9. $C_{19}H_{15}N_3O$ requires C, 75.7; H, 5.0; N, 13.9%).

$\nu_{max.}$ 1690 (C=O), 1640 (C=N), 1590, 1520, 1200, 1140, 990, 880, 850, 830, 780, 740 and 700 $cm.^{-1}$

τ($CDCl_3$) 1.67-1.90 (2H, m, phenyl protons), 2.23 (1H, d, J 9 Hz, 5-H), 2.38 (1H, s, 9-H), 2.50-2.67 (3H, m, phenyl protons), 2.88 (1H, d, J 9 Hz, 6-H), 3.67 (1H, s, 3-H), 7.45 (3H, s, 8-Me), 7.67 (3H, s, 4-Me).

9-Carbethoxy-4-methyl-2-phenyl-10H-pyrimido [1,2-a][1,8] naphthyridin-10-one (110).

7-(2,2-Dicarbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (95; 3 g) was added to boiling Dowtherm-A (24 g), and the solution boiled under reflux for 15 min. Petroleum ether (70 ml) was added to the cooled solution to precipitate a yellow solid which was collected, washed with petroleum ether and ethanol and dried to yield the pyrimidonaphthyridinone (2 g, 74%), pale yellow needles, m.p. 210-211° (from 2-ethoxyethanol).

(Found: C, 70.2; H, 4.8; N, 11.7%; M^+ 359. $C_{21}H_{17}N_3O_3$ requires C, 69.9; H, 4.9; N, 11.6%; M^+ 359).

$\lambda_{max.}(CHCl_3)$ 299 nm (log ε 4.24) and 415 (4.17).

$\nu_{max.}$ 1730 (ester C=O), 1690 (amide C=O), 1590, 1520, 1290, 1130, 830, 790 and 700 $cm.^{-1}$

$\tau(CDCl_3)$ 1.28 (1H, s, 8-H), 1.64 (2H, m, phenyl protons), 2.01 (1H, d, J 9 Hz, 5-H), 2.30 (1H, s, 3-H), 2.42-2.65 (3H, m, phenyl protons), 2.75 (1H, d, J 9 Hz, 6-H), 5.55 (2H, q, J 7 Hz, $-CO_2\underline{CH_2}Me$), 7.37 (3H, s, 4-Me), 8.58 (3H, t, J 7 Hz, $-CO_2CH_2\underline{Me}$).

m/e 361(1), 360(10), 359(42), 286(8), 285(19), 260(19), 259(100), 220(6), 219(28), 205(40), 204(8), 190(4), 168(6), 147(15), 109(9), 77(9), 59(10).

m* 258 (260→259), 227.9 (359→286).

9-Carbethoxy-5-ethoxy-4-methyl-2-phenyl-10H-pyrimido [1,2-a] [1,8] naphthyridin-10-one (111).

7-(2,2-Dicarbethoxyvinylamino)-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (96; 0.1 g) was added to boiling Dowtherm-A (4 g) and the solution boiled under reflux for 10 min. The solution was cooled and petroleum ether (15 ml) added; the precipitate was collected, washed with petroleum ether and dried to yield the pyrimidonaphthyridinone (0.06 g, 68%), small yellow needles, m.p. 195-198° (from ethanol).

(Found: C, 68.6; H, 5.4; N, 10.3%; M^+ 403. $C_{23}H_{21}N_3O_4$ requires C, 68.5; H, 5.3; N, 10.4%; M^+ 403).

$\nu_{max.}$ (KBr) 1740 (ester C=O), 1690 (amide C=O), 1620 (C=N), 1590, 1520, 1470, 1280, 1120, 1110, 830, 800, 780, and 700 $cm.^{-1}$

$\tau(CDCl_3)$ 1.32 (1H, s, 8-H), 1.58-1.90 (2H, m, phenyl protons), 2.32 (1H, s, 3-H), 2.37-2.62 (3H, m, phenyl protons), 3.47 (1H, s, 6-H), 5.70 (4H, q, J 7 Hz, $-CO_2\underline{CH}_2Me$ and $-O\underline{CH}_2Me$), 7.13 (3H, s, 4-Me), 8.42 (3H, t, J 7 Hz, $-OCH_2\underline{Me}$), 8.58 (3H, t, J 7 Hz, $-CO_2CH_2\underline{Me}$).

m/e 405(3), 404(21), 403 (79), 375(8), 357(16), 330(22), 329(13), 305(24), 304(100), 303(16), 277(23), 276(69), 275(4), 247(16), 246(45), 236(32), 219(34), 206(10), 191(12), 165(16), 153(7), 142(14), 118(13), 115(14), 102(20), 77(20), 45(23).

m* 348.9(403→375), 305 (357→330), 250.5 (304→276).

Attempted cyclisation of 7-(2,2-dicarbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine.

7-(2,2-Dicarbethoxyvinylamino)-2,4-dimethyl-1,8-naphthyridine (94; 2 g) was added to boiling Dowtherm-A (24 g) and the mixture boiled under reflux for 15 min. Addition of petroleum ether (25 ml) to the cooled solution precipitated unchanged vinylaminonaphthyridine (1.8 g), identified by undepressed mixed m.p. and IR spectroscopy. Some charred material was also present in the mixture.

Attempted cyclisation of 7-(2,2-dicarbethoxyvinylamino)-2,4-dimethyl-5-ethoxy-1,8-naphthyridine.

7-(2,2-Dicarbethoxyvinylamino)-2,4-dimethyl-5-ethoxy-1,8-naphthyridine (97; 0.25 g) was added to boiling Dowtherm-A (20 g) and the solution boiled under reflux for 15 min. Addition of petroleum ether to the cooled solution gave unchanged vinylaminonaphthyridine (0.25 g), identified by IR spectroscopy.

9-Acetyl-4-methyl-2-phenyl-10H-pyrimido [1,2-a] [1,8]-naphthyridin-10-one (112).

7-(2-Acetyl-2-carbethoxyvinylamino)-4-methyl-2-phenyl-1,8-naphthyridine (100; 0.5 g) was added to boiling Dowtherm-A (12 g) and the solution boiled for 5 min. The mixture was cooled, and the solid which precipitated on addition of petroleum ether (25 ml) was collected, washed with petroleum ether and dried to yield the pyrimidonaphthyridinone (0.11 g, 25%), yellow needles, m.p. 229° (decomp.) (from 2-ethoxyethanol).

(Found: C, 72.7; H, 4.7; N, 13.0. $C_{20}H_{15}N_3O_2$ requires C, 72.9; H, 4.6; N, 12.8%).

$\nu_{max.}$ 1710 (ketone C=O), 1660 (amide C=O), 1630 (C=N), 1590, 1520, 1340, 810, 790, 740, and 710 $cm.^{-1}$

$\tau(CDCl_3)$ 1.65-2.60 (9H, m, 3-H, 5-H, 6-H, 8-H and phenyl protons), 7.17 (3H, s, 4-Me), 7.27 (3H, s, -COMe).

9-Acetyl-5-ethoxy-4-methyl-2-phenyl-10H-pyrimido [1,2-a] [1,8] naphthyridin-10-one (113).

7-(2-Acetyl-2-carbethoxyvinylamino)-5-ethoxy-4-methyl-2-phenyl-1,8-naphthyridine (101; 0.4 g) was added to boiling Dowtherm-A (12 g) and the solution boiled under reflux for 10 min. The solid which precipitated when petroleum ether (20 ml) was added to the cooled solution was washed with petroleum ether and dried to yield the pyrimidonaphthyridinone (0.27 g, 71%), small orange needles, m.p. 249-251° (from 2-ethoxyethanol).
(Found: C, 70.5; H, 5.1; N, 11.4%; M^+ 373. $C_{22}H_{19}N_3O_3$ requires C, 70.7; H, 5.1; N, 11.3%; M^+ 373).

$\nu_{max.}$(KBr) 1720 (ketone C=O), 1660 (C=O), 1620 (C=N), 1590, 1520, 1500, 1470, 1330, 1280 (C-O), 1200, 1120, 830, 790, and 700 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.82 (1H, s, 8-H), 1.37 (1H, s, 3-H), 1.67-2.29 (6H, m, 6-H, phenyl protons), 5.17 (2H, q, J 7 Hz, $-OCH_2Me$), 6.62 (3H, s, 4-Me), 7.05 (3H, s, -COMe), 8.18 (3H, t, J 7 Hz, $-OCH_2Me$).

m/e 375(3), 374(21), 373(57), 359(24), 358(100), 343(28), 329(20), 328(83), 316(21), 315(57), 302(38), 289(23), 237(49), 220(21); 180(11), 165(14), 103(14), 102(14), 91(12), 77(14), 43(18).

m* 289.3 (343→315)

SYNTHESES OF 2,6-DIVINYLAMINOPYRIDINES AND RELATED COMPOUNDS

2,6-Di(2,2-dicarbethoxyvinylamino)pyridine (114).

A solution of 2,6-diaminopyridine (1.09 g) in ethyl ethoxymethylenemalonate (6 g) was heated under reflux at 250° for 15 min. The solid which deposited in the cooled solution was collected, washed with ether and dried to yield the divinylaminopyridine (3.2 g, 72%), buff needles, m.p. 133-134° (from ethanol).

(Found: C, 56.4; H, 6.3; N, 9.2. $C_{21}H_{27}N_3O_8$ requires C, 56.1; H, 6.1; N, 9.4%).

$\nu_{max.}$ 3150 (N-H), 1700 (C=O), 1650, 1620, 1560, 1420, 1250, 1170, 1110, 1050, 830 and 850 $cm.^{-1}$

$\tau(CDCl_3)$ -1.13 (2H, d, J 12.5 Hz, 2 x -NH-CH=), 0.86 (2H, d, J 12.5 Hz, 2 x -NH-CH=), 2.30 (1H, t, J 7 Hz, 4-H), 3.35 (2H, d, J 7 Hz, 3-H and 5-H), 5.65 (8H, q, J 7 Hz, 4 x $-CO_2CH_2Me$), 8.60 (12H, t, J 7 Hz, 4 x $-CO_2CH_2Me$).

2,6-Di(2-acetyl-2-carbethoxyvinylamino)pyridine (115).

A solution of 2,6-diaminopyridine (1.35 g) in ethyl ethoxymethyleneacetoacetate (6 g) was refluxed at 230° for 10 min. The solid which deposited in the mixture on cooling was collected, washed with ethanol and dried to yield the divinylaminopyridine (3.6 g, 74%), colourless prisms, m.p. 166-168° (from 2-ethoxyethanol).

(Found: C, 58.4; H, 6.0; N, 10.8. $C_{19}H_{23}N_3O_6$ requires C, 58.6; H, 6.0; N, 10.8%).

$\nu_{max.}$ 3350 (N-H), 1710 (ester C=O), 1700 (ketone C=O), 1630, 1570, 1260, 1170, 830 and 780 $cm.^{-1}$

$\tau(CDCl_3)$ -2.69 (2H, d, J 13 Hz, 2 x -NH-CH=), 0.90 (2H, d, J 13 Hz, 2 x -NH-CH=), 2.28 (1H, t, J 7 Hz, 4-H), 3.29 (2H, d, J 7 Hz, 3-H and 5-H), 5.70 (4H, q, J 7 Hz, 2 x CO_2CH_2Me), 7.45 (6H, s, 2 x -COMe), 8.63 (6H, t, J 7 Hz, 2 x $-CO_2CH_2Me$).

2,6-Di(2,2-dicarbethoxyvinylamino)-4-ethoxypyridine (116).

A mixture of 2,6-diamino-4-ethoxypyridine (0.3 g), ethanol (10 ml) and diethyl ethoxymethylenemalonate (0.8 g) was heated under reflux on a steam bath for 2 hr. The cooled mixture was stirred for 24 hr before filtering; the collected solid was washed with ethanol and dried to yield the divinylaminopyridine (0.6 g, 60%), colourless prisms, m.p. 148-149° (from methanol/water).

(Found: C, 56.1; H, 6.4; N, 8.7. $C_{23}H_{31}N_3O_9$ requires C, 56.0; H, 6.3; N, 8.5%).

$\nu_{max.}$ 3300 (N-H), 1710 (C=O), 1670, 1620, 1560, 1250, 1220, 1150, 1090, 870 and 820 $cm.^{-1}$

$\tau(CCl_4)$ -0.94 (2H, d, J 12 Hz, 2 x -NH-CH=), 1.03 (2H, d, J 12 Hz, 2 x -NH-CH=), 3.96 (2H, s, 3-H and 5-H), 5.52 (10H, m, 4 x $-CO_2CH_2Me$ and $-OCH_2Me$), 8.60 (3H, t, J 7 Hz, $-OCH_2Me$), 8.64 (12H, t, J 7 Hz, 4 x $-CO_2CH_2Me$).

2,6-Di(2-acetyl-2-carbethoxyvinylamino)-4-ethoxypyridine (117).

A solution of 2,6-diaminopyridine (0.3 g) in ethanol (10 ml) and ethyl ethoxymethyleneacetoacetate (0.8 g) was heated under reflux on a steam bath for 2 hr. The precipitate which appeared in the cooled mixture was collected, washed with

ethanol and dried to yield the divinylaminopyridine (0.5 g, 58%), colourless prisms, m.p. 128° (from methanol).

(Found: C, 58.2; H, 6.2; N, 9.9. $C_{21}H_{27}N_3O_7$ requires C, 58.2; H, 6.3; N, 9.7%).

$\nu_{max.}$ 3350 (N-H), 1710 (ester C=O), 1700 (ketone C=O), 1630, 1550, 1270, 1250 (C-O), 1160, 1080, 860, 830 and 780 $cm.^{-1}$

$\tau(CDCl_3)$ -2.61 (2H, d, J 12 Hz, 2 x -NH-CH=), 0.95 (2H, d, J 12 Hz, 2 x -NH-CH=), 3.80 (2H, s, 3-H and 5-H), 5.68 (4H, q, J 7 Hz, 2 x $-CO_2CH_2Me$), 5.89 (2H, q, J 7 Hz, $-OCH_2Me$), 7.43 (6H, s, 2 x -COMe), 8.54 (3H, t, J 7 Hz, $-OCH_2Me$), 8.61 (6H, t, J 7 Hz, 2 x $-CO_2CH_2Me$).

3,9-Dicarbethoxypyrimido[1,2-a][1,8]naphthyridin-4,10(1H,10H)-dione (118).

2,6-Di(2,2-dicarbethoxyvinylamino)pyridine (114; 1.5 g) was added to boiling Dowtherm-A (8 g) and the solution refluxed for 15 min. The solution was cooled, and the resulting gelatinous suspension was diluted with petroleum ether (100 ml) and filtered. The residue was extracted with petroleum ether in a Soxhlet apparatus for 3 hr, to remove all traces of Dowtherm-A. The yield of crude pyrimidonaphthyridinedione was 0.9 g (74%), m.p. 220-230°.

The crude product was dissolved in the minimum quantity of chloroform and the solution applied to an alumina column. The column was eluted with chloroform 90 : methanol 10. The first 150 ml of eluate was discarded (TLC examination on alumina plates showed the presence of 2 components); elution of the column was continued until colourless solutions were obtained.

A total of 150 ml eluate was collected; TLC examination showed the presence of one component only. Evaporation of the latter solution to dryness gave 55 mgm colourless prisms, m.p. 230-232°. (A correct analysis was not obtained).

$\nu_{max.}$ 1710 (ester C=O), 1690 (amide C=O), 1640 (C=N), 1610, 1580, 1250, 1090 and 800 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.49 (1H, s, 8-H), 0.63 (1H, s, 2-H), 1.10 (1H, d, J 8 Hz, 5-H), 2.22 (1H, d, J 8 Hz, 6-H), 5.16-5.57 (4H, m, 2 x $-CO_2\underline{CH_2}Me$), 8.23-8.69 (6H, m, 2 x $-CO_2CH_2\underline{Me}$).

m/e 359 (4), 358 (6), 357 (10), 330 (20), 313(10), 312(13), 285(56), 284(20), 265(13), 240(17), 239(100), 212(17), 211(42), 198(6), 185(4), 172(8), 171(35), 155(4), 144(16), 116(4), 113(13), 53(14), 45(25), 44(20), 31(49), 29(23), 27(20). ($\underline{M}^+$ 357)

Ethyl 7-(2-carbethoxy-2-cyanovinylamino)-4-amino-1,8-naphthyridine-3-carboxylate (119).

A solution of 2,6-diaminopyridine (1.1 g) and ethyl ethoxymethylenecyanoacetate (4 g) in ethanol (30 ml) was heated under reflux on a steam bath for 10 min. The cooled suspension was stirred at room temperature for 18 hr, then filtered to collect the vinylaminonaphthyridine (2.3 g, 64%). The crude product was crystallised first from 2-ethoxyethanol then from dimethyl sulphoxide; the colourless prisms had m.p. 254-256°.

(Found: C, 57.2; H, 4.8; N, 19.9, $C_{17}H_{17}N_5O_4$ requires C, 57.5; H, 4.8; N, 19.7%).

$\nu_{max.}$ 3450, 3350, 3300, 3250 (N-H); 2250 (C≡N), 1690 (C=O), 1650, 1630, 1580, 1310, 1270, 1230, 810 and 790 $cm.^{-1}$

SYNTHESES OF ANTHYRIDINES.

4,8-Dimethylanthyridin-2,6(1H,9H)-dione (56a).

This compound was prepared from 7-amino-4-methyl-1,8-naphthyridin-2(1H)-one (7) by the method of Carboni et al (1966b). The n.m.r. spectrum was determined and the assignments recorded here.

τ(CF_3CO_2H) 0.77 (1H, s, 5-H), 2.87 (1H, s, 3-H or 7-H), 3.02 (1H, s, 3-H or 7-H), 7.01 (3H, s, 8-Me), 7.20 (3H, s, 4-Me).

7-Acetyl-4-methylanthyridin-2,6(1H,9H)-dione (122).

7-(2-Acetyl-2-carbethoxyvinylamino)-4-phenyl-1,8-naphthyridin-2(1H)-one (103; 0.6 g) was added to boiling Dowtherm-A (12 g) and the solution boiled for 10 min. The hot suspension was filtered through sintered glass to collect the anthyridinone (0.3 g, 55%), m.p. above 330°. The product was purified for analysis by treating in boiling 2-ethoxyethanol, and washing the solid with hot ethanol.

(Found: C, 62.2; H, 4.4; N, 15.7%; M^+ 269. $C_{14}H_{11}N_3O_3$ requires C, 62.4; H, 4.1; N, 15.6%; M^+ 269).

$\nu_{max.}$ 1680 (ketone C=O), 1660 (amide C=O), 1650 (amide C=O), 1630 (C=N), 1580, 1300, 900, 820, and 800 $cm.^{-1}$

τ(CF_3CO_2H) 0.02 (1H, s, 5-H), 0.40 (1H, s, 8-H), 2.87 (1H, s, 3-H), 7.04 (3H, s, 4-Me), 7.13 (3H, s, -COMe).

m/e 271(1), 270(13), 269(65), 255(17), 254(100), 227(12), 226(6), 199(5), 198(5), 171(6), 170(3), 143(4), 127(5), 113(8), 77(3), 53(3), 43(6).

m* 239.7 (269→254), 201.0 (254→226), 173.5 (226→198).

Attempted preparation of 7-cyano-4-methylanthyridin-2,6(1H,9H)-dione (123).

7-(2-carbethoxy-2-cyanovinylamino)-4-methyl-1,8-naphthyridin-2(1H)-one (106; 0.25 g) was added to liquid paraffin (40 ml) at 330°. The mixture was heated at 340-350° for 10 min; a precipitate appeared after 2 min. The cooled suspension was centrifuged to collect the precipitate which was washed thoroughly with petroleum ether, followed by diethyl ether, and dried. The yield of product, m.p. above 330°, was 0.025g. No suitable solvent for the recrystallisation of the material could be found, and a correct analysis for $C_{13}H_8N_4O_2$ was not obtained.

$\nu_{max.}$ 3100 (N-H), 2250 (C≡N), 1660 (amide C=O), 1650, 1600, 1540, 1500, 1470, 1400, 1370, 1330, 880, 860, 810 and 660 $cm.^{-1}$ (KBr)

Attempted preparation of 7-cyano-4-phenylanthyridin-2,6(1H,9H)-dione (124).

7-(2-Carbethoxy-2-cyanovinylamino)-4-phenyl-1,8-naphthyridin-2(1H)-one (107; 0.3 g) was added to liquid paraffin (45 ml) at 330°. The mixture was heated at 330-340° for 10 min. A precipitate appeared in the mixture after 2 min. The cooled suspension was centrifuged, and the residue washed with petroleum ether followed by diethyl ether, then dried. The yield of crude product, m.p. 300° (decomp.), was 0.12 g. No suitable solvent could be found for the recrystallisation of the material, and correct analysis for $C_{18}H_{10}N_4O_2$ was not obtained.

$\nu_{max.}$ 3450, 3200 (N-H); 2250 (C≡N), 1660 (C=O), 1640, 1530, 1500, 1380, 1290, 810, 800, 780 and 710 $cm.^{-1}$

Attempted preparation of 2,8-diaminoanthyridine.
(Schoeller and von Schickh's method).

2,6-Diaminopyridine (2.2 g) was mixed with formic acid (80%, 10 ml); hot formalin solution (20 g) was added to the mixture which was then refluxed on a steam bath for 18 hr. The mixture was steam distilled (to remove unchanged formaldehyde) then evaporated to about 1/5 its volume. Addition of an equal volume of dilute hydrochloric acid to the cooled concentrate precipitated an orange solid (1.5 g). The solid was recrystallised from ethanol to yield 0.3 g of material which showed one component only when examined by TLC. (Eastman 'chromagram' silica gel; chloroform 90 : methanol 10). M.p. was above 320°.

$\lambda_{max.}$ (Water) 455 nm.

$\nu_{max.}$ (KBr) 1650, 1620, 1540, 1400, 1340, 1060, 780 and 710 $cm.^{-1}$

2,6-Diamino-3,5-dicyanopyridine (127).

Potassium 1,1,3,3-tetracyanopropene was prepared from ethoxymethylenemalononitrile by the method of Cottis and Tieckelmann (1961); this compound was then converted to 2,6-diamino-3,5-dicyanopyridine via 2-amino-6-chloro-3,5-dicyanopyridine using the procedure published by Little et al (1958). The infra-red spectrum, which has not been published, is summarised here.

$\nu_{max.}$ (KBr) 3350, 3200 (N-H); 2250 (C≡N), 1660, 1630, 1580, 1540, 1490, 1400, 1270, 830, 770, 700 and 680 $cm.^{-1}$

Attempted reduction of 2,6-diamino-3,5-dicyanopyridine. (Page 51)

Dry hydrogen chloride was passed into a stirred suspension of anhydrous stannous chloride (1.5 g) in sodium-dried ether (10 ml) until the salt had dissolved and formed a separate, viscous lower layer. 2,6-Diamino-3,5-dicyanopyridine (0.32 g) was added to the mixture, and hydrogen chloride passed in for 10 min, with further stirring for 15 min. The mixture was filtered, and the collected solid treated in boiling water for 15 min; this solid (0.3 g) was shown by infra-red spectroscopy to be unchanged dicyanopyridine.

Attempted preparation of 2,6-diaminopyridine-3,5-dicarboxylic acid (128).

2,6-Diamino-3,5-dicyanopyridine (1 g) in 1N potassium hydroxide (60 ml) was boiled under reflux for $2\frac{1}{2}$ hr. After cooling the mixture to 5°, glacial acetic acid was used to acidify the mixture which was then diluted to 120 ml. The solution was allowed to stand in a refrigerator overnight. The precipitate which had formed was collected and dried; IR examination of the product (yield 1 g) showed it to be mainly unchanged starting material.*

The procedure was repeated using more vigorous conditions; 2,6-diamino-3,5-dicyanopyridine (1 g) in $2\frac{1}{2}$N KOH (60 ml) was refluxed for 24 hr. IR examination of the product showed that it was unchanged dicyanopyridine.

*This procedure was stated by Cottis (1962) to give 89% yield of 2,6-diaminopyridine-3,5-dicarboxylic acid.

3,7-Dicarbethoxy-5-ethoxyanthyridin-4,6(1H,9H)-dione (132).

A solution of 2,6-diamino-4-ethoxypyridine (0.3 g) in diethyl ethoxymethylenemalonate (3 g) was refluxed (air-condenser) with collection of distillate for 40 min. The suspension was cooled and filtered; the collected solid was washed with ethanol to yield the anthyridinedione (0.9 g, 11%), m.p. above 330°. No suitable solvent could be found for the recrystallisation of the material, and analysis of the acid-washed material gave incorrect figures for $C_{19}H_{19}N_3O_7$.

$\nu_{max.}$ 3150 (N-H), 1710 (ester C=O), 1640 (amide C=O), 1610, 1310, 830 and 780 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.72 (2H, s, 2-H and 8-H), 5.06-5.70 (6H, m, 2 x $-CO_2\underline{CH_2}Me$ and $-O\underline{CH_2}Me$), 8.50 (9H, t, 2 x $-CO_2CH_2\underline{Me}$ and $-OCH_2\underline{Me}$).

m/e 401(1), 400(1), 399(6), 372(3), 371(12), 359(3), 329(5), 328(14), 311(2), 303(6), 302(34), 284(17), 283(69), 255(100), 229(3), 199(3), 198(3), 170(4), 143(8), 141(4), 115(2), 93(1), 53(10), 44(6).

$\underline{M}^+$ 401

Reaction of 2-amino-3-cyano-1,8-naphthyridine with acetylacetone. (Page 53)

2-Amino-3-cyano-1,8-naphthyridine (24) was prepared from 2-aminonicotinaldehyde and malononitrile by the method of Hawes and Wibberley (1966). This compound (0.51 g) was mixed with acetylacetone (0.6 g) in ethanol (10 ml) containing piperidine (0.10 ml), and the mixture was heated on a steam bath under reflux for 24 hr. The hot solution was filtered.

The residue (0.37 g) was washed with ethanol and dried, and was shown by undepressed mixed m.p. and IR spectroscopy to be unchanged aminonaphthyridine. The filtrate was allowed to stand; crystals which separated were collected (0.13 g) and shown to be unchanged aminonaphthyridine.

2-Amino-4,6-dimethylnicotinaldehyde (134).

This compound was prepared in three stages from ethyl 2-amino-4,6-dimethylnicotinate. The latter was prepared by reaction of acetylacetone with ethyl α-ethoxycarbonylacetimidate, using the published procedure (Dornow and Karlson, 1940).

2-Amino-4,6-dimethylnicotinic hydrazide.

Ethyl 2-amino-4,6-dimethylnicotinate (7.1 g), hydrazine hydrate (10 g) and 2-ethoxyethanol (70 ml) were mixed and heated together under reflux with stirring at 140° for 60 hr. The solution was evaporated to dryness, and the solid washed with ethanol to yield the hydrazide (3.6 g, 53%), colourless prisms, m.p. 178-179° (from ethanol).

(Found: C, 53.2; H, 6.9; N, 31.2. $C_8H_{12}N_4O$ requires C, 53.3; H, 6.7; N, 31.1%).

$\nu_{max.}$ 3450, 3350, 3250, 3150 (N-H); 1620 (C=O), 1530, 1320, 890, 830, 810, 770 and 710 $cm.^{-1}$

N-(2-Amino-4,6-dimethylnicotinoyl)-N'-p-toluenesulphonyl hydrazine.

Toluene-p-sulphonyl chloride (3.8 g) in pyridine (10 ml) was added slowly (1 hr) to a solution of 2-amino-4,6-dimethylnicotinic hydrazide (3.6 g) in pyridine (100 ml) at 10°. The solution was allowed to stand for 1 hr, then most of the

solvent was removed by distillation under reduced pressure. Addition of acetone to the residue precipitated the hydrazine (5.2 g, 79%), colourless needles, m.p. 243° (decomp.) (from ethanol).

(A satisfactory analysis was not obtained).

$\nu_{max.}$ 3450, 3350, 3200 (N-H); 1690 (C=O), 1640, 1150 ($-SO_2-$), 810 $cm.^{-1}$

2-Amino-4,6-dimethylnicotinaldehyde (134).

N-(2-Amino-4,6-dimethylnicotinoyl)-N'-p-toluenesulphonyl hydrazine (4.4 g, recrystallised material only, m.p. 243°) was suspended in ethylene glycol (30 ml) and the suspension stirred at a temperature of 170° for 15 min to ensure complete dissolution of the material. Sodium carbonate (1 g) was then added to the hot solution which was stirred for 1 min then cooled rapidly. Water (20 ml.) was added to the mixture, and the solution was extracted with chloroform. The dried ($MgSO_4$) extracts yielded the nicotinaldehyde (0.5 g, 25%), m.p. 161-162° (from water).

(Found: C, 63.7; H, 6.8; N, 18.6. $C_8H_{10}N_2O$ requires C, 64.0; H, 6.7; N, 18.7%).

$\nu_{max.}$ 3400, 3300, 3250 (N-H); 1660 (C=O), 1610, 1580, 1410, 1280, 1220, 1210, 1020, 830, 790, 780, and 740 $cm.^{-1}$

Attempted preparation of ethyl 2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (135).

2-Amino-4,6-dimethylnicotinaldehyde (0.4 g) was dissolved in ethanol (15 ml) with ethyl cyanoacetate (0.8 g) and piperidine (0.10 ml), and the solution was refluxed on a steam bath for 4 hr. The mixture was cooled to 40°, then

filtered. The residue was reserved (see below); the filtrate was allowed to stand for 6 hours, and the solid which crystallised was collected and suspended in chloroform (10 ml). This suspension was filtered and the filtrate evaporated to yield the naphthyridine-3-carboxylate (.03 g), m.p. 255-257° (from ethanol).

(A satisfactory analysis was not obtained.)

$\nu_{max.}$ (KBr) 3300 (N-H), 1660 (C=O), 1600, 1580, 1470, 1350, 1320, 1180, 820, 810, 730 and 710 $cm.^{-1}$

The residue obtained from the above reaction mixture was washed with chloroform, then dried to yield 3-cyano-5,7-dimethylnaphthyridin-2(1H)-one (136) (0.30 g), m.p. 299-300° (decomp.) (from 2-ethoxyethanol).

(Found: C, 66.2; H, 4.6; N, 21.2. $C_{11}H_9N_3O$ requires C, 66.3; H, 4.6; N, 21.1%).

$\nu_{max.}$ 3250 (N-H), 2250 (C≡N), 1680 (C=O), 1620, 1550, 1450, 1390, 1260, 1200, 850, 810, 790, 690, and 670 $cm.^{-1}$

SYNTHESES OF IMIDAZO[1,2-a][1,8]NAPHTHYRIDINES.

4,8-Dimethyl-2-phenylimidazo[1,2-a][1,8]naphthyridine (138).

A mixture of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 1.2 g), bromoacetone (0.35 g) and acetone (20 ml) was stirred and heated under reflux at 80° for 24 hr. The cooled solution was filtered and evaporation of the filtrate yielded the imidazonaphthyridine (0.5 g, 37%), colourless prisms, m.p. 172-174° (from petroleum ether of b.p. 100-120°).

(Found: C, 78.7; H, 5.3; N, 15.0. $C_{18}H_{15}N_3$ requires C, 79.1; H, 5.5; N, 15.4%).

$\nu_{max.}$ 3050, 1620, 1580, 1550, 1360, 770, 750, and 690 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 1.78-2.02 (3H, m, 5-H and phenyl protons), 2.35-2.67 (6H, m, 3-H, 6-H, 9-H and phenyl protons), 7.48 (3H, s, 4-Me or 8-Me), 7.52 (3H, s, 4-Me or 8-Me).

2,8-Dimethyl-4-methylimidazo[1,2-a][1,8]naphthyridine (139).

A mixture of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (80; 1.6 g), phenacyl bromide (0.8 g) and acetone (40 ml) was stirred and heated under reflux at 80° for 7 hr. The cooled solution was filtered and the filtrate evaporated to yield a semi-solid residue. This residue was stirred with petroleum ether to yield the imidazonaphthyridine (1.2 g, 82%), yellow needles, m.p. 174-175° (from ethanol).

(Found: C, 82.2; H, 5.3; N, 12.4. $C_{23}H_{17}N_3$ requires C, 82.4; H, 5.1; N, 12.5%).

$\lambda_{max.}(CHCl_3)$ 286 nm (log ε 4.40) and 349 (4.21).

$\nu_{max.}$(KBr) 3060, 3020, 2960, 1620, 1575, 1550, 1450, 1435, 1350, 1210, 1190, 805, 765, 740, and 690 $cm.^{-1}$ (Spectrum recorded on Perkin-Elmer 237 Spectrometer).

$\tau(CF_3CO_2H)$ 0.92 (1H, s, 9-H), 1.41 (1H, d, J 9 Hz, 5-H), 1.80 (1H, s, 3-H), 1.70-2.50 (3-H, 6-H and phenyl protons), 7.04 (3H, s, 4-Me).

8-Carbethoxy-4-methyl-2-phenylimidazo[1,2-a][1,8]naphthyridine (140).

7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (1.18 g), ethyl bromopyruvate (0.49 g) and acetone were stirred and heated together under reflux at 80° for 24 hr. The cooled mixture was filtered and the filtrate evaporated to yield the imidazonaphthyridine (0.6 g, 72%), m.p. 120-130°. This crude material was dissolved in benzene 95 : ethanol 5, and the solution was passed through an alumina column; this filtered solution was then applied to a silica gel column, and the column eluted with the same solvent. Evaporation of the eluate gave a red-brown powder, m.p. 167-170°.

(Analysis was not satisfactory. Calculated for $C_{20}H_{17}N_3O_2$ M^+ 331. Found M^+ = 331).

$\nu_{max.}(CHCl_3)$ 3100, 2950, 1700 (C=O), 1660, 1610, 1570, 1550, 1510, 1440, 1350, 1290, 1220, 1140, 1010, 810 and 690 $cm.^{-1}$

$\tau(CDCl_3)$ 1.32 (1H, s, 9-H), 2.08-2.30 (1H, m, 5-H), 2.60-2.94 (7H, m, 3-H, 6-H and phenyl protons), 5.64 (2H, q, J 9 Hz, $-CO_2\underline{CH_2}Me$), 7.50 (3H, s, 4-Me), 8.58 (3H, t, J 9 Hz, $-CO_2CH_2\underline{Me}$).

m/e 333(1), 332(9), 331(38), 286(15), 260(19), 259(100), 243(6), 235(4), 220(5), 219(28), 190(3), 165(4),

152(3), 144(7), 143(25), 130(10), 128(4), 121(5), 115(6), 110(4), 102(6), 78(7), 77(13), 51(5), 43(7), 29(7), 27(5).

2,4-Dimethylimidazo[1,2-a][1,8]naphthyridine (141).

A solution of bromacetal (2.2 g) in dioxan (15 ml) and water (10 ml) containing conc. hydrochloric acid (0.2 ml) was boiled for 30 min. Sodium hydrogen carbonate (1.7 g) was added to the cooled solution followed by a slurry of 7-amino-2,4-dimethyl-1,8-naphthyridine (5; 1.73 g) in dioxan (15 ml) and water (5 ml). The stirred mixture was boiled under reflux for 24 hr. The cooled mixture was acidified to Congo-red (pH 3-4) and filtered; the filtrate was evaporated to dryness and the residual solid extracted with chloroform. Evaporation of the extract yielded 1 g (50%) of the crude product. Sublimation of the crude product at 180° (1 mmHg) gave a small yield of the imidazonaphthyridine, colourless prisms, sublimes at 178°.

(A satisfactory analysis was not obtained).

$\nu_{max.}$ 1640 (C=N), 1600, 1280, 1250, 1190, 850, 820 and 770 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.52 (1H, d, J 2.5 Hz, 9-H), 1.28 (1H, d, J 9 Hz, 5-H), 1.69 (1H, d, J 9 Hz, 6-H), 1.79 (1H, d, J 2.5 Hz, 8-H), 1.97 (1H, s, 3-H), 6.79 (3H, s, 2-Me), 6.89 (3H, s, 4-Me).

4-Methyl-2-phenylimidazo[1,2-a][1,8]naphthyridine (142).

A solution of bromacetal (2.2 g) in dioxan (15 ml) and water (10 ml) containing conc. hydrochloric acid (0.2 ml) was boiled for 30 min. Sodium hydrogen carbonate (1.7 g) was added to the cooled solution followed by a slurry of 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (2.35 g) in dioxan (20 ml) and water (5 ml). The stirred mixture was boiled under reflux for 24 hr, then cooled, acidified to Congo-red (pH 3-4) and filtered. The residual solid obtained from evaporation of the filtrate was extracted with chloroform. Evaporation of this extract yielded 1.5 g (58%) of crude product. Sublimation of the latter at 220° (1 mmHg) yielded pure imidazonaphthyridine, colourless prisms, sublimes at 218°.

(A satisfactory analysis was not obtained).

$\nu_{max.}$ (KBr) 1640 (C=N), 1590, 1380, 1270, 760 and 700 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.92 (1H, d, J 2 Hz, 9-H), 1.38 (1H, d, J 9 Hz, 5-H), 1.67-2.0 (3H, m, 3-H and phenyl protons), 1.90 (1H, d, J 9 Hz, 6-H), 1.93 (1H, d, J 2 Hz, 8-H), 2.30-2.48 (3H, m, phenyl protons), 6.99 (3H, s, 4-Me).

SYNTHESES OF PYRIMIDO[4,5-b][1,8]NAPHTHYRIDINES.

2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (28a).

A solution of 2-amino-4,6-dimethylnicotinaldehyde (134; 0.15 g), cyanoacetamide (0.16 g) in ethanol (10 ml) containing piperidine (0.05 ml) was refluxed on a steam bath for 1 hr. The hot suspension was filtered, and the residue washed with hot ethanol. The yield of naphthyridine-3-carboxamide was 0.1 g (48%), pale yellow needles, m.p. 262° (decomp.) (from methanol).

(Found: C, 59.8; H, 6.2; N, 25.5. $C_{11}H_{12}N_4O$ requires C, 61.0; H, 5.6; N, 25.9%).

$\nu_{max.}$ (KBr) 3500, 3460, 3380, 3340 (N-H); 1680 (C=O), 1630 (C=N), 1600, 1370, 1340, 800, and 710 $cm.^{-1}$ (Spectrum determined on Perkin-Elmer 237 Spectrometer).

2-Acetamido-1,8-naphthyridine-3-carboxamide (148).

A solution of 2-amino-1,8-naphthyridine-3-carboxamide (25; 0.95 g) in acetic anhydride (12 ml) was heated under reflux at 130° for 2 hr. The suspension was filtered, and the collected solid washed with acetone and dried to yield the acetamidonaphthyridine (1.1 g, 95%), m.p. above 350° (from 2-ethoxyethanol).

(Found: C, 57.3; H, 4.5; N, 24.5%; $\underline{M}^+$ 230. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.4; N, 24.3%; $\underline{M}^+$ 230).

$\nu_{max.}$ 3350, 3200 (N-H); 1700 and 1680 (Amide I), 1630 (Amide II), 1600, 1570 (Amide II), 1520, 1350, 1320, 1260, 820, 780 and 710 $cm.^{-1}$

τ(CF_3CO_2H) 0.61 (1H, s, 4-H), 0.65-1.07 (2H, m, 5-H and 7-H), 1.65-2.41 (2H, m, 6-H and -NHCOMe), 7.37 (3H, s, -NHCOMe).

m/e 232(1), 231(8), 230(55), 216(12), 215(100), 213(26), 212(90), 198(29), 188(35), 186(55), 172(32), 171(42), 145(68), 144(55), 143(48), 129(23), 118(22), 117(26), 116(24), 102(30), 90(19), 76(15), 75(16), 64(15), 63(21), 51(14), 43(61), 28(29).

m* 197.2 (230→213), 137.6 (215→172), 120.6 (172→144).

2-Acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide (149).

A solution of 2-amino-7-phenyl-1,8-naphthyridine-3-carboxamide (28; 0.4 g) in acetic anhydride was heated at 130° under reflux for 2 hr. The suspension was cooled, and filtered; the collected solid was washed with acetone and dried to yield the acetamidonaphthyridine (0.32 g, 69%), colourless prisms, m.p. above 350°. An analytical sample was prepared by treating the crude product in boiling 2-ethoxyethanol; the hot suspension was filtered and the residue washed with warm ethanol before drying.

(Found: C, 66.5; H, 4.5; N, 18.5%; M^+ 306. $C_{17}H_{14}N_4O_2$ requires C, 66.7; H, 4.6; N, 18.3%; M^+ 306).

$\nu_{max.}$ 3350, 3200 (N-H); 1700 and 1670 (Amide I), 1630 (Amide II), 1600, 1570 (Amide II), 1530, 1470, 1320, 1270, 760, 730, and 690 $cm.^{-1}$

τ(CF_3CO_2H) 0.59 (1H, s, 4-H), 1.08 (1H, d, J 9 Hz, 5-H), 1.58 (1H, d, J 9 Hz, 6-H), 1.45-2.40 (6H, m, phenyl protons, and -NHCOMe), 7.35 (3H, s, -NHCOMe).

m/e 308(1), 307(4), 306(16), 292(50), 290(33), 289(100), 288(47), 274(7), 265(12), 264(12), 263(47), 247(15),

240(11), 221(33), 220(28), 219(14), 218(16), 192(16), 178(8), 177(8), 164(7), 150(8), 115(7), 112(10), 77(15), 51(10), 43(24), 28(24).

m* 259.8 (289→274).

2-Acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (150).

A stirred mixture of 2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (28a; 0.22 g) and acetic anhydride (8 ml) was heated under reflux at 130° for 2 hr. The mixture was cooled, filtered and the residual solid washed with acetone before drying to yield the acetamidonaphthyridine (0.21 g, 82%); an analytical sample was prepared by treating the crude product in boiling 2-ethoxyethanol then with hot ethanol. The pure product had m.p. 246° (decomp.).

(Found: C, 60.3; H, 5.3; N, 21.4%; M^+ 258. $C_{13}H_{14}N_4O_2$ requires C, 60.4; H, 5.5; N, 21.7%; M^+ 258).

$\nu_{max.}$ 3400 (N-H), 1700 and 1680 (Amide I), 1640 (Amide II), 1610, 1570 (Amide II), 1370, 1340, 1250, 980, 950 and 700 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.72 (1H, s, 4-H), 1.83-2.50 (1H, br, -NHCOMe), 2.20 (1H, s, 6-H), 6.93 (6H, s, 5-Me and 7-Me), 7.40 (3H, s, -NHCOMe).

m/e 259(4), 258(24), 243(80), 241(26), 240(100), 226(13), 215(55), 200(19), 199(30), 173(40), 172(29), 171(22), 157(13), 156(12), 130(13), 103(12), 77(18), 43(31), 42(20), 28(31).

m* 165.0 (240→199).

2-Methylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (152).

2-Acetamido-1,8-naphthyridine-3-carboxamide (148; 0.23 g) was mixed with water (3 ml) and 0.880 ammonia (3 ml) and the mixture was warmed on a steam bath under reflux for 40 min. The cooled mixture was filtered, and the collected solid washed with water and dried to yield the pyrimidonaphthyridinone (0.21 g, 95%). The crude product was treated with boiling 2-ethoxyethanol, filtered, and the solid washed with ethanol. The pure material had m.p. above 350°.

(Found: C, 61.7; H, 3.8; N, 26.4%; M^+ 212. $C_{11}H_8N_4O$ requires C, 62.3; H, 3.8; N, 26.4%; M^+ 212).

$\nu_{max.}$ 3400 (N-H), 1700 (C=O), 1630 (C=N), 1600, 1550, 1490, 1320, 1290, 1270, 1220, 1090, 820, 810 and 780 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.24 (1H, s, 5-H), 0.29-0.51 (2H, m, 6-H and 8-H), 1.33-1.69 (1H, m, 7-H), 6.80 (3H, s, 2-Me).

m/e 213(4), 212(17), 211(100), 197(9), 184(12), 171(22), 171(4), 154(4), 144(16), 143(35), 128(4), 116(13), 112(5), 75(50), 63(50), 42(10), 28(10).

m* 159.7 (212→184).

2-Methyl-8-phenylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (153).

2-Acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide (149; 0.2 g) was mixed with water (3 ml) and 0.880 ammonia (3 ml) and the mixture heated under reflux on a steam bath for 40 min. The cooled mixture was filtered to yield the pyrimidonaphthyridinone (0.19 g, 95%), small yellow needles, m.p. above 350° (from dimethylformamide).

(Found: C, 70.5; H, 4.4; N, 19.3%; M^+ 288. $C_{17}H_{12}N_4O$ requires: C, 70.8; H, 4.2; N, 19.4%; M^+ 288).

$\nu_{max.}$ 3150 (N-H), 1680 (C=O), 1630 (C=N), 1590, 1290, 820, 800, 770, and 690 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.13 (1H, s, 5-H), 0.58 (1H, d, J 9 Hz, 6-H), 1.33 (1H, d, J 9 Hz, 7-H), 1.52-2.30 (5H, m, phenyl protons), 6.81 (3H, s, 2-Me).

m/e 289(3), 288(22), 287(100), 286(43), 246(8), 245(5), 219(12), 218(17), 217(17), 216(5), 192(13), 191(9), 160(9), 140(4), 139(4), 115(5), 102(9), 89(4), 77(8), 76(5), 75(5), 63(6), 51(8), 42(27).

m* 210.8 (287→246), 166.5 (219→191).

2,6,8-Trimethylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-one (154).

A mixture of 2-acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (150; 0.15 g), water (3 ml) and 0.880 ammonia (3 ml) was heated on a steam bath for 15 min. The mixture was evaporated to dryness and the residue washed with water and dried to yield the pyrimidonaphthyridinone (0.14 g, 95%), which crystallised as yellow needles of the monohydrate, m.p. above 350° (from water).

(Found: C, 60.6; H, 5.0; N, 21.7%; M^+ 240. $C_{13}H_{12}N_4O.H_2O$ requires C, 60.4; H, 5.5; N, 21.7%; M^+ 240).

$\nu_{max.}$ 1680 (C=O), 1600, 1510, 1340, 1280 and 820 $cm.^{-1}$

$\tau(CF_3CO_2H)$ 0.07 (1H, s, 5-H), 1.97 (1H, s, 7-H), 6.78 (6H, s, 6-Me and 8-Me), 6.85 (3H, s, 2-Me).

m/e 241(2), 240(18), 239(100), 238(4), 225(4), 212(5), 200(3), 199(19), 198(3), 182(1), 173(2), 172(10), 171(10), 170(4), 157(3), 156(4), 155(3), 144(4), 143(3), 130(3), 129(3), 128(3), 120(2), 116(3), 103(3), 102(3), 98(3), 89(2), 78(2), 77(3), 63(2), 51(3), 42(9), 39(3).

m* 211.2 (240→225), 187.2 (240→212), 165.0 (240→199).

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