PREPARATION AND PROPERTIES OF SOME PYRIDO[3,4-d]PYRIMIDINES

BY

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SUMMARY

The chemistry of the few known pyrido[3,4-d]pyrimidines is reviewed, and the biological properties of related compounds are summarised.

Two main routes are employed for the synthesis of the pyrido[3,4-d]pyrimidines.

The pyrido[3,4-d]pyrimidin-4(3H)-ones and pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones are prepared from 3-aminopyridine-4-carboxylic acids, by condensation with amides or urea.

Treatment of 3-aminopyridine-4-carboxylic acid and its 2,6-dimethyl derivative with acetic anhydride yields 2-methylpyrido[3,4-d][1,3]oxazin-4-ones. Replacement of the acetic anhydride by benzoyl chloride in pyridine gives the corresponding 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones. The 2-methylpyrido-oxazines react readily with primary amines to form 3-substituted-2-methylpyridopyrimidines. Similar reactions with the 2-phenylpyrido-oxazines generally result in the isolation of the intermediate diamides, which cyclise to pyridopyrimidines on heating. The mechanisms of these reactions are discussed.

Methylation of a series of pyrido[3,4-d]pyrimidin-4(3H)-ones and pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones, with dimethyl sulphate or methyl iodide, yields the N-methyl derivatives. The reluctance of 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione to undergo methylation at the 1-position is thought to be due to steric hindrance.

Some ring-opening reactions of pyrido[3,4-d]pyrimidin-4(3H)-ones and pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones with nucleophiles are investigated and possible mechanisms for these reactions outlined.

The reaction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one with benzaldehyde and p-nitrobenzaldehyde yields a monostyryl derivative.

The reduction of pyrido[3,4-d]pyrimidin-4(3H)-ones with lithium aluminium hydride results in reductive cleavage of the 2,3-bond in the pyrimidine ring. The products obtained are 3-alkylamino-4-alkyl (or aryl) aminomethylpyridines, which can be recyclised to pyridopyrimidines by the action of phosgene. Possible mechanisms are discussed; the reaction seems to be general for the pyrido[3,4-d]pyrimidin-4(3H)-ones and the ease of cleavage appears to depend on the substituent at the 3-position.

The infrared and n.m.r. spectra of the new pyrido[3,4-d]pyrimidines are recorded.

The mass spectra of a selection of pyrido[3,4-d]pyrimidin-4(3H)-ones, pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones and pyridine derivatives are recorded, and possible fragmentation pathways are suggested for many of these compounds.

The author would like to thank his supervisor Dr. D. G. Wibberley for his help and encouragement during the course of this work, and Smith Kline and French Ltd. for carrying out tests for biological activity.

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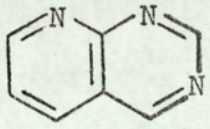
EXPERIMENTAL

INTRODUCTION

INTRODUCTION

The fusion of a pyridine and pyrimidine ring, other than through a nitrogen atom, may occur in four different ways. The resultant compounds are named pyrido[2,3-d]pyrimidine (1), pyrido[3,2-d]pyrimidine (2), pyrido[3,4-d]pyrimidine (3) and pyrido[4,3-d]pyrimidine (4); this is the nomenclature and numbering of Chemical Abstracts, an alternative system used in the literature is 1,3,5-(2), 1,3,6-(4), 1,3,7-(3) and 1,3,8-triazanaphthalene (1).



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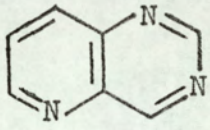

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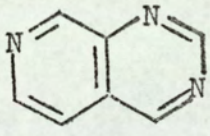

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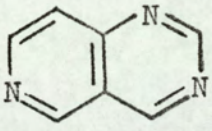

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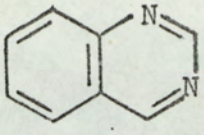
The pyridopyrimidines have recently been reviewed by Irwin and Wibberley.[1] Many pyridopyrimidines were initially synthesised for a study of their biological or physical properties, because of the close structural relationship of these systems to the quinazolines (5) and pteridines (6). Recent reviews [2,3,4] have discussed these related compounds



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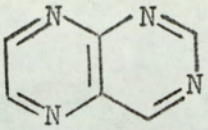

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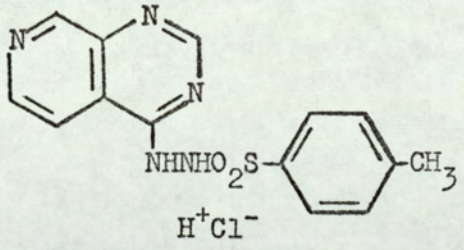
SYNTHESIS OF PYRIDO[3,4-d]PYRIMIDINES

Of the four systems of pyridopyrimidine the least investigated is the[3,4-d]isomer and few derivatives are known. The parent pyrido[3,4-d]pyrimidine (3) was first prepared by Armarego[5] in 1961, by decomposition of 4-N'-toluene-p-sulphonyl-hydrazinopyrido[3,4-d]pyrimidine hydrochloride (7).



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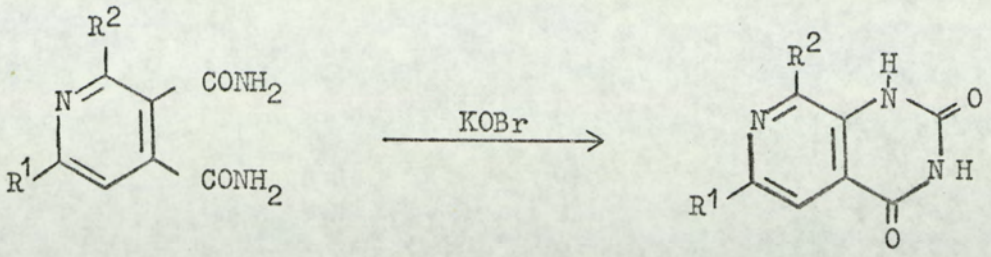
The first recorded pyridopyrimidine was pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=H$), prepared by the Hofmann degradation of pyridine-3,4-dicarboxamide (9; $R^1=R^2=H$) by Gabriel and Colman[6] in 1902.



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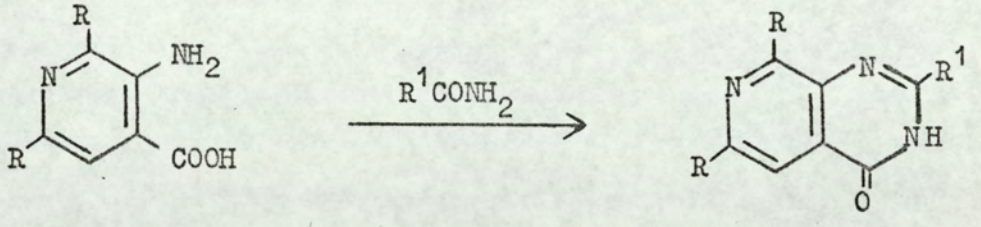
The same type of synthesis has been extended to the preparation of 6-methylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione[7] (8; $R^1=CH_3$, $R^2=H$) and 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione[8] (8; $R^1=R^2=CH_3$). Gabriel and Colman[6] also prepared pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=H$) by condensation of urea with 3-aminopyridine-4-carboxylic acid (10; R=H).

The amino acid (10; R=H) was also condensed with formamide to give pyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=H$), and a similar reaction with acetamide yielded the 2-methyl derivative (11; R=H, $R^1=CH_3$).



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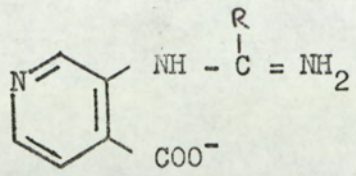
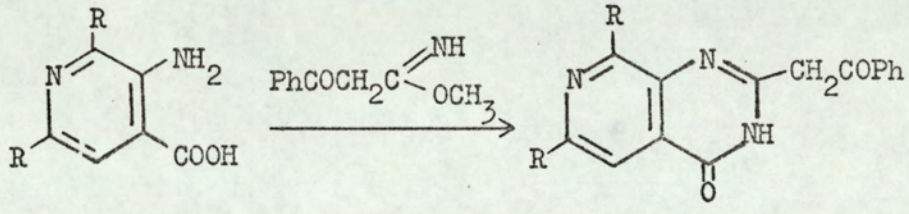
Reid[9] prepared 2-methylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=H, $R^1=CH_3$) by the reaction of 3-aminopyridine-4-carboxylic acid with acetadimic acid. The reaction proceeds *via* an amidine intermediate (12), which cyclises with loss of water to yield the pyridopyrimidinone.



(12)

A similar reaction between 3-aminopyridine-4-carboxylic acid (10; R=H) and methyl α-benzoylacetimidate yielded 2-benzoylmethylpyrido[3,4-d]pyrimidin-4(3H)-one (13; R=H).[10]



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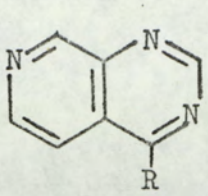
CHEMICAL PROPERTIES.

No examples of electrophilic substitution in the pyridopyrimidines have been reported in the literature.

Nucleophilic substitution generally occurs at the 2- and 4- positions in the pyridopyrimidines, as is the case with the pyrimidines and the quinazolines.[11]

Chlorination of pyrido[3,4-d]pyrimidin-4(3H)-one with phosphoryl chloride gives 4-chloropyrido[3,4-d]pyrimidine (14; R=Cl)[6] and phosphorus pentasulphide yields the 4-mercapto derivative (14; R= SH)[12]. 4-Chloropyrido[3,4-d]pyrimidine on reduction with hydriodic acid and red phosphorus yields 3,4-dihydropyrido[3,4-d]pyrimidine (15), the only reduced pyrido[3,4-d]pyrimidine reported in the literature.[6]



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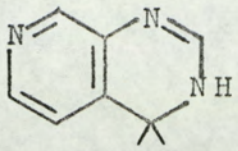
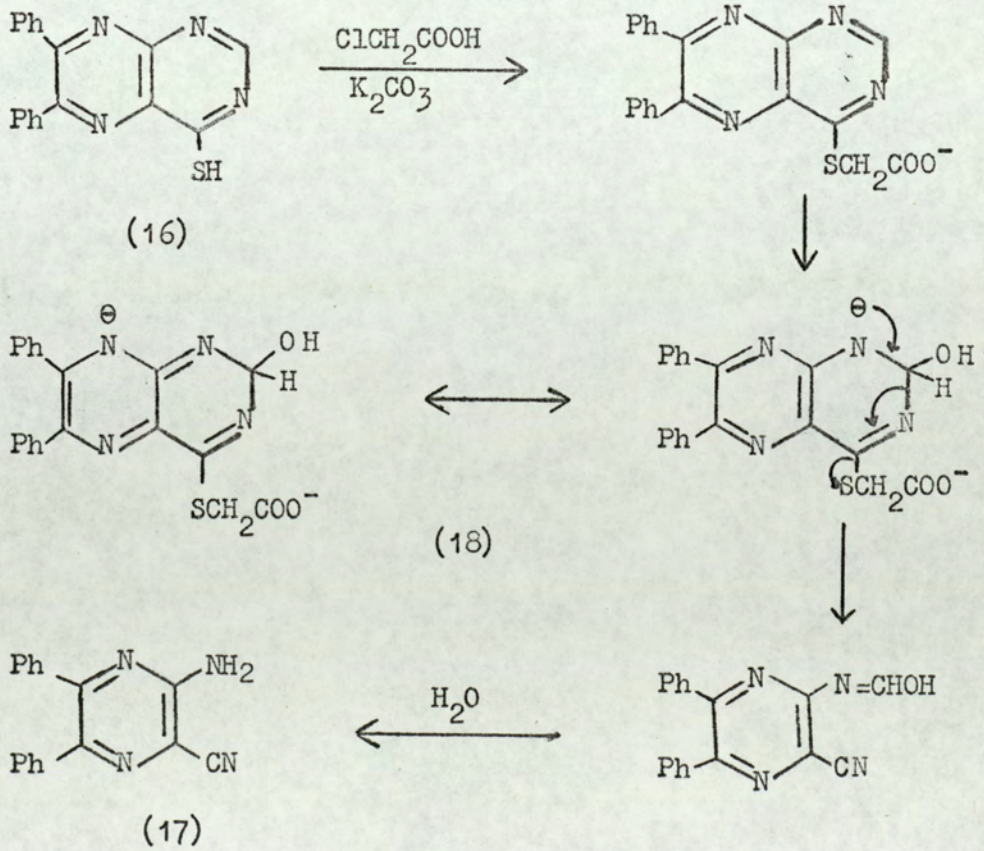


(15)

4-Mercapto-6,7-diphenylpteridine (16), on reaction with chloroacetic acid and potassium carbonate yields 2-amino-3-cyano-5, 6-diphenylpyrazine (17). E. C. Taylor[12] postulated the following mechanism; stating the requirements for ring-opening as (a) the anion (18), formed by attack of the hydroxide ion at C_2, be capable of stabilisation by appropriate structural features in the remainder of the molecule and (b) the substituent in the 4-position be capable of ejection with its bonding pair of electrons in an irreversible cleavage step.



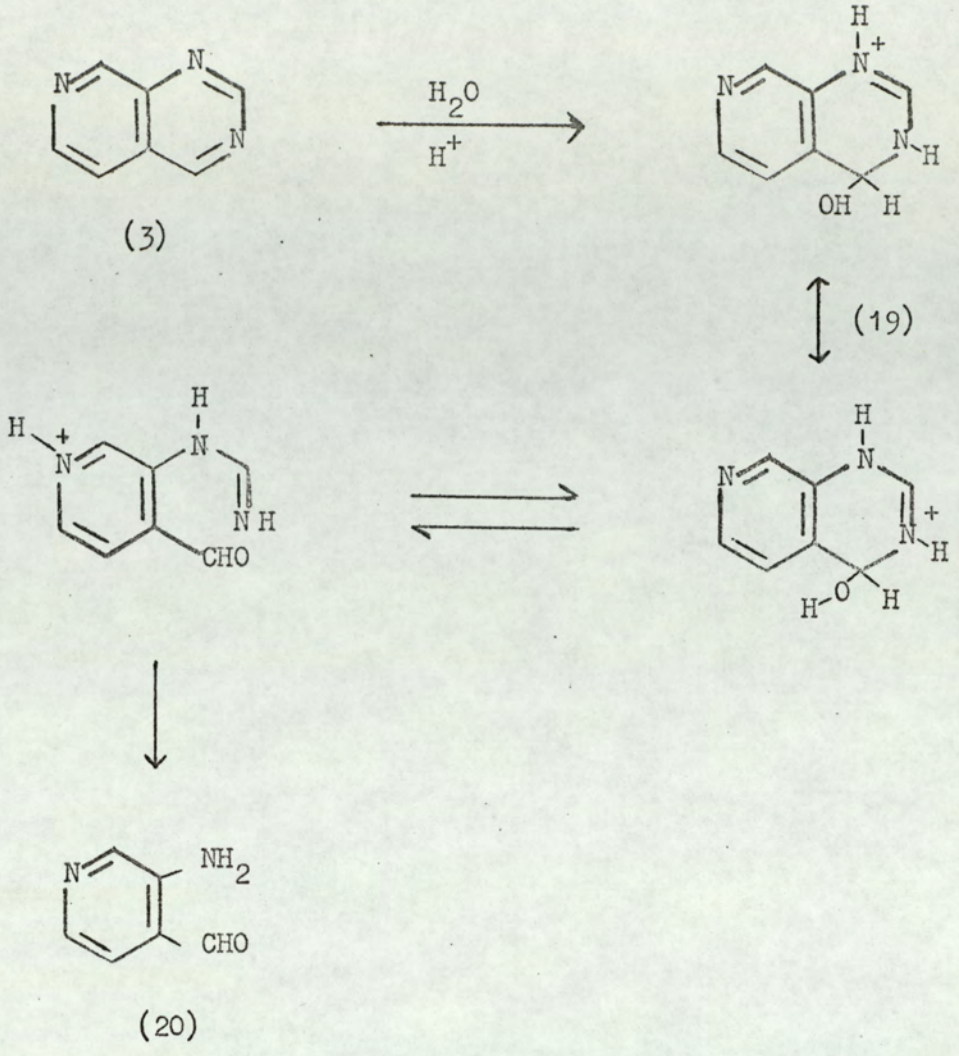
(16)

(18)

(17)

If this mechanism is correct, 4-mercaptopyrido[3,4-d]pyrimidine (14; R=SH) should not ring-open as the anion corresponding to (18) is not capable of being resonance stabilised. The only products obtained by Taylor under ring-opening conditions were 4-carboxymethylthiopyrido[3,4-d]pyrimidine (14; R=SCH_2COOH) and a small amount of pyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=H), thus confirming his postulated mechanism. 4-Methylthiopyrido[3,4-d]pyrimidine (14; R=SCH_3) was also prepared in the course of this work, by reaction of dimethyl sulphate with the 4-mercapto derivative (14; R=SH).

The pyridopyrimidines, in common with other fused pyrimidines,[13] are susceptible to nucleophilic addition of water across a C=N bond. The covalent hydration of pyrido[3,4-d]pyrimidine (3) has been studied by Armarego[14], together with the three other isomers. The ultraviolet spectra of pyrido[3,4-d]pyrimidine in water and cyclohexane are similar, indicating the absence of any appreciable amounts of the hydrated species. However, when an aqueous solution of pyrido[3,4-d]pyrimidine was acidified, the absorption spectrum taken ten to fifteen minutes after mixing was found to be at shorter wavelengths compared to that of the neutral molecule. Hence pyrido[3,4-d]pyrimidine is predominantly hydrated (19) as the cation. Unlike the neutral molecule the hydrated cations of pyrido[3,4-d]pyrimidine gradually decompose, until after 5 days at 20° the ultraviolet spectrum is identical with that obtained from 3-aminopyridine-4-aldehyde (20).



The degradation of pyrido[3,4-d]pyrimidine in acid solution to 3-aminopyridine-4-aldehyde excludes the addition of water to the pyridine ring. Addition of p-nitrophenylhydrazine at pH2 resulted in precipitation of the hydrazone. This rules out the preliminary addition of water across the 1,2-double bond followed by ring-opening, because only 3,4- or 1,4-addition followed by ring-opening would lead to a positive aldehyde test. Mild oxidation with hydrogen peroxide, yielded pyrido[3,4-d]pyrimidin-4(3H)-one (11; R =R^1=H) thus hydroxylation occurs at the 4-position and confirms the fact that hydration must occur at the 3,4- or 1,4-positions. These two

positions cannot be distinguished from each other because they are resonance stabilised structures (19).

PHYSICAL PROPERTIES

The physical properties of the pyridopyrimidines closely resemble those of their nearest N-heterocyclic neighbours, the quinazolines and pteridines. Thus in common with the pteridines[15], the presence of groups capable of hydrogen-bonding markedly raises the melting points and lowers the solubility[16].

Pyrido[3,4-d]pyrimidine has the same π electron structure as naphthalene and hence would be expected to have a similar ultra-violet spectrum. This has proved to be the case with pteridine[3] and quinazoline[2], which have similar π electron structures. Favini [17,18], calculated the transition energies and intensities of the $\pi \rightarrow \pi^*$ bands for pyrido[3,4-d]pyrimidine. The results are in fair agreement with the experimentally determined values[14] in a non ionic solvent, which are quoted below.

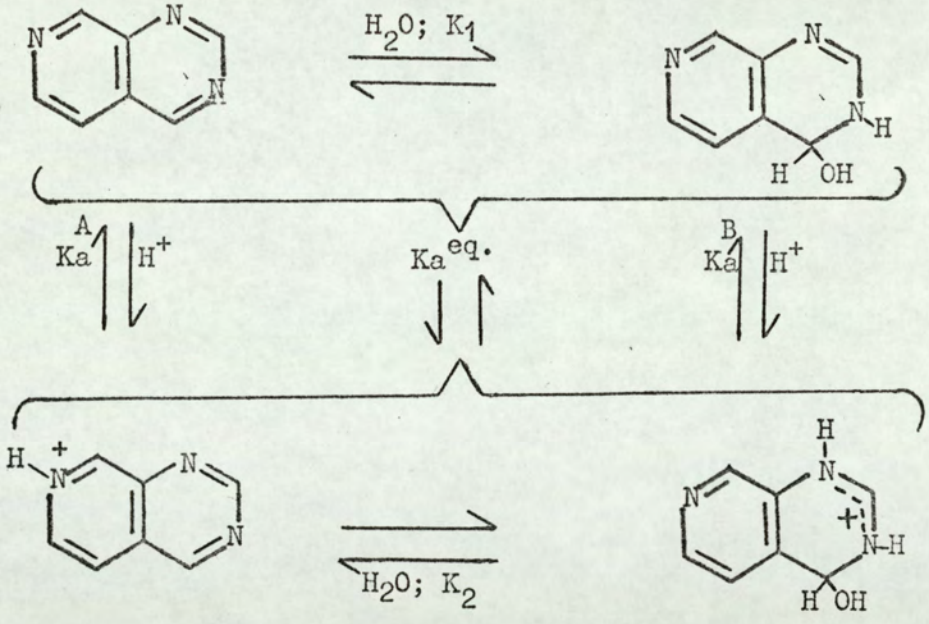
Wavelength maxima (mμ)	$\pi \rightarrow \pi^*$ transition band N°		
	1	2	3
Calculated	307	269	219
Experimental			
a) Water	314	249	214
b) Cyclohexane	316	245	214

The infrared spectrum of pyrido[3,4-d]pyrimidine has been recorded by Armarego[19]. Thirteen in-plane skeletal vibrations and 10 C-H bending vibrations are theoretically possible in the 1700-650 $cm.^{-1}$ region, although slightly less than this number of bands were observed. C-H out of plane bending vibrations were thought to account for most of the intense bands found in the 1000-650 $cm.^{-1}$ region.

The only nuclear magnetic resonance (n.m.r.) spectrum of a pyrido[3,4-d]pyrimidine recorded in the literature is that of the parent compound.[20]

$\tau(CDCl_3)$ 0.43(1H,s,2-H), 0.42(1H,d,J=0.7 c./sec., 4-H), 2.21(1H,d,J=5.8 c./sec., 5-H), 1.15(1H,d,J=5.8 c./sec., 6-H), 0.45(1H,d,J=0.7 c./sec., 8-H).

The ionisation constant of pyrido[3,4-d]pyrimidine was measured by Armarego[14] during his investigation into covalent hydration in the pyridopyrimidines. Like quinazoline, pyrido [3,4-d]pyrimidine is subject to the equilibria illustrated below;

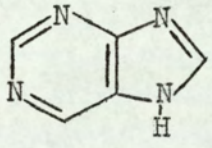


The solution was allowed to come to equilibrium before the measurements were taken. The pKa^{eq} value obtained by the method of Albert and Phillips[21] was 4.70 ± 0.02. This value is meaningless for purposes of comparison with other systems, as it depends on (i) K_a^A, (ii) K_a^B, and (iii) the ratio of anhydrous to hydrated species in the neutral molecule and the cation. However, the kinetics of hydration-dehydration in the pH 4-10 range were slow enough to give reliable values of the pKa of the

hydrated species (pK_a^B). The pK_a^B value obtained (6.35 ± 0.05) is approximately one unit less than that for hydrated quinazoline,[22] thus showing the base weakening effect of the extra nitrogen atom.

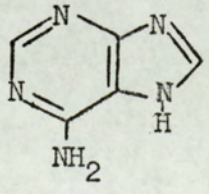
BIOLOGICAL PROPERTIES.

The pyrido[3,4-d]pyrimidines are bicyclic compounds containing the pyrimidine ring fused through its "d face" with a pyridine ring. Two other bicyclic systems of outstanding biological importance, which contain a similarly fused pyrimidine ring, are the purines (21.) and pteridines (6), derivatives of which are essential metabolites in both the plant and animal kingdoms.



(21)

Several purine bases are very widely distributed in living organisms and often occur as complex derivatives of the greatest biological interest. Adenine (22) is the most common, its derivatives are involved in oxidation-reduction,[23,24] phosphorylation,[25] methylation,[26] sulphonation[27] and acylation[28] systems *in vivo*.



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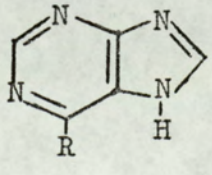
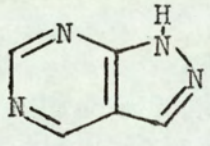


(23)

Purine bases are also one of the main constituents of nucleic acids, which are the primary constituents of living cells. Because of this fundamental role, the possibility of using purine derivatives as chemotherapeutic agents in the treatment of malignant diseases was investigated. The success of 6-mercaptopurine (23; R=SH)[29] against experimental animal neoplasms prompted clinical study, and it has been used in the treatment of cancers in man. 6-Chloropurine (23; R=Cl)[30] has been used to treat patients with acute leukaemia. Many other purine derivatives have also been found to possess antitumor activity.[31,32] Diuretic[33] and antiviral[34,35,36] activity has been observed with certain purines.

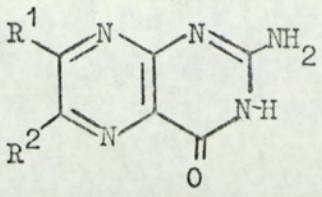
The pyrazolo[3,4-d]pyrimidine (24) system is isomeric with purine (21).



(24)

4-Aminopyrazolo[3,4-d]pyrimidine[37] has been studied extensively as an antitumor agent[38] and as an inhibitor of the growth of microbiol systems[39] and cells[40] in tissue cultures.

The first known naturally occurring pteridines were isolated from butterflies wings in 1889,[41] however it was not until 1940 that the structures of these compounds, xanthopterin[42] (25; R^1=H,R^2=OH), leucopterin[43] (25; R^1=R^2=OH) and isoxanthopterin[44] (25; R^1=OH,R^2=H) were elucidated.



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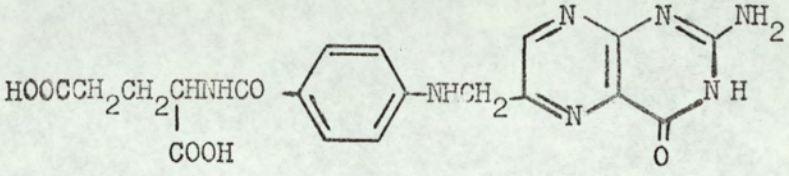
Pteroyl-L-glutamic acid (26) is one of the naturally occurring pteridines found in man.



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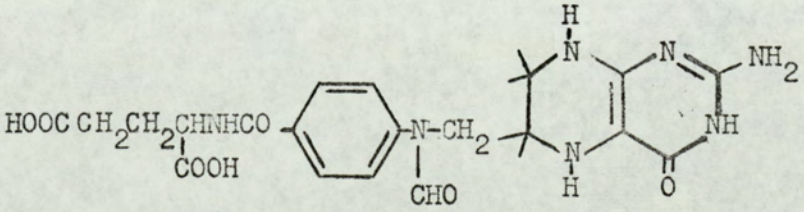
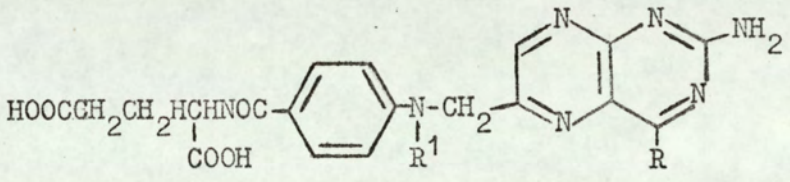
The N^{10}-formyl-5,6,7,8-tetrahydro derivative (27) serves as a source of one-carbon atom fragments in the biosynthesis of a host of physiologically important substances.



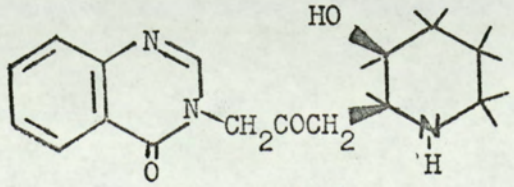
(27)

The biosynthesis of nucleic acids appears to be vitally dependent on this compound (27), and hence the possibility that analogues of it may be capable of selectively interfering with the development of neoplastic cells in comparison with normal cells was investigated.[45] Amethopterin (28; R=NH_2, R^1=CH_3) and aminopterin (28; R=NH_2, R^1=H) have both been used in the treatment of leukaemia.[46] They apparently function by blocking the conversion of pteroylglutamic acid (26) to the N^{10}-formyltetrahydro derivative (27), which in turn prevents incorporation of the one-carbon unit in the biosynthesis.



(28)

Alkaloids containing a quinazoline nucleus form a small but important group of natural products. Many quinazolines possessing a wide variety of biological activities are known. The antimalarial activity of febrifugine (29), one of the naturally occurring quinazoline alkaloids, spurred the preparation and testing of a number of quinazolines. The compounds (30; a and b) were shown to have significant antimalarial activity.[47]



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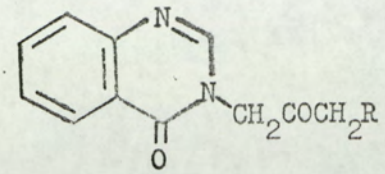
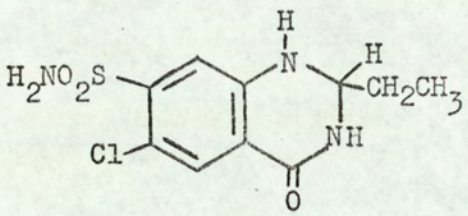


(30)

a) R = ω-N-morpholypropyl

b) R = ω-N-piperidyl-n-butyl

7-Chloro-6-sulphonamidoquinazolin-4(3H)-ones are more effective than the mercury diuretics and can be administered orally,[48] even better are the 1,2-dihydro derivatives and one (31) has been marketed under the name "Quinethazone".[49]



(31)

Amino and hydrazino quinazolines exhibit antibacterial activity[50,51] and 2-methyl-3-o-tolylquinazolin-4(3H)-one was shown to be superior to sodium phenobarbitone as an anticonvulsant against metrazol induced seizures.[52]

There are no known naturally occurring pyridopyrimidines, but because of their close relationship to other fused pyrimidines certain of these compounds have been investigated for biological activity. G. H. Hitchings and his co-workers have made a comprehensive study of antifolic acid activity in both the pyrimidines and bicyclic systems containing pyrimidine. They have demonstrated that very many such

compounds, both simple and fused, show such activity.[53,54] In the course of this work some pyrido[3,2-d]pyrimidines and a large number of pyrido[2,3-d]pyrimidines were shown to be highly active against a variety of pathogenic bacteria.[53,54,55,56,57,58] A series of 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidines have been studied and are claimed to exhibit antipyretic, diuretic, bacteriostatic, sedative and coronary dilating properties.[59,60]

There are no reports in the literature of any pyrido[3,4-d]pyrimidines possessing biological activity.

DISCUSSION

DISCUSSION

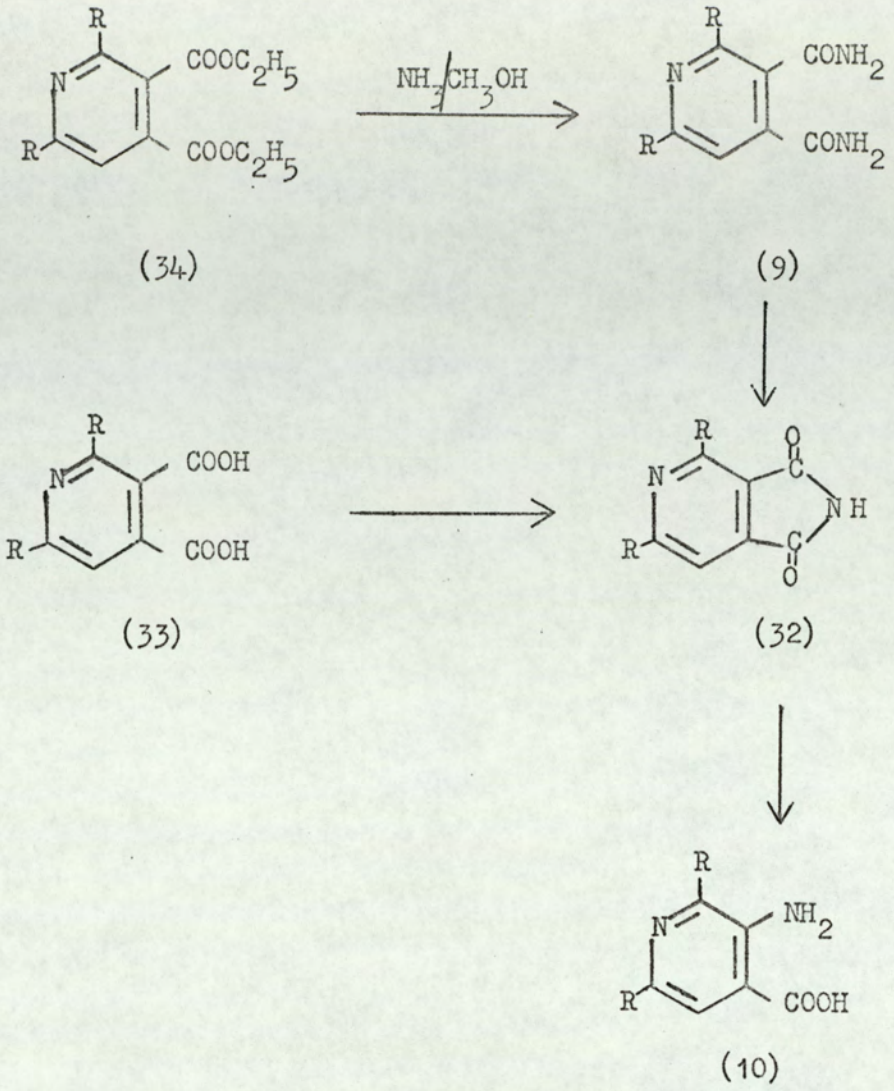
The synthesis and properties of the few known pyrido[3,4-d]pyrimidines have been reviewed in the introduction. The aim of this investigation was to develop new synthetic routes and to study some of the chemical, physical and biological properties of the pyrido[3,4-d]pyrimidine system.

SYNTHESIS OF PYRIDO[3,4-d]PYRIMIDINES.

(i) From 3,4-substituted pyridines.

3-Aminopyridine-4-carboxylic acids were essential intermediates in the synthetic routes employed.

3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3) was prepared from 2,6-dimethylcinchomeronimide (32; R=CH_3) by a Hofmann degradation.[61] Gulland and Robinson[62] obtained the imide (32; R=CH_3) from 2,6-dimethylpyridine 3,4-dicarboxylic acid (33; R=CH_3) by reaction with urea. A more satisfactory method for the synthesis of the imide (32; R=CH_3) was developed. Ethyl 2,6-dimethylpyridine-3,4-dicarboxylate (34; R=CH_3) was converted to the diamide (9; R^1=R^2=CH_3), which on thermal cyclisation at 230-250° gave a good yield of 2,6-dimethylcinchomeronimide (32; R=CH_3). There is a report in the literature[63] of the direct preparation of the amino acid (10; R=CH_3), in a good yield, from the diamide by a Hofmann degradation with sodium hypochlorite. This reaction was repeated but only very low yields of the amino acid (10; R=CH_3) were obtained, the main product was 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; R^1=R^2=CH_3).



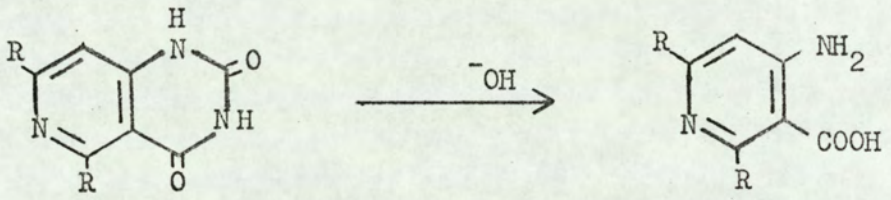
The infrared spectrum of 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3) showed the expected absorptions at 3310 and 3400 $cm.^{-1}$, due to the asymmetrical and symmetrical N-H stretching vibrations, and at 1695 $cm.^{-1}$ due to the carbonyl stretching vibration.

3-Aminopyridine-4-carboxylic acid (10; R=H) was prepared in a similar manner from the corresponding imide (32; R=H). Pyridine-3,4-dicarboxylic acid (33; R=H), obtained from the oxidation of isoquinoline[64], was treated with acetic anhydride and acetamide, by the

method of Bachmann and Barker[65], to yield the imide (32; R=H).

6,8-Dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) has been reported[8] as the product obtained from a Hofmann degradation on 2,6-dimethylpyridine-3,4-dicarboxamide (9; $R^1=R^2=CH_3$). Treatment of this product with 30% aqueous sodium hydroxide solution gave an amino acid with an identical infrared spectrum and melting point to that of an authentic sample of 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; $R=CH_3$).

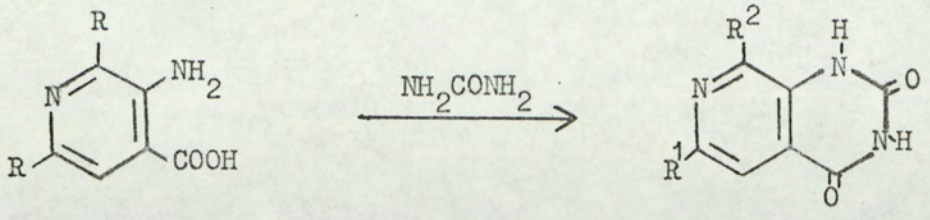
The 4-amido group could conceivably have been the one to undergo rearrangement in the Hofmann reaction, but this would then have yielded a pyrido[4,3-d]pyrimidine (35; $R=CH_3$) which would be hydrolysed to 4-amino-2,6-dimethylpyridine-3-carboxylic acid (36; $R=CH_3$)



(35) (36)

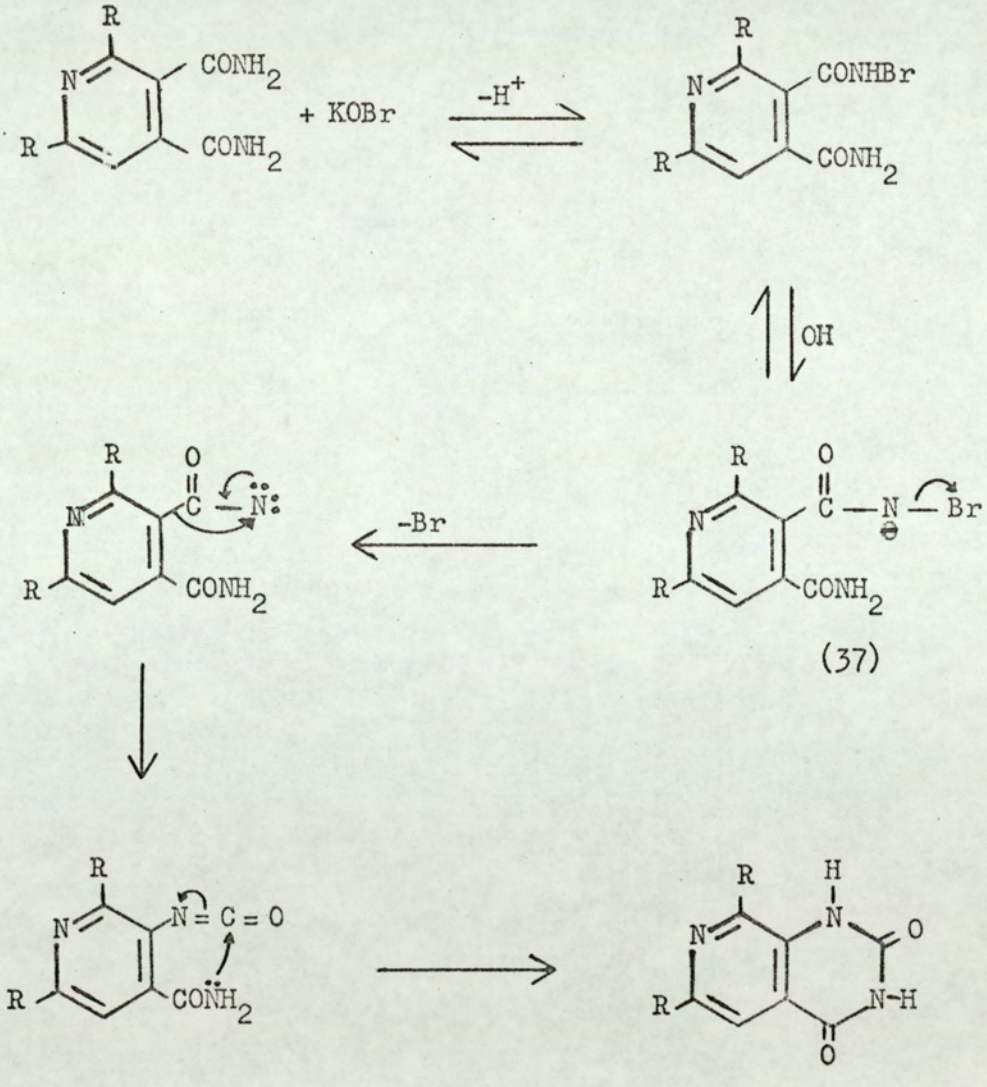
The n.m.r. spectrum in trifluoroacetic acid also confirmed that the product was the 3-amino-4-carboxylic acid (10; $R=CH_3$). The aromatic singlet due to the 5-H was visible at 1.89τ, whereas the spectrum of the 4-aminopyridine-3-carboxylic acid (36=H) showed the 5-H at 2.9τ in this system.[66]

An independent synthesis, by reaction of an authentic sample of 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; $R=CH_3$) with urea at 170°, yielded 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) which was identical to the product obtained by the Hofmann degradation route.



(10) (8)

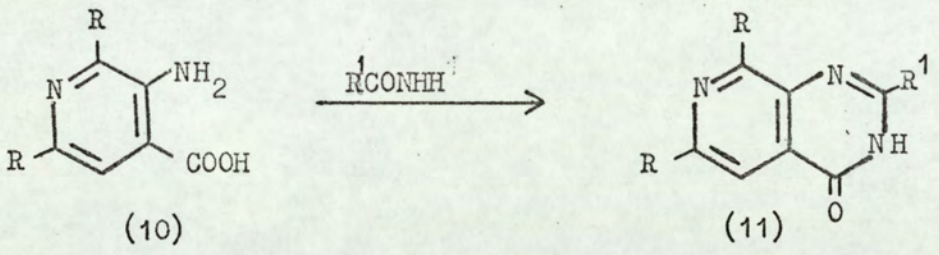
A plausible mechanism for the Hofmann degradation of pyridine-3,4-dicarboxamides is as follows :



(37)

The loss of Br^- from the anion (37) is probably the rate determining step, since the rate of decomposition of substituted N-bromobenzamides in alkaline solution is more rapid when electron releasing groups are present in the aromatic ring and slower when electron attracting groups are present.[67,68] Thus the amide meta to the N atom in the pyridine ring will be the more favoured to undergo a Hofmann degradation, by virtue of the fact that Br^- loss from the anion (37) is more favoured. The isocyanate formed is then attacked by the nitrogen atom of the other amide group to yield the pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione.

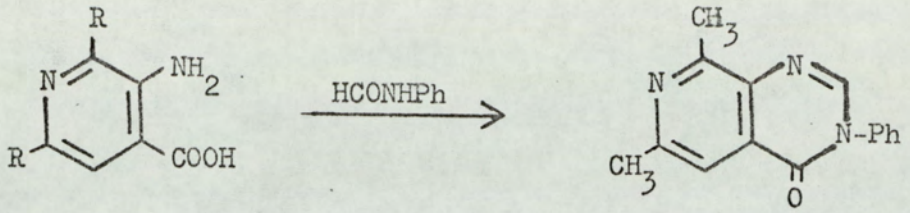
Pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=H$) and pyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=H$) were prepared by the method of Gabriel and Colman[6] in order to study their chemical and physical properties.



(10) (11)

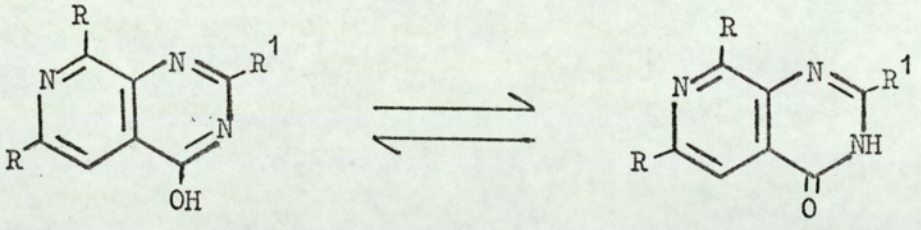
The Niementowski reaction was employed for the synthesis of 6,8-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=CH_3$, $R^1=H$) and 6,8-dimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (38). Reaction of 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10;$R=CH_3$) with formamide at 170° yielded the pyridopyrimidine (11; $R=CH_3$,$R^1=H$). Replacement of formamide with formanilide gave the 3-phenyl derivative (38) in low yield. The Niementowski reaction has been

reported to proceed via an intermediate N-formyl derivative.[69]

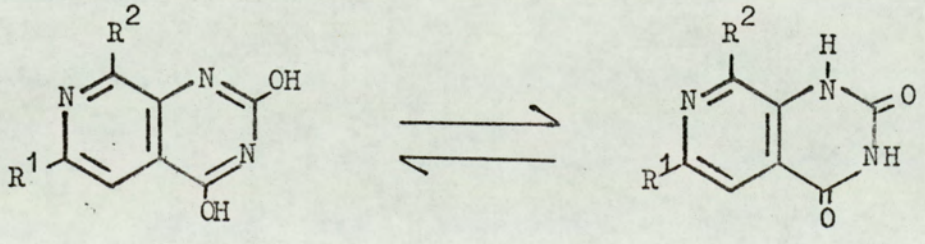


(10) (38)

The infrared spectra of these pyrido[3,4-d]pyrimidine-2, 4(1H,3H)-diones (8) and pyrido[3,4-d]pyrimidin-4(3H)-ones (11) all showed carbonyl absorptions in the 1680-1710 cm.$^{-1}$ region of the spectrum. This, together with the N-H absorptions, is only compatible with these compounds existing predominatly in the tautomeric oxo forms (11 and 8).



(11)

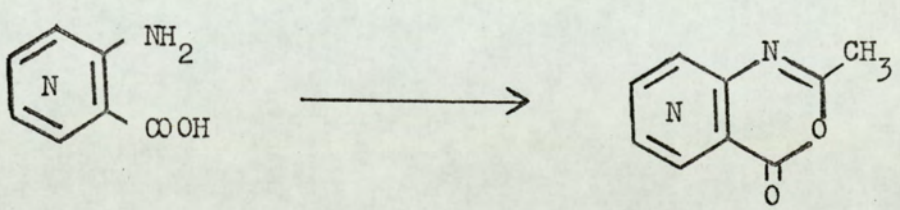


(8)

The n.m.r. spectra of these pyrido[3,4-d]pyrimidin-4(3H)-ones (11) and pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones were studied. The poor solubility of these compounds in deuteriochloroform necessitated the use of trifluoroacetic acid as a solvent, which resulted in the expected powerful deshielding effects. Because of this solvent effect direct comparison of these n.m.r. spectra with that of the parent pyrido[3,4-d]pyrimidine[20] are difficult. The 2- and 5-protons gave singlets at 1.08 and 0.99 τ respectively in the spectrum of pyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=H$). The introduction of two methyl groups into the molecule, at the 6- and 8-positions, brought about an upfield shift of these protons to 1.23 and 1.48 τ respectively.

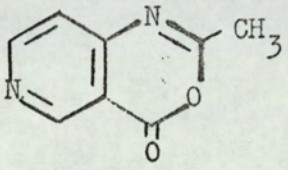
(ii) Via pyrido[3,4-d][1,3]oxazin-4-ones.

Before the commencement of this work only one pyrido[3,4-d][1,3]oxazin-4-one (39) was known. Little and Allan[70] showed that the condensation of the appropriate aminopyridine carboxylic acid (40) with acetic anhydride afforded the corresponding 2-methylpyrido[1,3]oxazin-4-one (41).



(40) (41)

The method yielded the four 2-methylpyrido[1,3]oxazin-4-ones; 2-methylpyrido[4,3-d][1,3]oxazin-4-one (42), 2-methylpyrido[3,4-d][1,3]oxazin-4-one (39), 2-methylpyrido[3,2-d][1,3]oxazin-4-one (44) and 2-methylpyrido[2,3-d][1,3]oxazin-4-one (43).



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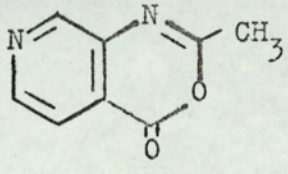
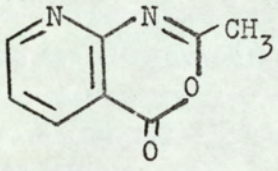


(39)



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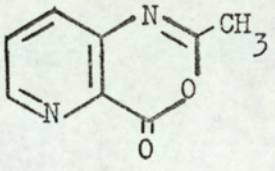
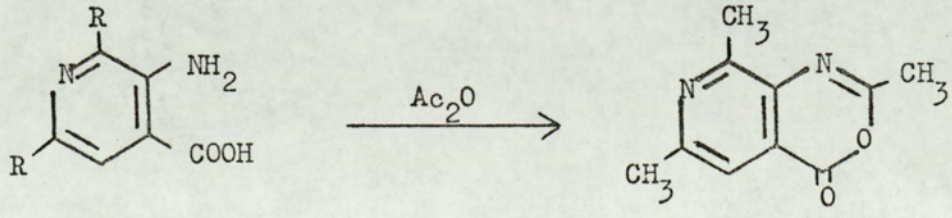


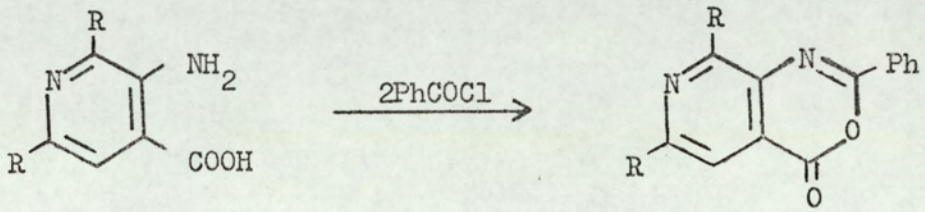
(44)

2-Methylpyrido[3,4-d][1,3]oxazin-4-one (39) was prepared by the method of Little and Allan[70], but with direct crystallisation of the crude product from ethyl acetate. 3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3) yielded the corresponding trimethyl analogue (45) under similar conditions.



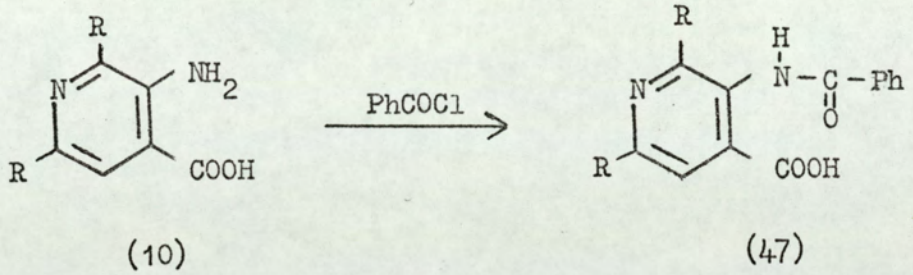
(10; R=CH_3) (45)

2-Phenylpyrido[3,4-d][1,3]oxazin-4-ones were also prepared from the corresponding 3-aminopyridine-4-carboxylic acids. Reaction of 3-aminopyridine-4-carboxylic acid (10; R=H) with benzoyl chloride (2 mole.) in pyridine yielded 2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H). 6,8-Dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; $R=CH_3$) was obtained by a similar reaction from the corresponding amino acid (10; $R=CH_3$).

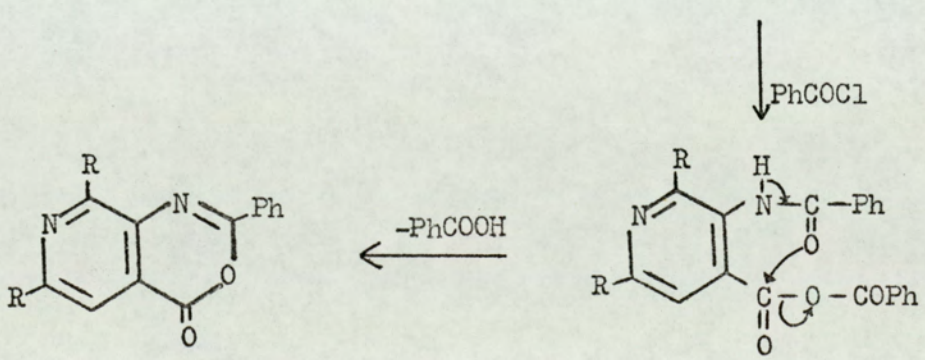


(10) (46)

The following mechanism appears to be the most plausible:



(10) (47)

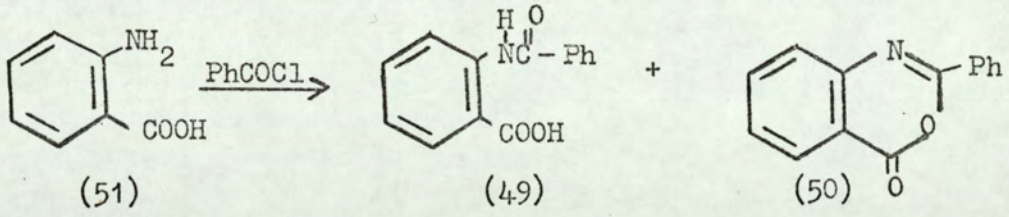


(46) (48)

One mole. of benzoyl chloride is used in the formation of the benzoyl derivative (47). The other mole. of benzoyl chloride undergoes a normal acid chloride reaction[71] with the carboxylic acid group in the benzamido derivative (47), to yield the unsymmetrical anhydride (48). This intermediate (48) then undergoes an intramolecular nucleophilic displacement of benzoate ion from the anhydride group by the carbonyl oxygen of the neighbouring amide function. Cyclisation is presumably facilitated by 1,6-interaction between the reacting groups.

The formation of 2-methylpyrido[3,4-d][1,3]oxazin-4-ones presumably proceeds by a similar mechanism. Acetic anhydride also reacts with carboxylic acid groups to form anhydrides.[72]

The preparation of benzoxazines has been postulated to proceed by a similar mechanism. Bain and Smalley[73] isolated N-benzoyl-anthranilic acid (49) and the benzoxazin-4-one (50) from the reaction of anthranilic acid (51) with one mole. of benzoyl chloride.

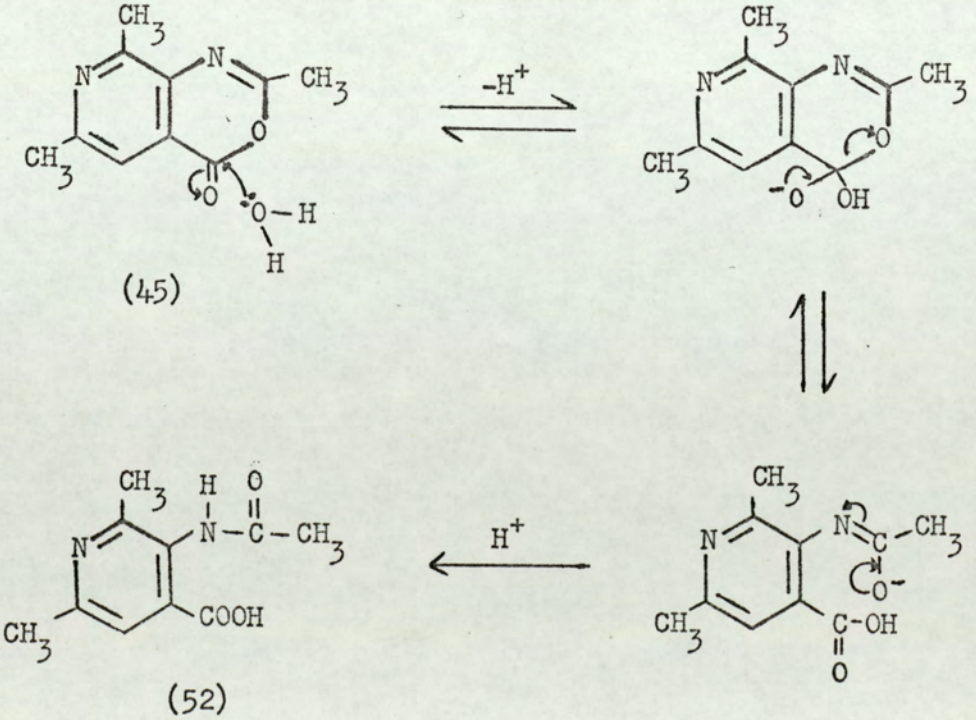


(51) (49) (50)

The infrared spectra of the pyrido[3,4-d][1,3]oxazin-4-ones all showed the high carbonyl stretching vibration expected of an unsaturated δ-lactone[74] in the 1745-1760 cm.$^{-1}$ region of the spectrum. The spectrum of 2-methylpyrido[3,4-d][1,3]oxazin-4-one was very similar to the corresponding pyrido[4,3-d]-[75] and pyrido[3,2-d][1,3]oxazin-4-ones.[76]

The n.m.r. spectra of the pyrido[3,4-d][1,3]oxazin-4-ones were recorded and all the peaks assigned.

2-Methylbenz-1,3-oxazin-4-ones[77], 2-methylpyrido[3,2-d][1,3]oxazin-4-one[76] and the pyrido[4,3-d]isomer[75] are all susceptible to hydrolysis by moisture in the atmosphere. 2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) was left exposed to the atmosphere for 12 hr. Periodic infrared spectra of the sample revealed the emergence of peaks at 1650 and 1680 $cm.^{-1}$, due to the amide and carboxylic acid carbonyl stretching vibrations of the hydrolysed product (52). After two weeks approximately 50% of the pyrido-oxazine (45) had been hydrolysed to 3-acetamido-2,6-dimethylpyridine-4-carboxylic acid (52). Hydrolysis in water at room temperature was complete after twelve hours. The reaction is probably initiated by nucleophilic attack of water at the exocyclic C=O band.

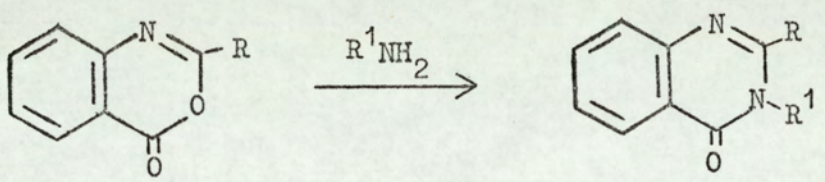


(45)

(52)

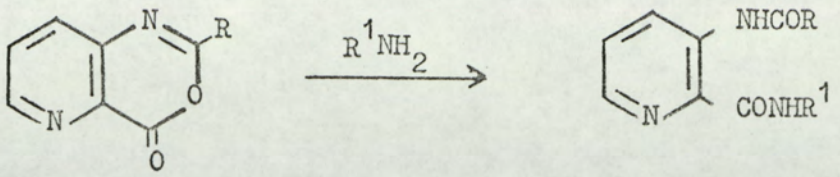
2-Phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H) and its 6,8-dimethyl derivative (46; R=CH_3) were stable. Both compounds were recovered unchanged from water at 35-40° after three days.

Benz-1,3-oxazin-4-ones (53) react exothermally with ammonia in aqueous media to give high yields of quinazolones (54).[77,78,79] A wide variety of amines has been successfully used, including aliphatic, aromatic, heterocyclic amines and hydrazine.[80]

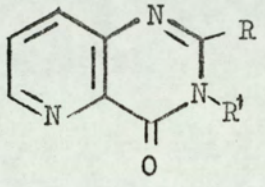


(53) (54)

This route has been extended to the synthesis of pyridopyrimidines. Pyrido[3,2-d][1,3]oxazin-4-ones (55) yielded the corresponding pyrido[3,2-d]pyrimidin-4(3H)-ones (56) on reaction with various primary amines.[76] In the 2-phenylpyrido[3,2-d][1,3]oxazin-4-one (55; R=Ph) series, the product was invariably the 3-benzamido-pyridine-2-carboxamide (57; R=Ph). These diamides (57; R=Ph) were cyclised to the pyrido-pyrimidine (56; R=Ph) by dissolution in phosphoryl chloride.



(55) (57)

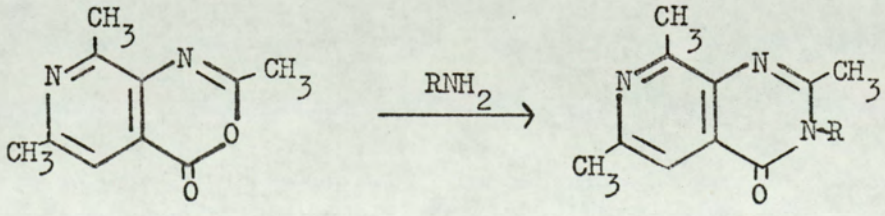


(56)

Similar treatment of pyrido[4,3-d][1,3]oxazin-4-ones yielded the corresponding pyrido[4,3-d]pyrimidin-4-one.[75]

This method of synthesis was applied to the pyrido[3,4-d]pyrimidine system. The 2-methyl-pyrido[3,4-d][1,3] oxazin-4-ones yielded the corresponding pyrido[3,4-d]pyrimidin-4(3H)-ones directly, but 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones generally yielded the intermediate diamides.

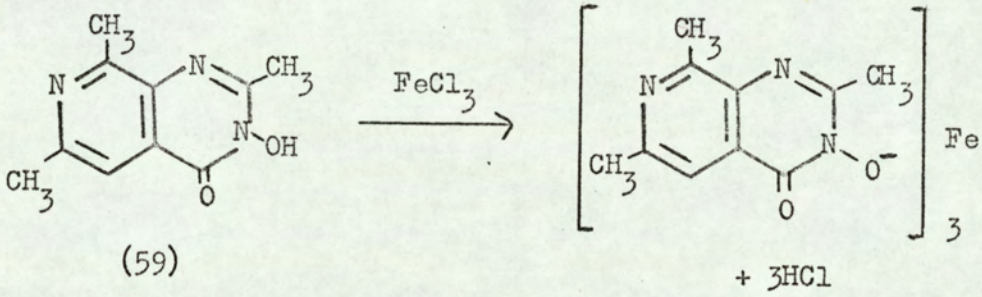
2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) was reacted with a series of primary amines. Aqueous ammonia yielded 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=CH_3$) in an exothermic reaction at room temperature.



(45) (58)

Hydrazine hydrate underwent a similar reaction with the trimethyl-pyrido-oxazine (45), although in this case seven days at room temperature were required for the complete conversion of the pyrido-oxazine (45) into 3-amino-2,6,8-trimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (58; R=NH_2).

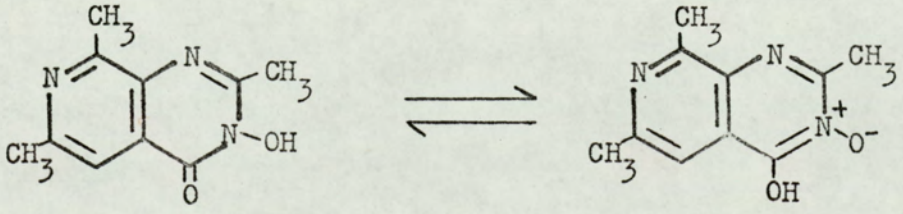
Reaction of 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) with hydroxylamine at room temperature was very slow. The addition of sodium hydroxide as catalyst yielded 3-hydroxy-2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (59) after five days. The product gave a wine red colour with ferric chloride, characteristic of hydroxamic acids.



(59)

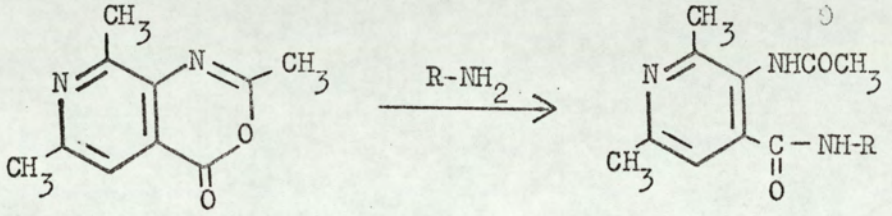
+ 3HCl

Tautomerism is possible in these hydroxamic acids, they can be represented as o-hydroxy N-oxides.

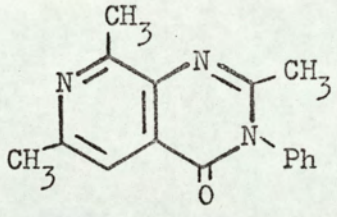


The evidence from other hydroxamic acids indicates that in most solutions and in all solids the hydroxamic acids exist in the N-hydroxy-amide form.[81,82]

The reaction of 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) with aniline at room temperature for five days yielded a mixture of 3-acetamido-2,6-dimethyl-N-phenyl-pyridine-4-carboxamide (60; R=Ph) and 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72).



(45) + (60)

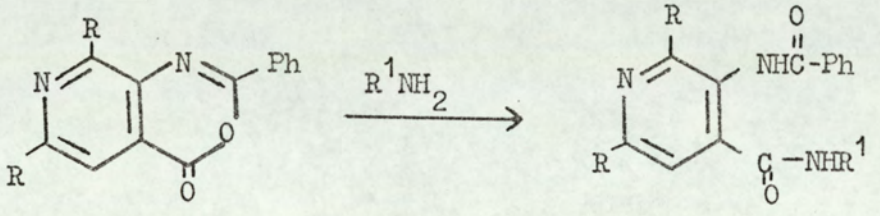


(72)

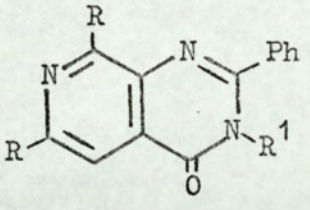
Shorter reaction times (twelve hours) gave solely the diamide (60; R=Ph), however attempted purification by crystallisation from hot ethanol resulted in cyclisation to the pyridopyrimidine (72). When the reaction was carried out at elevated temperatures for short periods the sole product was the pyridopyrimidine (72).

2-Methylpyrido[3,4-d][1,3]oxazin-4-one (39) yielded 2-methylpyrido[3,4-d]pyrimidin-4- (3H)-one (11; R=H, $R^1=CH_3$) on reaction with ammonia under those conditions which were employed for the trimethyl derivative (45).

2-Phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H) and its 6,8-dimethyl derivative (46; $R=CH_3$) were both treated with aqueous ammonia under the conditions employed for the 2-methylpyrido-oxazines. The product in both cases was the diamide (61; R=H or CH_3, R^1=H).



(46) (61)



(62)

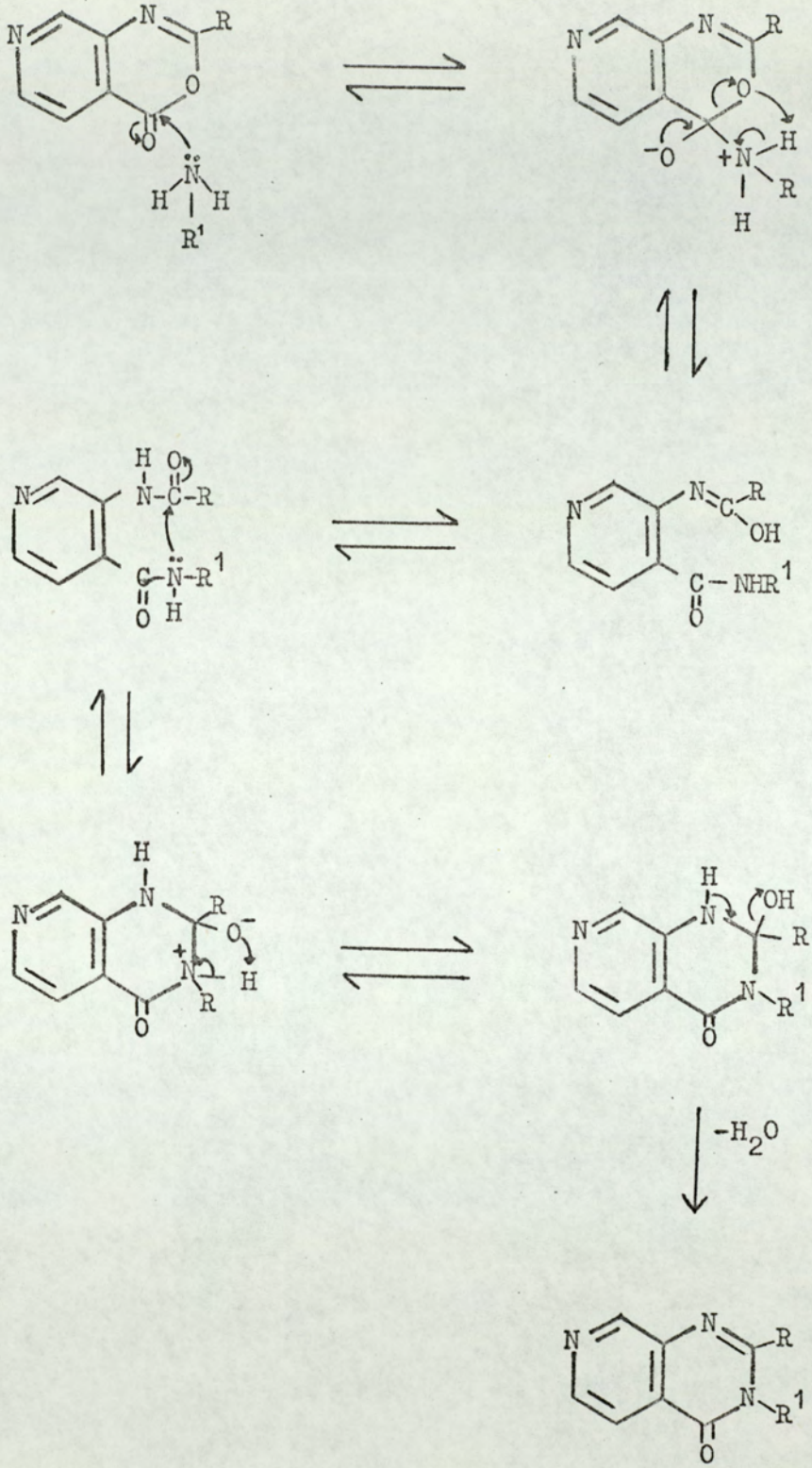
3-Benzamido-2,6-dimethyl-N-phenylpyridine-4-carboxamide (61; $R=CH_3$, R^1=Ph) was obtained from 6,8-dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; $R=CH_3$) by reaction with aniline at room temperature. The diamides (61) were cyclised to the pyridopyrimidines (62) by heating at 200-260° for periods of up to eighteen hours.

The reaction of 6,8-dimethyl-2-phenyl-pyrido[3,4-*d*][1,3]oxazin-4-one (46; R=CH_3) with *m*-nitroaniline at elevated temperatures yielded a mixture of 3-benzamido-2,6-dimethyl-N-(3^1-nitrophenyl) pyridine-4-carboxamide (61; R=CH_3, R^1= 3^1-NO_2Ph) and 6,8-dimethyl-3-(3^1-nitrophenyl)-2-phenyl-pyrido[3,4-*d*]pyrimidin-4(3H)-one (62; R=CH_3, R^1=3^1-NO_2Ph). Attempted cyclisation of the diamide (61; R=CH_3, R^1=3^1-NO_2Ph) by heat was unsatisfactory, the high temperatures required tended to cause the diamide to decompose.

The infrared spectra of these pyridopyrimidines all showed the expected carbonyl absorptions in the 1670-1700 cm^{-1} region of the spectrum. The carbonyl absorptions for the diamides were generally at lower frequency than the corresponding pyridopyrimidine.

The n.m.r. spectra of a selection of diamides and pyrido-pyrimidines were studied and all the peaks assigned.

The most probable mechanism for the formation of pyrido[3,4-*d*]pyrimidin-4(3H)-ones from the corresponding pyrido-oxazine is as follows:



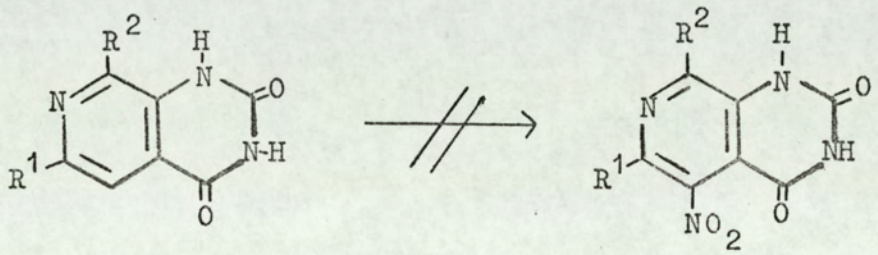
The initial step in the reaction is nucleophilic attack of the lone pair of electrons on the nitrogen atom of the primary amine at the exocyclic C=O bond of the pyrido-oxazine. The overall rate determining step is probably attack of the nitrogen atom of the 4-amido group on the carbonyl carbon of the 3-amido group. If this is the rate determining step, any factors which increase the nucleophilicity of the 4-amido nitrogen should increase the rate of reaction. On this basis the availability of the electrons on the nitrogen atom of the reacting amine, its basic strength, should control the reaction rate. This view was supported by the reaction between 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) and a series of amines. Ammonia yielded the pyridopyrimidine (58;R=H) in twelve hours at room temperature, while with less basic amines much longer reaction times were required.

The diamides (61), derived from 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones (46), were much more reluctant to undergo cyclisation to the pyridopyrimidnes (62) than the diamides derived from 2-methyl-pyrido[3,4-d][1,3]oxazin-4-ones, which were rarely isolated. This reluctance of 3-benzamidopyridine-4-carboxamides to yield pyrido-pyrimidines is not surprising in view of the known reduction in electrophilic properties of a carbonyl group when attached to an aromatic nucleus.[83]

CHEMICAL PROPERTIES

All the pyridopyrimidines are π electron deficient systems, and hence nucleophilic substitution is more favoured than electrophilic substitution. There are many examples of nucleophilic substitution, the majority of which involve substitution in the pyrimidine ring,[11,55,84,85] but no reports of electrophilic substitution occurring at a carbon atom have been recorded.

Derivatives with electron donating substituents are more likely to undergo electrophilic substitution than the parent pyridopyrimidines. Attempted nitration of 6,8-dimethyl-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) with nitric acid (d. 1.4) in acetic and sulphuric acids under a variety of conditions failed, starting material was recovered from the reaction mixtures.

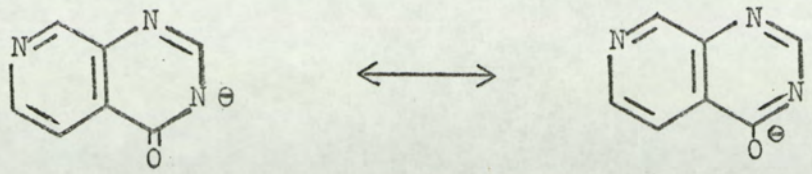


(8)

(1) Methylation of pyrido[3,4-d]pyrimidin-4(3H)-ones and -[3,4-d]pyrimidine-2,4(1H,3H)-diones.

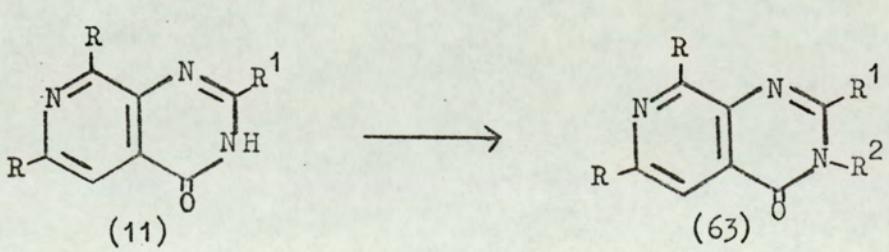
Electrophilic substitution at ring nitrogen atoms has been limited to protonation and N-alkylation of the anion derived from a pyridopyrimidinone.[11]

The question of the position of alkylation of pyrido[3,4-d]pyrimidinones is similar to the problem encountered in all aromatic nitrogen heterocyclic systems, in which a hydroxyl group is found ortho or para to the nitrogen position. In alkaline solution the anions of such compounds exist as resonance hybrids, the two major forms differing only by the position of a pair of electrons as shown;



Thus in the alkylation of the pyrido[3,4-d]pyrimidinones the entering group may become attached to either the nitrogen atom, giving N-alkylpyrido[3,4-d]pyrimidinones, or to the oxygen atom giving alkoxypyrido[3,4-d]pyrimidines. Bogert and Seil [86] made a summary of all such reactions, and found that in general the alkylating agent and the conditions of alkylation, and not the heterocyclic nucleus, were the factors determining the course of the alkylation. Methylation of pteridinones[87] and quinazolones[88] with dimethyl sulphate and methyl iodide in alkaline solution yielded N-methyl derivatives. The pyrido[3,4-d]pyrimidinones under these reaction conditions also yielded N-methyl derivatives.

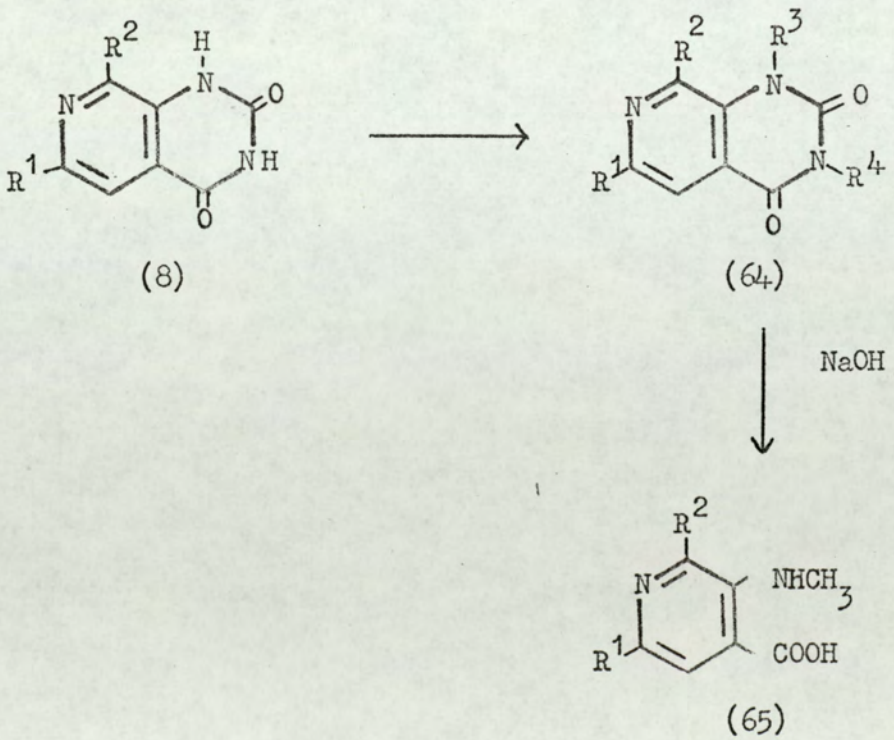
Methylation of 6,8-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=CH_3, R^1=H) and 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=CH_3) with dimethyl sulphate in aqueous sodium hydroxide solution yielded the trimethyl (63; R=R^2=CH_3, R^1=H) and the tetramethyl (63; R=R^1=R^2=CH_3) derivatives respectively.



(11) (63)

Attempted methylation of pyrido[3,4-d]pyrimidin-4(3H)-one (11;R=R^1=H) and the 2-methyl analogue (11; R=H, R^1=CH_3) with the same methylating agent yielded only intractable tars. However methyl iodide in sodium ethoxide solution yielded the two N-methylated products, 3-methylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=H, R^2=CH_3) and 2,3-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=H, R^1=R^2=CH_3).

The methylation of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; R^1=R^2=CH_3) with dimethyl sulphate yielded 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; R^1=R^2=R^4=CH_3, R^3=H). The structure of the product was proved by hydrolysis. The trimethylpyridopyrimidine (64; R^1=R^2=R^4=CH_3, R^3=H) was heated under reflux in 10% aqueous sodium hydroxide solution to yield 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3). If methylation had occurred at the 1-position the expected product would have been 2,6-dimethyl-3-methylaminopyridine-4-carboxylic acid (65; R^1=R^2=CH_3).



Further reaction of 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^4=CH_3$, $R^3=H$) with dimethyl sulphate at 35-40° in aqueous sodium hydroxide solution gave a low yield of 1,3,6,8-tetramethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^3=R^4=CH_3$). Methylation of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) with methyl iodide yielded a mixture of the trimethyl (64; $R^1=R^2=R^4=CH_3$, $R^3=H$) and the tetramethyl (64; $R^1=R^2=R^3=R^4=CH_3$) compounds.

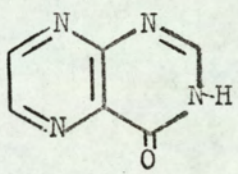
The reluctance of the dione (8; $R^1=R^2=CH_3$) to methylate at the 1-position can best be explained by the steric hindrance of the 8-methyl group. Construction of a model of 1,3,6,8-tetramethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^3=R^4=CH_3$) shows the close proximity of the 1- and 8-methyl groups. This view is also supported by the fact that methylation of pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=H$) yielded 1,3-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=H$, $R^3=R^4=CH_3$). When the reaction was carried out for short periods the only materials isolated were the 1,3-dimethylpyridopyrimidine (64; $R^1=R^2=H$, $R^3=R^4=CH_3$) and starting material.

The n.m.r. spectra of 3,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one and 1,3,6,8-tetramethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione were recorded in deuteriochloroform and trifluoroacetic acid as solvents. The expected downfield shift due to trifluoroacetic acid was observed, being greatest for hydrogens attached directly to the nucleus. The 5-H in both compounds was shifted approximately 0.75 τ downfield when the spectra were recorded in trifluoroacetic acid, compared to deuteriochloroform as solvent. Methyl groups attached to the pyridopyrimidine nucleus were affected to a much lesser extent.

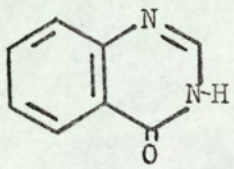
A comparison of the spectra of 3-methylpyrido[3,4-d]pyrimidin-4(3H)-one and pyrido[3,4-d]pyrimidine[20] in deuteriochloroform showed that the 4-carbonyl group considerably lowered the position of the 5-H, even with the 3-methyl group present in the molecule.

(ii) Ring-opening Reactions.

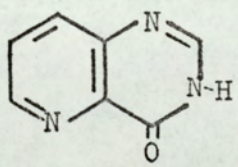
The ring-opening of fused pyrimidin-4(3H)-ones has been widely studied. Those in which ring-openings have been observed include pteridin-4(3H)-ones (66)[89-94] quinazolin-4(3H)-ones[95,96](67) and pyrido[3,2-d]pyrimidin-4(3H)-ones (68)[76].



(66)



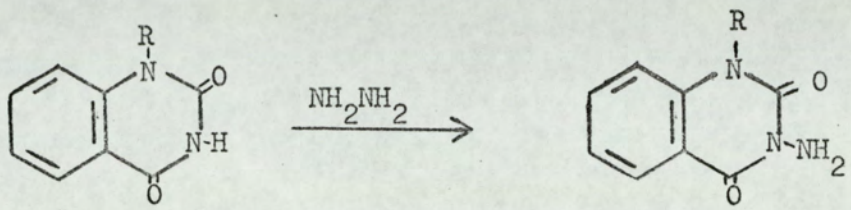
(67)



(68)

Treatment of these compounds with nucleophiles, such as hydroxide ion, ammonia, amines and hydrazine generally leads to rupture of one of the heterocyclic rings.

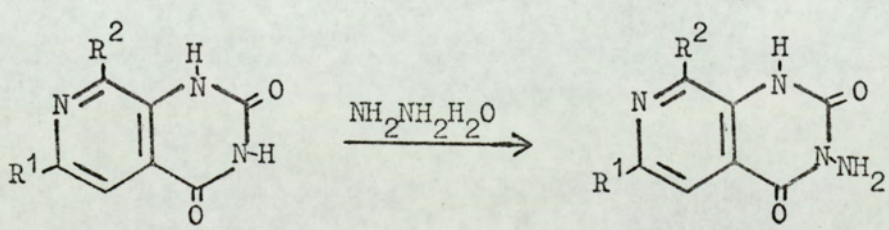
Certain fused pyrimidine-2,4(1H.3H)-diones have also been studied. Quinazoline-2,4(1H,3H)-diones (69) yielded 3-amino-quinazoline-2,4(1H,3H)-diones (70) on reaction with hydrazine hydrate.[97,98].



(69) (70)

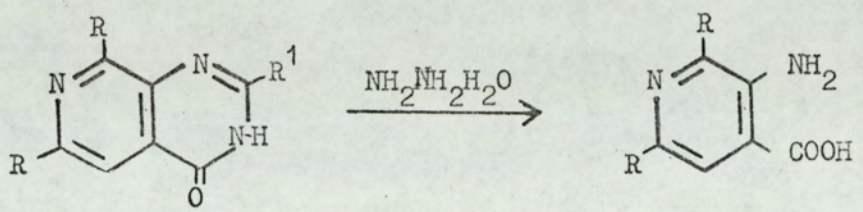
The alkaline hydrolysis of 6,8-dimethyl-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) and the 3-methyl analogue (64; $R^1=R^2=R^4=CH_3$, $R^3=H$) has already been mentioned (p. 18 and 37)

Reaction of pyrido[3,4-d]pyrimidine-2, 4(1H,3H)-dione (8; $R^1=R^2=H$) and 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$) with hydrazine hydrate yielded the corresponding 3-amino derivatives (71; $R^1=R^2=H$ or CH_3).



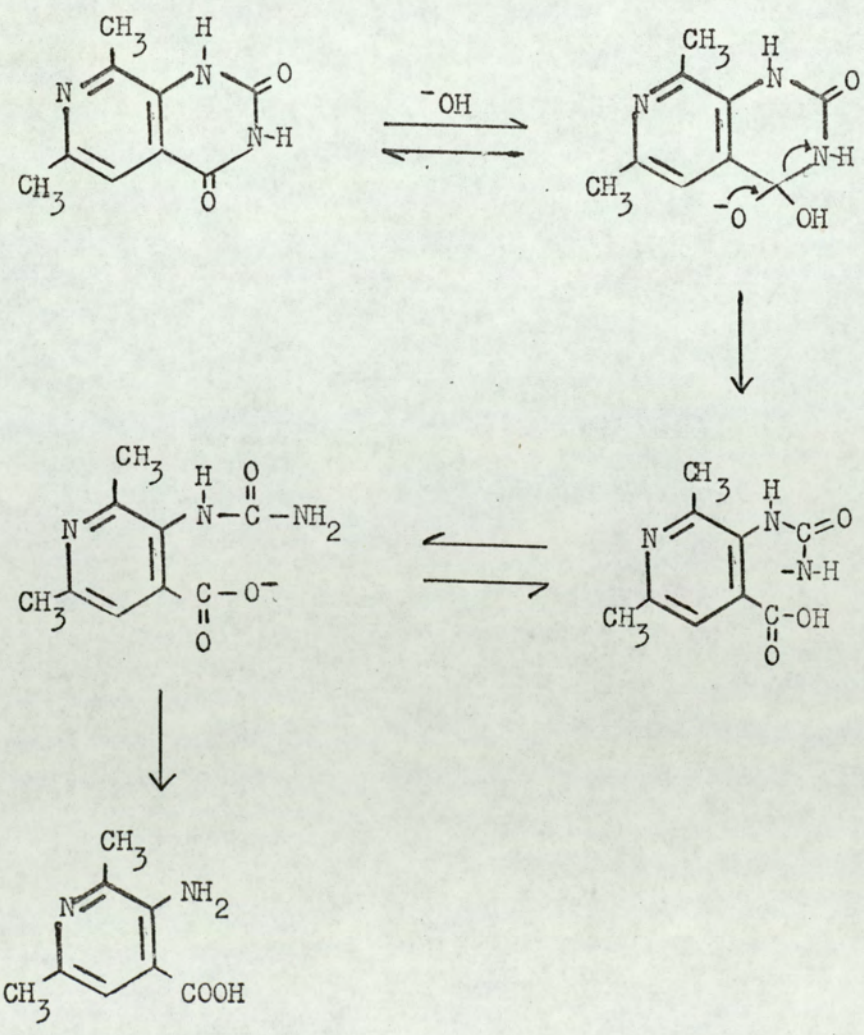
(8) (71)

Pyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=H) and 6,8-dimethylpyrido [3,4-d]pyrimidin-4(3H)-one (11; R=CH_3, R^1=H) with the same reagent yielded 3-aminopyridine-4-carboxylic acid (10; R=H) and the 6,8-dimethyl analogue (10; R=CH_3).



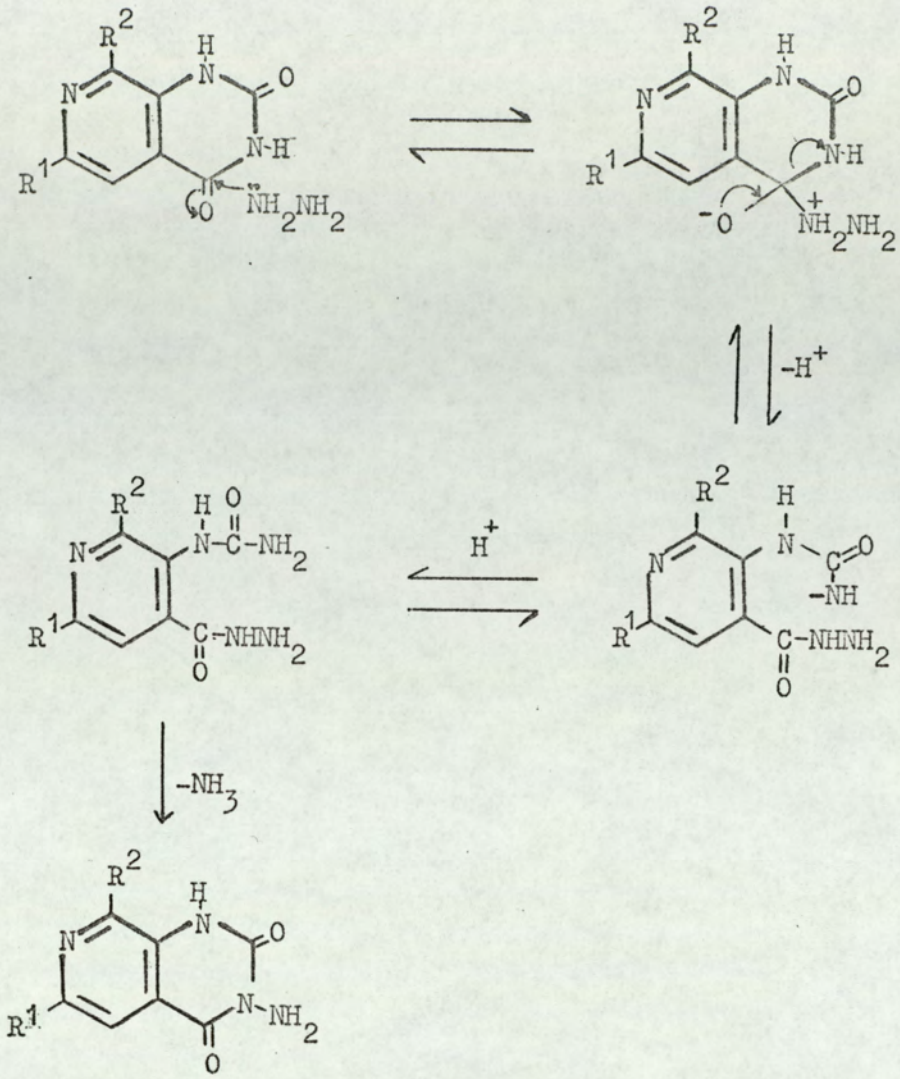
(11) (10)

A plausible mechanism for the ring-opening of 6,8-dimethyl-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione is as follows ;



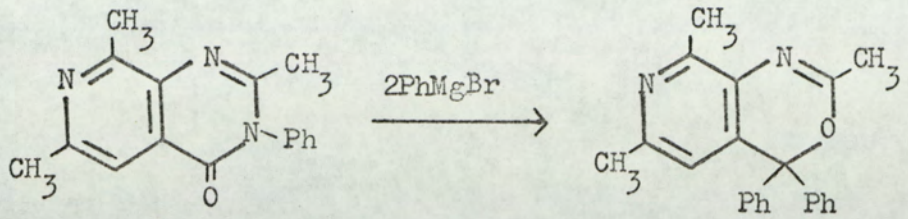
In sodium hydroxide solution the dione (8; $R^1=R^2=CH_3$) will exist as the di-anion in which electrostatic repulsion will tend to protect the carbonyl positions from attack by hydroxide ions. 30% Aqueous sodium hydroxide solution at 100° for eighteen hours was required to ring-open 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$). The introduction of a methyl group at the 3-position should increase the ease of ring-opening, as structural modifications which prevent ionisation are well known to make hydroxy-heterocycles more labile to alkali.[87,93,99-101] This was found to be the case, 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^3=CH_3$, $R^3=H$) with 10% aqueous sodium hydroxide solution yielded 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; $R=CH_3$) under the same conditions as were employed for the 6,8-dimethyl-pyridopyrimidine dione (8; $R^1=R^2=CH_3$).

The mechanism of the reaction between hydrazine hydrate and the pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones (8; $R^1=R^2=H$ or CH_3) is also presumably initiated by nucleophilic attack at the 4-carbon atom, which is followed by ring-opening and ring closure to yield the 3-amino-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones (71; $R^1=R^2=H$ or CH_3).



Initial attack of hydrazine hydrate on the pyrido[3,4-d]pyrimidin-4(3H)-ones can occur at either the endocyclic C=N or exocyclic C=O bond. Related cleavages have been stated to occur by initial attack at the endocyclic C=N bond[93,99] and the exocyclic C=O bond.[92,93,95,96] Reaction of both quinazolin-4(3H)-one (67)[95,96] and pteridin-4(3H)-ones (66)[94] with hydrazine hydrate has been stated to occur by initial attack at the 4-carbonyl position.

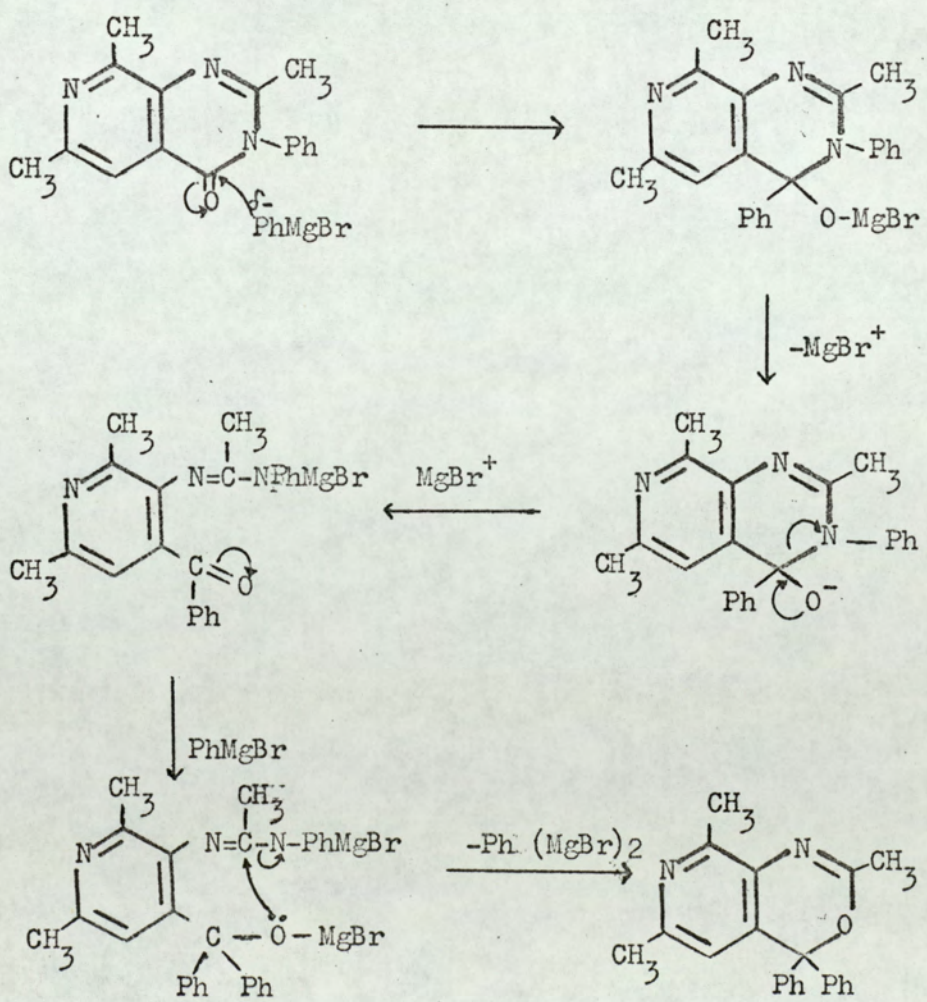
2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72) on reaction with excess phenyl magnesium bromide yielded 2,6,8-trimethyl-4,4-diphenylpyrido[3,4-d][1,3]oxazine (73).



(72) (73)

2-Methyl-3-phenyl quinazolin-4(3H)-one has been stated to yield the corresponding benzoxazine under similar reaction conditions.[102]

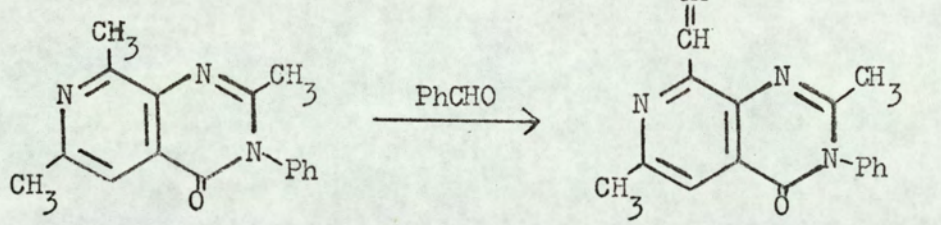
This reaction can be explained by assuming that it proceeds through a ring-opened intermediate. A plausible mechanism is outlined below ;



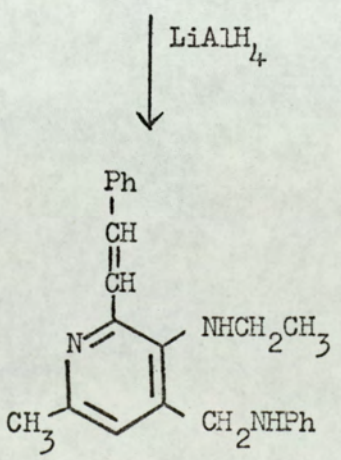
(iii) Reactive Methyl Groups

Little data is available in the four pyridopyrimidine systems, but methyl groups α and γ to ring nitrogen atoms appear to be activated, as is the case with other heterocyclic systems.[2,103] 2-and 6-Methyl substitutents in the pyrido[3,2-d]pyrimidines undergo bromination,[104,105,106] oxidative decarboxylation[76] and form styryl compounds.[76]

Reaction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with 1 mole. of benzaldehyde at 180° yielded a product shown to be 2,6-dimethyl-3-phenyl-8-styryl-pyrido [3,4-d]pyrimidin-4(3H)-one (74).



(72) (74)

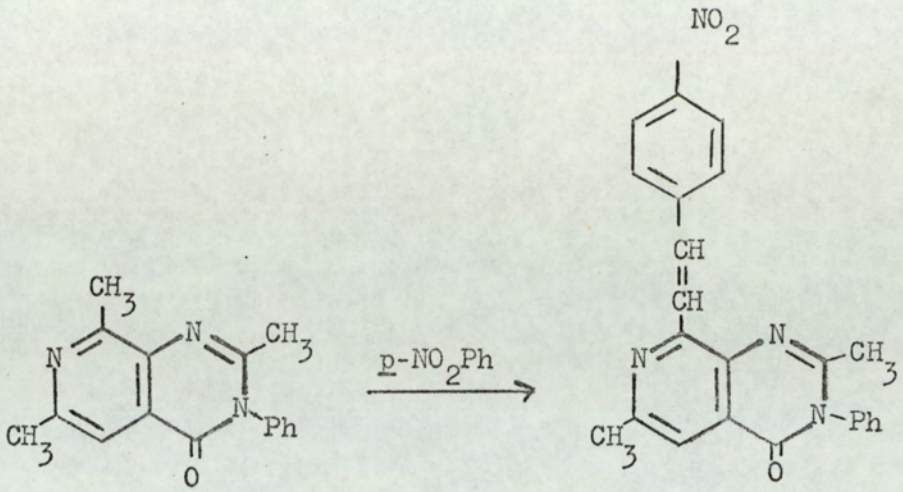


(75)

Reduction of 2,6-dimethyl-3-phenyl-8-styryl-pyrido[3,4-d]pyrimidin-4(3H)-one (74) with an excess of lithium aluminium hydride yielded 4-anilinomethyl-3-ethylamino-6-methyl-2-styryl-pyridine (75). The crude product could not be obtained sufficiently pure for a correct elemental analysis, but a mass spectrum gave a molecular weight of 343. The n.m.r. spectrum clearly showed the presence of the 3-ethylamino group at 6.92 τ(2H, q, J=7.0c./sec.) and 8.85 τ(3H, t, J=7.0c./sec.), thus the 2-methyl group had not undergone reaction.

The n.m.r. spectrum of the styryl compound (74) showed the presence of two methyl groups at 7.32 and 7.78 τ, the three methyl groups in 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4-(3H)-one (72) were at 7.8 (2-CH_3), 7.4(6-CH_3) and 7.17 τ(8-CH_3). The fact that reaction did not occur at the 2-methyl group is also shown by these n.m.r. spectra. The high methyl group in the 2,6,8-trimethyl-pyridopyrimidine (72), assigned as the 2-methyl group, is still present in the styryl derivative (74). The replacement of either the 6-or 8-methyl in 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one by a styryl group would be expected to shift the methyl group at the other position to a lower field value. Thus it appears from these spectra that reaction occurred at the 8-position, and the product is 2,6-dimethyl-3-phenyl-8-styryl-pyrido[3,4-d]pyrimidin-4(3H)-one (74).

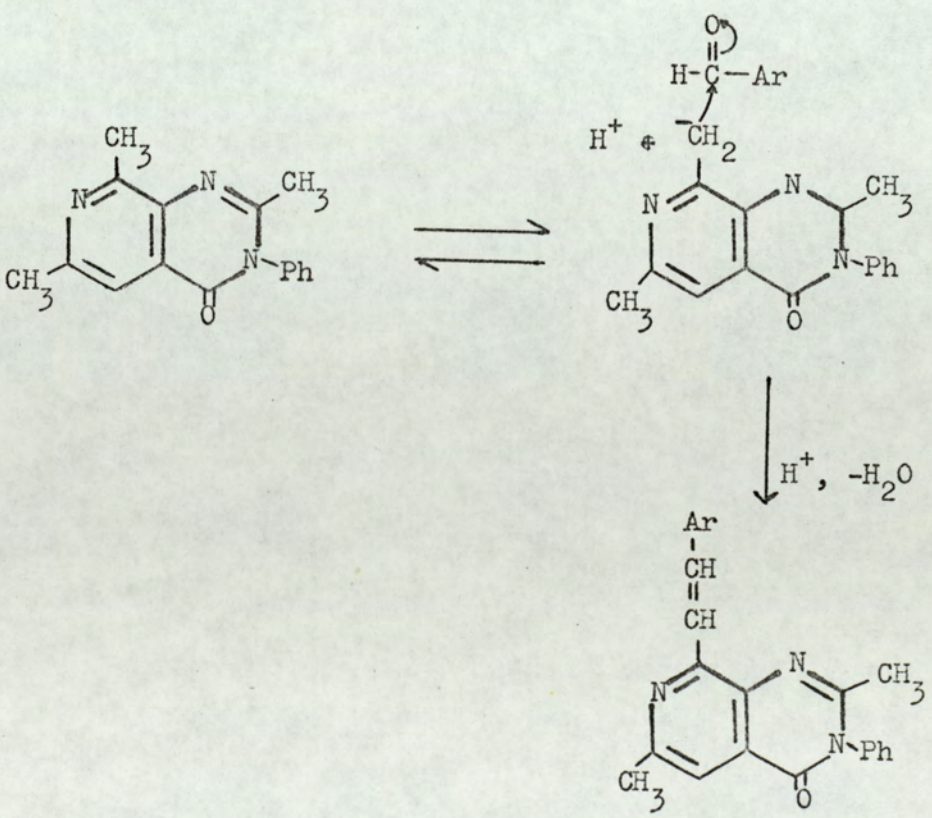
Reaction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with p-nitrobenzaldehyde under similar conditions gave 2,6-dimethyl-8-(p-nitrostyryl)-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (76) in excellent yield. Attempted preparation of a di(p-nitrostyryl) derivative failed. The only product isolated when the reaction was carried out in acetic anhydride, besides the monostyryl derivative (76), was p-nitrobenzylidene diacetate, formed by reaction between p-nitro benzaldehyde and acetic anhydride.[107,108]



(72) (76)

Reaction of p-dimethylaminobenzaldehyde with the trimethyl-pyridopyrimidine (72) under a wide variety of conditions, including acidic and basic catalysis, only resulted in the isolation of starting materials.

The formation of styryl compounds probably proceeds by the following mechanism;

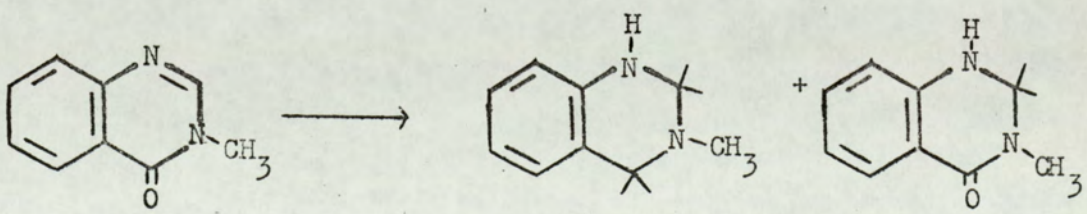


The electrophilicity of the carbonyl group in these benzaldehydes depends on the para substituent. Thus the order of the reactivity of the three benzaldehydes employed should be p-NO_2 > p-H > p-$N(CH_3)_2$. This is in agreement with the experimental results obtained, p-nitrobenzaldehyde yielded the styryl derivative readily, whereas p-dimethylaminobenzaldehyde failed to react.

Attempted bromination of 2,6,8-trimethyl-3- phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with bromine in an acetic acid/sodium acetate buffer yielded a complex mixture, which could not be separated. The n.m.r. spectrum of the mixture showed that bromination was occurring at two methyl positions.

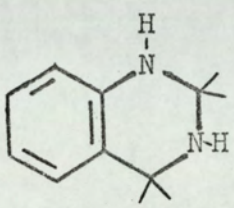
(iv) Reduction of pyrido[3,4-d]pyrimidin-4(3H)-ones.

Pyrimidines, quinazolines, pyridopyrimidines, pteridines and purines are all susceptible to nucleophilic attack at the 2-and 4-positions of the pyrimidine ring. Consequently many of these compounds yield di-and tetrahydro derivatives when treated with metal hydrides.[109,110] Fused pyrimidin-4(3H)-ones are also known to yield similar compounds,[111,112,113] for example the reduction of 3-methylquinazolin-4(3H)-one (77) with lithium aluminium hydride yields 1,2,3,4-tetrahydro-3-methylquinazoline (78) and a small amount of the 1,2-dihydro compound (79).[114]

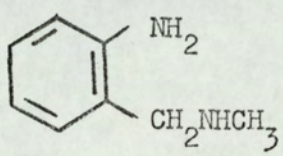


(77) (78) (79)

Reduction of quinazoline[115] with lithium aluminium hydride, for short periods, yields the expected tetrahydroquinazoline (80). When the reaction was carried out for longer periods, with an excess of reagent, a mixture was obtained consisting of the tetrahydro derivative (80) and o-methylaminomethylaniline (81).

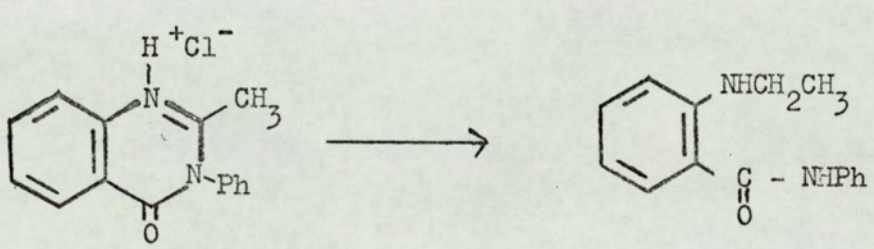


(80)



(81)

4-Chloro-2-phenylquinazoline yields analogous products on prolonged reduction with the same reagent. The ring-opened products, o-methylaminomethylaniline and o-benzylamino-methylaniline, result from the reductive cleavage of the 1,2-bond in these compounds. 2-Methyl-3-phenylquinazolin-4(3H)-one hydrochloride (82) on reaction with sodium borohydride in diethyleneglycol dimethylether also underwent reductive cleavage.[116] In this case however it was the 2,3-bond which was cleaved to give 2-ethylaminobenzanilide (83).

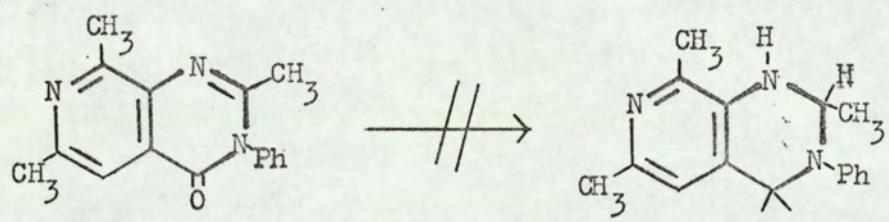


(82)

(83)

The reduction of a series of pyrido[3,4-d]pyrimidin-4(3H)-ones with lithium aluminium hydride was investigated.

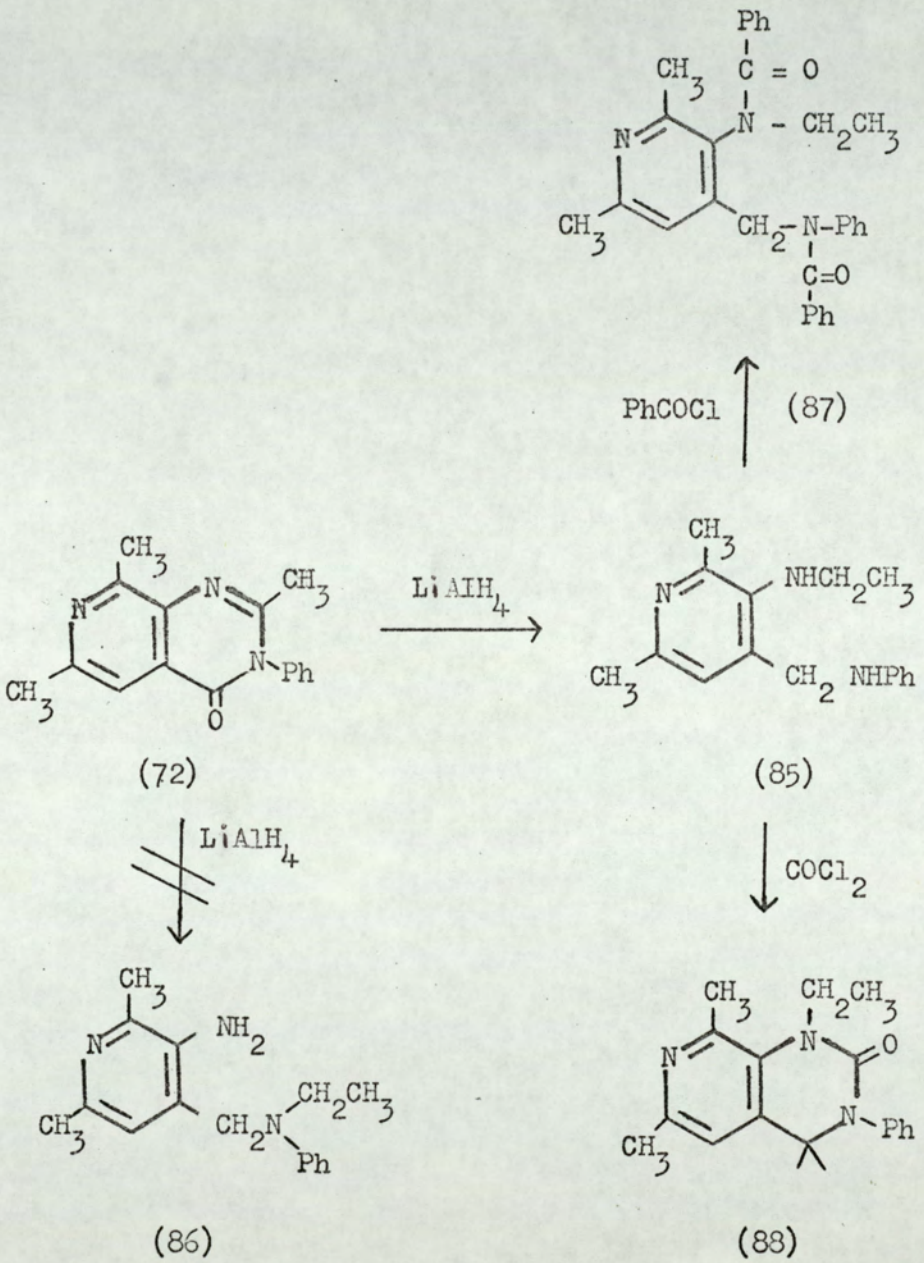
Treatment of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with an excess of lithium aluminium hydride in diethyl ether at room temperature for periods of one hour to seven days gave the same product in excellent yield. An infrared spectrum revealed the presence of N-H stretching vibrations at 3310, 3220 and 3090 $cm.^{-1}$, but the absorption at 1670 $cm.^{-1}$ due to C=O, which had been present in the starting material, was now absent. The n.m.r. spectrum showed the presence of an ethyl group in the molecule, hence excluding the possibility that the product was the tetrahydro derivative (84).



(72) (84)

An elemental analysis gave an empirical formula of $C_{10}H_{21}N_3$ and the mass spectrum a molecular weight of 255. These facts can only be rationalised by assuming that reductive cleavage has occurred at the 1,2- or 2,3-bond to give either 4-anilinomethyl-3-ethylamino-2,6-dimethyl-pyridine (85) or 3-amino-4-N-ethylanilinomethyl-2,6-dimethylpyridine (86). The formation of a dibenzoyl derivative (87) by reaction of the product with benzoyl chloride in pyridine was the first chemical evidence in favour of the di-secondary amine structure (85). If the product is 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85) it should be possible to regenerate the pyrimidine ring. Reaction with phosgene at

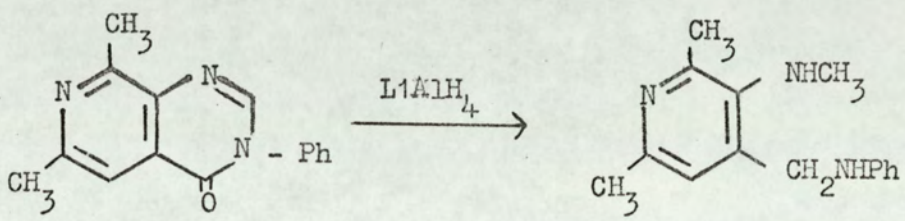
room temperature yielded 1-ethyl-3,4-dihydro-6,8-dimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-2(1H)-one (88), thus confirming this structure (85).



An n.m.r. spectrum of the pyrido[3,4-d]pyrimidin-2(1H)-one (88) showed the expected downfield shift of the ethyl group, 5.91 τ (2H, q, J=7.0 c./sec., 1-$\underline{CH_2}CH_3$) compared to the diaminopyridine (85), 7.02 τ (2H, q, J=7.0 c./sec., 3-NH$\underline{CH_2}CH_3$). The infrared spectrum

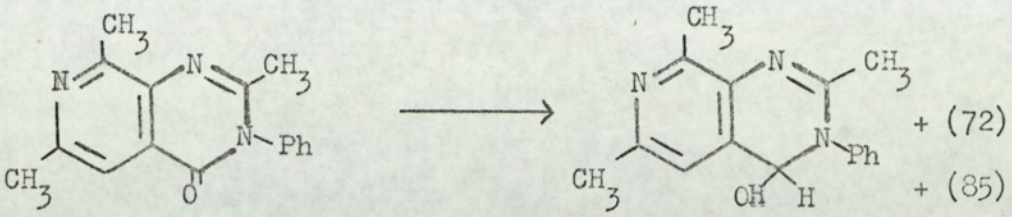
showed the presence of a carbonyl stretching vibration at 1650 cm.$^{-1}$ but absorptionsin the 3000-3300 cm.$^{-1}$ region, due to N-H stretchings, which had been present in the diaminopyridine (85) were now absent.

6,8-Dimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (38) underwent a similar reductive cleavage on reaction with lithium aluminium hydride to yield4-anilinomethyl-2,6-dimethyl-3-methyl-aminopyridine (89).



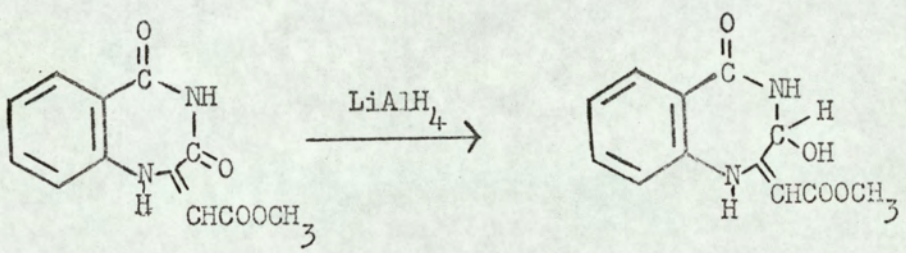
(38) (89)

The reduction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with 1.3 moles of lithium aluminium hydride at room temperature for half an hour gave a mixture of products. The main reaction products obtained were 4-anilino-methyl-3-ethylamino-2,6-dimethylpyridine (30%), starting material (35%) and another compound (25%) which was shown to be 3,4-dihydro-4-hydroxy-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (90). An infrared spectrum showed the absence of C=O and N-H absorptions, the peaks at 3400 and 1610 cm.$^{-1}$ were due to O-H and C=N stretching vibrations respectively. The 4-proton was visible at 4.31 τ in the n.m.r. spectrum. An accurate mass determination gave the molecular formula as $C_{16}H_{17}N_3O$, the initial fragmentation in the mass spectrum was loss of a hydroxyl radical.



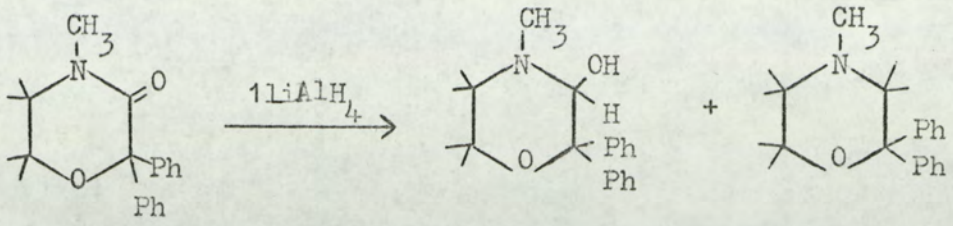
(72) (90)

The isolation of hydroxy derivatives from the reduction of amides with lithium aluminium hydride is unusual, although several instances have been reported in the literature. Reduction of 2-methoxycarbonylmethylene-2H,1,4-benzodiazepine-3,5(1H,4H)-dione (91) yields the hydroxy derivative (92).[117]



(91) (92)

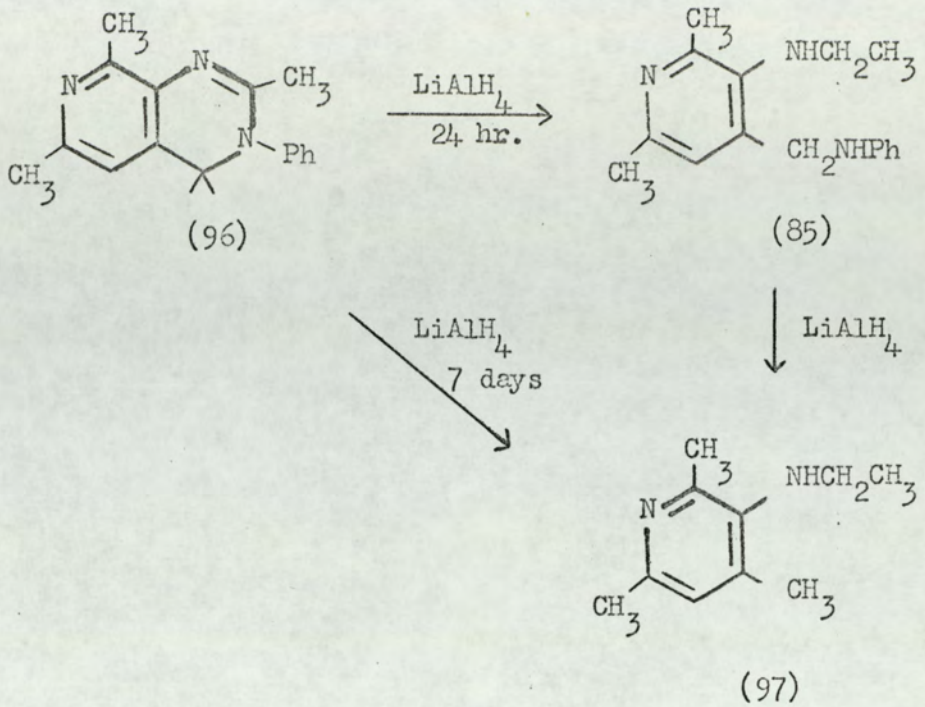
4-Methyl-2,2-diphenylmorpholin-3-one (93) on reduction with two moles. of lithium aluminium hydride yields a mixture of 3-hydroxy-4-methyl-2,2-diphenylmorpholine (94) and 4-methyl-2,2-diphenylmorpholine (95). Further reduction of the 3-hydroxymorpholine (94) gave the fully reduced product (95).[118]



(93) (94) (95)

Further reduction of 3,4-dihydro-4-hydroxy-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (90) with an excess of lithium aluminium hydride at room temperature gave 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85), the same product that was obtained on reduction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with an excess of lithium aluminium hydride.

3,4-Dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (96) was prepared by reduction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with granulated tin and hydrochloric acid. The n.m.r. spectrum of the 3,4-dihydro derivative (96) showed singlets for the 4-H protons (5.29 τ) and the 5-H proton (4.38 τ). The further reduction of this 3,4-dihydro derivative (96) with lithium aluminium hydride at room temperature also yielded 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85). The fact that the 3,4-dihydro derivative (96) and the 4-hydroxy analogue (90) both yielded the diaminopyridine (85) on reduction with lithium aluminium hydride suggests that these compounds may be intermediates in the reduction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) to the diaminopyridine (85).



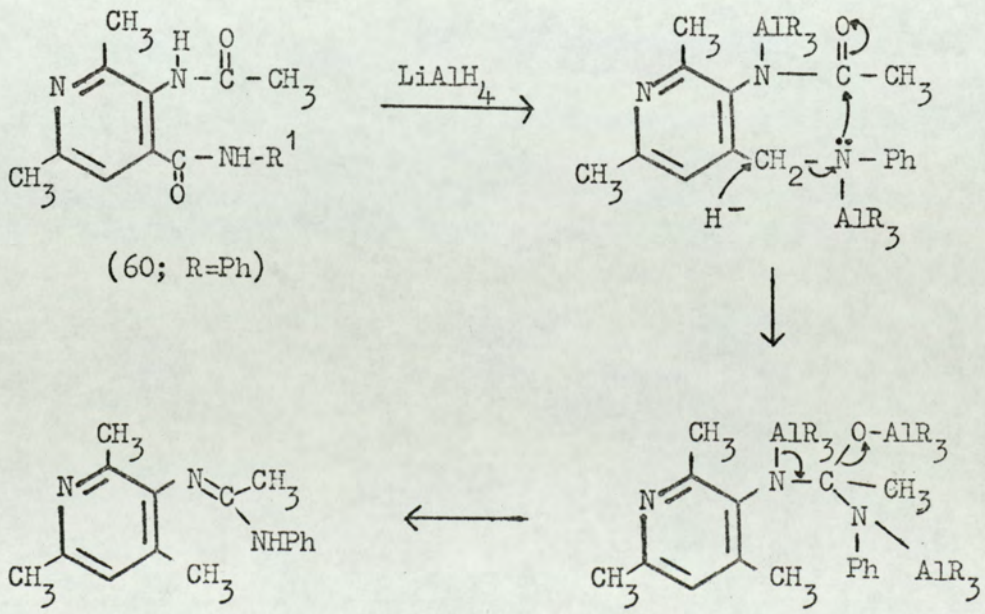
(97)

Prolonged reduction of 3,4-dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (96) with lithium aluminium hydride under reflux in diethyl ether for one week yielded 3-ethylamino-2,4,6-trimethylpyridine (97). The n.m.r. spectrum showed three singlet methyl groups, the highest at 7.81 τ due to the 4-methyl group, which is in accordance with the spectrum of 2,4,6-trimethylpyridine.[119] 3-Ethylamino-2,4,6-trimethylpyridine presumably results from reductive cleavage of the 4-anilinomethyl group in the diaminopyridine (85). This view was supported by the prolonged reduction of 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine with lithium aluminium hydride under reflux in diethyl ether. The n.m.r. spectrum of the reaction product revealed the presence of the trimethylpyridine (97) (25%), the remaining material was unchanged diaminopyridine (85).

As a final proof of the structure of the diaminopyridine (85), obtained by the reductive cleavage of 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72), an independent synthesis was attempted. Reduction of 3-acetamido-2,6-dimethyl-N-phenyl-

pyridine-4-carboxamide (60; R=Ph) with lithium aluminium hydride under reflux in diethyl ether for seven days did not give the required product. An elemental analysis gave an empirical formula of $C_{16}H_{19}N_3$ and the mass spectrum a molecular weight of 253. The product appeared to be N-2,4,6-trimethylpyrid—3-yl-N^1-phenyl-acetamidine (98), an infrared spectrum showed absorptions at 3300 and 1650 $cm.^{-1}$ due to N-H and C=N stretching vibrations respectively. The n.m.r. spectrum revealed the presence of four methyl groups in the molecule; the three pyridyl methyl groups at 7.57, 7.64 and 7.92, and a higher methyl singlet at 8.22 τ. The presence of a phenyl group in the molecule was confirmed by the downfield region of the spectrum. The structure (98) was supported by the fragmentation pathway in the mass spectrum.

The most likely mechanism seems to be that postulated below; initial reduction of the 4-amido carbonyl, followed by intramolecular attack of the 4-amino nitrogen atom on the acetamido carbonyl with concerted attack of a hydride ion.



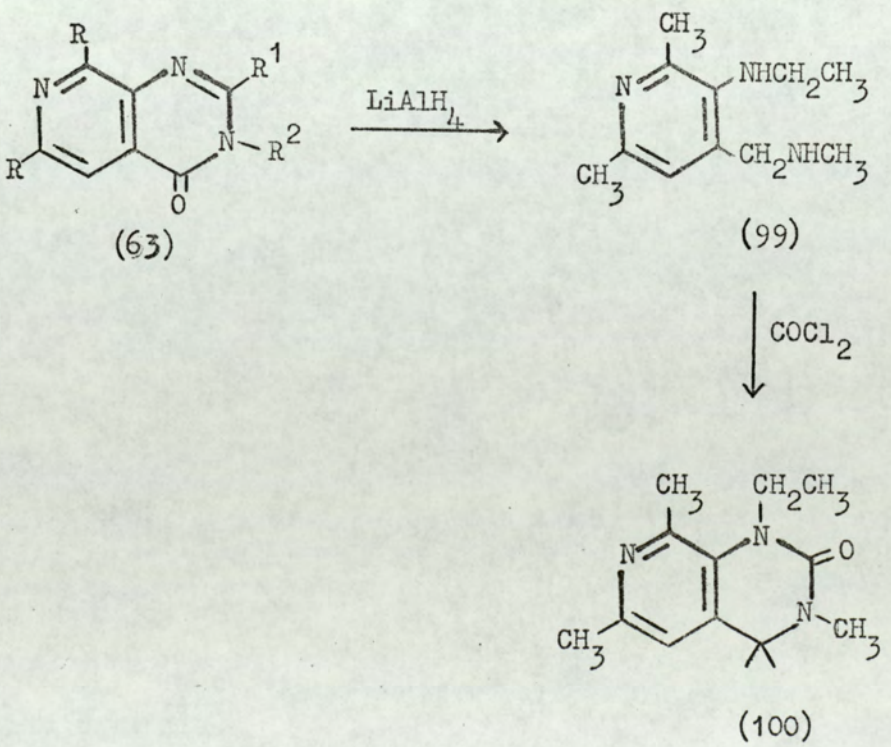
(60; R=Ph)

(98)

The attempted reduction of 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (72) with sodium borohydride under reflux in diethyl ether, methanol and diethyleneglycol dimethyl ether at 100° only resulted in the isolation of starting material.

Certain 3-alkyl-substituted pyrido[3,4-d]pyrimidin-4(3H)-ones also underwent a reductive cleavage with lithium aluminium hydride, but far more drastic conditions were required.

Thus 3-ethylamino-2,6-dimethyl-4-methylaminomethyl pyridine (99) was obtained from the reduction of 2,3,6,8-tetramethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (63; $R=R^1=R^2=CH_3$) with lithium aluminium hydride under reflux in diethyl ether for six days. The structure of the product was confirmed by reaction with phosgene, which yielded 1-ethyl-3,4-dihydro-3,6,8-trimethyl-pyrido[3,4-d]pyrimidin-2(1H)-one (100).

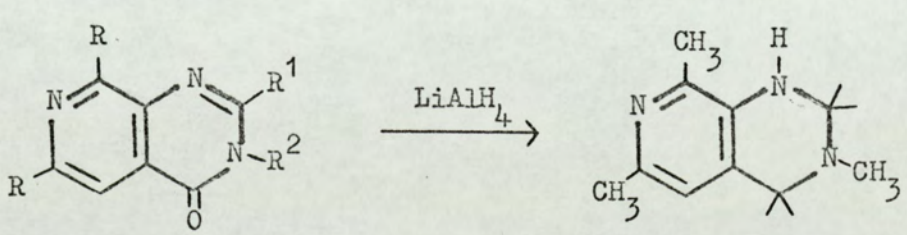


(63) (99) (100)

A comparison of the n.m.r. spectra of the diaminopyridine (99) and the pyridopyrimidinone (100) showed the expected downfield shift of the ethyl group, from 6.98 τ (3-NHCH$_2$CH$_3$) in the former to 5.95 τ (1-CH$_2$CH$_3$) in the latter case.

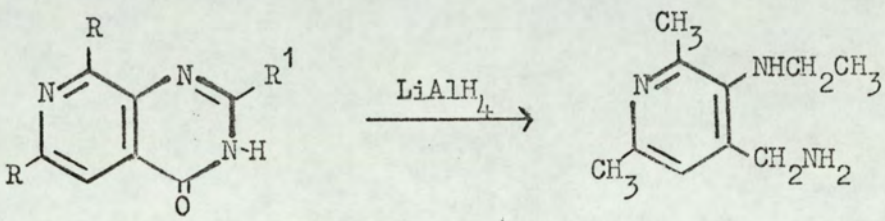
Reduction of the tetramethylpyridopyrimidine (63 ; R=R^1=R^2=CH$_3$) with lithium aluminium hydride for periods of one to three days at room temperature gave complex mixtures. The only compounds isolated were starting material and the ring-opened final product (99).

3,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^2=CH$_3$, R^1=H) on reduction with lithium aluminium hydride in diethyl ether at room temperature yielded 1,2,3,4-tetrahydro-3,6,8-trimethylpyrido[3,4-d]pyrimidine (101). An infrared spectrum showed the N-H stretching vibration at 3200 cm.$^{-1}$, but the absorption at 1680 cm.$^{-1}$ due to C=O, which had been present in the starting material was now absent. The n.m.r. spectrum revealed the expected upfield shift in the position of the 5-H, from 2.43 τ in the trimethylpyridopyrimidine (63; R=R^2=CH$_3$, R^1=H) to 3.5 τ in the tetrahydro derivative (101). The two methylene groups were observed as singlets at 6.17 and 6.48 τ.



(63) (101)

Pyrido[3,4-d]pyrimidin-4(3H)-ones with no substituent at the 3-position also underwent specific ring-opening reactions. 2,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=CH_3$) yielded 4-aminomethyl-3-ethylamino-2,6-dimethylpyridine (102) on reduction with lithium aluminium hydride under reflux in diethyl ether for six days.

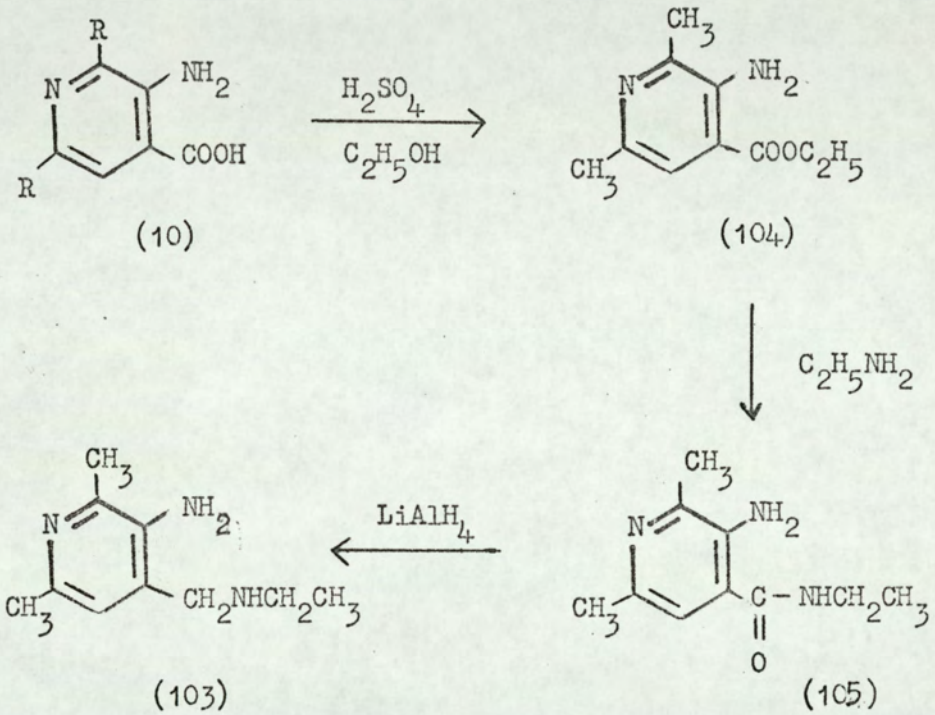


(11) (102)

The n.m.r. spectrum of the product revealed the presence of the ethyl group at 7.0 τ(2H,q,J=7.0 c./sec., 3-NHCH$_2$CH$_3$), 8.81τ(3H,t,J=7.0 c./sec., 3-NHCH$_2$CH$_3$). The ethyl group in the spectrum of the 4-anilinomethyl analogue (85) showed absorptions at 7.02 τ(2H,q,J=7.0 c./sec.,3-NHCH$_2$CH$_3$) and 8.86(3H ,t,J=7.0 c./sec., 3-NHCH$_2$CH$_3$). If reductive cleavage had occurred at the 1,2-bond and not the 2,3-bond, the product would have been 3-amino-4-ethylaminomethyl-2,6-dimethylpyridine (103). The ethyl group in the n.m.r. spectrum of this compound would be expected at a higher field, because of its removal from the deshielding influence of the aromatic ring.

To confirm the structure of the product 3-amino-4-ethylaminomethyl-2,6-dimethylpyridine (103) was prepared by an independent synthesis. Ethyl-3-amino-2,6-dimethylpyridine-4-carboxylate (104)[120] was prepared by esterification of 3-amino-2,6-dimethylpyridine-4-carboxylic acid (10; $R=CH_3$). The reaction required vigorous conditions, because of the steric hindrance of the ortho amino group to the incoming alcohol

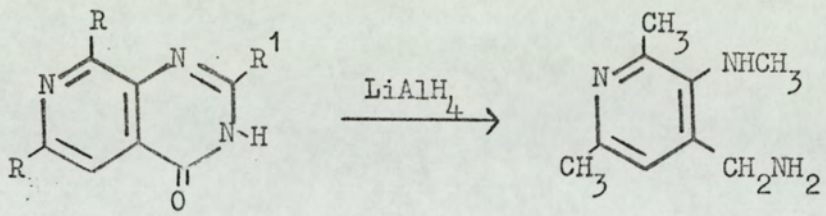
molecule[121] and also because of its electronic effect. The ester (104) was then treated with anhydrous ethylamine to yield ethyl-3-amino-2,6-dimethylpyridine-4-carboxamide (105), which on reduction with lithium aluminium hydride under reflux in diethyl ether for seven days gave 3-amino-4-ethylaminomethyl-2,6-dimethylpyridine (103).



The n.m.r. spectrum of the ethylaminomethylpyridine (103) showed the ethyl group in this compound at 7.53τ(2H,q,J=7.0 c./sec., 4-$CH_2NHCH_2CH_3$) and 8.98τ(3H,t,J=7.0 c./sec., 4-$CH_2NHCH_2CH_3$), thus confirming that the product obtained from the reduction of 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one is not 3-amino-4-ethylaminomethyl-2,6-dimethyl-pyridine (103).

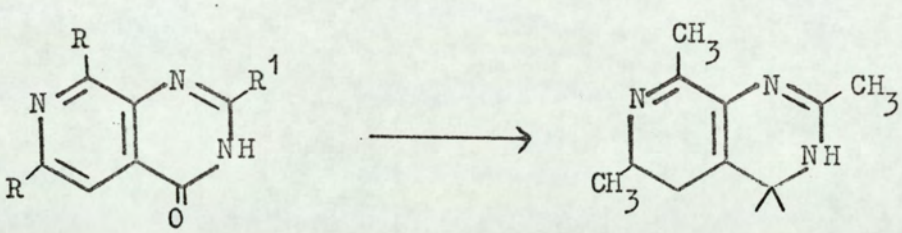
6,8-Dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=CH_3, R^1=H) also underwent reductive cleavage of the 2,3-bond on reaction with lithium aluminium hydride under reflux in diethyl ether for seven days,

to yield 4-aminomethyl-2,6-dimethyl-3-methylaminopyridine (106)



(11) (106)

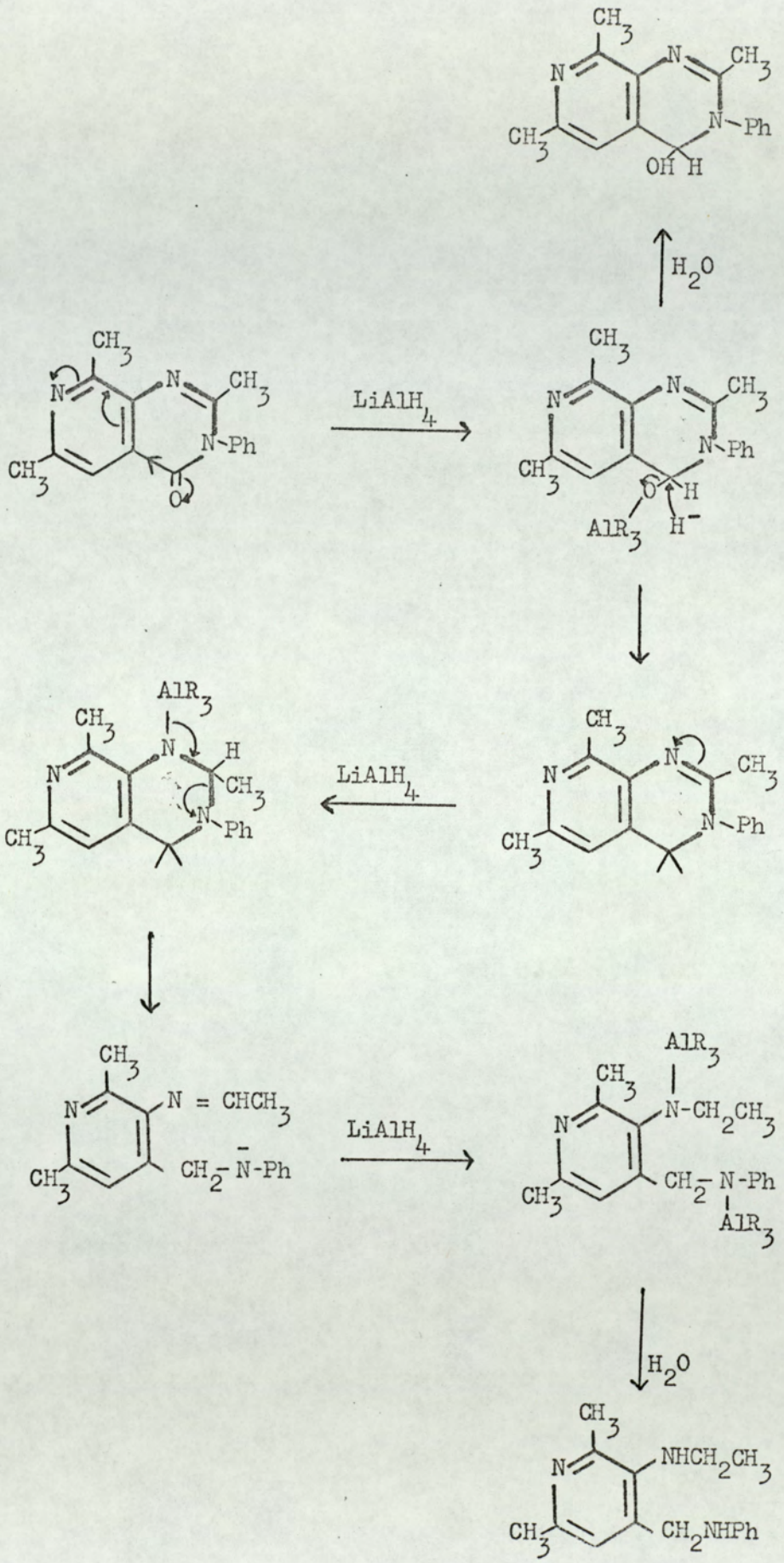
The reduction of 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=CH_3$) with lithium aluminium hydride at room temperature for twenty hours gave a low yield of 3,4-dihydro-2,6,8-trimethylpyrido[3,4-d]pyrimidine (107). Starting material was also isolated from the reaction mixture.



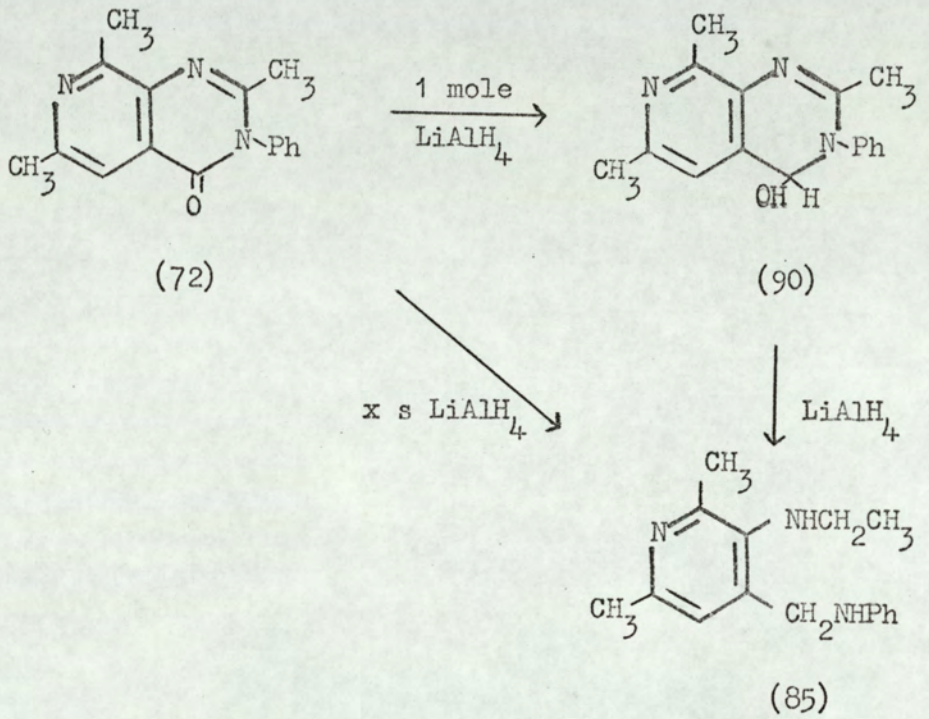
(11) (107)

An infrared spectrum of the dihydro derivative (107) showed absorptions at 3360 and 1620 $cm.^{-1}$ due to N-H and C=N stretching vibrations. The n.m.r. spectrum, accurate mass determination and mass spectrum confirmed the structure of the product.

Pyrido[3,4-d]pyrimidin-4(3H)-ones have two sites which are susceptible to hydride attack, the endocyclic C=N and the exocyclic C=O bonds. If initial attack of a hydride ion occurs at the exocyclic C=O bond in 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72), then ring-opening could occur by the following mechanism;


CH3
N
CH3
N
Ph
CH3
OH H
H2O
LiAlH4
O
AlR3
H
LiAlH4
N = CHCH3
CH2 N-Ph
N-CH2CH3
NHCH2CH3
CH2NHPh

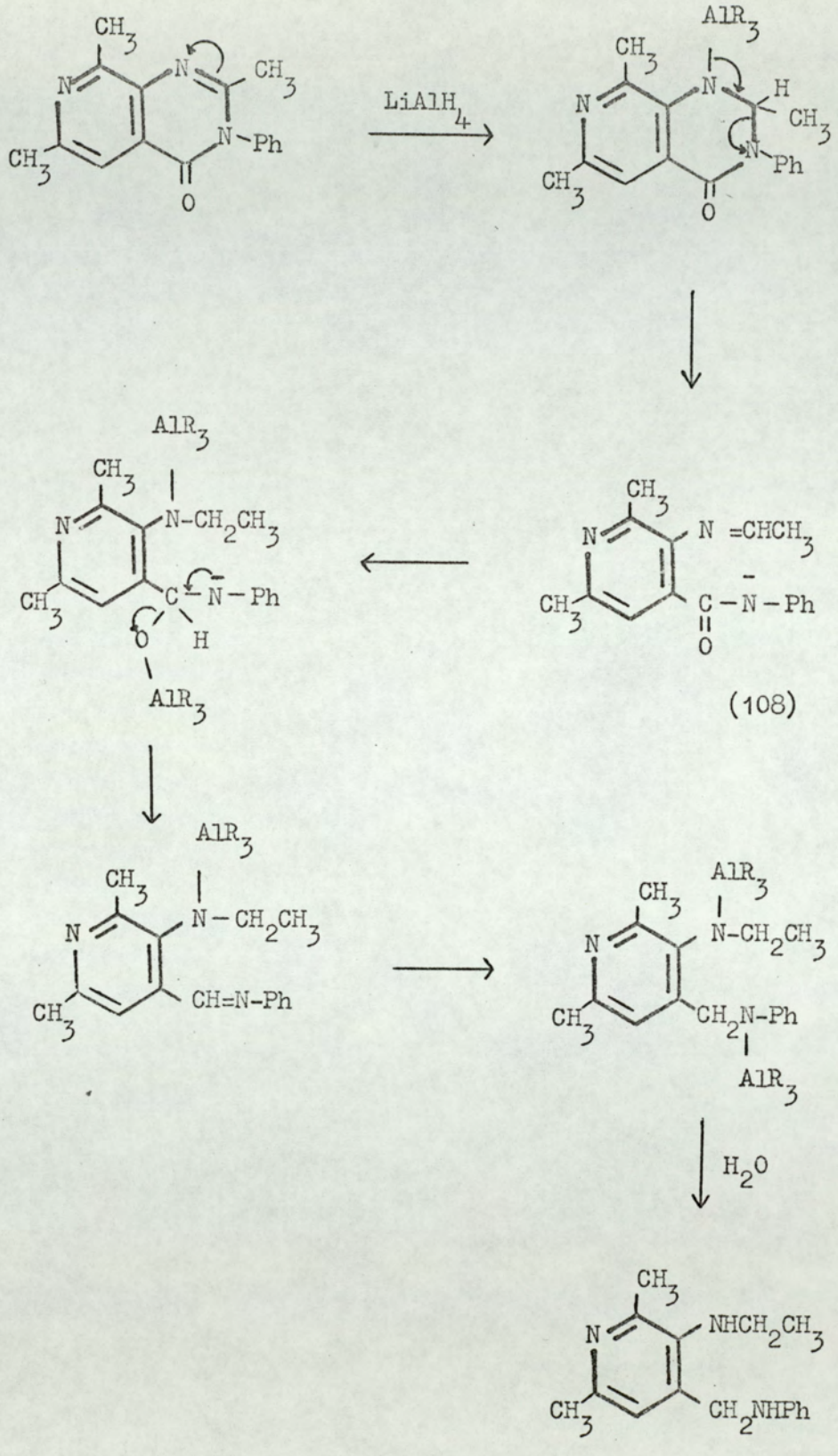
This type of mechanism is supported by the fact that 3,4-dihydro-4-hydroxy-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (90), isolated from the controlled reduction of 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72), also yielded the diaminopyridine (85) on further reduction with lithium aluminium hydride.



(72) (90) (85)

Further evidence is supplied by the fact that 3,4- dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (96), a proposed intermediate in the reaction scheme gave 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85) on reduction with lithium aluminium hydride under mild conditions.

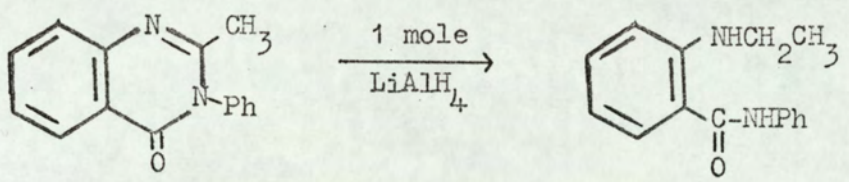
An alternative scheme involves initial reduction of the 1,2-bond of 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one;



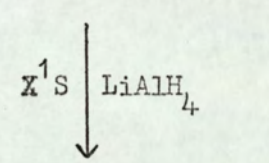
(108)

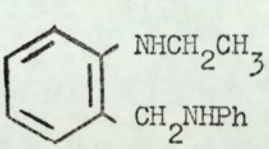
The delocalisation of the charge in the anion (108) over both the phenyl group and the amide carbonyl group would be expected to be a major factor influencing the operation of this type of cleavage.

The reduction of 2-methyl-3-phenylquinazolin-4(3H)-one (109) appears to proceed by the above mechanism. Reaction with an excess of lithium aluminium hydride yielded 2-anilinomethyl-N-ethylaniline (110), while 2-ethylaminobenzanilide (83) a proposed intermediate, if cleavage occurs by the above type of mechanism, was isolated from the reduction with one mole. of lithium aluminium hydride.[122]



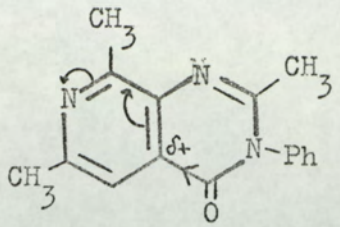
(109) (83)



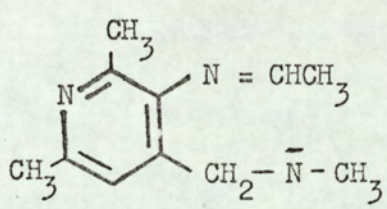


(110)

The evidence points to the initial reduction of 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72) occurring at the exocyclic C=O bond. The change in the initial reaction site from the endocyclic C=N to the exocyclic C=O bond, on going from the quinazolinone (109) to the pyridopyrimidine (72), may be explained by the electron withdrawing effect of the nitrogen atom in the pyridine ring, which further activates the 4-carbon atom to nucleophilic attack.



Presumably the reductive cleavage of 2,3,6,8-tetramethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=R^2=CH_3) goes by a similar mechanism to that postulated for the 3-phenyl analogue (72). The anion (111) in this case is less favoured because of the absence of the stabilising phenyl substituent. This fact is reflected in the much more vigorous conditions required for ring-opening.



(111)

The isolation of the 3,4-dihydro derivative (107) from the controlled reduction of 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=CH_3) indicates that initial reduction also occurs at the exocyclic C=O bond in this compound. The vigorous reaction conditions required for reductive cleavage in compounds with no substituents at the 3-nitrogen atom is due at least in part to the insolubility of the starting materials.

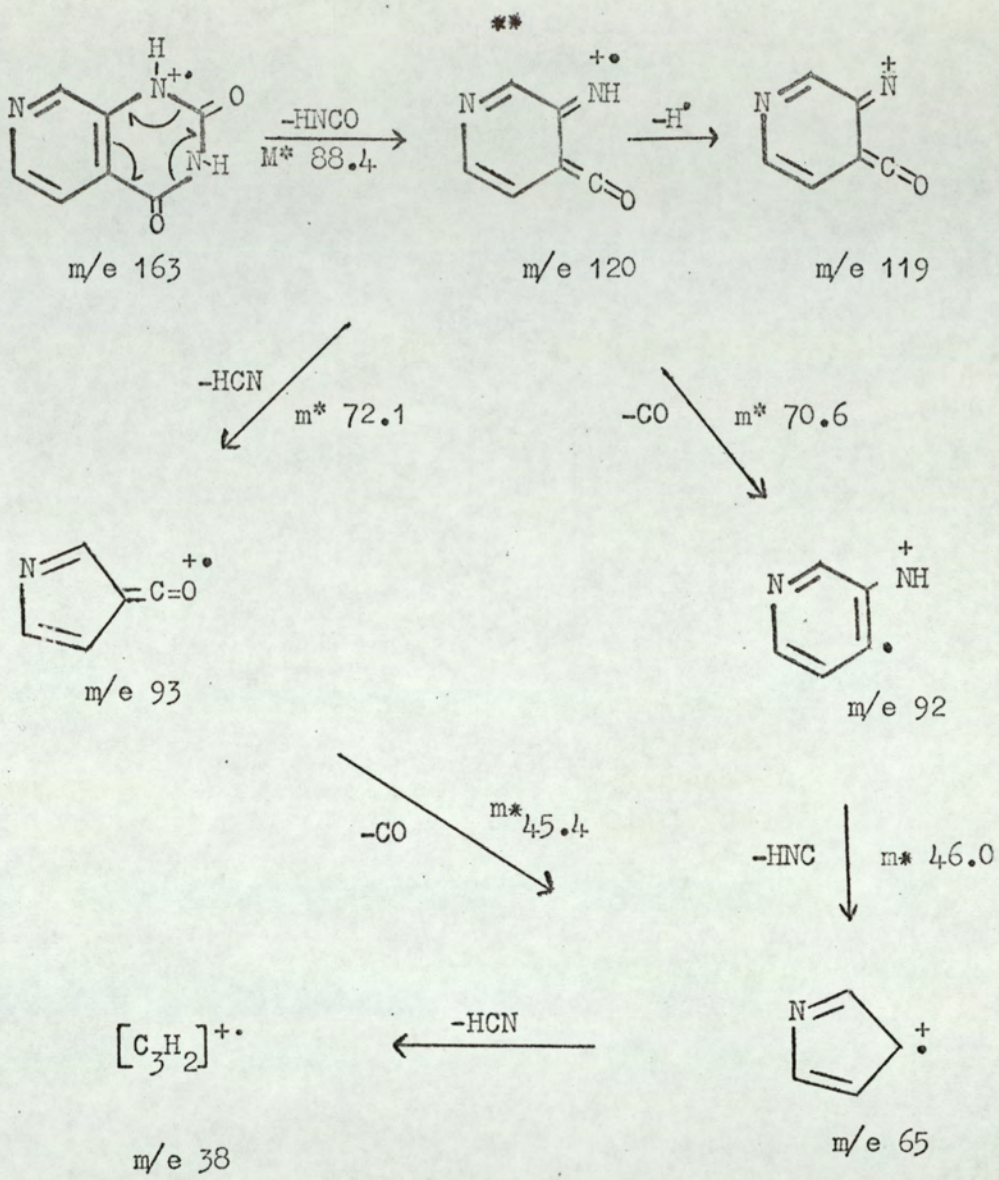
In all the pyrido[3,4-d]pyrimidin-4(3H)-ones which underwent reductive cleavage it was the 2,3-bond which was broken. The 3-substituent appears to control the ease of reductive cleavage.

MASS SPECTRA

(i) Pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones

The initial fragmentation of quinazoline-2,4(1H,3H)-dione[123] and pteridine-2,4(1H,3H)-dione[124] is the loss of HNCO from the molecular ion. By analogy with these compounds pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8 ; R^1=R^2=H) may be expected to show a similar initial fragmentation, and this was found to be the case (SchemeI). This loss of HNCO has been suggested to occur by a retro-Diels-Alder rearrangement for other fused pyrimidines.[125]

Scheme I



** The structure shown for this, and subsequent fragmentation ions, represent only one of several possible forms.

The ion at $^{m}/_{e}$ 120, formed by elimination of HNCO from the molecular ion, further fragments by loss of $H^{\bullet}$, HNC and CO to give the ions at $^{m}/_{e}$ 119 (3%), $^{m}/_{e}$ 93(33%) and $^{m}/_{e}$ 92 (12%). The $^{m}/_{e}$ 93 and $^{m}/_{e}$ 92 ions then eliminate CO and HCN respectively to form the same ion at $^{m}/_{e}$ 65 (13%). All the major fragmentations are substantiated by metastable peaks. An ion present in low concentration (4%) at $^{m}/_{e}$ 147 indicates an oxygen loss, a similar loss is quoted for quinazoline-2, 4(1H,3H)-dione.[123]

6,8-Dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=CH_3$, $R^3=R^4=H$) shows a fragmentation pathway very similar to that of pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione, except that the ion formed at $^{m}/_{e}$ 120 (32%) by loss of CO from $(M-HNCO)^+$ is now the major fragmentation ion. The intensities of the ions for loss of $H^{\bullet}$ and HCN are less than 3%. The $(M-HNCO-CO)^+$ ion then eliminates either HCN or CH_3CN to give the ions at $^{m}/_{e}$ 93(8%) and $^{m}/_{e}$ 79 (32%).

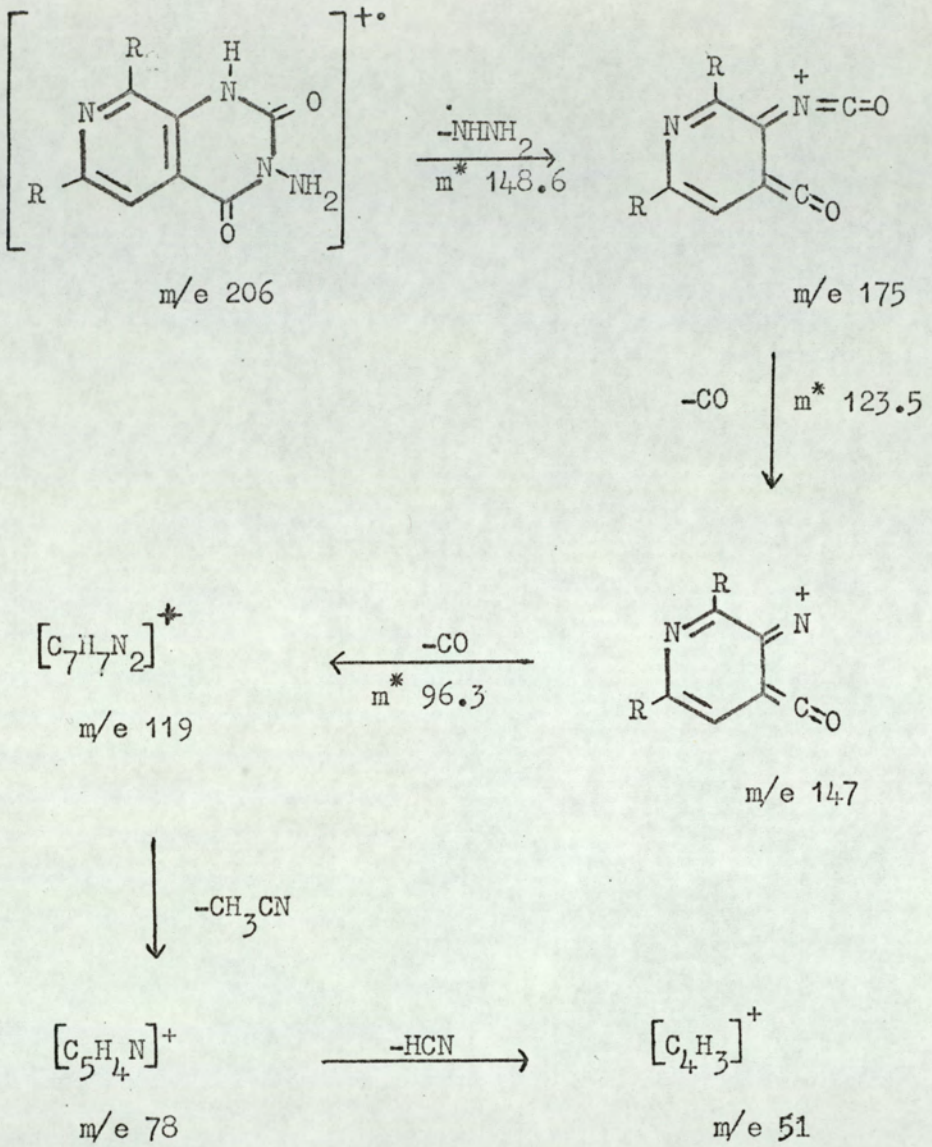
The mass spectrum of 3,6,8-trimethyl-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^4=CH_3$, $R^3=H$) clearly shows that it is the 3-N atom which is involved in the retro-Diels-Alder rearrangement. CH_3NCO is eliminated from the molecular ion to form the fragmentation ion at $^{m}/_{e}$ 148 (63%), without any appreciable loss of HNCO. Further fragmentation then occurs in a similar manner to that of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione.

Compounds with a methyl substituent at the 1-position showed alternative fragmentation pathways, the initial loss of CH_3NCO now being less important. 1,3-Dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=H$, $R^3=R^4=CH_3$) fragments by initial elimination of CH_3NCO and CO to give the ions at $^{m}/_{e}$ 134(8%) and $^{m}/_{e}$ 163 (5%) respectively. The $(M-CH_3NCO)^+$ ion then eliminates a molecule of CO to give the most abundant fragmentation ion (73%) in the spectrum. The introduction of

four methyl groups produced considerable changes in the mode of decomposition of the molecule under electron impact. 1,3,6,8-Tetramethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^3=R^4=CH_3$) shows $(M-H)^+$ and $(M-CH_3NCO)^+$ fragmentation ions of low abundance (4%). The principle initial decomposition is now the loss of a methyl radical to give the ion at $^m/_e$ 204(22%). Expulsion of CH_3NCO then yields the ion at $^m/_e$ 147 (23%). The loss of HCN from the $(M-CH_3NCO)^+$ ion in this tetramethyl derivative suggests that a rearrangement, possibly involving the incorporation of the 1-methyl group in a ring expansion process, occurs with this ion.

In all the pyridopyrimidine-diones previously mentioned the molecular ion was the base peak, however when the compounds have a 3-amino substituent they become less stable to electron impact. 3-Aminopyrido[3,4-d]pyrimidine-2,4(1H3H)-dione (71; $R^1=R^2=H$) and the 6,8-dimethyl analogue (71; $R^1=R^2=CH_3$) both fragment in a similar manner (Scheme II). The molecular ions eliminate $NHNH_2$ to give the ions at $^m/_e$ 147 (99%) and $^m/_e$ 175 (100%), which in each case is followed by two successive losses of a molecule of CO.

Scheme II

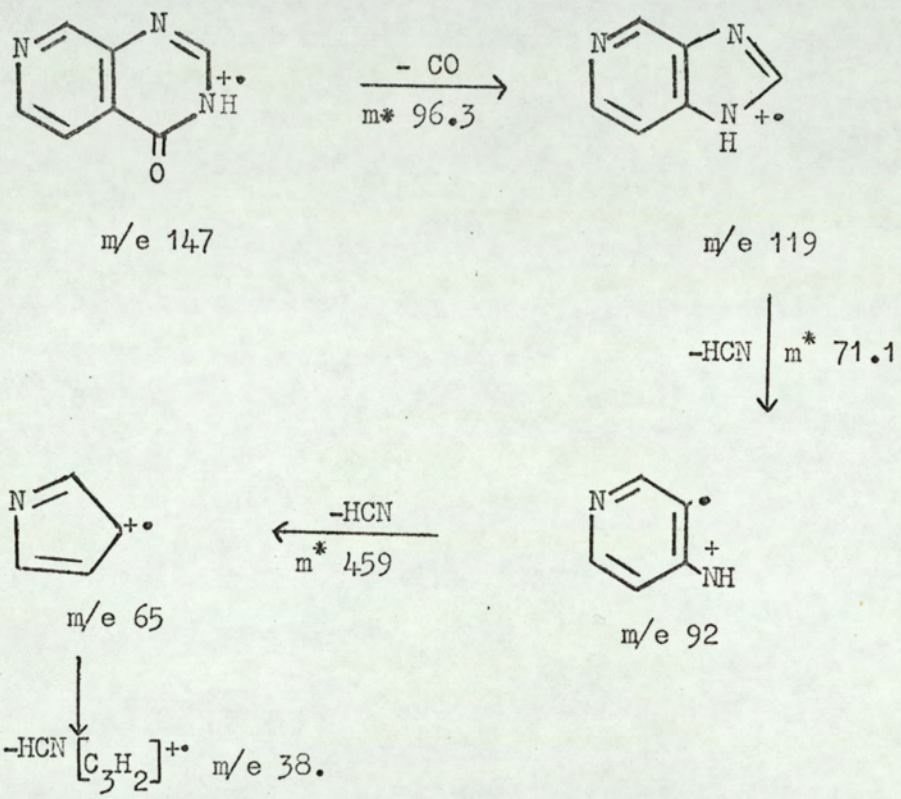


(ii) Pyrido[3,4-d]pyrimidin-4(3H)-ones.

The mass spectra of pyridones,[126,127] quinolones,[128] quinazolinones[123] and pteridinones[124] have all been reported in the literature. The mass spectrum of pyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=H) shows a strong molecular ion peak and a principal degradation pathway of an initial loss of CO, followed by three successive losses of one molecule of HCN (scheme III). Similar

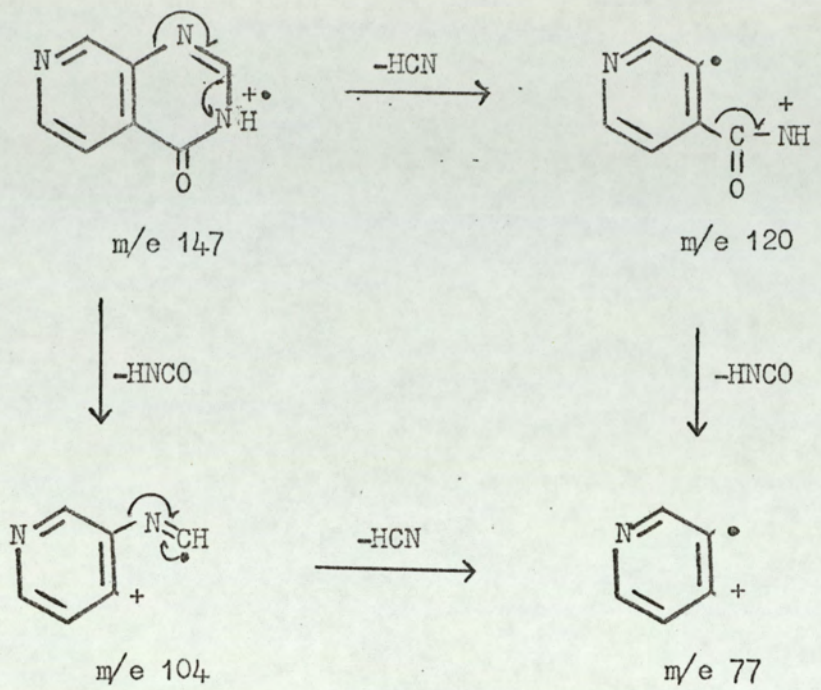
fragmentation pathways have been reported for quinazolin-4(3H)-one[123] and pteridin-4(3H)-one.[124]

Scheme III



Three other fragmentation pathways are also observed, initiated by loss of $H^{\bullet}$, HCN and HNCO (scheme IV) to give the ions at $^{m}/_{e}$ 146 (8%), $^{m}/_{e}$ 120 (6%) and $^{m}/_{e}$ 104(9%). The initial loss of HNCO has been observed in the spectra of quinazolin-4(3H)-one[123] and pteridin-4(3H)-one[124].

Scheme IV



A study of the mass spectra of 3-methyl- (63; R=R^1=H, R^2=CH_3), 6,8-dimethyl- (11; R=CH_3, R^1=H), 2,6,8-trimethyl- (11; R=R^1=CH_3) and 3,6,8-trimethylpyrido [3,4-d]pyrimidin-4(3H)-one (63; R=R^2=CH_3, R^1=H) showed that an increased number of methyl substituents resulted in

(a) an increased resistance to electron induced fragmentation,

(b) a decreased tendency for the molecular ion to lose CO, and

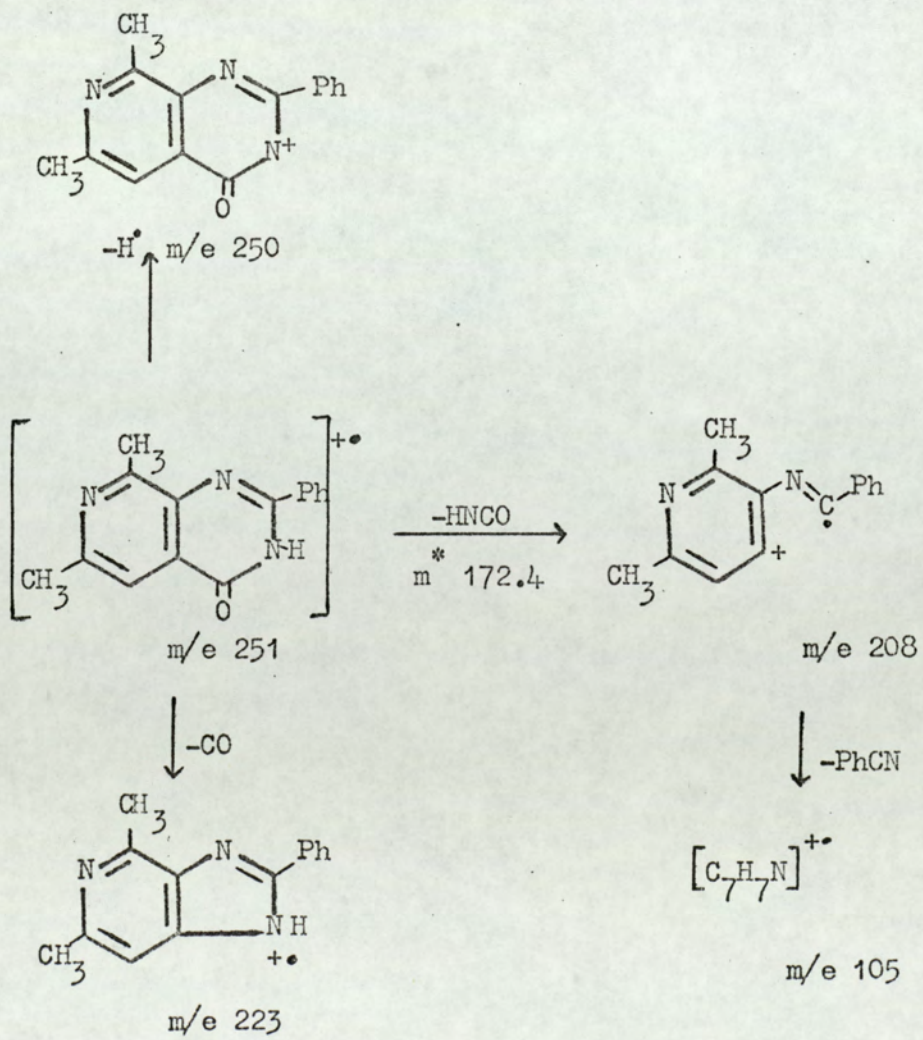
(c) an increased proportion of the ion current carried by the $(M-H)^+$ ion.

Compound	$(M-CO)^+$	$(M-H)^+$
63; R=R^1=H, R^2=CH_3	22%	13%
11; R=CH_3, R^1=H	5%	5%
11; R=R^1=CH_3	4%	7%
6 ; R=R^2=CH_3, R^1=H	2%	8%

$CH_3^{\bullet}$ and CH_3CN loss from the molecular ion becomes significant (3-4%) for the trimethyl substituted compounds (63; $R=R^2=CH_3$, $R^1=H$ and 11; $R^1=R=CH_3$). Introduction of another methyl further enhances loss of a methyl radical from the molecular ion. The main initial fragmentation from 2,3,6,8-tetramethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; $R=R^1=R^2=CH_3$) is loss of a methyl radical to give the ion at m/e 188 (15%), which is the major fragmentation ion in the spectrum.

6,8-Dimethyl-2-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; $R=CH_3$, $R^1=H$) shows a similar fragmentation pattern to the corresponding 2-methyl derivative, fragmentation being initiated by loss of $H^{\bullet}$, CO and HNCO (scheme V).

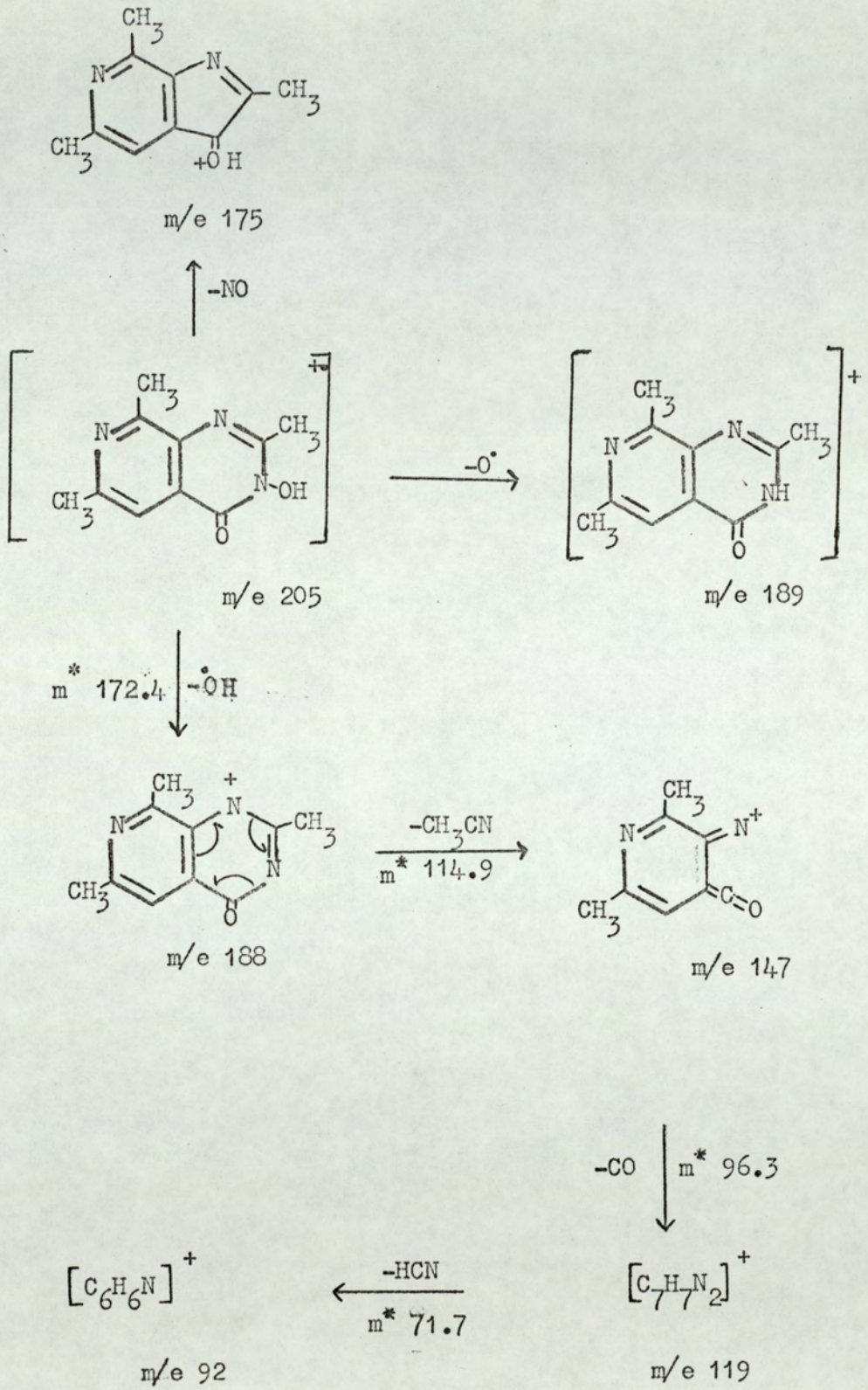
Scheme V



The pyrido[3,4-d]pyrimidin-4(3H)-ones and their methylated derivatives are more stable to electron impact than the corresponding pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones.

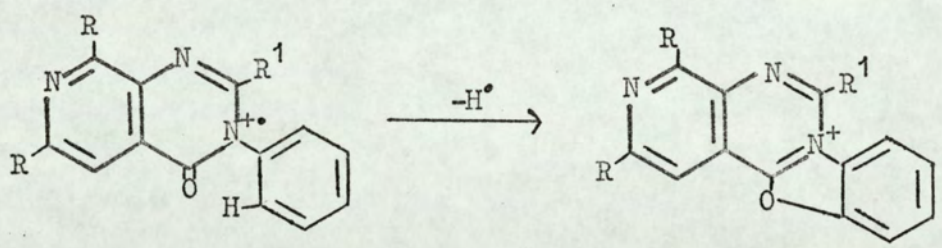
The fact that substituents at the 2- and 3-positions of the pyrimidine ring affects the fragmentation pathways has already been observed in the methylated pyrido[3,4-d]pyrimidin-4(3H)-ones. 3-Hydroxy-2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (59) shows three fragmentation pathways (scheme VI.) The base peak in the spectrum is the ion at $^{m}/_{e}$ 147, formed by successive losses of $^{\bullet}OH$ and CH_3CN from the molecular ion; both these fragmentations being substantiated by metastable peaks. In the reported mass spectrum of 3-hydroxy-2-methyl quinazolin-4(3H)-one[129] one of the initial fragmentations is elimination of O=C=NOH. This loss in the present spectrum could also account for the ion at $^{m}/_{e}$ 147, although there is no metastable peak to support this fragmentation. The molecular ion also fragments by loss of an oxygen atom to give the ion at $^{m}/_{e}$ 189 (45%), which has the same composition as the molecular ion obtained from 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one; a similar subsequent fragmentation pathway is observed in both cases. Cyclic hydroxamic acids can also be considered as o-hydroxy-N-oxides and it is probably from this structure that $O^{\bullet}$ loss occurs. A minor fragmentation pathway is initiated by loss of NO. There is only one report in the literature[129] of a compound of this type fragmenting by expulsion of NO, although some aromatic nitro compounds and oximes are known to fragment by loss of nitric oxide from the molecular ion.[125]

Scheme VI


m/e 175
-NO
m/e 205
-O·
m/e 189
m* 172.4
-·OH
m/e 188
-CH3CN
m* 114.9
m/e 147
-CO
m* 96.3
m/e 119
-HCN
m* 71.7
m/e 92

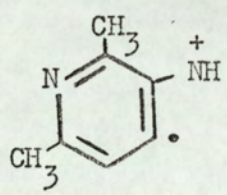
The main fragmentation pathway of3-amino-2,6,8-trimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (58; R=NH_2) is initiated by loss of HCO to give the ion at $^{m}/_{e}$ 175 (44%). This ion then ejects a molecule of nitrogen to yield the ion at $^{m}/_{e}$ 106 (10%). A minor fragmentation pathway is apparently initiated by loss of NH to give the ion at $^{m}/_{e}$ 189 (6%), which is the same ion that was obtained by loss of O from the 3-hydroxypyridopyrimidine (59). The stability of this ion is demonstrated by the fact that the largest fragmentation ion in the spectrum of 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one is the $(M-H)^+$ ion $^{m}/_{e}$ 188 (8%).

The most interesting feature of a series of 3-phenyl substituted pyrido[3,4-d]pyrimidin-4(3H)-ones was the initial loss of a hydrogen atom, presumably from the ortho position of the phenyl group, to form a five membered ring.

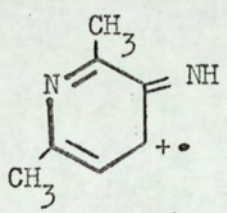


This type of rearrangement has also been observed in the mass spectra of N-phenyl-2-pyridones, in which the $H^{\bullet}$ loss was shown to occur from the ortho position of the phenyl group by deuterium labelling and substitution by methyl groups. The base peak in the spectrum 6,8-dimethyl-2,3-diphenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3, R^1=Ph) was the ion at $^{m}/_{e}$ 326 formed by loss of $H^{\bullet}$ from the molecular ion.

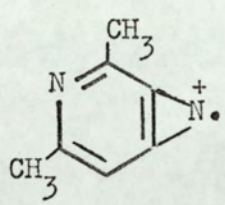
The pyrido[3,4-d]pyrimidin-4(3H)-ones and pyrido[3,4-d]pyrimidine-2,4(1H,3H)-diones all fragment *via* the pyrimidine ring. In all the spectra there is a strong peak for a pyridinium ion, the composition of the ion depending on the fragmentation pathway but the exact nature of these pyridinium ions is uncertain. One of the main fragmentation ions observed in these spectra is the ion at $^{m}/_{e}$ 120, which may be written as (a) or could also be represented by the structures (b), (c) and (d).



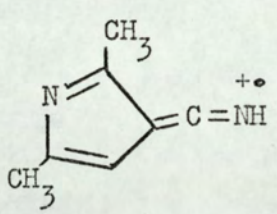
(a)



(b)



(c)



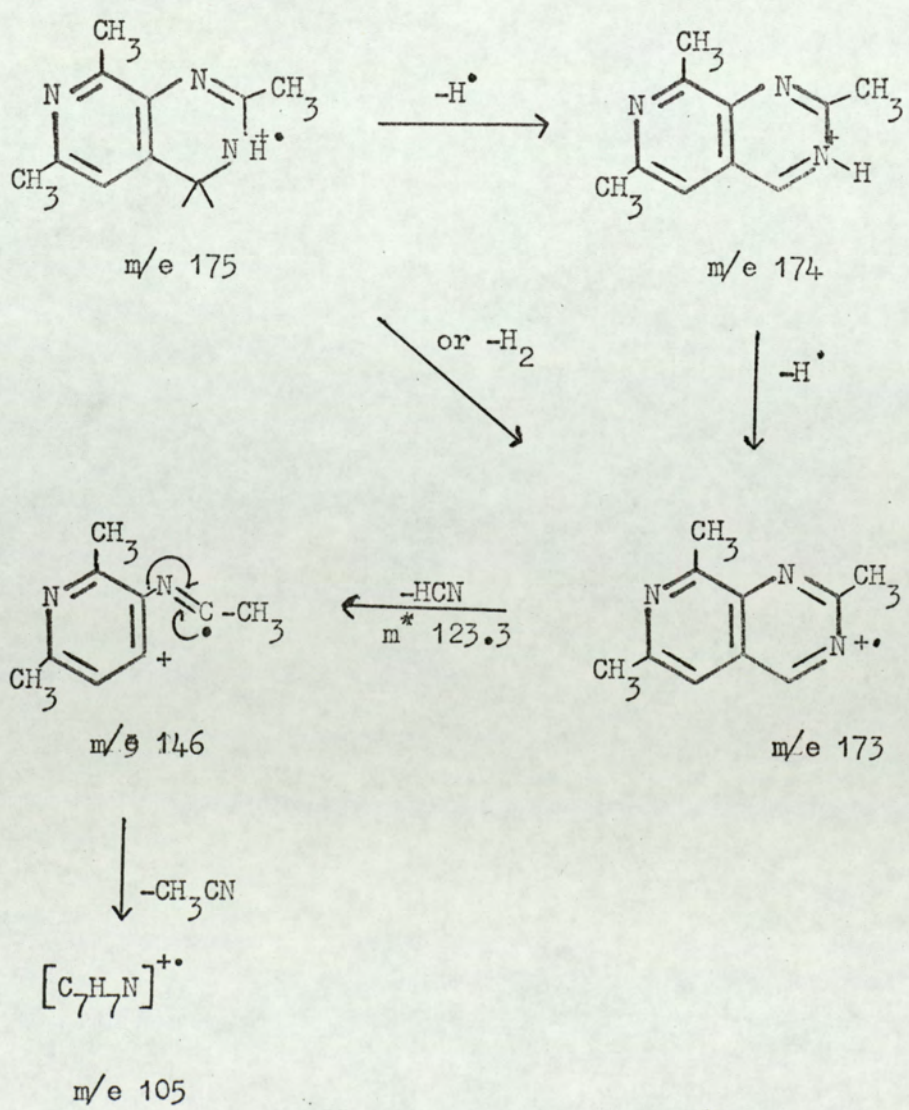
(d)

It is unlikely that this ion exists as a di-azatropylium ion, because of its odd electron nature. Djerassi[130] has shown, by ^{13}C labelling, that the odd electron ion, which can be written for the $C_6H_7N^{+\bullet}$ ion derived from aniline, does not exist as an azatrophlium ion. All the ions which exist as an azatropylium ion have an even electron structure, thus the ion $^{m}/_{e}$ 119 $(C_7H_7N_2)^+$, which is also observed in many of these spectra could conceivably exist as a di-azatrophlium ion, although there is no evidence to suggest this type of structure.

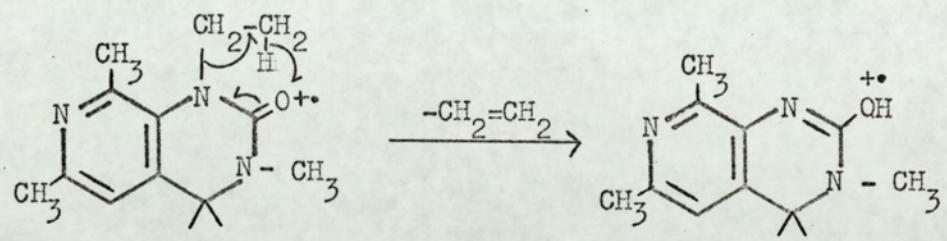
(iii) 3,4-Dihydropyrido[3,4-d]pyrimidines.

The dihydropyrido[3,4-d]pyrimidines are less stable to electron impact than the pyrido[3,4-d]pyrimidin-4(3H)-ones and -pyrimidine-2,4(1H,3H)-diones. The base peak in the spectrum of 3,4-dihydro-2,6,8-trimethylpyrido[3,4-d]pyrimidine (107) is the ion at $\frac{m}{e}$ 173, resulting from either the loss of two hydrogen atoms or a molecule of hydrogen from the molecular ion. The $\frac{m}{e}$ 173 ion then looses HCN, followed by CH_3CN as would be expected for a fused pyrimidine system.[125] (scheme VII). A minor fragmentation pathway is also observed, initiated by loss of a methyl radical.

Scheme VII

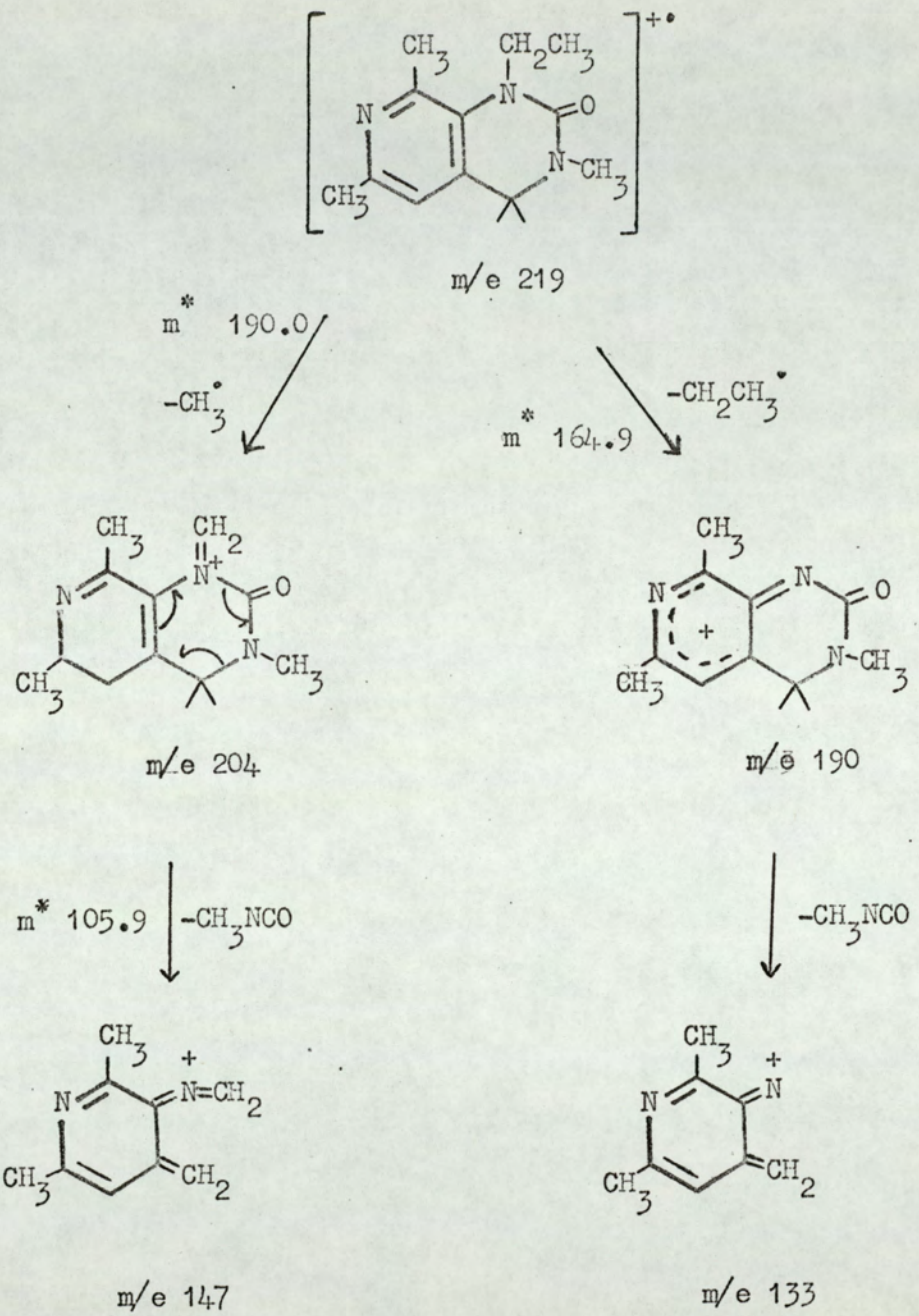


The spectrum of 1-ethyl-3,4-dihydro-3,6,8-trimethyl-pyrido[3,4-d]pyrimidin-2(1H)-one (100) also shows an initial hydrogen loss, however in this case the $(M-H)^+$ ion is only 7% of the base peak. The main fragmentation pathways are initiated by elimination of an ethyl and a methyl radical (scheme VIII). The elimination of the methyl radical must occur by an α-cleavage of the 1-ethyl group, because of the subsequent loss of CH_3NCO, which is substantiated by a metastable peak. The base peak in the spectrum is the ion at $^{m}/_{e}$ 147. A minor fragmentation pathway is initiated by loss of 28 mass units, which could be due to elimination of a molecule of CO or more likely ejection of a molecule of ethylene by a McLafferty rearrangement. The mass spectrum of 3,4-dihydro-1-methyl-3-phenylquinazolin-2(1H)one[130] does not show an initial loss of 28 mass units, thus supporting the view that ethylene is eliminated in the case of the ethyl derivative.

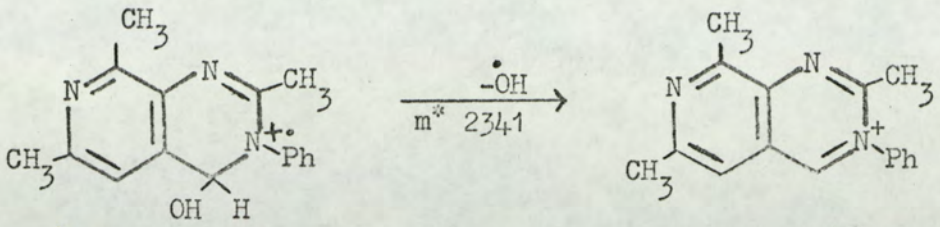


m/e 219 m/e 191

Scheme VIII



The base peak in the spectrum of 3,4-dihydro-4-hydroxy-2,6,8-trimethylpyrido[3,4-d]pyrimidine (90) is the ion at $^{m}/_{e}$ 250, formed by loss of $\cdot OH$ from the molecular ion. This $^{m}/_{e}$ 250 ion is extremely stable, further fragmentation ions being of low intensity.



m/e 267 m/e 250

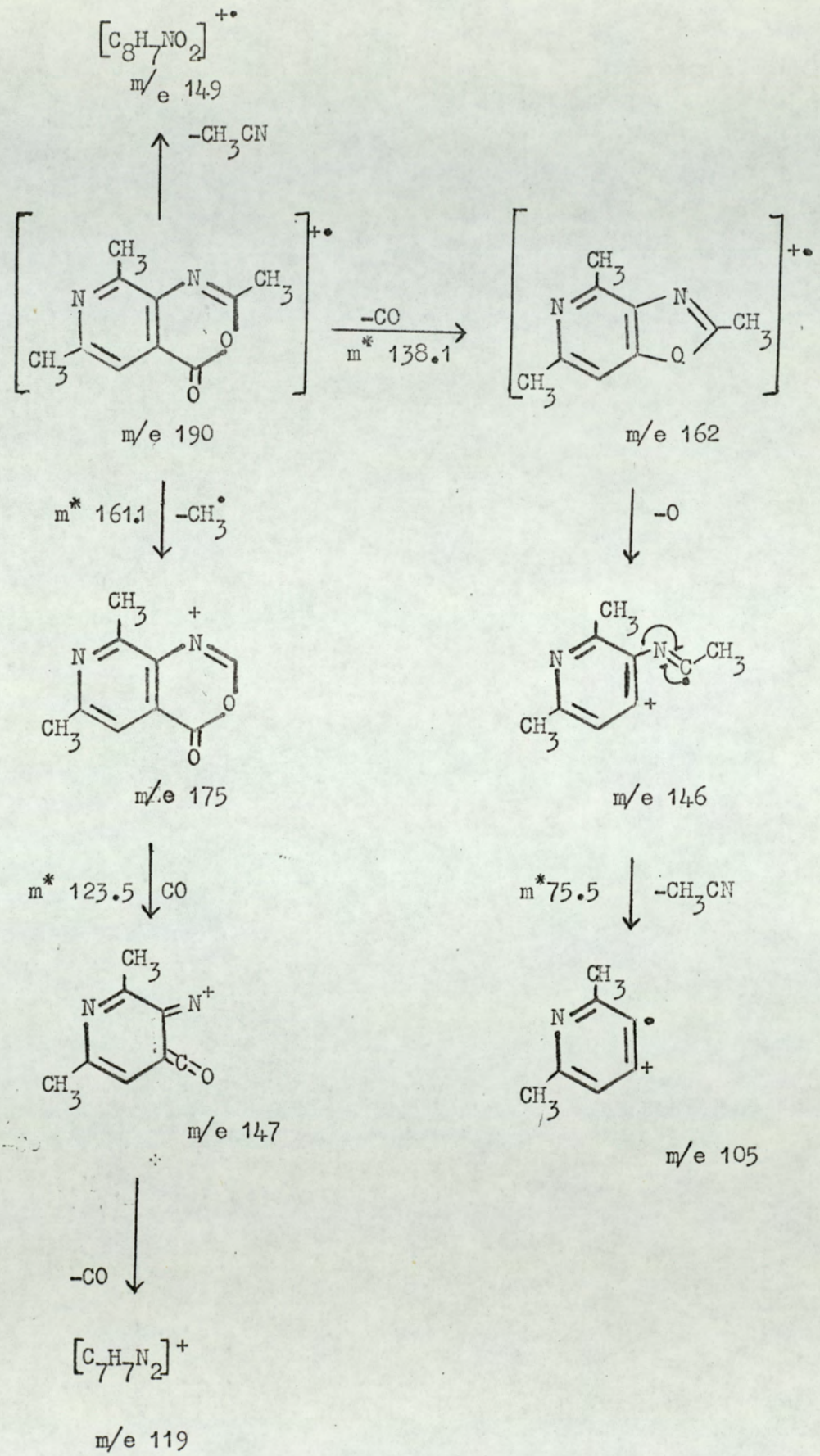
(iv) Pyrido[3,4-d][1,3]oxazines.

The mass spectra of three pyrido[3,4-d][1,3]oxazin-4-ones showed that they were more susceptible to fragmentation by electron impact than the corresponding pyridopyrimidines, but with the two 6,8-dimethyl compounds (45 and 46; R=CH_3) the molecular ion was still the base peak. The main fragmentation pathway of 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (45) is initiated by loss of CO. The next step appears to be an oxygen loss, although this is not substantiated by a metastable peak. The ion at $\frac{m}{e}$ 146 (14%) then eliminates a molecule of CH_3CN. Two minor fragmentation pathways are also observed, initiated by loss of a methyl radical and CH_3CN (scheme IX).

The two 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones (46; R=CH_3 or H) fragment by initial loss of CO and CO_2. The carbon monoxide loss being followed by elimination of the $(PhCO)^+$ ion to yield the main fragmentation ion (87%) in the spectrum of 6,8-dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=CH_3), and the base peak in spectrum of 2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H). The initial loss of CO from both these compounds is substantiated by the appropriate metastable peaks.

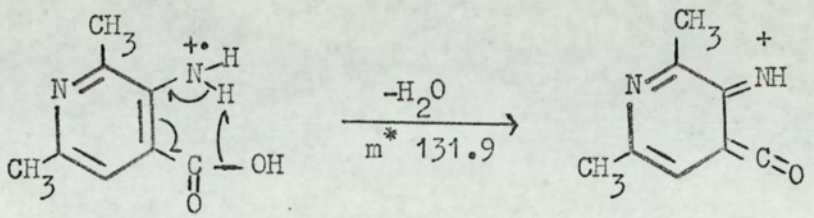
2,6,8-Trimethyl-4,4-diphenylpyrido[3,4-d][1,3]oxazine (73) fragments by initial loss of a molecule of ketene, followed by a hydrogen atom to give the base peak in the spectrum at $\frac{m}{e}$ 185. The molecular ion also exhibits two minor fragmentation pathways, initiated by loss of a methyl radical and a molecule of methyl isocyanate.

Scheme IX


[C8H7NO2]+•
m/e 149
-CH3CN
m/e 190
-CO
m* 138.1
m/e 162
m* 161.1
-CH3•
-O
m/e 175
m/e 146
m* 123.5
CO
m* 75.5
-CH3CN
m/e 147
m/e 105
-CO
[C7H7N2]+
m/e 119

(v) Pyridine Derivatives

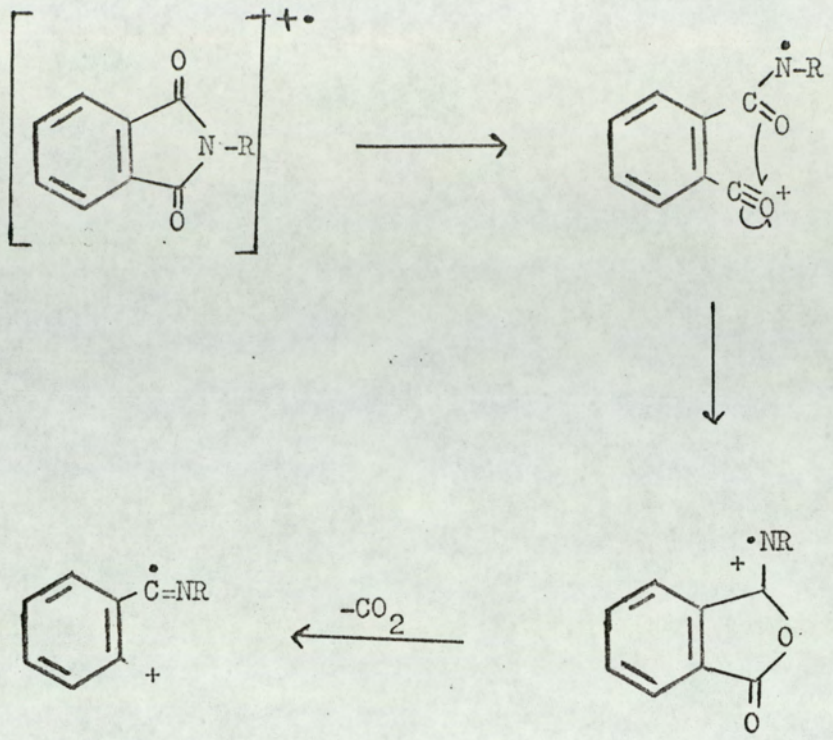
3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3) fragments by initial loss of water from the molecular ion.



m/e 166 m/e 148

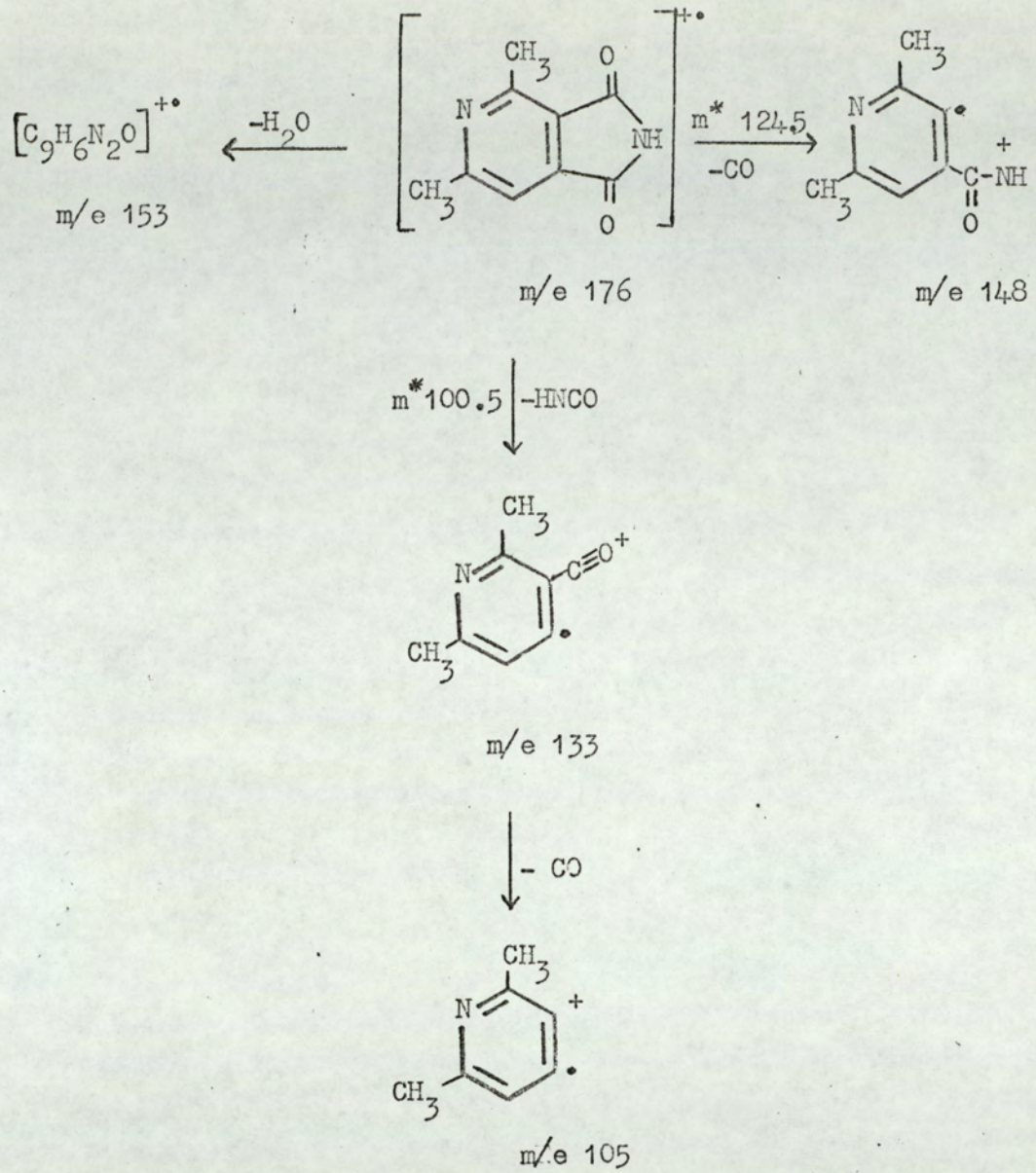
This water loss is a common feature of aromatic acids with a hydrogen bearing ortho substituent[131,132]; salicylic acid fragments in a similar manner. The ion formed at $^{m}/_{e}$ 148 (53%), by loss of water, then eliminates a molecule of carbon monoxide to give the ion at $^{m}/_{e}$ 120 (36%), which fragments in the usual manner.

The main fragmentation pathway in the spectrum of 2,6-dimethyl-cinchomeronimide (32; R=CH_3) is initiated by loss of HNCO to yield the ion $^{m}/_{e}$ 133(60%). Two minor fragmentation processes are also observed, water and carbon monoxide being eliminated from the molecular ion (scheme X). The loss of water must involve a rearrangement, if this elimination is correct. The mass spectra of N-methyl- and N-phenylphthalimide have been reported in the literature.[133] The main fragmentation from the molecular ions is loss of carbon dioxide, which is stated to occur by the rearrangement shown.



In the present spectrum any loss of carbon dioxide is negligible.

Scheme X

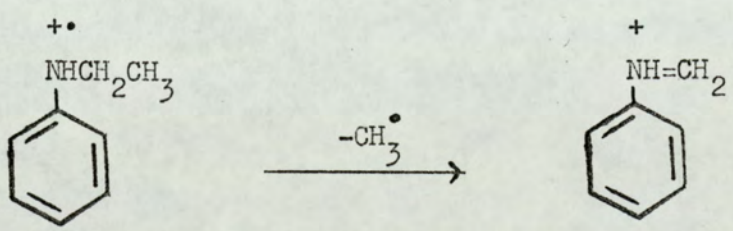


The mass spectrum of two pyridine-3,4-dicarboxamides were studied, both compounds were unstable to electron impact, in neither case was the molecular ion the base peak. The molecular ion in the spectrum of 3-benzamido-2,6-dimethyl-N-(3^1-nitrophenyl)pyridine-4-carboxamide (61; R=CH_3, R^1=3^1-NO_2Ph) is not visible, the highest significant peak in the spectrum being the ion at $^m/_e$ 253, due to loss

of $^{\bullet}NHPhNO_2$ from the molecular ion. This loss of $^{\bullet}NHPhNO_2$ from the molecular ion is substantiated by a metastable peak at 164.1. There is a small peak at $^{m}/_{e}$ 371, which is probably due to cyclisation of the diamide, by elimination of water, before ionisation. The main fragmentation pathway of 3-benzamido-6,8-dimethyl-pyridine-4-carboxamide (61; R=CH_3. R^1=H) is initiated by loss of ammonia, followed by a molecule of carbon monoxide.

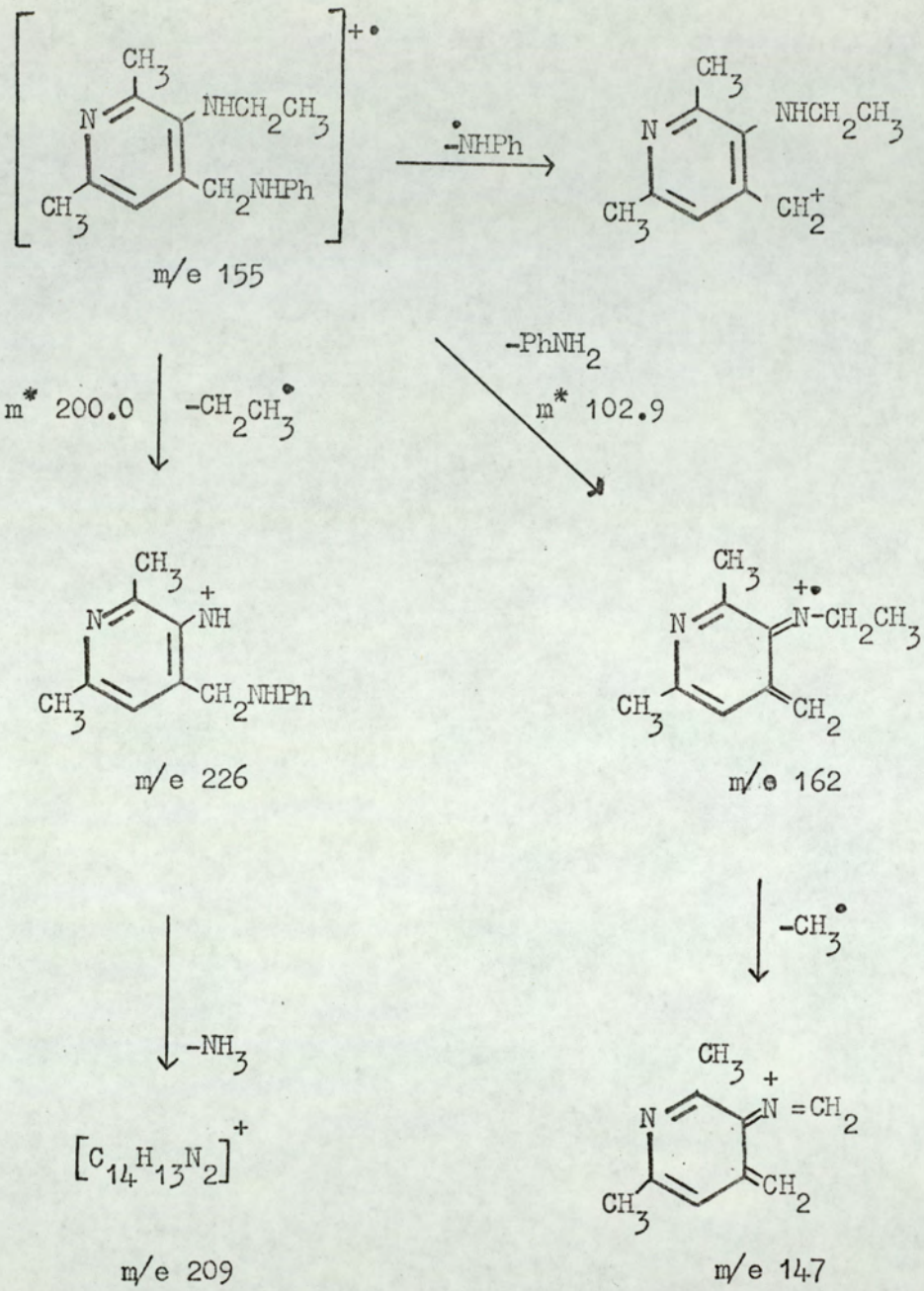
In the three 4-anilinomethyl-3-alkylaminopyridines studied the base peaks were not the molecular ions. 4-Anilinomethyl-3-ethyl-amino-2,6-dimethylpyridine (85) fragments by loss of an ethyl radical to give the base peak in the spectrum at $^{m}/_{e}$ 226. Another major fragmentation pathway is initiated by loss of aniline, followed by elimination of a methyl radical to give the ion at $^{m}/_{e}$ 147 (93%) (scheme XI). There is also a large peak in the spectrum at $^{m}/_{e}$ 163, which appears to be due to a $PhNH^{\bullet}$ loss, although this is not substantiated by a metastable peak. The 8-styryl derivative (75) fragments in a similar manner, by initial loss of an ethyl radical and aniline.

There is only a very small (< 2%) methyl loss from these compounds, although this is the preferred initial fragmentation from N-ethylaniline.[134]



4-Anilinomethyl-2,6-dimethyl-3-methylaminopyridine (89) fragments in a similar manner, the initial fragmentation ions now being formed by loss of $CH_3^{\bullet}$, $PhNH_2$ and $PhNH^{\bullet}$ from the molecular ion.

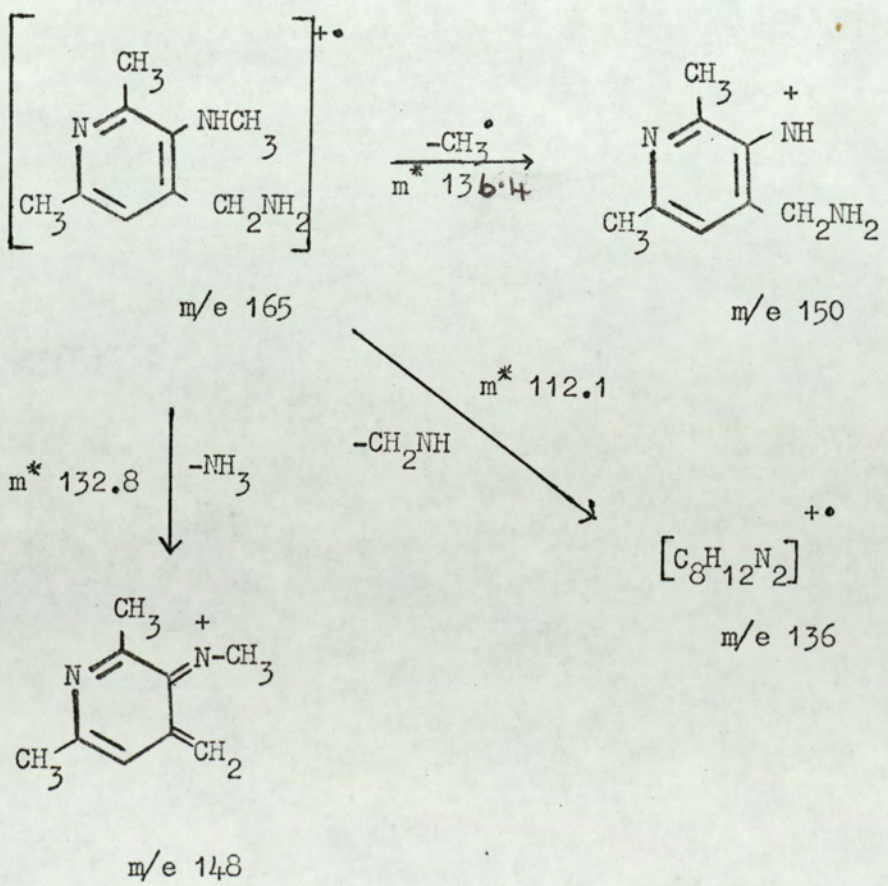
Scheme XI



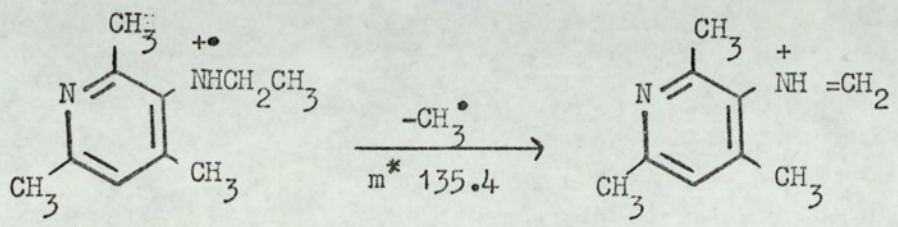
4-Aminomethyl-3-ethylamino-2,6-dimethylpyridine (102) and 4-aminomethyl-2,6-dimethyl-3-methylaminopyridine (106) fragment in a similar manner to the corresponding 4-anilinomethyl compounds. Replacement of the phenyl group by a hydrogen results in the loss of ammonia instead of aniline. The other main fragmentation pathway is

still initiated by loss of an ethyl or methyl radical. 4-Amino-methyl-3-ethylamino-2,6-dimethylpyridine also exhibits the expected methyl loss from the ethylamino substituent,[125] although it is only a minor fragmentation ion (16%). The base peak in this spectrum is the ion at $^{m}/_{e}$ 147, formed by loss of ammonia and a methyl radical from the molecular ion. The base peak in the spectrum of 4-aminomethyl-2,6-dimethyl-3-methylaminopyridine (106) is the molecular ion, which besides the fragmentation already noted loses 29 mass units from the molecular ion to give the ion at $^{m}/_{e}$ 136 (50%), (scheme XII). This loss makes it uncertain whether the corresponding loss of 29 mass units from the ethylamino compound (102) is due to elimination of an ethyl radical.

Scheme XII



3-Ethylamino-2,4,6-trimethylpyridine (97) fragments by initial loss of a methyl radical, in an analogous manner to N-ethylaniline[134], to give the base peak in the spectrum at $^{m}/_{e}$ 149.

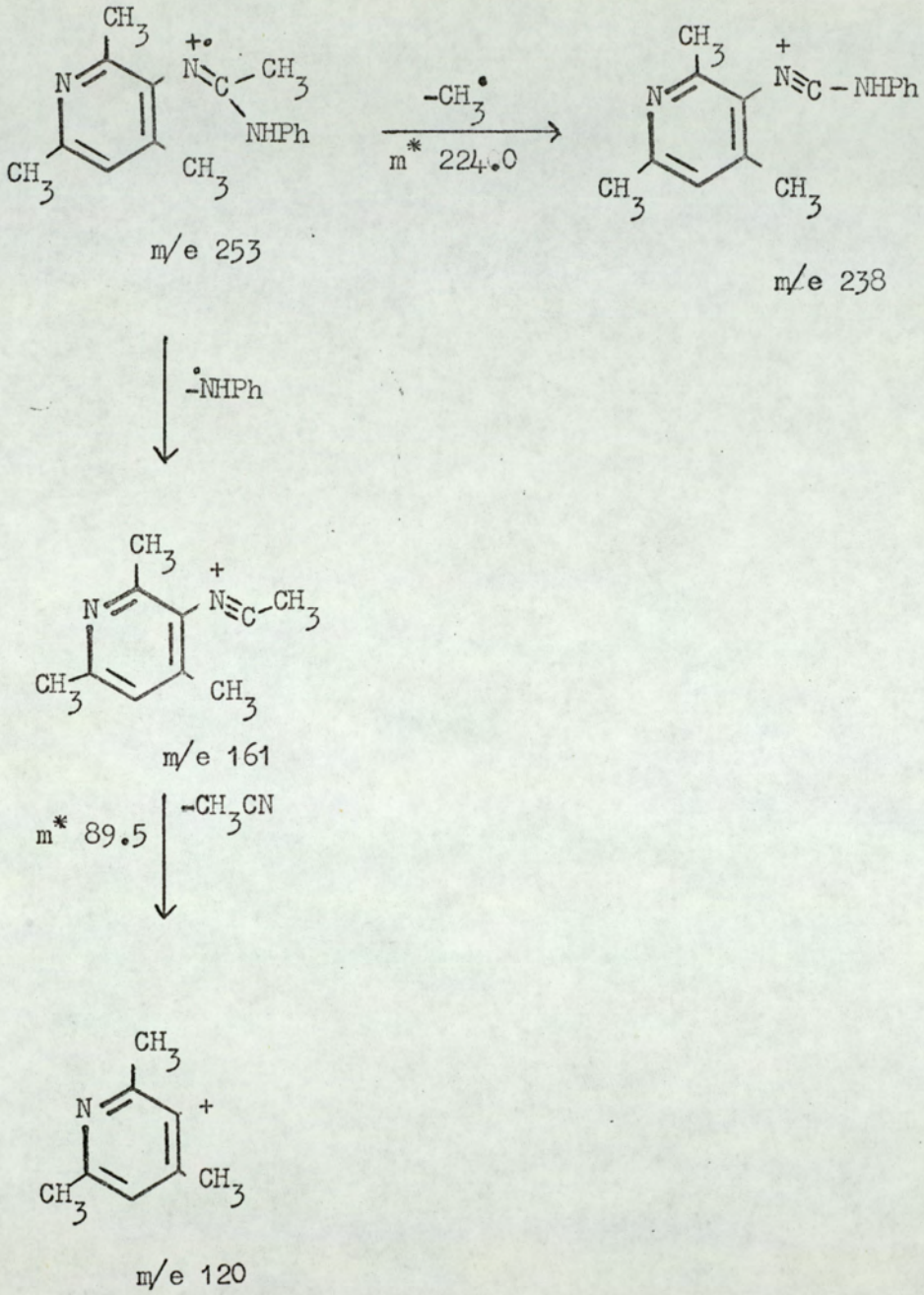


m/e 164 m/e 149

The $^{m}/_{e}$ 149 ion further fragments by elimination of CH_2=NH. A minor fragmentation pathway is initiated by loss of an ethyl radical to give the ion at $^{m}/_{e}$ 135 (12%).

The expected initial fragmentation of N-2,4,6-trimethyl-pyrid-3-yl-N^{1}-phenylacetamidine (98) would be loss of PhNH•. This fragmentation occurs to give the base peak in the spectrum at $^{m}/_{e}$ 161, which then eliminates a molecule of methyl cyanide (scheme XII). A minor fragmentation pathway is initiated by loss of a methyl radical from the molecular ion.

Scheme XIII



EXPERIMENTAL

EXPERIMENTAL

Infrared spectra were determined as nujol mulls with a Unicam S.P. 200 spectrophotometer.

Nuclear magnetic resonance spectra were determined, unless otherwise stated, with tetramethyl-silane as internal standard, on a Varian A-60A spectrometer. All the peaks are assigned in terms of τ values. Abbreviations used in the interpretation of n.m.r. spectra; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; J = coupling constant; a = removed on deuteration.

Mass spectra were determined with an A.E.I. MS9 spectrometer operating at 50 μa and 70 EV. M^+ signifies the molecular ion peak.

Melting points are uncorrected. Sublimation and reaction temperatures are those of the external oil bath.

SYNTHESIS OF PYRIDO[3,4-d]PYRIMIDINES.

(i) From pyridine derivatives

Diethyl-2,6-dimethylpyridine-3,4-dicarboxylate (34; R=CH_3).-Ethyl acetylpyruvate[135] (15.8 g.) was added to a cooled solution of ethyl β-aminocrotonate[136] (12.9 g.) in ether (50 ml.) The solution was stirred overnight and then heated on the steam bath for 2 hr. Cooled, extracted with ether, the ether removed and the residue distilled under reduced pressure to give the di-ester (21.0 g., 84%), b.p. 150-155°/4.0 mm. (lit.[61] 163°/13 mm.)

2,6-Dimethylpyridine-3,4-dicarboxamide (9; R^1=R^2=CH_3).-Diethyl-2,6-dimethylpyridine-3,4-dicarboxylate (14.5 g.) in dry methanol (50 ml.) was saturated with ammonia. The solution was left to stand for 3 days to yield the diamide (8.8 g., 79%), m.p. 220-221° (dec.),(lit.[61] 220°), ν_{max} 3090, 3200, 3310 and 3410 (N-H), 1665 (C=O) $cm.^{-1}$

2,6-Dimethylcinchomeronimide (32; R=CH_3). -2,6-Dimethyl-pyridine-3,4-dicarboxamide (11.0 g.) was heated at 200-220° until no more ammonia was evolved. The residue was sublimed (175°/1.0 mm.) to give the imide (8.4 g., 84%), m.p. 230-232° (lit.[62] 230°), ν_{max} 2740 (N-H), 1730 (C=O) $cm.^{-1}$

Methyl pyridine-3,4-dicarboxylate.-Sulphuric acid (240 ml., d.1.84) was added dropwise to ice cold isoquinoline (106.4 g.), anhydrous copper sulphate (2.8 g.) and mercuric nitrate monhydrate (6.0 g.) with cooling. Nitric acid (282 ml., d. 1.4) was added dropwise to the mixture at 210-230° over a period of 2.5 hr. Air was then drawn through for a further 0.5 hr., and the solution cooled. Urea (30.0 g.) was added and the mixture heated at 100° for 0.5 hr. Methanol (360 ml.) and benzene (240 ml.) were added and the solution heated under reflux for 7 hr. The resulting solution was poured onto ice and the pH adjusted to 10 with ammonia (d.0.88). The benzene layer was separated off, and the aqueous layer extracted with chloroform (3 x 360 ml.) The chloroform layer was washed with aqueous sodium carbonate solution and water. The residue from the chloroform extraction was distilled under reduced pressure to give the ester (75.8 g., 47%), b.p. 95-100°/1.5 mm. (lit.[64] 95-100°/1.5 mm.), ν_{max} 1730 (C=O) $cm.^{-1}$

Pyridine-3,4-dicarboxylic acid (33; R=H).-Methyl-pyridine-3,4-dicarboxylate (75.8 g.) and 3.5 N hydrochloric acid were heated under reflux for 4 hr. Evaporation gave the acid (61.0 g., 95%), m.p. 252-254° (lit.[64] 253-255°), ν_{max} 1710 (C=O) $cm.^{-1}$

Cinchomeronimide (32; R=H.)-Pyridine-3,4-dicarboxylic acid (22.5 g.) and acetic anhydride (75 ml.) were heated together under reflux for 3 hr. Half the acetic anhydride was distilled off, acetamide

(14.0 g.) added, and the reaction mixture heated at 120-125° for 8 hr. The mixture was cooled to yield the imide (14.0 g., 68%), m.p. 228-230° (from ethanol) (lit.[65] 229-230°), ν_{max} 2750 (N-H), 1720 (C=O) cm.$^{-1}$

3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3).-Finely powdered 2,6-dimethylcinchomeronimide (5.0 g.) was dissolved in a well stirred, ice cold, solution of potassium hypobromite, prepared from bromine (4.6 g.) and 10% aqueous potassium hydroxide solution (75 ml.) After 2 hr. 10% aqueous potassium hydroxide solution (40 ml.) was added and the solution heated on the steam bath for 10 min. The solution was acidified with hydrochloric acid (d. 1.16) and evaporated to dryness under reduced pressure. The residue was extracted with boiling absolute ethanol and the filtered solution concentrated to a small volume to yield the hydrochloride of the amino acid (4.0 g., 69.5%), m.p. 252-254° (lit.[61] 253-254°), ν_{max} 3310 and 3400 (N-H), 1695 (C=O)cm.$^{-1}$ τ(T.F.A) 1.89 (1H, s, 5-H), 7.28 (3H, s, 2-CH_3), 7.32 (3H, s, 6-CH_3).

3-Aminopyridine-4-carboxylic acid (10; R=H).-Similar treatment of cinchomeronimide (10.0 g.) with potassium hypobromite gave the corresponding amino acid dihydrochloride (7.5 g., 81%), m.p. 243-244° (lit.[6] 244-245°), ν_{max} 3330 and 3430 (N-H), 1690 (C=O) cm.$^{-1}$

6,8-Dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=CH_3 R^1=H).-3-Amino-2, 6-dimethylpyridine-4-carboxylic acid (2.5g) and formamide (5.0 g.) were heated together at 165-170° for 2 hr. to yield the pyridopyrimidine (1.7 g., 64%), needles, m.p. 289-291° (from acetic acid) (Found : C, 61.4; H, 5.3; N, 23.7% M^+, 175. $C_9H_9N_3O$ requires C, 61.7; H, 5.2; N, 24.0% M^+, 175), ν_{max} 1675 (C=O) cm.$^{-1}$ τ(T.F.A.) 1.23 (1H, s, 2-H), 1.48 (1H, s, 5-H), 7.02 (3H, s, 6-CH_3), 6.77 (3H, s, 8-CH_3).

Pyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=H$). -Similar treatment of 3-aminopyridine-4-carboxylic acid (2.5 g.) and formamide (5.0 g.) yielded the corresponding pyridopyrimidine (1.8 g., 67%), m.p. 314-317° (lit.[6] 315-317°), ν_{max} 1710 (C=O) cm.$^{-1}$

τ (T.F.A.) 1.08 (1H, s, 2-H), 0.99 (2H, s, 5-H and 6-H), 0.18, (1H, s, 8-H).

6,8-Dimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (38). —3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10.0 g.) and formanilide (12.0 g.) were heated together at 170-180° for 10 hr. The melt was cooled, 30% aqueous sodium hydroxide solution (10 ml.) added and the mixture extracted with ether to give the pyridopyrimidine (3.3 g., 22%), needles, m.p. 185° (from light petroleum) (Found: C, 71.9; H, 5.3; N, 16.7. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%), ν_{max} 1685 (C=O) cm.$^{-1}$

τ ($CDCl_3$) 1.92 (1H, s, 2-H), 2.53 (5H, broad s, 3-Ph), 2.27 (1H, s, 5-H), 7.37 (3H, s, 6-CH_3), 7.16 (3H, s, 8-CH_3).

6,8-Dimethylpyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (8; $R^1=R^2=CH_3$). —a) 2,6-Dimethylpyridine-3, 4-dicarboxamide (5.0g.) was dissolved in a well stirred, ice cold, solution of potassium hypobromite, prepared from bromine (8.3 g.) in 12% aqueous potassium hydroxide solution (140 ml.) The solution was stirred for 2 hr., warmed on the steam bath and acidified with acetic acid to give the dione (4.3 g., 87%), m.p. 354-356° (from acetic acid) (lit.[8] 355-357°), ν_{max} 3200 and 3150 (N-H), 1710 (C=O) cm.$^{-1}$

τ (T.F.A.) 1.8 (1H, s, 5-H), 7.08 (3H, s, 6-CH_3), 6.95 (3H, s, 8-CH_3).

(b) 3-Amino-2,6-dimethylpyridine-4-carboxylic acid (0.5 g.) and urea (0.4 g.) were heated together at 170° for 3 hr. The melt was cooled and

washed with water to give the dione (0.35 g., 61%), m.p. 355-357° and on admixture with an authentic sample.

6,8-Dimethylpyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (0.5 g.) and 30% aqueous sodium hydroxide solution (15 ml.) were heated together under reflux for 18 hr. Evaporation to dryness and extraction with absolute alcohol yielded 3-amino-2,6-dimethylpyridine-4-carboxylic acid (0.3 g., 69%), undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

Pyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (8; R^1=R^2=H). -Similar treatment of 3-aminopyridine-4-carboxylic acid (2.5 g.) and urea (2.5 g.) yielded the dione (1.9 g., 69%), m.p. sublimes above 300° (from acetic acid) (lit.[6] >300°) ν_{max} 1700 and 1710 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 1.75 (2H, s, 5-H and 6-H), 1.39 (1H, s, 8-H)

(ii) Via pyrido[3,4-d][1,3]oxazin-4-ones.

2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (45).—3-Amino-2,6-dimethylpyridine-4-carboxylic acid (1.0 g.) and acetic anhydride (12 ml.) were heated together under reflux for 2 hr. The excess acetic anhydride was removed under reduced pressure and the residue was cooled to yield the pyrido-oxazine (0.8 g., 70%), needles, m.p. 139-140° (from ethyl acetate) (Found: C, 63.0; H, 5.4; N, 14.6% M^+, 190. $C_{10}H_{10}N_2O_2$ requires C, 63.2; H, 5.3; N, 14.7%, M^+, 190.) ν_{max} 1745 (C=O), 1635 (C=N) and 1240 (C-O)$_{cm.}^{-1}$

$\tau_{(CDCL_3)}$ 7.55 (3H, s, 2-CH_3), 2.46 (1H, s, 5-H), 7.47 (3H, s, 6-CH_3), 7.29 (3H, s, 8-CH_3).

A suspension of the pyrido-oxazine (0.15 g.) in water (10 ml.) was stirred for 16 hr. at room temperature to yield 3-acetamido-2,6-dimethyl-

pyridine-4-carboxylic acid (52) (0.12 g., 75%), m.p. 274-276° (from ethanol) (Found: C, 57.3; H, 6.0; N, 13.6. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.5%), ν_{max} 3150 (N-H), 2500-2400 (bonded OH), 1680 and 1650 (C=O) cm.$^{-1}$

2-Methylpyrido[3,4-d][1,3]oxazin-4-one (39).-Similar treatment of 3-aminopyridine-4-carboxylic acid (3.6 g.) and acetic anhydride (42 ml.) gave the corresponding pyrido-oxazine (2.6 g., 66%) m.p. 99-101° (lit.[70] 99-102°), ν_{max} 1750 (C=O) , 1635 (C=N) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 7.66 (3H, s, 2-CH_3), 1.3 (1H, d, J= 8.0 c./sec., 5-H), 2.16 (1H, d, J=8.0 c./sec., 6-H), 1.12 (1H, s, 8-H).

6,8-Dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=CH_3).--3-Amino-2,6-dimethylpyridine-4-carboxylic acid hydrochloride (1.0 g.) and benzoyl chloride (1.5 ml.) in pyridine were heated together under reflux for 20 min. The solution was diluted with water to yield the pyrido-oxazine (0.75 g., 61%), needles, m.p. 156-157° (from benzene) (Found: C, 71.5: H, 4.9; N, 11.2% M^+, 252. $C_{15}H_{12}N_2O_2$ requires C, 71.5; H, 4.8; N, 11.1% M^+, 252), ν_{max} 1750 (C=O), 1610 (C=N) and 1240 (C-O) cm.$^{-1}$

$\tau_{(CDCL_3)}$ 1.62-1.73 and 2.28 - 2.5 (2H and 3H, m, 2-Ph), 2.64 (1H, s, 5-H), 7.3 (3H, s, 6-CH_3), 7.09 (3H, s, 8-CH_3).

The pyrido-oxazine was not hydrolysed by treatment with water at 35-40° for 3 days.

2-Phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H).- Similar treatment of 3-aminopyridine-4-carboxylic acid (1.0 g.) with benzoyl chloride (2.0 ml.) in pyridine yielded the pyrido-oxazine (1.0 g., 64%), m.p. 131-132° (from light petroleum) (Found: C, 69.7; H, 3.8; N, 12.3% M^+, 224. $C_{13}H_8N_2O_2$ requires C, 69.6; H, 3.6; N, 12.5% M^+, 224), ν_{max} 1760 (C=O), 1610 (C=N) and 1240 (C-O) cm.$^{-1}$

$\tau_{(CDCL_3)}$ 1.59-1.75 and 2.41-2.51 (2H and 3H, m, 2-Ph), 1.22 (1H, d, J=5.0 c./sec., 5-H), 1.99 (1H, d, J=5.0 c./sec., 6-H), 0.89 (1H, s, 8-H).

The pyrido-oxazine was not hydrolysed by treatment with water at 35-40° for 3 days.

2,6,8-Trimethylpyrido[3,4-d]pyrimidin-4 (3H)-one. (11; $R=R^1=CH_3$). -2,6,8-Trimethylpyrido[3,4-d][1,3] oxazin-4-one (0.4 g.) was added to ammonia (10 ml., d.0.88) and the mixture was stirred at room temperature until dissolution was complete (12 hr.) Evaporation under reduced pressure yielded the pyridopyrimidine (0.33 g., 83%), m.p. 287-289° (from ethanol) (Found: C, 63.2; H, 5.9; N, 22.0% M^+, 189. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.8; N, 22.2% M^+, 189), ν_{max} 3180 (N-H) and 1680 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 7.12 (3H, s, 2-CH_3), 1.51 (1H, s, 5-H), 7.03 (3H, s, 6-CH_3), 6.8 (3H, s, 8-CH_3).

2-Methylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=H, $R^1=CH_3$).-Similar treatment of 2-methylpyrido[3,4,-d][1,3]oxazin-4-one (3.0 g.) with ammonia (d.0.88) yielded the pyridopyrimidine (2.5 g., 83%), m.p. 308-309° (lit.[9] 309-310°), ν_{max} 1685 (C=O) and 1610 (C=N) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 7.02 (3H, s, 2-CH_3), 0.88 (1H, s, 5-H), 0.95 (1H, s, 6-H), 0.47 (1H, s, 8-H).

3-Hydroxy-2,6,8-trimethylpyrido[3,4,-d]pyrimidin-4(3H)-one (59). - 2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (0.32 g.) was added to a solution of sodium hydroxide (0.5 g.) in ethanol (25 ml.) containing hydroxylamine (0.2 g.) and the mixture was stirred at room temperature for 5 days. The solution was acidified, filtered, and the

filtrate evaporated to yield the pyridopyrimidine (0.23 g., 66%), m.p. 256-258° (from ethanol) (Found: C, 58.2; H, 5.6; N, 20.7% M^+, 205. $C_{10}H_{11}N_3O_2$ requires C, 58.5; H, 5.4; N, 20.5% M^+, 205), ν_{max} 2600-2450 (OH), 1700 (C=O) cm.$^{-1}$

$\tau_{(T.F.A.)}$ 7.37 (3H, s, 2-CH_3), 1.6 (1H, s, 5-H), 7.3 (3H, s, 6-CH_3), 7.16 (3H, s, 8-CH_3).

The product is a cyclic hydroxamic acid and gave the typical wine red colour with ferric chloride.

3-Amino-2,6-8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (58; R=NH_2).—Hydrazine hydrate (1.5 ml.) was added to 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (0.5 g.) in ethanol (15 ml.) and the mixture was stirred at room temperature until dissolution was complete (7 days). Concentration of the solution yielded the pyridopyrimidine (0.46 g., 86%) m.p. 205-206° (from ethanol) (Found: C, 58.9; H, 6.1; N, 27.5% M^+, 204. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.9; N, 27.5% M^+, 204.), ν_{max} 3330 and 3100 (N-H), 1680 (C=O) cm.$^{-1}$

$\tau_{(CDCL_3)}$ 7.08 (6H, s, 2-and 6-CH_3), 5.09 (2H, broad s, 3-NH_2)[a], 2.3 (1H, s, 5-H), 6.8 (3H, s, 8-CH_3).

2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72).—2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (0.26 g.) and aniline (0.6 g.) were heated together at 180-190° for 0.75 hr. The cooled melt was titurated with ether to give the pyridopyrimidine (0.34 g., 94%), needles, m.p. 216-217° (from benzene) (Found: C, 72.7; H, 5.4; N, 15.9% M^+, 265. $C_{16}H_{15}N_3O$ requires C, 72.5; H, 5.7; N, 15.9% M^+, 265), ν_{max} 1670 (C=O) cm.$^{-1}$

$\tau_{(CDCL_3)}$ 7.8 (3H, s, 2-CH_3), 2.46-2.53 and 2.68-2.73 (3H and 2H, m, 3-PH), 2.34 (1H, s, 5-H), 7.4 (3H, s, 6-CH_3), 7.17 (3H, s, 8-CH_3).

Reaction of 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (0.5 g.) and aniline (1.2 ml.) in absolute ethanol (50 ml.) at room temperature for 12 hr. yielded 3-acetamido-2,6-dimethyl-N-phenylpyridine-4-carboxamide (60; R=Ph) (0.4 g., 55%), ν_{max} 3300 (N-H), 1660 (C=O) $cm.^{-1}$

Attempted purification by crystallisation from ethanol gave 2,6,8-trimethyl-3-phenylpyrido[3,4,-d]pyrimidin-4(3H)-one, m.p. 216-217° and on admixture with an authentic sample.

6,8-Dimethyl-2-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; $R=CH_3, R^1=H$).— 6,8-Dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (0.8 g.) and ammonia (10 ml., d. 0.88) were stirred together at 20° for 24 hr. to yield 3-benzamido-2,6-dimethylpyridine-4-carboxamide (61; $R=CH_3$. $R^1=H$) (0.7 g., 86%), m.p. 277-278° (from ethanol) (Found: C, 66.6; H, 5.7; N, 15.4% M^+, 269. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6% M^+, 269), ν_{max} 3300 and 3250 (N-H), 1665 and 1640 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 7.01 (6H, s, 2-and 6-CH_3), 1.92-2.33 (6H, m, 5-H and 2-Ph).

The diamide was heated at 240° for 12 hr. to yield the pyridopyrimidine (100%), m.p. 270-271° (Found: C, 71.5; H, 5.4; N, 16.6% M^+, 251. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7% M^+,251), ν_{max} 1690 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 2.2-2.32 and 2.79-2.9 (5H, m, 2-Ph), 2.1 (1H,s, 5-H), 7.42 (3H, s, 6-CH_3), 7.1 (3H, s, 8-CH_3).

2-Phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; $R=R^1=H$).- Similar treatment of 2-phenylpyrido[3,4-d][1,3]oxazin-4-one (1.0 g.) with ammonia yielded 3-benzamidopyridine-4-carboxamide (61; $R=R^1=H$) (0.88 g., 82%), m.p. 210 - 211° (from ethanol) (Found : C, 64.5; H, 43; N, 17.3.

$C_{13}H_{11}N_3O_2$ requires C, 64.7; H, 4.6; N, 17.4%), ν_{max} 3450 and 3150 (N-H), 1680 and 1650 (C=O) $cm.^{-1}$

Cyclisation by heat at 260° for 18 hr. gave the pyrido-pyrimidine (100%), m.p. 266-267° (Found: C, 69.7; H, 3.9; N, 18.7% M^+, 233. $C_{13}H_9N_3O$ requires C, 70.0; H, 4.0; N, 18.8% M^+, 233), ν_{max} 1690 (C=O) $cm.^{-1}$

6,8-Dimethyl-2,3-diphenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3, R^1=Ph).- 6,8-Dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (0.5 g.) and aniline (1.0 ml.) in ethanol (25 ml.) were stirred together at 20° for 24 hr. to give 3-benzamido-2,6-dimethyl-N-phenyl-pyridine-4-carboxamide (61; R=CH_3, R^1=Ph) (0.52 g., 76%) m.p. 253-254° (from ethanol) (Found: C, 73.0; H, 5.4; N, 12.0. $C_{21}H_{19}N_3O_2$ requires C, 73.1; H, 5.5; N, 12.2%), ν_{max} 3250 (N-H), 1650 (C=O) $cm.^{-1}$ $\tau_{(T.F.A.)}$ 7.03 (6H, s, 2 and 6 CH_3), 1.92-2.61 (11H, m, 5-H, 2 and 3-Ph).

The diamide was heated at 200° for 12 hr. to yield the pyrido-pyrimidine (100%), m.p. 187-188° (Found: C, 76.8; H, 5.2; N, 13.1. $C_{21}H_{17}N_3O$ C, 77.1; H, 5.2; N, 12.8%), ν_{max} 1680 (C=O) $cm.^{-1}$ $\tau_{(CDCl_3)}$ 2.72-2.92 (10H, m, 2-and 3-Ph), 2.32 (1H, s, 5-H), 7.24 (3H, s, 6-CH_3), 7.03 (3H, s, 8-CH_3).

6,8-Dimethyl-3-(3^1-nitrophenyl)-2-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3, R^1=3^1-NO_2Ph).- 6,8-Dimethyl-2-phenyl-pyrido[3,4-d][1,3]oxazin-4-one (0.9 g.) and m-nitroaniline (1.0 g.) were heated together at 150-160° for 2 hr. The residue was stirred with chloroform and filtered to give 3-benzamido-2,6-dimethyl-N-(3^1-nitro-phenyl) pyridine-4-carboxamide (61; R=CH_3, R^1=3^1-NO_2Ph) (0.4 g., 30%), m.p. 303-304° (from acetone) (Found: C, 64.3; H, 4.6; N, 14.1. $C_{21}H_{18}N_4O_4$ requires C, 64.6; H, 4.6; N, 14.4%), ν_{max} 3175 (N-H), 1645 (C=O). $cm.^{-1}$

$\tau_{(T.F.A.)}$ 7.09(6H, s, 2-and 6-CH_3), 1.6 (1H, s, 5-H),
1.98 - 2.7 (9H, m, 2-Ph and 3^1-nitrophenyl)

Evaporation of the chloroform extract gave the pyrido-pyrimidine (0.3 g., 23%), m.p. 240-241° (from light petroleum) (Found: C, 67.8 , H, 4.4; N, 15.2% M^+, 372 $C_{21}H_{16}N_4O_3$ requires C, 67.8; H, 4.3: N, 15.1% M^+, 372), ν_{max} 1680 (C=O). $cm.^{-1}$

$\tau_{(CDCL_3)}$ 2.68-2.92 (9H, m, 2-Ph and 3^1-nitrophenyl),
2.47 (1H, s, 5-H), 7.4 (3H, s, 6-CH_3), 7.18 (3H, s, 8-CH_3).

METHYLATION OF PYRIDO[3,4-d]PYRIMIDINES.

3,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (63: R=R^2=CH_3, R^1=H).- Dimethyl sulphate (1.5 ml.) was added to a stirred solution of 6,8-dimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (0.75 g.) in 5% aqueous sodium hydroxide solution (20 ml.) over 1 hr, and the mixture stirred for a further 1 hr. Extraction with chloroform yielded the trimethyl derivative (0.7 g., 81%), m.p. 155-156° (from light petroleum) (Found: C, 63.7; H, 5.8; N, 21.9% M^+, 189. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.8; N, 22.2% M^+, 189), ν_{max} 1675 (C=O), 1580 (C=N) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 1.97 (1H, s, 2-H), 6.4 (3H, s, 3-CH_3), 2.25 (1H, s, 5-H),
7.34(3H, s, 6-CH_3), 7.15 (3H, s, 8-CH_3).

$\tau_{(T.F.A.)}$ 1.2 (1H, s, 2-H), 6.18 (3H, s, 3-CH_3), 1.49 (1H, s, 5-H),
7.06 (3H, s, 6-CH_3), 6.81 (3H, s, 8-CH_3).

2,3,6,8-Tetramethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=R^2=CH_3).--Similar treatment of 2,6,8-trimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (3.5 g.) with dimethyl sulphate gave the tetramethyl derivative (2.9 g., 77%),m.p. 157-158° (from light petroleum) (Found: C, 65.0; H, 6.4; N, 20.4% M^+, 203 $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.4; N, 20.7% M^+, 203) ν_{max} 1680 (C=O) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 7.42 (6H, s, 2-and 6-CH_3), 6.45(3H, s, 3-CH_3), 2.43(1H, s, 5-H), 7.28(3H, s, 8-CH_3).

3-Methylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=H, R^2=CH_3).- Methyl iodide (1.2 ml.) was added to a solution of pyrido[3,4-d]pyrimidin-4(3H)-one (0.75 g.) in sodium ethoxide solution, prepared from sodium (0.12 g.) and ethanol (50 ml.). The solution was heated under reflux for 4 hr. The cooled mixture was filtered, and the filtrate was concentrated, diluted with water, and extracted with chloroform to yield the monomethyl derivative (0.48 g., 67%), needles, m.p. 176-177° (from light petroleum) (Found: C, 59.5; H, 4.3; N, 26.2% M^+, 161. $C_8H_7N_3O$ requires C, 59.6; H, 4.3; N, 26.1% M^+, 161), ν_{max} 1670 (C=O) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 1.87 (1H, s, 2-H), 6.39(3H, s, 3-CH_3), 1.29(1H, d, J=5.0 c./sec., 5-H), 1.95(1H, d, J=5.0 c./sec., 6-H), 0.86 (1H, s, 8-H).

2,3-Dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=H, R^1=R^2=CH_3)- Similar treatment of 2-methylpyrido[3,4-d]pyrimidin-4(3H)-one (1.0 g.) with methyl iodide gave the corresponding 2,3-dimethyl derivative (0.79 g., 73%), needles, m.p. 148-149° (from light petroleum) (Found: C, 61.4; H, 4.9; N, 23.8% M^+, 175. $C_9H_9N_3O$ requires C, 61.7; H, 5.1; N, 24.0% M^+, 175) ν_{max} 1675(C=O) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 7.37 (3H, s, 2-CH_3), 6.37(3H, s, 3-CH_3), 1.40(1H, d, J=5.0 c./sec., 5-H), 2.07(1H, d, J=5.0 c./sec., 6-H), 0.96 (1H, s, 8-H).

1,3-Dimethylpyrido [3,4-d]pyrimidine-2,4(1H, 3H)-dione (64; $R^1=R^2=H$, $R^3=R^4=CH_3$).—Methyl iodide (1.6 ml.) was added to a solution of pyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (0.5 g.) in sodium ethoxide solution, prepared from sodium, (0.25 g.) and ethanol (50 ml.) The solution was heated under reflux for 4 hr., cooled and filtered to give starting material (0.2 g.) The filtrate was concentrated, diluted with water, and extracted with chloroform to yield the dimethyldione (0.22 g., 37.5%), needles, m.p. 158-159° (from light petroleum) (Found: C, 56.1; H, 4.7; N, 21.6% M^+, 191. $C_9H_9N_3O$ requires C, 56.5; H, 4.7; N, 22.0% M^+, 191), ν_{max} 1705 and 1665 (C=O) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 6.51 (3H, s, 1-CH_3), 6.34 (3H, s, 3-CH_3), 1.43 (1H, d, J=5.0 c./sec., 5-H), 1.99 (1H, d, J=5.0 c./sec., 6-H), 1.25 (1H, s, 8-H).

3,6,8-Trimethylpyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (64; $R^1=R^2=R^4=CH_3$, $R^3=H$). - Dimethyl sulphate (2.0 ml.) was added to a stirred solution of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (1.0 g.) in 5% aqueous sodium hydroxide solution (30 ml.) over 1.5 hr. to give a precipitate of the trimethyldione (0.8 g., 75%), m.p. 350-353° (from acetic acid) (Found: C, 58.5; H, 5.4; N, 20.4%, M^+, 205. $C_{10}H_{11}N_3O_2$ requires C, 58.5; H, 5.4; N, 20.5% M^+, 205), ν_{max} 3200 (N-H), 1715 and 1655 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 6.38 (3H, s, 3-CH_3), 7.12 (3H, s, 6-CH_3), 6.97 (3H, s, 8-CH_3), 1.6 (1H, s, 5-H).

3,6,8-Trimethylpyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (0.8 g.) and 10% aqueous sodium hydroxide solution were heated together under reflux for 18 hr. Evaporation of the solution to dryness and

extraction with absolute ethanol yielded 3-amino-2,6-dimethylpyridine-4-carboxylic acid (0.5 g., 77%), undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

1,3,6,8-Tetramethylpyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (64; $R^1=R^2=R^3=R^4=CH_3$). - a) Dimethyl sulphate (4.0 ml.) was added to a stirred solution of 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (2.0 g.) in 5% aqueous sodium hydroxide solution (30 ml.) at 35-40° during 2 hr. The mixture was filtered free from unchanged starting material (1.5 g.) after a further 1 hr., and the filtrate was extracted with chloroform to yield the tetramethyl derivative (0.2 g., 10%), m.p. 167-168° (from light petroleum) (Found : C. 60.5; H, 6.1; N, 18.9% M^+, 219. $C_{11}H_{13}N_3O_2$ requires C, 60.3; H, 5.9; N, 19.2% M^+, 219), ν_{max} 1695 and 1655 (C=O) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 6.53 (3H, s, 1-CH_3), 6.29 (3H, s, 3-CH_3), 2.29 (1H, s, 5-H), 7.45 (3H, s, 6-CH_3), 7.18 (3H, s, 8-CH_3).

$\tau_{(T.F.A.)}$ 6.36 (3H, s, 1-CH_3), 6.05 (3H, s, 3-CH_3), 1.48 (1H, s, 5-H), 7.08 (3H, s, 6-CH_3), 6.78 (3H, s, 8-CH_3).

b) Methyl iodide (5.0 ml.) was added to a solution of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (1.0 g.) in sodium ethoxide solution, prepared from sodium (0.25 g.) and ethanol (50 ml.). The solution was heated under reflux for 15 hr., evaporated to dryness, diluted with water and extracted with chloroform to yield the tetramethyldione (0.41 g., 38%). The aqueous layer contained the trimethyldione (0.46 g., 40%).

STYRYL COMPOUNDS.

2,6-Dimethyl-3-phenyl-8-styrylpyrido[3,4-d]pyrimidin-4(3H)-one (74). - 2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidine-4(3H)-one (0.5 g.) and benzaldehyde (0.2 ml.) were heated together at 180° for 1 hr. The cooled oil was titurated with ether to yield the styryl derivative (0.43 g., 65%), m.p. 205-206° (from ethanol) (Found: C,78.4, H, 5.5; N, 11.7% M^+, 353. $C_{23}H_{19}N_3O$ requires C, 78.2; H, 5.4; N, 11.9% M^+, 353), ν_{max} 1690 (C=O), 1630 (C=N) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 7.78 (3H, s, 2-CH_3), 2.24-2.71 (11H, m, 3-Ph, 5-H and styryl Ph), 7.32 (3H, s, 6-CH_3), 1.78 (1H, s, CH=CH) and 1.86 (1H, s, CH=CH).

2,6-Dimethyl-8-(p-nitrostyryl)-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one (76). - 2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)- one (0.5 g.) and p-nitrobenzaldehyde (0.29 g.) were heated together at 180° for 0,75 hr. Cooled and washed with ethanol to yield the p-nitrostyryl derivative (0.71 g., 95%), m.p. 278-279°, needles (from pyridine) (Found : C, 69.0; H, 4.7; N, 14.0. $C_{23}H_{18}N_4O_3$ requires C, 69.2; H, 4.5; N, 14.1%), ν_{max} 1685 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 7.41 (3H, s, 2-CH_3), 7.0 (3H, s, 6-CH_3),
1.5 - 2.5 (12H, m, 3-Ph, 5-H and p nitrostyryl).

4-Anilinomethyl-3-ethylamino-6-methyl-2-styrylpyridine (75). - A suspension of 2,6-dimethyl-3-phenyl-8-styryl pyrido[3,4-d]pyrimidin-4 (3H)- one (0.75 g.) in dry ether (200 ml.) was added to a stirred suspension of lithium aluminium hydride (1.0 g.) in dry ether (50 ml.) and the mixture heated under reflux for 3 days.

Water (1.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried ($MgSO_4$). Evaporation of the ether yielded a viscous oil (0.6 g.), which on tituration with ether yielded the diaminostyrylpyridine (0.15 g.), m.p. 172-173° (from light petroleum) (Found: M^+, 343 $C_{23}H_{25}N_3$ requires M^+, 343), ν_{max} 3350 and 3250 (N-H) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 6.92 (2H, q, J=7.0 c./sec., 3-NHC$\underline{H_2}$$CH_3$),
8.85(3H, t, J=7.0 c./sec., 3-NHCH$_2$C$\underline{H_3}$),
5.79 (2H, s, 4-C$\underline{H_2}$NHPh), 7.5 (3H, s, 6-CH_3),
2.35-3.3(13H, m, 5-H, 4-CH_2N$\underline{H}$Ph and 8-CH=CH-Ph).

The ether solution from the tituration was evaporated to dryness. A n.m r. spectrum showed that the oil contained approximately 60% of the diaminostyrylpyridine (75), plus an unknown compound. Attempted separation of the mixture by thin layer chromatography failed.

RING-OPENING REACTIONS OF PYRIDO[3,4-d]PYRIMIDIN-4(3H)-ONES AND PYRIDO[3,4-d]PYRIMIDINE-2,4 (1H, 3H)-DIONES.

a) Pyrido[3,4-d]pyrimidin-4(3H)-one (0.5 g.) and hydrazine hydrate (10 ml.) were heated together under reflux for 20 hr. The excess hydrazine hydrate was evaporated off under reduced pressure and the residual oil was titurated with aqueous ethanol to yield 3-amino-pyridine-4-carboxylic acid (0.35 g., 74%), m.p. 244-245° and on admixture with an authentic sample.

b) Similar treatment of 6,8-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (0.7 g.) gave 3-amino-2,6-dimethylpyridine-4-carboxylic acid (0.5g, 75%), m.p. 253-254° and on admixture with an authentic sample.

c) Similar treatment of 6,8-dimethylpyrido[3,4-d]pyrimidine-2,4 (1H, 3H)-dione (1.0 g.) yielded 3-amino-6,8-dimethyl-pyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (71; $R^1=R^2=CH_3$) (0.6g., 56%), needles, m.p. > 300° (from water) (Found: C, 52.6; H, 4.7; N, 27.0% M^+, 206. $C_9H_{10}N_4O_2$ requires C, 52.4; H, 4.9; N, 27.2% M^+, 206), ν_{max} 3350, 3150 and 3050 (N-H), 1725 and 1665 (C=O) $cm.^{-1}$

$\tau_{(T.F.A.)}$ 1.59 (1H, s, 5-H), 7.09 (3H, s, 6-CH_3), 6.93 (3H, s, 8-CH_3).

d) Similar treatment of pyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (1.0 g.) gave 3-amino-pyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (71; $R^1=R^2=H$) (0.65 g., 60%), needles, m.p. 278-279° (from water) (Found: C, 47.4; H, 3.1; N, 31.6% M^+, 178. $C_7H_6N_4O_2$ requires C, 47.2; H, 3.4; N, 31.5% M^+, 178), ν_{max} 3310, 3110 and 3030 (N-H), 1710-1680 (C=O) $cm.^{-1}$

2,6,8-Trimethyl-4,4-diphenylpyrido[3,4-d][1,3]oxazine (73). - 2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4 (3H)-one (1.0 g.) and phenylmagnesium bromide, prepared from magnesium (1.0 g.) and bromobenzene (6.5 g.), in dry ether (250 ml.) were heated under reflux for 48 hr. Aqueous ammonium chloride solution was added and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether gave an oil, which on tituration with a small amount of ether yielded the pyrido-oxazine (0.82 g., 66%), m.p. 219-220° (from light petroleum) (Found : C, 80.0; H, 6.3; N, 8.7% M^+, 328. $C_{22}H_{20}N_2O$ requires C, 80.4; H, 6.1; N, 8.5% M^+, 328), ν_{max} 1630 (C=N) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 7.82 (3H, s, 2-CH_3), 2.7 (10H, broad s, 4-Phs), 3.64 (1H, s, 5-H), 7.57 (3H, s, 6-CH_3), 7.36(3H, s, 8-CH_3).

REDUCTION OF PYRIDO[3,4-d]PYRIMIDIN-4(3H)-ONES.

4-Anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85). - A suspension of 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (2.85 g.) in dry ether (200 ml.) was added to a stirred suspension of lithium aluminium hydride (3.0 g.) in dry ether (100 ml.) The mixture was stirred for a further 1 hr. at room temperature and the metal salts decomposed with 10% aqueous sodium hydroxide solution (25 ml.) The ether layer was dried over anhydrous sodium sulphate and evaporated to yield the diamino-pyridine (2.43 g., 89%), m.p. 96-97° (from light petroleum) (Found: C, 75.0; H, 8.2; N, 16.4% M^+, 255. $C_{16}H_{21}N_3$ requires C, 75.3; H, 8.2; N, 16.5% M^+, 255), ν_{max} 3310, 3220 and 3090 (N-H) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 7.02 (2H, q, J=7.0 c./sec., 3-NHC$\underline{H_2}$CH$_3$), 8.86 (3H, t , J=7.0 c./sec., 3-NHCH$_2$C$\underline{H_3}$), 5.79 (2H, s, 4-C$\underline{H_2}$NHPh), 2.67-3.45(6H, m, 5-H and 4-CH$_2$NH$\underline{Ph}$), 7.5 (3H, s, 2-CH$_3$), 7.6 (3H, s, 6-CH$_3$).

4-Anilinomethyl-3-ethylamino-2,6-dimethylpyridine (0.58 g.), benzoyl chloride (1.2 ml.) and pyridine (6.0 ml.) were heated together under reflux for 0.75 hr. The resulting solution was evaporated to dryness under reduced pressure and the residue chloroform extracted to yield the dibenzoyl derivative (87) (0.9 g., 86%), m.p. 119-120° (from light petroleum) (Found: C, 77.5; H, 6.4; N, 8.8 $C_{30}H_{29}N_3O_2$ requires C, 77.8; H, 6.3; N, 9.1%, ν_{max} 1630 (C=O) $cm.^{-1}$

1-Ethyl-3,4-dihydro-6,8-dimethyl-3-phenylpyrido[3,4-d]pyrimidin-2(1H)-one (88).—4-Anilinomethyl-3-ethylamino-2,6-dimethylpyridine (0.5 g.), sodium carbonate (0.6 g.) and phosgene (1.62 ml., 12% $^{w}/_{v}$ in benzene) in dry benzene (10 ml.) were

stirred together at room temperature for 12 hr. Water (10 ml.) was then added and the solution stirred for a further 0.5 hr. The benzene layer was dried over anhydrous sodium sulphate and evaporated to yield the pyridopyrimdine (0.4 g., 73%), m.p. 166-167° (from light petroleum) (Found : C, 72.4; H, 7.0; N, 15.0. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%), ν_{max} 1650 (C=O) cm.$^{-1}$

$\tau_{(CDCL_3)}$ 5.93 (2H, q, J=7.0 c./sec., 1-CH_2CH_3), 8.83 (3H,t, J=7.0 c./sec., 1-CH_2CH_3), 2.72 (5H, broad s, 3-Ph), 5.44 (2H, s, 4-Hs), 3.21 (1H, s, 5-H), 7.59 (3H, s, 6-CH_3), 7.39 (3H, s, 8-CH_3).

Attempted preparation of 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine from 3-acetamido-2,6-dimethyl-N-phenylpyridine-4-carboxamide.

A suspension of 3-acetamido-2,6-dimethyl-N-phenylpyridine-4-carboxamide (0.5 g.) in dry ether (150 ml.) was added to a stirred suspension of lithium aluminium hydride (1.5 g.) in dry ether (100 ml.) and the mixture heated under reflux for 7 days. Water (2.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried (Mg SO_4). Evaporation of the ether yielded N-2,4,6-trimethylpyrid-3-yl-N^1-phenylacetamidine (98) (0.4 g.), m.p. 159-160° (from light petroleum) (Found: C, 76.2; H, 7.6;, N, 16.6% M^+, 253. $C_{16}H_{19}N_3$ requires C, 75.9; H, 7.5; N, 16.6% M^+, 253), ν_{max} 3300 (N-H), 1650 (C=N) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 3.14 (1H, s, 5-H), 7.57 and 7.64 (3H, s, 2-and 6-pyridyl CH_3), 7.9 (3H, s, 4-pyridyl CH_3), 2.33-3.0 (5H, m, N^1-Ph), 3.75 (1H, broad s, NHPh)[a], 8.22 (3H, s, -N=C(CH_3)NHPh).

3,4-Dihydro-4-hydroxy-2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidine (90). -A suspension of lithium aluminium hydride (0.2 g.) in dry ether (50 ml.) was added to 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (1.0 g.) in dry ether (250 ml.) and sufficient dry benzene to achieve solution. The mixture was stirred at room temperature for 0.5 hr., water (1.0 ml.) and 10% aqueous sodium hydroxide solution (10 ml.) added and the ether/benzene solution dried over anhydrous sodium sulphate. The dried solution was reduced to a small volume and filtered to yield the hydroxy-pyridopyrimidine (0.25 g., 25%), m.p. 174-177° (from benzene) (Found: M^+, 267.137155 $C_{16}H_{17}N_3O$ requires M^+, 176.14042), ν_{max} 3400 (O-H), 1610 (C=N)cm.$^{-1}$

τ ($CDCL_3$) 8.3 (3H, s, 2-CH_3), 2.61 (5H, s, 3-Ph), 4.31 (1H, s, 4-H), 3.13 (1H, s, 5-H), 7.5 and 7.53 (3H, s, 6-and 8-CH_3).

The filtrate was evaporated to dryness and titurated with light petroleum to yield starting material, 2,6,8-trimethyl-3-phenyl-pyrido [3,4-d]pyrimidin-4(3H)-one (0.35 g.), m.p. 216-217°, undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

The light petroleum fraction was examined by thin layer chromatography, silica plates and chloroform as eluant. The major component was identified as 4-anilinomethyl-3-ethylamino-2,6-dimethyl-pyridine, one of the minor components was 2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidin-4(3H)-one and the other was unidentified.

Reaction of 3,4-dihydro-4-hydroxy-2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidine (0.1 g.) with lithium aluminium hydride (0.1 g.) in dry ether (100 ml.), at room temperature for 24 hr., yielded 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (0.08 g., 84%), m.p. 96-97°; undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

3,4-Dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (96). - Granulated tin (6.0 g.) was added to 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (0.75 g.) in hydrochloric acid (75 ml., d. 1.16) and the mixture warmed on the steam bath for 4 hr. The cooled solution was made alkaline with 30% aqueous sodium hydroxide solution, filtered and both the filtrate and filter cake extracted with chloroform to yield the dihydropyridopyrimidine (0.5 g., 70%), m.p. 119-121° (from light petroleum) (Found: C, 76.7; H, 6.8; N, 16.5. $C_{16}H_{17}N_3$ requires C, 76.5; H, 6.8; N, 16.7%).

τ ($CDCl_3$) 8.04 (3H, s, 2-CH_3), 2.6-2.71(5H, m, 3-Ph), 3.48 (1H, s, 5-H), 7.58(3H, s, 6-CH_3), 7.39(3H, s, 8-CH_3), 5.29 (2H, s, 4-Hs).

Reduction of 3,4-dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (0.2 g.) with lithium aluminium hydride (0.2 g.) in dry ether (100 ml.), at room temperature for 24 hr., yielded 4-anilinomethyl-3-ethylamino-2,6-dimethylpyridine (0.15 g., 74%), m.p. 96-97° undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

3-Ethylamino-2,4,6-trimethylpyridine (97). - A suspension of 3,4-dihydro-2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidine (0.7 g.) in dry ether (150 ml.) was added to a stirred suspension of lithium aluminium hydride (1.5 g.) in dry ether (100 ml.) and the mixture heated under reflux for 5 days. Water (2.0 ml.) was cautiously added, followed by 20% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether gave a viscous oil (0.6 g.), which was distilled under reduced pressure to yield the trimethylpyridine (0.3 g., 65%), b.p. 92-96°/5.0 mm.

(Found: M^+ 164.13227. $C_{10}H_{16}N_2$ requires 164.13134), ν_{max} 3350(N-H) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 7.55 (3H, s, 2-CH_3), 7.06 (2H, q, J=7.0 c./sec., 3-NHC$\underline{H_2}$$CH_3$), 8.86 (3H, t, J=7.0 c./sec., 3-NHCH$_2$C$\underline{H_3}$), 7.81 (3H, s, 4-CH_3), 3.25 (1H, s, 5-H), 7.62 (3H, s, 6-CH_3).

Thin layer chromatography, silica plates and chloroform as eluant, on the residue from the distillation revealed two components. The first component was identified as aniline and the second was shown to be more 3-ethylamino-2,4,6-trimethylpyridine.

4-Anilinomethyl-2,6-dimethyl-3-methylaminopyridine (89). - A solution of 6,8-dimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (0.6 g.) in dry ether (200 ml.) was added to a suspension of lithium aluminium hydride (0.6 g.) in dry ether (50 ml.) and the mixture stirred at room temperature for 24 hr. Water (1.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether yielded the diaminopyridine (0.5 g., 88%), m.p. 122-123° (from light petroleum) (Found: C, 74.8; H, 7.8; N, 17.7 $C_{15}H_{19}N_3$ requires C, 74.7; H, 7.9; N, 17.4%), ν_{max} 3400 and 3290 (N-H) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 7.3 (3H, s, 3-NHC$\underline{H_3}$), 2.93-3.6 (6H, m, 5-H and 4-C$\underline{H_2}$NHPh), 5.9 (2H, s, 4-C$\underline{H_2}$NHPh), 6.48-7.1 (2H, broad s, 3-N$\underline{H}$CH$_3$ and 4-CH$_2$N$\underline{H}$Ph)[a] 7.6 and 7.7 (3H, s, 2- and 6-CH_3).

4-Aminomethyl-3-ethylamino-2,6-dimethylpyridine (102). -A suspension of 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (0.75 g.) in dry ether (150 ml.) was added to a stirred suspension of lithium aluminium hydride (1.0 g.) in dry ether (100 ml.) and the mixture heated under

reflux for 6 days. Water (1.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer evaporated to give an oil (0.6 g.) The crude oil was distilled under reduced pressure to yield the diaminopyridine (0.3 g., 42%), b.p. 135-139°/5.0 m.m. An analytically pure sample could not be obtained (Found: M^+, 179.14113. $C_{10}H_{17}N_3$ requires M^+, 179.14224).

$\tau_{(CDCl_3)}$ 7.5 (3H, s, 2-CH_3), 7.0 (2H, q, J=7.0 c./sec., 3-$NHCH_2CH_3$), 8.81(3H, t, J=7.0 c./sec., 3-$NHCH_2CH_3$), 6.15(2H, s, 4-CH_2NH_2), 3.12(1H, s, 5-H), 7.57 (3H, s, 6-CH_3).

An n.m.r. spectrum of the residue from the distillation showed the main component to be the diaminopyridine (102). The minor component was identified as 3,4-dihydro-2,6,8-trimethylpyrido[3,4-d]pyrimidine (107).

Ethyl-3-amino-2,6-dimethylpyridine-4-carboxylate (104). - 3-Amino-2,6-dimethylpyridine-4-carboxylic acid (2.5 g.) and sulphuric acid (2.8 ml., d. 1.84) in absolute ethanol (40 ml.) were heated together under reflux for 48 hr. The excess ethanol was removed under reduced pressure and the residue added to ice, addition of aqueous ammonia (d.0.88) yielded the ester (2.1 g., 87%), m.p. 48-49° (from light petroleum) (lit.[120] 47-48°), ν_{max} 3410 and 3300 (N-H), 1690 (C=O) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 4.4 (2H, broad s, 3-NH_2)[a], 5.92 (2H, q, J=7.0 c./sec., 4-$CO_2CH_2CH_3$), 8.67 (3H, t, J=7.0 c./sec., 4-$CO_2CH_2CH_3$), 2.65 (1H, s, 5-H), 7.61 (6H, s, 2-and 6-CH_3).

Ethyl-3-amino-2,6-dimethylpyridine-4-carboxamide (105). -Ethyl-3-amino-2,6-dimethylpyridine-4-carboxylate (0.6 g.) and anhydrous ethylamine (4.0 ml.) were heated together in a sealed tube at 100-110° for

48 hr. to yield the amidopyridine (0.5 g., 83%), m.p. 133.5-134.5° (from benzene) (Found: C, 61.9; H, 8.0; N, 22.0. $C_{10}H_{15}N_3O$ requires C, 62.2; H, 7.8; N, 21.8%), ν_{max} 3450, 3350 and 3260(N-H), 1640(C=O) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 4.33 (2H, broad s, 3-NH_2)[a], 3.3(1H, broad s, 4-CONHCH$_2$CH$_3$)[a] 6.58 (2H, m, 4-CONHCH_2CH$_3$)* 8.81 (3H, t, J=7.0 c./sec., 4-CONHCH$_2$CH_3), 3.08 (1H, s, 5-H), 7.64 and 7.69 (3H, s, 2- and 6-CH_3)

* Collapses to quartet on deuteration (J=7.0 c./sec.)

3-Amino-4-ethylaminomethyl-2,6-dimethylpyridine (103). -Ethyl-3-amino-2,6-dimethylpyridine-4-carboxamide (0.3 g.) and lithium aluminium hydride (0.3 g.) in dry ether (100 ml.) were heated under reflux for 7 days. Water (1.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether yielded the diaminopyridine (0.2 g., 72%), b.p. 228-232° (Found: M^+, 179.1437. $C_{10}H_{17}N_3$ requires 179.14224), ν_{max} 3450 and 3350 (N-H) cm.$^{-1}$

$\tau_{(CDCl_3)}$ 5.8-7.25(3H, broad s, 3-NH_2 and 4-CH$_2$NHCH$_2$CH$_3$)[a], 7.53 (2H, q, J=7.0 c./sec., 4-CH$_2$NHCH_2CH$_3$), 8.98(3H,t , J=7.0 c./sec., 4-CH$_2$NHCH$_2$CH_3), 6.49 (2H, s, 4-CH_2NHCH$_2$CH$_3$), 3.64 (1H, s, 5-H), 7.75 and 7.78 (3H, s, 2-and 6-CH_3).

3,4-Dihydro-2,6,8-trimethylpyrido[3,4-d]pyrimidine (107). - A suspension of 2,6,8-trimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (0.75 g.) in dry ether 150 ml.) was added to a stirred suspension of lithium aluminium hydride (0.75 g.) in dry ether (100 ml.) After 20 hr., water (1.0 ml.) was added, followed by 20% aqueous sodium hydroxide solution (50 ml.) and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether yielded the dihydropyridopyrimidine (0.15 g, 21%),

m.p. 144-146° (from acetone) (Found : M^+ 175.11162. $C_{10}H_{13}N_3$ requires M^+, 175.110942), ν_{max} 3360 (N-H), 1620 (C=N) $cm.^{-1}$

$\tau_{((CH_3)_2CO)}$ 8.08 (3H, s, 2-CH_3), 5.53(2H, s, 4-H_s), 3.47 (1H, s, 5-H), 7.7 (3H, s, 6-CH_3), 7.6 (3H, s, 8-CH_3).

The aqueous layer was neutralised with hydrochloric acid and evaporated to dryness under reduced pressure. Extraction with hot absolute ethanol yielded starting material, 2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (0.4 g.), m.p. 287-289°, undepressed mixed m.p. and identical infrared spectrum with an authentic sample.

4-Aminomethyl-2,6-dimethyl-3-methylaminopyridine (106). - A suspension of 6,8-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (0.5 g.) in dry ether (200 ml.) was added to a stirred suspension of lithium aluminium hydride (1.0 g.) in dry ether (100 ml.) and the mixture heated under reflux for 7 days. Water (1.0 ml.) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried over anhydrous sodium sulphate. Evaporation of the ether yielded the diaminopyridine (0.35 g., 75%), m.p. 79-81° (from light petroleum) (Found: M^+, 165.1270. $C_aH_{15}N_3$ requires 165.12659), ν_{max} 3400 and 3250 (N-H) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 6.38 (2H, s, 4-$\underline{CH_2}NH_2$), 3.35 (1H, s, 5-H), 7.68 (9H, s, 2- and 6-CH_3 and 3-NH$\underline{CH_3}$), 5.9-6.8 (3H, broad s, 3-N$\underline{H}CH_3$ and 4-$CH_2\underline{NH_2}$)[a]

1,2,3,4-Tetrahydro-3,6,8-trimethylpyrido[3,4-d]pyrimidine (101). - A solution of 3,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (1.1 g.) in dry ether (250 ml.) was added to a stirred suspension of lithium aluminium hydride (1.5 g.) in dry ether (50 ml.). After 3 days, water(1.0 ml.) was cautiously added, followed by 10% aqueous sodium

hydroxide solution (25 ml.) and the ether layer dried ($MgSO_4$). Evaporation of the ether yielded the tetrahydropyridopyrimidine (0.95 g., 92%), m.p. 61-62° (from light petroleum) (Found: C, 67.4; H, 8.6; N, 23.7. $C_{10}H_{15}N_3$ requires C, 67.8; H, 8.5; N, 23.8%), ν_{max} 3200 (N-H) $cm.^{-1}$

$\tau_{(CDCl_3)}$ 5.88 (1H, broad s, 1-H)[a], 6.17 (2H, s, 2-Hs), 7.75 (3H, s, 3-CH_3), 3.5 (1H, s, 5-H), 7.68 (6H, s, 6-and 8-CH_3), 6.48 (2H, s, 4-Hs).

3-Ethylamino-2,6-dimethyl-4-methylaminomethylpyridine (99). - A solution of 2,3,6,8-tetramethylpyrido[3,4-d]pyrimidin-4(3H)-one (0.5 g.) in dry ether (250 ml.) was added to a stirred suspension of lithium aluminium hydride (0.5 g.) in dry ether (50 ml.) and the mixture heated under reflux for 6 days. Water (1.0 ml) was cautiously added, followed by 10% aqueous sodium hydroxide solution (25 ml.) and the ether layer dried ($MgSO_4$). Evaporation of the ether yielded the crude diaminopyridine (0.4 g.) (Found: M^+, 193. $C_{11}H_{19}N_3$ requires M^+, 193)

$\tau_{(CDCl_3)}$ 6.98 (2H, q, J=7.0 c./sec., 3-NHCH$_2$CH$_3$), 8.85 (3H, t, J=7.0 c./sec., 3-NHCH$_2$CH$_3$), 6 .31 (2H, s, 4-CH$_2$NHCH$_3$), 7.63 (3H, s, 4-CH$_2$NHCH$_3$), 3.12 (1H, s, 5-H), 7.51 and 7.48 (3H, s, 2-and 6-CH_3).

The crude 3-ethylamino-2,6-dimethyl-4-methylaminomethylpyridine (0.3 g.), sodium carbonate (0.4 g.) and phosgene (1.5 ml., 12%$^{w}/_{v}$ in benzene) in dry benzene (25 ml.) were stirred together at room temperature for 24 hr. Water (10 ml.) was added and the mixture stirred for a further 0.5 hr. The benzene layer was dried ($MgSO_4$) and

evaporated to dryness to yield 1-ethyl-3,4-dihydro-3,6,8-trimethyl-pyrido[3,4-d]pyrimidin-2 (1H)-one (100) (0.18 g., 53%), m.p. 105-106° (from light petroleum) (Found: C, 65.6; H, 7.6; N, 18.9% M^+, 219. $C_{12}H_{17}N_3O$ requires C, 65.8; H, 7.8; N, 19.2% M^+, 219), ν_{max} 1660 (C=O) $cm.^{-1}$

$\tau_{(CDCL_3)}$ 5.95 (2H, q, J=7.0 c./sec., 1-CH_2CH_3),
8.89 (3H, t, J=7.0 c./sec., 1-CH_2CH_3),
7.0 (3H, s, 3-CH_3), 5.76 (2H, s, 4-Hs),
3.1 (1H, s, 5-H), 7.48 (3H, s, 6-CH_3), 7.4 (3H, s, 8-CH_3).

MASS SPECTRAL TABLE

(1) Pyrido[3,4-d]pyrimidines.

Pyrido[3,4-d]pyrimidin-4(3H)-one (11; R=R^1=H)

m/e	148	147(M^+)	146	120	119	118	117	106
I%	12	100	8	6	18	12	6	6
m/e	105	104	103	96	93	92	91	77
I%	4	9	6	6	12	32	12	9
m/e	76	73.5	66	65	64	63	53	52
I%	6	2	6	18	18	5	6	15
m/e	51	50	49	44	43	42	41	40
I%	15	21	6	9	4	6	6	6
m/e	39	38	37					
I%	9	18	12					

m^* 145(147→146), 96.3(147→119), 71.1(119→92), 45.9(92→65).

6,8-Dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; R=CH_3, R^1=H).

m/e	176	175(M^+)	174	147	146	132
I%	10	100	5	5	5	3

m/e	120	119	106	105	79	78
I%	10	5	4	3	7	5

m/e	52	51	42
I%	8	6	6

m^* 123 (175 → 147), 98(147 → 120), 58.9(106 → 79).

3-Methylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=H, R^2=CH_3).

m/e	162	161(M^+)	160	134	133	132
I%	13	100	3	5	22	11

m/e	131	120	105	104	103	93
I%	3	6	12	6	6	9

m/e	92	91	80.5	79	78	77
I%	5	3	3	6	5	3

m/e	76	66	65	64	52	51
I%	5	3	5	8	3	6

m/e	50	43	42	41
I%	12	3	31	6

2,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=R^1=CH_3$)

m/e	190	189(M^+)	188	174	160	149
I%	12	100	8	3	2	2

m/e	148	147	146	133	131	121
I%	3	5	3	2	2	2

m/e	120	119	118	107	106	105
I%	4	6	2	2	2	3

m/e	104	93	92	80	79	78
I%	2	2	2	2	7	5

m/e	77	76	69	66	65	64
I%	2	2	2	2	2	4

m/e	63	62	53	52	51	50	45
I%	4	2	2	7	5	3	2

m/e	44	43	42	41	39	38	36
I%	4	2	18	3	2	3	7

m^* 187 (189 → 188), 160.2(189 → 174), 137.1(189 → 161), 118(120 → 119), 116(189 → 148), 112.8(189 → 146).

3,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^2=CH_3, R^1=H).

m/e	190	189(M^+)	188	176	174	161	160
I%	14	100	7	3	4	4	3
m/e	148	147	146	134	120	119	79
I%	3	4	4	2	6	6	4
m/e	78	64	63	52	51	42	41
I%	5	4	3	6	5	27	4
m/e	39						
I%	3						

m^* 160.2(187 → 174), 137.2(189 → 161), 118(120 → 119), 116(189 → 148), 89.5(161 → 118).

2,3,6,8-Tetramethylpyrido[3,4-d]pyrimidin-4(3H)-one (63; R=R^1=R^2=CH_3).

m/e	204	203(M^+)	202	189	188	175
I%	14	100	5	3	15	6
m/e	174	161	160	147	146	119
I%	3	3	4	4	6	3
m/e	106	105	101.5	79	78	66
I%	2	2	2	2	3	2
m/e	65	64	63	57	56	52
I%	3	4	3	2	20	3
m/e	51	42	41	39		
I%	3	4	2	2		

m^* 174.2(203 → 188), 151.2(203 → 175), 105(203 → 146), 88.5(160 → 119).

3-Amino-2,6,8-Trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (58; R=NH_2)

m/e	206	205	204(M^+)	191	189	188	177
I%	2	14	100	6	6	5	3
m/e	176	175	174	173	161	160	159
I%	7	44	2	2	2	3	5
m/e	158	148	147	146	145	135	124
I%	5	4	17	10	4	2	4
m/e	133	132	122	121	120	119	118
I%	2	4	2	4	4	7	2
m/e	107	106	104	93	92	91	79
I%	2	10	3	4	4	2	7
m/e	78	77	76	75	67	66	65
I%	10	9	3	2	3	4	7
m/e	64	63	62	57	53	52	51
I%	25	11	3	7	3	7	8
m/e	42	40	39	38			
I%	13	2	5	3			

m^* 175.1(204 → 189), 150.1(204 → 175), 123.4(175 → 147).

3-Hydroxy-2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (59)

m/e	206	205(M^+)	190	189	188	175	174
I%	12	90	7	45	12	5	3

m/e	161	160	159	158	148	147	146
I%	3	3	3	3	12	100	7

m/e	144	121	120	119	118	106	105
I%	3	3	7	13	3	3	4

m/e	104	93	92	87	79	78	77
I%	3	3	6	3	8	13	7

m/e	76	73	67	66	65	64	63
I%	5	3	3	3	5	15	10

m/e	62	58	53	52	51	50	45
I%	3	3	3	13	13	3	3

m/e	44	43	41	40	39	38
I%	7	5	3	4	5	3

m^* 172.4(205 → 188), 114.9(188 → 147), 97.8, 96.3(147 → 119), 71.1(119 → 92).

2,6,8-Trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72)

m/e	266	265(M^+)	264	253	252	251
I%	18	100	18	3	16	4

m/e	250	224	223	222	219	195
I%	23	4	2	2	5	2

m/e	189	173	172	162	154	148
I%	3	4	18	2	2	2

m/e	147	145	133	132.5	132	131
I%	4	2	3	6	2	3

m/e	120	119	118	117	106	105	104
I%	3	9	33	2	4	15	5

m/e	103	91	78	77	76	64	63
I%	3	2	7	35	2	4	2

m/e	52	51	44	42	36
I%	2	5	2	3	2

m^* 263(265 → 264), 235.9(265 → 250), 189.3(265 → 224), 111.6(265 → 172), 56.5(105 → 77).

6,8-Dimethyl-2,3-diphenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3, R^1=Ph)

m/e	328	327(M^+)	326	325	324	312
I%	3	23	100	73	5	3

m/e	298	250	235	234	209	208
I%	2	4	3	8	2	8

m/e	207	195	193	181	180	179
I%	6	2	2	4	13	2

m/e	178	167	166	128	127	120	119
I%	3	2	2	3	2	3	3

m/e	116	105	104	103	93	91	79
I%	2	5	7	3	2	3	3

m/e	78	77	76	75	65	64	63
I%	9	46	4	2	4	27	8

m/e	62	61	52	51	50	45	43
I%	2	3	4	17	3	3	13

m/e	42	41	39	38
I%	8	2	4	2

m^* 324(326 → 325), 206(208 → 207).

6,8-Dimethyl-3-(3^1-nitrophenyl)-2-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3; R^1=3^1-NO_2Ph).

m/e	373	372(M^+)	371	370	343	342
I%	5	24	100	24	2	4

m/e	341	327	326	325	324	301
I%	3	3	9	18	5	2

m/e	300	297	296	295	255	250
I%	6	3	2	2	2	2

m/e	249	235	234	226	225	209
I%	2	2	6	2	8	4

m/e	208	207	194	193	181	180
I%	18	10	2	3	2	4

m/e	179	178	177	168	167	166
I%	12	4	2	2	4	5

m/e	163	153	152	149	148	141
I%	4	2	3	7	16	2

m/e	140	139	133	132	131	130
I%	3	2	4	2	2	4

m/e	128	127	121	120	119	118
I%	3	2	2	7	5	2

m/e	117	116	115	106	105	104
I%	2	3	7	3	10	10

m/e	103	102	93	92	91	90
I%	6	2	2	5	2	4

m/e	89	79	78	77	76	75	66
I%	3	7	10	18	43	5	2

m/e	65	64	63	62	53	52	51
I%	4	62	20	3	2	3	11

m/e	50	42	41	39	38
I%	10	16	2	8	4

m^{*} 369(371 → 370), 284.7(371 → 325), 206(208 → 207).

2,6-Dimethyl-3-phenyl-8-styrylpyrido[3,4-d]pyrimidin-4(3H)-one (74).

m/e	355	354	353(M^+)	352	338	326	
I%	3	21	87	21	4	4	
m/e	325	324	311	310	284	283	
I%	17	27	2	6	7	9	
m/e	276	252	248	235	234	233	
I%	7	8	3	4	4	4	
m/e	224	222	219	209	208	207	206
I%	3	2	2	12	75	11	5
m/e	205	193	192	181	180	176.5	174
I%	4	6	7	3	3	3	2
m/e	165	152	151	150	140	139	128
I%	2	6	6	3	4	4	3
m/e	126	119	118	117	115	105	103
I%	3	13	87	3	4	10	4
m/e	102	91	89	78	77	76	75
I%	5	4	2	13	100	5	2
m/e	65	64	63	55	52	51	50
I%	3	4	3	2	4	25	4
m/e	46	45	43	42			
I%	23	5	23	11			

m^* 350.9(353 → 352), 322.9(325 → 324), 299.2(353 → 325), 282.

6,8-Dimethyl-2-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (62; R=CH_3, R^1=H)

m/e	252	251(M^+)	250	249	227	225		
I%	10	52	22	2	3	3		
m/e	224	223	209	208	207	176		
I%	19	2	3	7	3	2		
m/e	175	167	166	149	148	147		
I%	2	2	2	2	3	2		
m/e	126	125.5	124	123	122	121		
I%	3	3	3	15	5	5		
m/e	120	119	107	106	105	104		
I%	3	3	2	10	100	8		
m/e	103	97	95	94	93	92		
I%	3	2	2	2	2	2		
m/e	91	81	80	79	78	77		
I%	2	2	2	5	12	60		
m/e	76	75	74	69	67	66		
I%	7	3	3	2	2	2		
m/e	65	64	63	62	58	57	56	55
I%	3	10	5	2	3	2	2	3
m/e	53	52	51	50	44	43	42	
I%	5	8	20	7	2	2	8	

m^* 198.1(251 → 223), 172.4(251 → 208), 87.3, 56.5(105 → 77).

1-Ethyl-3,4-dihydro-3,6,8-trimethylpyrido[3,4-d]pyrimidin-2(1H)-one (100).

m/e	220	219(M^+)	218	205	204	203	
I%	10	68	7	8	25	3	
m/e	192	191	190	176	162	161	
I%	3	13	25	4	5	13	
m/e	160	149	148	147	146	145	
I%	3	4	15	100	4	3	
m/e	135	134	133	132	131	128	
I%	3	10	23	3	3	10	
m/e	121	120	119	118	117	107	106
I%	8	38	13	18	5	5	10
m/e	105	104	93	92	91	80	79
I%	5	4	8	10	8	5	10
m/e	78	77	76	67	66	65	64
I%	10	18	4	5	18	30	8
m/e	63	56	54	53	52	51	50
I%	5	5	5	10	10	10	5
m/e	42	41					
I%	33	10					

m^* 190 (219 → 204), 164.9(219 → 190), 105.9(204 → 147).

3,4-Dihydro-4-hydroxy,2,6,8-trimethyl-3-phenyl-pyrido[3,4-d]pyrimidine (90)

m/e	268	267(M^+)	266	265	253	252	251
I%	6	23	6	4	2	7	26
m/e	250	249	248	238	225	224	209
I%	100	4	8	2	2	2	2
m/e	208	207	193	181	176	175	173
I%	2	2	2	2	3	14	2
m/e	172	168	167	166	163	149	148
I%	2	3	6	2	2	2	2
m/e	147	146	134	133	131	130	119
I%	3	2	2	2	2	2	3
m/e	118	117	115	106	105	104	103
I%	11	2	2	3	2	5	2
m/e	93	92	91	80	79	78	77
I%	3	3	3	2	2	5	27
m/e	76	66	65	64	63	53	52
I%	2	2	5	5	4	4	3
m/e	51	50	43	42	41	39	
I%	8	2	4	6	2	4	

m^* 234.1(267 → 250).

3,4-Dihydro-2,6,8-trimethylpyrido[3,4-d]pyrimidine (107).

m/e	176	175(M^+)	174	173	172	160	159	158
I%	7	53	86	100	16	3	2	5

m/e	147	146	145	135	134	133	132	131
I%	7	38	9	2	14	16	7	7

m/e	120	119	118	117	107	106	105	104
I%	3	18	3	2	5	12	9	6

m/e	93	92	91	90	79	78	77	76
I%	4	5	4	3	4	5	9	3

m/e	75	74	67	66	65	64	63	62
I%	2	3	3	9	16	41	9	5

m/e	59	54	53	52	51	50	45	42
I%	4	3	4	6	7	3	3	21

m/e	41	40	39	38
I%	7	5	18	5

Pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; R^1=R^2=H).

m/e	164	163(M^+)	147	121	120	119	94
I%	11	100	4	5	43	2	2

m/e	93	92	91	82	81	80	79
I%	33	12	4	25	10	25	10

m/e	67	66	65	64	63	60	52
I%	2	4	13	11	2	4	5

m/e	50	45	44	43
I%	4	2	5	5

m^* 88.4(163 → 120), 72.1(120 → 93), 70.6(120 → 92), 46.0(92 → 65), 45.4(93 → 65), 22.2(65 → 38).

6,8-Dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (8; $R^1=R^2=CH_3$).

m/e	192	191(M^+)	148	121	120	119
I%	10	100	36	7	32	28

m/e	93	92	80	79	78	77
I%	8	4	3	32	9	3

m/e	76	66	65	63	53	52
I%	3	4	4	3	4	17

m/e	51	50	42	39
I%	11	5	8	3

m^* 118(120 → 119), 114.7(191 → 148), 97.3(148 → 120)

3,6,8-Trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; $R^1=R^2=R^4=CH_3$, $R^3=H$)

m/e	206	205(M^+)	191	179	178	149
I%	11	100	5	4	7	8

m/e	147	121	120	119	93	92	79
I%	7	8	46	26	8	5	29

m/e	78	77	76	67	66	65	64
I%	9	4	4	5	5	5	7

m/e	63	52	51	50	44	42	41
I%	8	18	12	5	5	9	5

m/e	39
I%	5

m^* 118(120 → 119), 106.9(205 → 148), 97.3(148 → 120).

1,3-Dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione
(64; $R^1=R^2=H$, $R^3=R^4=CH_3$)

m/e	192	191(M^+)	163	162	161	135	134
I%	12	100	5	4	3	3	8

m/e	133	107	106	105	93	91	81
I%	4	7	73	18	18	3	3

m/e	80	79	78	77	76	69	66	65
I%	3	13	8	3	3	3	4	6

m/e	64	63	56	53	52	51	50	42
I%	14	3	3	3	7	8	7	6

m/e	38	37
I%	8	4

m^* 104(106 → 105), 94.1(191 → 134), 83.9(134 → 106), 58.9(106 → 79).

1,3,6,8-Tetramethylpyrido[3,4-d]pyrimidine-2,4(1H, 3H)-dione (64; $R^1=R^2=R^3=R^4=CH_3$)

m/e	220	219(M^+)	218	205	204	191	
I%	14	100	4	3	22	3	
m/e	190	189	176	175	162	161	
I%	11	7	3	8	4	3	
m/e	148	147	146	134	133	120	
I%	11	23	3	13	11	5	
m/e	119	109.5	107	93	92	79	78
I%	14	3	4	3	6	4	10
m/e	77	72	66	65	64	63	56
I%	4	5	4	5	3	3	3
m/e	52	51	50	42	41	39	
I%	7	8	3	11	3	4	

m^* 190(219 → 204), 164.9(219 → 190), 132.8(135 → 134), 123.5(175 → 147), 120, 116, 111, 97, 96.3(147 → 119).

3-Amino-6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (71; $R^1=R^2=CH_3$)

m/e	207	206(M^+)	191	177	176	175
I%	10	72	4	3	11	100
m/e	154	148	147	120	119	106
I%	6	7	20	7	19	4

m/e	93	92	79	78	77	76	
I%	4	3	11	19	6	4	
m/e	66	65	64	63	53	52	51
I%	4	4	4	4	6	20	14
m/e	50	44	43	42	41	39	
I%	6	4	4	3	13	6	

m^* 148.5(206 → 175), 123.5(175 → 147), 96.3(147 → 119).

3-Aminopyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (71; R^1=R^2=H).

m/e	179	178(M^+)	163	149	148	147	
I%	9	100	3	3	9	99	
m/e	138	121	120	119	105	94	
I%	2	2	11	29	2	4	
m/e	93	92	91	78	77	70	
I%	19	8	11	5	2	4	
m/e	67	66	65	64	63	54	
I%	4	7	15	18	4	2	
m/e	53	52	51	50	49	44	41
I%	4	6	6	11	2	2	4
m/e	40	39	38	37			
I%	4	10	29	11			

m^* 121.4(178 → 147), 96.3(147 → 119), 69.6(119 → 91).

(ii) Pyrido[3,4-d][1,3]oxazines

2,6,8-Trimethylpyrido[3,4-d][1,3]oxazin-4-one (45)

m/e	191	190(M^+)	175	163	162	161
I%	12	100	6	5	39	6
m/e	148	147	146	121	120	119
I%	9	8	14	6	14	15
m/e	106	105	93	79	78	77
I%	5	6	5	18	12	5
m/e	65	64	63	52	51	50
I%	5	21	11	13	14	6
m/e	44	43	42			
I%	5	46	18			

m^* 161.1(190 → 175), 138.1(190 → 162), 123.5(175 → 147), 75.5(146 → 105).

2-Phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=H)

m/e	225	224(M^+)	180	122	106	105
I%	6	31	7	46	11	100
m/e	77	76	64	51	50	
I%	57	6	6	20	13	

m^* 144.7(224 → 180), 90.3(122 → 105), 56.5(105 → 77).

6,8-Dimethyl-2-phenylpyrido[3,4-d][1,3]oxazin-4-one (46; R=CH_3)

m/e	253	252(M^+)	224	219	208	204
I%	18	100	21	28	13	5

m/e	147	134	119	106	105	78
I%	6	5	7	8	87	17

m/e	77	64	63	52	51	50
I%	60	13	7	8	21	6

m/e	42
I%	11

m^* 199.9(252 → 224), 171.7(252 → 208), 56.5(105 → 77).

4,4-Diphenyl-2,6,8-trimethylpyrido[3,4-d][1,3]oxazine (73)

m/e	330	329	328(M^+)	313	288	287
I%	4	11	41	4	4	11

m/e	286	285	284	283	272	271
I%	41	100	14	5	7	25

m/e	270	269	251	245	244	243
I%	3	4	7	4	9	4

m/e	242	241	240	230	229	228
I%	5	4	4	3	5	7

m/e	227	217	216	215	214	213
I%	5	4	4	7	4	4

m/e	210	209	203	202	201	189
I%	5	14	4	9	3	4

m/e	178	176	167	166	165	152
I%	3	3	3	4	7	3

m/e	141	140	139	128	115	94
I%	3	3	4	5	5	3

m/e	92	91	78	77	76	65
I%	3	5	5	9	3	3

m/e	64	63	57	56	51	43
I%	3	4	3	3	5	21

m/e	42	41	39
I%	7	4	5

m^* 298.6(328 → 313), 283.9(286 → 285), 249.4(328 → 286).

(iii) Pyridine derivatives

3-Amino-2,6-dimethylpyridine-4-carboxylic acid (10; R=CH_3)

m/e	167	166(M^+)	165	149	148	147	122
I%	11	100	3	7	53	8	3

m/e	121	120	119	105	94	93	92
I%	11	36	45	6	4	14	4

m/e	80	79	78	68	67	66	65
I%	11	47	8	3	3	4	6

m/e	64	63	54	53	52	51	50
I%	3	3	7	17	25	14	6

m/e	45	44	43	42	41	40	39
I%	3	3	3	14	7	3	7

m^* 131.95(166 → 148), 118(120 → 119), 97.2(148 → 120)

2,6-Dimethylcinchomeronimide (32; R=CH_3)

m/e	177	176(M^+)	159	158	148	134	133
I%	33	100	6	39	19	8	60

m/e	132	131	130	119	107	106	105
I%	12	6	21	4	5	5	33

m/e	104	93	92	91	90	89	88
I%	7	8	57	13	7	11	4

m/e	79	78	77	76	70	66	65
I%	4	8	18	6	5	7	11

m/e	64	63	62	61	53	51	50
I%	96	49	18	8	9	12	8

m/e	44	43	42	41	39	38
I%	8	5	21	7	11	8

m^* 141.9(176 → 158), 124.5(176 → 148), 100.5(176 → 133), 82.9(133 → 105).

3-Benzamido-2,6-dimethylpyridine-4-carboxamide (61; R=CH_3, R^1=H).

m/e	270	269(M^+)	253	252	251	241	225
I%	3	12	6	29	3	4	2

m/e	224	208	164	148	147	119
I%	2	2	5	2	3	2

m/e	106	105	80	79	78	77
I%	8	100	2	2	6	45

m/e	76	76	65	53	52	51
I%	2	2	2	5	5	10

m/e	50	44	42
I%	10	3	3

m^* 236.1(269 → 252), 215.9(269 → 241), 199.05(252 → 224), 56.5(105 → 77).

3-Benzamido-2,6-dimethyl-N-(3^1-nitrophenyl) pyridine-4-carboxamide (61; R=CH_3, R^1=3^1-NO_2Ph).

m/e	254	253	252	225	224	208	175
I%	9	49	21	2	4	3	2

m/e	147	138	121	119	108	106	105
I%	2	6	2	3	2	8	100

m/e	104	93	92	80	79	78	77
I%	2	2	7	3	3	8	51

m/e	76	66	65	64	63	53	52
I%	3	2	5	3	3	3	6

m/e	51	50	43	42
I%	11	3	31	5

m^* 199.1(252 → 224), 164.1(390 → 253), 56.5(105 → 77).

4-Anilinomethyl-3-ethylamino-2,6-dimethylpyridine (85)

m/e	256	255(M^+)	227	226	225	224	210
I%	17	79	21	100	7	11	5

m/e	209	164	163	162	161	148	147
I%	11	14	79	45	5	16	93

m/e	135	133	127	123	122	121	120
I%	7	11	7	14	9	9	24

m/e	110	108	107	106	105	104	94
I%	7	5	7	14	7	17	11

m/e	93	92	91	81	80	79	78
I%	31	11	11	5	11	28	14

m/e	77	67	66	65	64	63	55
I%	48	14	17	24	5	5	7

m/e	54	53	52	51	50	42	41
I%	7	21	11	17	5	24	17

m/e	40	39
I%	11	24

m^* 200.3(255 → 226), 193.2(226 → 209), 133.4(162 → 147).

3-Ethylamino-2,4,6-trimethylpyridine (97)

m/e	165	164(M^+)	163	151	150	149	148
I%	9	58	9	5	12	100	5

m/e	147	136	135	128	121	120	109
I%	8	6	12	6	6	21	5

m/e	108	107	94	93	92	80	79
I%	12	5	5	9	5	5	8

m/e	78	68	67	66	65	55	54
I%	5	9	12	9	8	6	5

m/e	53	52	51	50	43	42	41
I%	6	6	6	5	6	9	12

m/e	40	39
I%	6	9

m^* 135.4(164 → 149), 96.6(149 → 120), 78.3(149 → 108).

3-Amino-4-ethylaminomethyl-2,6-dimethylpyridine (103).

m/e	180	179(M^+)	178	177	164	163	162	161	151
I%	5	45	5	3	3	3	5	3	15

m/e	150	149	148	147	137	136	135	134	133
I%	100	5	8	10	5	65	50	15	25

m/e	124	123	122	121	120	119	118	109	108
I%	3	25	10	10	5	35	3	5	10

m/e	107	106	105	96	95	94	93	92	91
I%	10	10	3	3	3	10	3	10	5

m/e	82	81	80	79	78	77	68	67	66
I%	5	5	10	5	5	5	3	15	15

m/e	65	64	63	58	56	55	54	53	52
I%	15	3	3	15	3	3	15	15	10

m/e	51	44	43	42	41	40	39
I%	5	30	5	25	13	5	10

m^* 103.3(179 → 136).

4-Aminomethyl-3-ethylamino-2,6-dimethylpyridine (102).

m/e	180	179(M^+)	164	163	162	161	160	159
I%	8	22	16	10	27	10	7	7

m/e	151	150	149	148	147	136	135	134
I%	19	56	30	19	100	16	30	10

m/e	133	123	122	121	120	119	108	107
I%	21	17	7	13	30	12	13	12

m/e	106	94	93	92	91	80	79	78
I%	21	8	10	10	17	11	21	10

m/e	77	67	66	65	64	63	54	53
I%	21	13	19	25	7	8	10	22

m/e	52	51	42	41	40	39
I%	15	11	33	17	8	24

m^* 146.6(179 → 162), 133.4(162 → 147).

4-Anilinomethyl-2,6-dimethyl-3-methylaminopyridine (89).

m/e	242	241(M^+)	227	226	224	210	209	151
I%	11	42	4	18	4	3	4	3

m/e	150	149	148	147	146	137	136	135
I%	18	100	47	49	4	3	4	5

m/e	134	133	132	123	122	121	120	119
I%	4	11	3	5	3	8	26	4

m/e	118	108	107	106	105	104	94	93
I%	3	10	10	16	4	7	8	40

m/e	92	91	80	79	78	77	68	67
I%	8	7	5	20	10	31	3	8

m/e	66	65	64	63	54	53	52	51
I%	14	19	4	4	4	10	8	11

m/e	50	42	41	40	39
I%	3	16	7	4	14

m^* 211.9(241 → 226), 146(148 → 147), 96.6(149 → 120), 90.9(241 → 148), 72.1(120 → 93).

4-Aminomethyl-2,6-dimethyl-3-methylaminopyridine (106).

m/e	166	165(M^+)	164	163	162	159	151	150
I%	12	100	9	18	6	3	9	65

m/e	149	148	147	137	136	135	134	133
I%	6	18	15	6	50	26	21	41

m/e	132	131	123	122	121	120	119	109
I%	3	3	24	15	15	6	44	6

m/e	108	107	106	105	104	96	95	94
I%	18	21	15	6	3	3	3	15

m/e	93	92	91	82	81	80	79	78
I%	12	9	3	3	6	15	9	12

m/e	77	68	67	66	65	64	63	54
I%	6	6	18	26	24	6	6	15

m/e	53	52	51	50	44	43	42	41
I%	21	15	12	6	38	6	41	18

m/e	40	39
I%	9	21

m^* 136.4(165 → 150), 132.8(165 → 148), 112.1(165 → 136).

4-Anilinomethyl-3-ethylamino-6-methyl-2-styrylpyridine (75).

m/e	343(M^+)	342	341	328	326	316
I%	5	2	2	5	5	2

m/e	315	314	313	312	286	285
I%	7	21	2	5	2	7

m/e	252	251	250	249	248	247
I%	7	23	47	100	7	5

m/e	237	236	235	234	233	223
I%	5	14	54	5	5	7

m/e	222	221	220	219	211	210
I%	16	9	5	5	2	2

m/e	209	208	207	206	205	204
I%	7	12	7	7	5	2

m/e	196	195	194	193	192	191
I%	2	5	7	5	5	2

m/e	182	181	180	179	178	174
I%	2	2	2	2	5	2

m/e	173	168	167	166	165	161	160
I%	12	2	5	2	5	2	9

m/e	159	153	152	151	147	146	145
I%	21	2	5	2	7	7	5

m/e	143	142	141	140	139	133	132
I%	2	2	2	2	2	5	5

m/e	131	130	129	128	127	120	119
I%	5	7	5	7	5	2	5

m/e	118	117	116	115	114	107	106
I%	7	5	5	12	2	5	12

m/e	105	104	103	102	101	94	93
I%	7	12	7	5	2	5	23

m/e	92	91	90	89	80	79	78
I%	14	68	2	2	5	9	37

m/e	77	76	75	71	67	66	65
I%	44	5	2	2	5	14	26

m/e	64	63	57	56	55	54	53
I%	5	7	5	5	5	5	12

m/e	52	51	50	43	42	41	40	39
I%	16	21	9	9	9	12	7	21

m^* 248(250 → 249), 182.2(343 → 250).

N-2,4,6-trimethylpyrid-3-yl-N^1-phenylacetamidine (98).

m/e	254	253(M^+)	252	239	238	163
I%	7	25	4	5	19	17
m/e	162	161	160	159	136	127
I%	14	100	5	2	4	3
m/e	121	120	119	118	104	93
I%	5	51	8	65	2	8
m/e	92	91	80	79	78	77
I%	4	6	3	14	9	51
m/e	67	66	65	57	53	52
I%	2	3	6	3	6	3
m/e	51	50	43	42	41	40
I%	21	2	4	9	13	2

m^* 224(253 → 238). 102.5(253 → 161). 89.5(161 → 120), 72.1(120 → 93), 50.3(118 → 77).

PHARMACOLOGICAL SCREENING RESULTS.

A selected number of pyrido[3,4-d]pyrimidines and pyridine derivatives were subjected to general and specific pharmacological screening tests in intact mice and rats. The compounds were also screened as anti-bacterial agents.

3-Aminopyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (71; $R^1=R^2=H$) 3-benzamido-2,6-dimethylpyridine-4-carboxamide (61; $R=CH_3 R^1=H$) and 2,6-dimethylpyridine-3,4-dicarboxamide (9; $R^1=R^2=CH_3$) administered orally to mice in the first two cases and rats in the latter, at a dose of 200 mg./Kg., failed to produce any overt side effects. 3-Amino-6,8-dimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (71; $R^1=R^2=CH_3$) administered to mice in a similar dose produced slight hypotonia in a third of the animals. In all cases one animal of each dose level was injected with tetrabenazine (10-20 mg./Kg. I.P.) approximately three hours after dosing, no tetrabenazine antagonism was observed.

Certain of the compounds were screened for tranquilliser activity, 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one (45), 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72) and 6,8-dimethylpyrido[3,4-d]pyrimidin-4(3H)-one (11; $R=CH_3$, $R^1=H$) administered orally at a dose of 200 mg./Kg. failed to antagonise Metrazol-induced convulsions in rats. 3,6,8-Trimethyl-pyrido[3,4-d]pyrimidine-2,4(1H.3H)-dione (64; $R^1=R^2=R^4=CH_3$, $R^3=H$) at a similar dosage produced protection in 20% of the animals against Metrazol-induced convulsions.

Anti-bacterial Activity.

None of the compounds tested; 6,8-dimethyl-pyrido[3,4-d]pyrimidin-4(3H)-one (11; R=CH_3, R^1=H), 3-hydroxy-2,6,8-trimethylpyrido[3,4-d]pyrimidin-4(3H)-one (59), 2,6,8-trimethyl-3-phenylpyrido[3,4-d]pyrimidin-4(3H)-one (72), 3,6,8-trimethylpyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (64; R^1=R^2=R^4=CH_3, R^3=H), 3-amino-6,8-dimethyl-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (71; R^1=R^2=CH_3), 2,6,8-trimethyl-pyrido[3,4-d][1,3]oxazin-4-one (45) and 3-benzamido-2,6-dimethyl-pyridine-4-carboxamide (61; R=CH_3, R^1=H) showed any significant antimicrobial activity against the organism in table I.

Table I

Streptococcus faecalis (Gram positive)

Straphylococcus aureus (resistant strain; Gram positive)

Straphylococcus aureus (sensistive strain; Gram positive)

Klebsiella pneumonia (Gram negative)

Pseudomonas aeruginosa (Gram negative)

Escherichia coli (Gram negative)

Salmonella typhi (Gram negative)

Trichophyton mentagnophytes (Fungus)

Mycobacterium smegmatis (Acid fast)

Candida albicans (Fungus)

Bacillus subtilis (Gram positive)

Trichomonas foetus (protozon)

Fusarium oxysporum var. lycopersici (fungus-Anscomycetes)

Penicillium citrinium var. leiter (fungus)

Aspergillus niger (fungus-Ascomycetes)

Cyptococcus neoformans (Yeast)

Histoplasma capsulatum (Fungi imperfecti)

Blastomyces dermatitidis (Yeast)

Xanthomonas vesicatoria ATCC 11551 (bacterium)

Streptococcus pyogenes C203 (Gram positive)

Sarcina lutea (non-pathogenic, Gram positive)

Mycobacterium tuberculosis (H37RV)(human strain)

Mycoplasma salivarium (PPLO; human strain)

Mycoplasma gallisepticum (STR #S19/5-6) (PPLO; avian strain)

Ascaris suum (helminth, large roundworm)

Hymenolepis nana (mouse tapeworm)

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Pyridopyrimidines. Part V.[1] Syntheses and Properties of Pyrido[3,4-*d*]-pyrimidin-4(3*H*)-ones and -pyrimidine-2,4-(1*H*,3*H*)-diones

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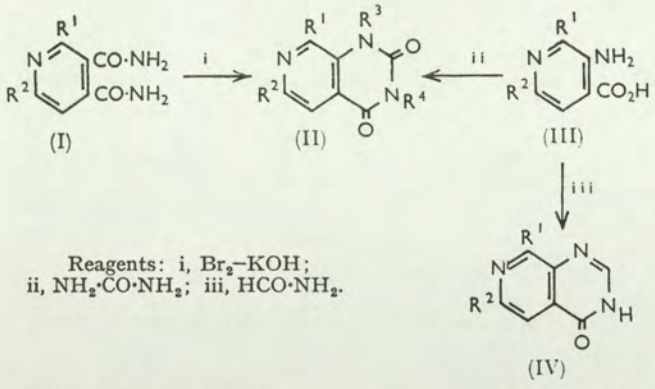
Pyridopyrimidines. Part V.[1] Syntheses and Properties of Pyrido[3,4-*d*]-pyrimidin-4(3*H*)-ones and -pyrimidine-2,4-(1*H*,3*H*)-diones

By **I. R. Gelling** and **D. G. Wibberley,*** Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham, 4

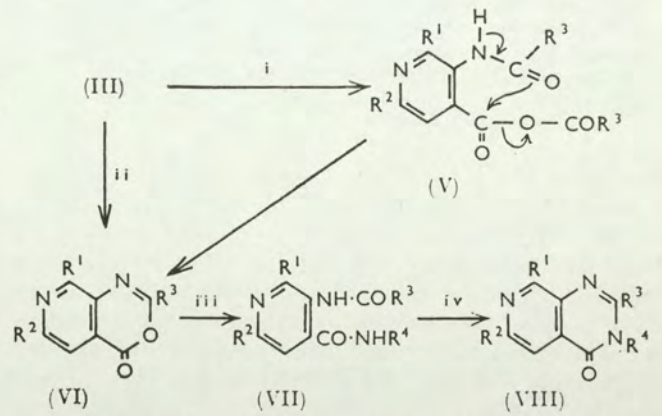
2,6,8-Trimethyl-, 6,8-dimethyl-2-phenyl-, and 2-phenyl-pyrido[3,4-*d*][1,3]oxazin-4-ones have been prepared from the corresponding 3-aminopyridine-4-carboxylic acids. Treatment of the pyrido-oxazines with amines yielded the corresponding pyrido[3,4-*d*]pyrimidines or intermediate 3-aminopyridine-4-carboxamides. Hydrazinolyses and methylations of a number of pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones and -pyrimidine-2,4(1*H*,3*H*)-diones are described. Some n.m.r. and mass spectra are discussed.

FEW pyrido[3,4-*d*]pyrimidines have been described in the literature. The parent compound was prepared by Armarego,[2] who demonstrated its susceptibility to covalent hydration. Pyrido[3,4-*d*]pyrimidine-2,4(1H,-3*H*)-dione (II; $R^1 = R^2 = R^3 = R^4 = H$), the first recorded pyridopyrimidine of any system, was prepared by the Hofmann degradation of pyridine-3,4-dicarboxamide (I; $R^1 = R^2 = H$).[3] This route has also been used for 6-methyl- (II; $R^1 = R^3 = R^4 = H$, $R^2 = Me$)[4] and 6,8-dimethyl- (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione and was our method of choice for the latter compound. The dione (II; $R^1 = R^2 = R^3 = R^4 = H$) we prepared by the alternative route[3] from 3-aminopyridine-4-carboxylic acid (III; $R^1 = R^2 = H$) and urea. A similar fusion process with formamide yielded pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one[3] (IV; $R^1 = R^2 = H$) and 6,8-dimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (IV; $R^1 = R^2 = Me$).



Reagents: i, Br_2–KOH; ii, NH_2·CO·NH_2; iii, HCO·NH_2.

We have previously demonstrated that pyrido-[3,2-*d*]-[5] and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones[6] can be synthesised from pyrido-oxazines and this type of route proved equally successful for the pyrido[3,4-*d*] pyrimidine system (VI). The scope of this synthetic route was extended by the adaptation of a method used by Bain and Smalley.[7] These authors have shown that an excess of an acyl chloride is necessary for the preparation of benzoxazines from anthranilic acid, and that mixed anhydrides are intermediates in the reaction. By this type of method a 3-aminopyridine-4-carboxylic acid (III; $R^1 = R^2 = H$ or $R^1 = R^2 = Me$) was treated with benzoyl chloride (2 mol.) in pyridine to yield the pyrido[3,4-*d*][1,3]oxazin-4-one (VI; $R^1 = R^2 = H$, $R^3 = Ph$ or $R^1 = R^2 = Me$, $R^3 = Ph$) in one step. The isolation of 4-benzamidopyridine-3-carboxylic acid in a closely similar reaction with 4-aminopyridine-3-carboxylic acid and less benzoyl chloride (1 mol.),[6] suggests that in the pyridopyrimidines, as in the benzoxazines,[7] mixed anhydrides are likely intermediates. 2,6,8-Trimethylpyrido[3,4-*d*][1,3]oxazin-4-one (VI; $R^1 = R^2 = R^3 = Me$) yielded the pyrido[3,4-*d*]pyrimidin-4-(3*H*)-ones (VIII; $R^1 = R^2 = R^3 = Me$, $R^4 = H$, OH, NH_2, and Ph) directly on treatment with ammonia, hydroxylamine, hydrazine, and aniline respectively. 2-Phenyl substituted compounds on the other hand, yielded the intermediate diamides (VII) on treatment with ammonia,



Reagents: i, BzCl (2 mol.)–pyridine; ii, Ac_2O; iii, R^4NH_2; iv, heat or R^4NH_2.

aniline, or *m*-nitroaniline. The diamides (VII) were cyclised to the corresponding pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones (VIII) by the action of heat for several hours.

The treatment of the pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones (IV; $R^1 = R^2 = H$ and $R^1 = R^2 = Me$) with hydrazine hydrate yielded the parent amino-acids (III; $R^1 = R^2 = H$ and $R^1 = R^2 = Me$), whereas the

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pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (II; $R^1 = R^2 = R^3 = R^4 = H$ and $R^1 = R^2 = Me$, $R^3 = R^4 = H$) yielded *N*-amino-compounds (II; $R^1 = R^2 = R^3 = H$, $R^4 = NH_2$ and $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = NH_2$).

Methylation at the 3-position was accomplished by the treatment of 6,8-dimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (IV; $R^1 = R^2 = Me$) and -2,4(1*H*,3*H*)-dione (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) with dimethyl sulphate in aqueous alkali at room temperature. The dione (II; $R^1 = R^2 = R^4 = Me$, $R^3 = H$) was converted into the 1,3,6,8-tetramethyl-dione (II; $R^1 = R^2 = R^3 = R^4 = Me$) with more dimethyl sulphate in aqueous alkali at 40°. This type of methylation was unsuccessful for the analogous compounds with no methyl groups in the pyridine ring (IV; $R^1 = R^2 = H$) and (II; $R^1 = R^2 = R^3 = R^4 = H$) and gave only intractable tars. Methyl iodide and sodium ethoxide, however, gave the required *N*-methyl derivatives (VIII; $R^1 = R^2 = R^3 = H$, $R^4 = Me$) and (II; $R^1 = R^2 = H$, $R^3 = R^4 = Me$) in these cases.

The n.m.r. spectra of a number of pyrido[3,4-*d*][1,3]-oxazines and pyrido[3,4-*d*]pyrimidines are recorded in Table 1. The poor solubilities of certain of the compounds in deuteriochloroform necessitated the use of trifluoroacetic acid as a solvent which resulted in the expected powerful deshielding effects. Because of the variations in solvent, direct comparison of the n.m.r. spectra of the pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones with that of the parent pyrido[3,4-*d*]pyrimidine (*cf.* footnote *b*, Table 1) are difficult. Where a direct comparison is possible, as in the case of 3-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one, the ring protons at the 2, 6, and 8-positions show an upfield shift compared with the parent compound,[8] whereas 5-H, which is deshielded by the adjacent carbonyl group, shows a downfield shift.

TABLE 1

N.m.r. spectra [a] of pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones, pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3H)-diones, and pyrido-[3,4-*d*][1,3]oxazin-4-ones. Chemical shifts (τ values)

Compound [b]	R^1	R^2	R^3	R^4	Solvent	Protons and substituents in the pyridine ring: 5	6	8	Protons and substituents in the pyrimidine and oxazine rings: 1	2	3
(IV)	H	H			TFA [c]	0·99(H) [d]	0·99(H)	0·18(H)		1·08(H)	
(IV)	Me	Me			TFA	1·48(H)	7·02(Me)	6·77(Me)		1·23(H)	
(VIII)	H	H	Me	H	TFA	0·88(H)	0·95(H)	0·47(H)		7·02(Me)	
(VIII)	Me	Me	H	Me	TFA	1·49(H)	7·34(Me)	6·81(Me)		1·2(H)	6·18(Me)
(VIII)	Me	Me	Me	H	TFA	1·51(H)	7·03(Me)	6·8(Me)		7·12(Me)	
(VIII)	Me	Me	Me	OH	TFA	1·6(H)	7·08(Me)	6·8(Me)		7·08(Me)	
(VIII)	Me	Me	Ph	H	TFA	2·1(H)	7·1(Me)	7·42(Me)		2·2—2·32 and 2·79—2·90 (Ph)	
(VIII)	H	H	H	Me	$CDCl_3$	1·29(H) [e]	1·95(H)	0·86(H)		1·87(H)	6·39(Me)
(VIII)	Me	Me	H	Me	$CDCl_3$	2·25(H)	7·34(Me)	7·15(Me)		1·97(H)	6·4(Me)
(VIII)	Me	Me	Me	NH_2	$CDCl_3$	2·3(H)	7·3(Me)	7·16(Me)		7·37(Me)	5·09 (NH_2) [f]
(VIII)	Me	Me	Me	Ph	$CDCl_3$	2·34(H)	7·8(Me)	7·4(Me)		7·17 (Me)	2·68—2·73 and 2·46—2·53 (Ph)
(VIII)	Me	Me	Ph	Ph	$CDCl_3$	2·32(H)	7·24(Me)	7·03(Me)		2·72—2·92(Ph)	
(VIII)	Me	Me	Ph	NO_2Ph	$CDCl_3$	2·47(H)	7·4(Me)	7·18(Me)		2·18(H)	2·68—2·92(Ph and nitrophenyl)
(II)	H	H	H	H	TFA	1·75(H)	1·75(H)	1·39(H)			
(II)	Me	Me	H	H	TFA	1·8(H)	7·08(Me)	6·95(Me)			
(II)	Me	Me	H	NH_2	TFA	1·59(H)	7·09(Me)	6·93(Me)			
(II)	Me	Me	H	Me	TFA	1·6(H)	7·12(Me)	6·97(Me)			6·38(Me)
(II)	Me	Me	Me	Me	TFA	1·48(H)	7·08(Me)	6·78(Me)	6·36(Me)		6·05(Me)
(II)	Me	Me	Me	Me	$CDCl_3$	2·29(H)	7·45(Me)	7·18(Me)	6·53(Me)		6·29(Me)
(II)	H	H	Me	Me	$CDCl_3$	1·43(H)	1·99(H)	1·25(H)	6·51(Me)		6·34(Me)
(VI)	H	H	Ph		$CDCl_3$	1·22(H)	1·99(H)	0·89(H)	1·59—1·73 and 2·41—2·52(Ph)		
(VI)	Me	Me	Me		$CDCl_3$	2·46(H)	7·55(Me)	7·47(Me)	7·29(Me)		
(VI)	Me	Me	Ph		$CDCl_3$	2·64(H)	7·3(Me)	7·09(Me)	1·62—1·73 and 2·28—2·5(Ph)		

[a] Measured at 60 Mc./sec. [b] Pyrido[3,4-*d*]pyrimidine: τ ($CDCl_3$) 0·48(s, 2-H), 0·42(d, *J* 0·7 c./sec., 4-H), 2·21(d, *J* 5·8 c./sec., 5-H), 1·15(d, *J* 5·8 c./sec. 6-H), 0·45 d, *J* 0·7 c./sec. 8-H). [c] TFA = trifluoroacetic acid. [d] Singlets except where stated otherwise. [e] Doublets (*J* 5·0 c./sec.). [f] Disappears on shaking with D_2O.

TABLE 2

Mass spectra of pyrido[3,4-*d*][1,3]oxazin-4-ones *

2,6,8-Trimethylpyrido[3,4-*d*][1,3]oxazin-4-one: 191 (12), 190 (100) M^+, 175 (6), 163 (5), 162 (39), 161 (6), 148 (9), 147 (8), 146 (14), 121 (6), 120 (14), 119 (15), 106 (5), 105 (6), 93 (5), 79 (18), 78 (12), 77 (5), 65 (5), 64 (21), 63 (11), 52 (13), 51 (14), 50 (6), 44 (5), 43 (46), 42 (18); *m* * 161·1 (190 ⟶ 175), 138·1 (190 ⟶ 162), 123·5 (175 ⟶ 147), 75·5 (146 ⟶ 105)

6,8-Dimethyl-2-phenylpyrido[3,4-*d*][1,3]oxazin-4-one: 253 (18), 252 (100) M^+, 224 (21), 219 (28), 208 (13), 204 (5), 147 (6), 134 (5), 119 (7), 106 (8), 105 (87), 78 (17), 77 (60), 64 (13), 63 (7), 52 (8), 51 (21), 50 (6), 42 (11); *m* * 199·9 (252 ⟶ 224), 171·7 (252 ⟶ 208), 56·5 (105 ⟶ 77)

2-Phenylpyrido[3,4-*d*][1,3]oxazin-4-one: 225 (6), 224 (31) M^+, 180 (7), 122 (46), 106 (11), 105 (100), 77 (57), 76 (6), 64 (6), 51 (20), 50 (13); *m* * 144·7 (224 ⟶ 180), 90·3 (122 ⟶ 105), 56·5 (105 ⟶ 77)

* Intensities of ions above 4% of the base peak are shown in parenthesis. Ions below *m/e* 42 are not shown.

The mass spectra of the pyrido[3,4-*d*]pyrimidines are to be recorded elsewhere. Those of three pyrido[3,4-*d*]-

[8] W. L. F. Armarego and T. J. Batterham, *J. Chem. Soc.* (*B*), 1966, 750.

[1,3]oxazin-4-ones are given in Table 2. The pyrido-oxazines were more susceptible to fragmentation by electron impact than the corresponding pyridopyrimidines but with the two 6,8-dimethyl compounds (VI; $R^1 = R^2 = R^3 = Me$ and $R^1 = R^2 = Me$, $R^3 = Ph$) the molecular ion was still the base peak. The two most important fragmentation losses from all three compounds were CO and CO_2. The principal fragmentation ion was an acyl group, CH_3CO^+ for the 2,6,8-trimethyl compound (VI; $R^1 = R^2 = R^3 = Me$), and $PhCO^+$ for both 6,8-dimethyl-2-phenyl- (VI; $R^1 = R^2 = Me$, $R^3 = Ph$) and 2-phenyl- (VI; $R^1 = R^2 = H$, $R^3 = Ph$) pyrido[3,4-*d*]oxazin-4-one; in the latter case this was the peak in the spectrum.

EXPERIMENTAL

I.r. spectra were determined with a Unicam SP 200 spectrophotometer, n.m.r. spectra with a Varian A-60A spectrometer, and mass spectra with an A.E.I. M.S.9 spectrometer operating at 50 μA and 70 ev.

2,6,8-*Trimethylpyrido*[3,4-d][1,3]*oxazin-4-one* (VI; $R^1 = R^2 = R^3 = Me$).— 3-Amino-2,6-dimethylpyridine-4-carboxylic acid (1·0 g.) and acetic anhydride (12 ml.) were heated together under reflux for 2 hr. The excess of acetic anhydride was removed under reduced pressure, and the residue was cooled to yield the *pyrido-oxazine* (0·8 g., 70%), needles, m.p. 139—140° (from ethyl acetate) (Found: C, 63·0; H, 5·4; N, 14·6. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·7%), $\nu_{max.}$ 1745 (C=O), 1635 (C=N), and 1240 (C–O) cm.$^{-1}$. The pyrido-oxazine was substantially unchanged after exposure to the air for 1 week. A suspension of the pyrido-oxazine (0·15 g.) in water (10 ml.) was stirred for 16 hr. at room temperature to yield 3-*acetamido*-2,6-*dimethylpyridine*-4-*carboxylic acid* (0·12 g., 75%), m.p. 274—276° (Found: C, 57·3; H, 6·0; N, 13·6. $C_{10}H_{12}N_2O_3$ requires C, 57·7; H, 5·8; N, 13·5%), $\nu_{max.}$ 3150 (N–H), 2500—2400 (bonded O–H), 1680 and 1650 (C=O) cm.$^{-1}$.

2,6-*Dimethyl*-2-*phenylpyrido*[3,4-d][1,3]*oxazin-4-one* (VI; $R^1 = R^2 = Me$, $R^3 = Ph$).—3-Amino-2,6-dimethylpyridine-4-carboxylic acid hydrochloride (1·0 g.) and benzoyl chloride (1·5 ml.) were heated together under reflux for 20 min. The solution was diluted with water to yield the *pyrido-oxazine* (0·75 g., 61%), needles, m.p. 156—157° (from benzene) (Found: C, 71·5; H, 4·9; N, 11·2. $C_{15}H_{12}N_2O_2$ requires C, 71·5; H, 4·8; N, 11·1%), $\nu_{max.}$ 1750 (C=O), 1610 (C=N), and 1240 (C–O) cm.$^{-1}$. The pyrido-oxazine was not hydrolysed by treatment with water at 35—45° for 3 days.

2-*Phenylpyrido*[3,4-d][1,3]*oxazin-4-one* (VI; $R^1 = R^2 = H$, $R^3 = Ph$).—Similar treatment of 3-aminopyridine-4-carboxylic acid with benzoyl chloride (2·0 mol.) in pyridine yielded the *pyrido-oxazine* (64%), m.p. 131—132° (from light petroleum) (Found: C, 69·7; H, 3·8; N, 12·3. $C_{13}H_8N_2O_2$ requires C, 69·6; H, 3·6; N, 12·5%), $\nu_{max.}$ 1760 (C=O) 1610 (C=N), and 1240 (C–O) cm.$^{-1}$. The pyrido-oxazine was not hydrolysed by similar treatment with water at 35—45° for 3 days.

6,8-*Dimethylpyrido*[3,4-d]*pyrimidin* 4(3H)-*one* (IV; $R^1 = R^2 = Me$).—3-Amino-2,6-dimethylpyridine-4-carboxylic acid (2·5 g.) and formamide (5·0 g.) were heated together at 165—175° for 2 hr. to yield the *pyridopyrimidine* (1·7 g., 64%), needles, m.p. 289—291° (from acetic acid) (Found: C, 61·4; H, 5·3; N, 23·7. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%), $\nu_{max.}$ 1675 (C=O) cm.$^{-1}$.

2,6,8-*Trimethylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^3 = Me$, $R^4 = H$).—2,6,8-Trimethylpyrido-[3,4-*d*][1,3]oxazin-4-one (0·4 g.) was added to ammonia (10 ml.; *d* 0·88) and the mixture was stirred at room temperature until dissolution was complete (12 hr.). Evaporation under reduced pressure yielded the *pyrido-pyrimidine* (0·33 g., 83%), m.p. 287—289° (from ethanol) (Found: C, 63·2; H, 5·9; N, 22·0. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·8; N, 22·2%), $\nu_{max.}$ 3180 (N–H) and 1680 (C=O) cm.$^{-1}$.

3-*Hydroxy*-2,6,8-*trimethylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^3 = Me$, $R^4 = OH$).—2,6,8-Trimethylpyrido[3,4-*d*][1,3]oxazin-4-one (0·32 g.) was added to a solution of sodium hydroxide (0·5 g.) in ethanol (25 ml.) containing hydroxylamine (0·2 g.) and the mixture was stirred at room temperature for 5 days. The solution was acidified, filtered, and the filtrate was evaporated to yield the *pyridopyrimidine* (0·23 g., 66%), m.p. 256—258° (from ethanol) (Found: C, 58·2; H, 5·6; N, 20·7. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%), $\nu_{max.}$ 2600—2450 (O–H), 1700 (C=O) cm.$^{-1}$. The product is a cyclic hydroxamic acid and gave the typical wine red colour with ferric chloride.

3-*Amino*-2,6,8-*trimethylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^3 = Me$, $R^4 = NH_2$).—Hydrazine hydrate (1·5 ml.) was added to 2,6,8-trimethylpyrido-[3,4-*d*][1,3]oxazin-4-one (0·5 g.) in ethanol (15 ml.) and the mixture was stirred at room temperature until dissolution was complete (7 days). Concentration yielded the *pyrido-pyrimidine* (0·46 g., 86%), m.p. 205—206° (from ethanol) (Found: C, 58·9; H, 6·1; N, 27·5. $C_{10}H_{12}N_4O$ requires C, 58·8; H, 5·9; N, 27·5%), $\nu_{max.}$ 3300 and 3100 (N–H), 1680 (C=O) cm.$^{-1}$.

2,6,8-*Trimethyl*-3-*phenylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^3 = Me$, $R^4 = Ph$).—2,6,8-Trimethylpyrido[3,4-*d*][1,3]oxazin-4-one (0·26 g.) and aniline (0·6 g.) were heated together at 180—190° for 45 min. The cooled melt was triturated with ether to give the pyridopyrimidine (0·34 g., 94%), needles, m.p. 216—217° (from benzene) (Found: C, 72·7; H, 5·4; N, 15·9. $C_{16}H_{15}N_3O$ requires C, 72·5; H, 5·7; N, 15·9%), $\nu_{max.}$ 1670 (C=O) cm.$^{-1}$.

6,8-*Dimethyl*-2-*phenylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = H$).—6,8-Dimethyl-2-phenylpyrido[3,4-*d*][1,3]oxazin-4-one (0·8 g.) and ammonia (10 ml.; *d* 0·88) were stirred together at 20° for 24 hr. and the precipitated 3-*benzamido*-2,6-*dimethylpyridine*-4-*carboxamide* (0·7 g., 86%) was collected, m.p. 277—278° (from ethanol) (Found: C, 66·6; H, 5·7; N, 15·4. $C_{15}H_{15}N_3O_2$ requires C, 66·9; H, 5·6; N, 15·6%), $\nu_{max.}$ 3330 and 3250 (N–H), 1665 and 1640 (C=O) cm.$^{-1}$. The diamide was heated at 240° (oil-bath temperature) for 12 hr. to yield the *pyridopyrimidine* (100%), m.p. 270—271° (Found: C, 71·5; H, 5·4; N, 16·6. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%) $\nu_{max.}$ 1690 (C=O) cm.$^{-1}$.

2-*Phenylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^4 = H$, $R^3 = Ph$).—Similar treatment of 2-phenylpyrido[3,4-*d*][1,3]oxazin-4-one with ammonia yielded 3-*benzamidopyridine*-4-*carboxamide* (82%), m.p. 210—211° (Found: C, 64·5; H, 4·3; N, 17·3. $C_{13}H_{11}N_3O_2$ requires C, 64·7; H, 4·6; N, 17·4%), $\nu_{max.}$ 3450 and 3150 (N–H), 1680, and 1650 (C=O) cm.$^{-1}$. Cyclisation by heat at 260° for 18 hr. gave the *pyridopyrimidine* (100%), m.p. 266—267° (Found: C, 69·7; H, 3·9; N, 18·7. $C_{13}H_9N_3O$ requires C, 70·0; H, 4·0; N, 18·8%), $\nu_{max.}$ 1690 (C=O) cm.$^{-1}$.

6,8-*Dimethyl*-2,3-*diphenylpyrido*[3,4-d]*pyrimidin*-4(3H)-

one (VIII; $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$).— 6,8-Dimethyl-2-phenylpyrido[3,4-*d*][1,3]oxazin-4-one (0·5 g.), aniline (1·0 ml.), and ethanol (25 ml.) were stirred together at 20° for 24 hr. to yield 3-*benzamido*-2,6-*dimethyl*-N-*phenylpyridine*-4-*carboxamide* (0·52 g., 76%), m.p. 253—254° (from ethanol) (Found: C, 73·0; H, 5·4; N, 12·0. $C_{21}H_{19}N_3O_2$ requires C, 73·1; H, 5·5; N, 12·2%), $\nu_{max.}$ 3250 (N–H) and 1650 (C=O) cm.$^{-1}$. The amide was heated at 200° for 12 hr. to yield the *pyridopyrimidine* (100%), m.p. 187—188° (Found: C, 76·8; H, 5·2; N, 13·1. $C_{21}H_{17}N_3O$ requires C, 77·1; H, 5·2; N, 12·8%), $\nu_{max.}$ 1680 (C=O) cm.$^{-1}$.

6,8-*Dimethyl*-3-(3′-*nitrophenyl*)-2-*phenylpyrido*[3,4-d]-*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = 3\text{-}NO_2C_6H_4$).— 6,8-Dimethyl-2-phenylpyrido[3,4-*d*]-[1,3]oxazin-4-one (0·9 g.) and *m*-nitroaniline (1·0 g.) were heated together at 150—160° for 2 hr. The residue was stirred with chloroform and filtered to leave 3-*benzamido*-2,6-*dimethyl*-N-(3-*nitrophenyl*)*pyridine*-4-*carboxamide* (0·4 g., 30%), m.p. 303—304° (from acetone) (Found: C, 64·3; H, 4·6; N, 14·1. $C_{21}H_{18}N_4O_4$ requires C, 64·6; H, 4·6; N, 14·4%), $\nu_{max.}$ 3175 (N–H) and 1645 (C=O) cm.$^{-1}$. Evaporation of the chloroform extract gave the *pyridopyrimidine* (0·3 g., 23%), m.p. 240—241° (light petroleum) which was also formed by heating the amide at 280° for 2 hr. (Found: C, 67·8; H, 4·4; N, 15·2. $C_{21}H_{16}N_4O_3$ requires C, 67·8; H, 4·3; N, 15·1%), $\nu_{max.}$ 1680 (C=O) cm.$^{-1}$.

Reaction of Pyrido[3,4-d]*pyrimidin*-4(3H)-*ones and* -2,4(1H,3H)-*diones with Hydrazine Hydrate.*—(*a*) Pyrido-[3,4-*d*]pyrimidin-4(3H)-one (0·5 g.) and hydrazine hydrate (10 ml.) were heated together under reflux for 20 hr. The excess of hydrazine was evaporated off under reduced pressure and the residual oil was triturated with ethanol to yield 3-aminopyridine-4-carboxylic acid (0·35 g., 74%) (undepressed mixed m.p. and identical i.r. spectrum with an authentic sample).

(*b*) Similar treatment of 6,8-dimethylpyrido[3,4-*d*]-pyrimidin-4(3H)-one (0·7 g.) gave 3-amino-2,6-dimethylpyridine-4-carboxylic acid (0·5 g., 75%).

(*c*) 6,8-Dimethylpyrido[3,4-*d*]pyrimidine-2,4(1H,3H)-dione (1·0 g.) gave 3-*amino*-6,8-*dimethylpyrido*[3,4-d]-*pyrimidine*-2,4(1H,3H)-dione (II; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = NH_2$) (0·6 g., 56%), needles, m.p. >300° (from water) (Found: C, 52·6; H, 4·7; N, 27·0. $C_9H_{10}N_4O_2$ requires C, 52·4; H, 4·9; N, 27·2%), $\nu_{max.}$ 3350, 3150, and 3050 (N–H), 1725 and 1665 (C=O) cm.$^{-1}$.

(*d*) Pyrido[3,4-*d*]pyrimidine-2,4(1H,3H)-dione (1·0 g.) gave 3-*aminopyrido*[3,4-d]*pyrimidine*-2,4(1H,3H)-*dione* (II; $R^1 = R^2 = R^3 = H$, $R^4 = NH_2$) (0·65 g., 60%), needles, m.p. 278—279° (from water) (Found: C, 47·4; H, 3·1; N, 31·6. $C_7H_6N_4O_2$ requires C, 47·2; H, 3·4; N, 31·5%), $\nu_{max.}$ 3310, 3110, and 3030 (N–H), 1710—1680 (C=O) cm.$^{-1}$.

Methylations.— 3,6,8-*Trimethylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^4 = Me$, $R^3 = H$). Dimethyl sulphate (1·5 ml.) was added to a stirred solution of 6,8-dimethylpyrido[3,4-*d*]pyrimidin-4(3H)-one (0·75 g.) in sodium hydroxide solution (20 ml., 5·0%) at 35—40° during 1 hr. and the mixture was stirred for a further 1 hr. Extraction with chloroform yielded the *methylated derivative* (0·7 g., 81%), m.p. 155—156° (light petroleum) (Found: C, 63·7; H, 5·8; N, 21·9. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·8; N, 22·2%), $\nu_{max.}$ 1675 (C=O) and 1580 (C=N) cm.$^{-1}$.

3,6,8-*Trimethylpyrido*[3,4-d]*pyrimidine*-2,4(1H,3H)-*dione* (II; $R^1 = R^2 = R^4 = Me$, $R^3 = H$). Similar treatment of 6,8-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (1·0 g.) with dimethyl sulphate for 1·5 hr. gave a precipitate of the *trimethyl-dione* (0·8 g., 75%), m.p. 350—353° (from acetic acid) (Found: C, 58·5; H, 5·4; N, 20·4. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%), $\nu_{max.}$ 3200 (N–H), 1715, and 1655 (C=O) cm.$^{-1}$.

1,3,6,8-*Tetramethylpyrido*[3,4-d]*pyrimidine*-2,4(1H,3H)-*dione* (II; $R^1 = R^2 = R^3 = R^4 = Me$). Dimethyl sulphate (4·0 ml.) was added to a stirred solution of 3,6,8-trimethylpyrido[3,4-*d*]pyrimidine-2,4(1H,3H)-dione in sodium hydroxide (30 ml., 5·0%) at 35—40° during 2 hr. The mixture was filtered free from unchanged starting material (1·5 g.) after a further 1 hr., and the filtrate was extracted with chloroform to yield the *tetramethyl-dione* (0·2 g., 10%), m.p. 167—168° (from light petroleum) (Found: C, 60·5; H, 6·1; N, 18·9. $C_{11}H_{13}N_3O_2$ requires C, 60·3; H, 5·9; N, 19·2%), $\nu_{max.}$ 1695 and 1655 (C=O) cm.$^{-1}$.

3-*Methylpyrido*[3,4-d]*pyrimidin*-4(3H)-*one* (VIII; $R^1 = R^2 = R^3 = H$, $R^4 = Me$). Methyl iodide (1·2 ml.) was added to a solution of pyrido[3,4-*d*]pyrimidin-4(3H)-one (0·75 g.) in ethanol (50 ml.) and sodium ethoxide [from sodium (0·12 g.)] and the solution was heated under reflux for 4 hr. The mixture was filtered, and the filtrate was concentrated, diluted with water, and extracted with chloroform to yield the *methylated derivative* (0·48 g., 67%), needles, m.p. 176—177° (from light petroleum) (Found: C, 59·5; H, 4·3; N, 26·2. $C_8H_7N_3O$ requires C, 59·6; H, 4·3; N, 26·1%), $\nu_{max.}$ 1670 (C=O) cm.$^{-1}$.

1,3-*Dimethylpyrido*[3,4-d]*pyrimidine*-2,4(1H,3H)-*dione* (II; $R^1 = R^2 = H$, $R^3 = R^4 = Me$). Similar treatment of pyrido[3,4-*d*]pyrimidine-2,4(1H,3H)-dione (0·5 g.) with methyl iodide (1·6 ml.) (4 hr. reflux) yielded unchanged starting material (0·2 g.) and, by extraction with chloroform as above, the *dimethyl-dione* (0·22 g., 37·5%), needles, m.p. 158—159° (from light petroleum) (Found: C, 56·1; H, 4·7; N, 21·6. $C_9H_9N_3O_2$ requires C, 56·5; H, 4·7; N, 22·0%), $\nu_{max.}$ 1705 and 1665 (C=O) cm.$^{-1}$.

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Pyridopyrimidines. Part VI.[1] Fragmentation of Some Pyridopyrimidin-4(3*H*)-ones and Pyridopyrimidine-2,4(1*H*,3*H*)-diones induced by Electron Impact

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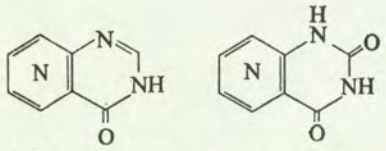
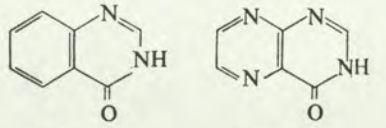
The mass spectra of the four pyrido[2,3-*d*]-, pyrido[3,2-*d*]-, pyrido[3,4-*d*]-, and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones, and the corresponding four -pyrimidine-2,4(1*H*,3*H*)-diones, and a number of methyl-, hydroxy-, and phenyl-substituted derivatives of these compounds have been measured. Fragmentation pathways are postulated on the basis of these spectra and, in certain cases, with the aid of deuterium labelling. Variations are observed in the mode of fragmentation according to the nature of the substitutent group and the position of the nitrogen atom in the pyridine ring, and comparisons are drawn with the quinazolones and pteridones.

THE mass spectra of pyridones,[2] quinolones,[3] quinazolones,[4] and pteridones [5] are recorded in the literature. We have now determined the mass spectra of the four isomeric pyridopyrimidin-4(3*H*)-ones (I), the four pyridopyrimidine-2,4(1*H*,3*H*)-diones (II) and certain of their substituted derivatives (*cf.* Table 1).

The mass spectra of the four pyridopyrimidin-4(3*H*)-ones (I) showed an overall similarity; they are also similar to the reported mass spectra of quinazolin-4(3*H*)-one (III) [4] and pteridin-4(3*H*)-one (IV).[5] Thus the pyridopyrimidin-4(3*H*)-ones all showed strong



(I)[a] (II)[a]



(III) (IV)

The N atom is located in the pyridine ring at the 5-([3,2-*d*]), 6-([4,3-*d*]), 7-([3,4-*d*]), or 8-positions ([2,3-*d*]).

molecular ion peaks (*m/e* 147), small *m/2e* peaks, and a principal degradation pathway in all four cases of an initial loss of CO, followed by two successive losses of one molecule of HCN.

Pyrido[3,2-*d*]pyrimidin-4(3*H*)-one showed the simplest mass spectrum (Table 1) with this degradation pathway (Scheme 1) accounting for the bulk of the ion current (the $[M - CO]^{+\cdot}$ ion at *m/e* 119 has an intensity of 76%). The only other fragmentation pathways of any appreciable importance in this system involved the loss of HCN to yield the fragmentation ion at *m/e* 120, and that of HCNO or HNCO to yield the ion at *m/e* 104. These ions can then fragment further by loss of HNCO and HCN respectively to yield the ion at *m/e* 77 (14%) which is conventionally regarded as a pyridyne radical-ion (Scheme 2). A similar minor fragmentation pathway involving HNCO loss may be deduced from the published mass spectra of quinazolin-4(3*H*)-one [4] and pteridin-4(3*H*)-one [5] but has received no previous mention.

TABLE 1

Mass spectra of pyridopyrimidin-4(3*H*)-ones and pyridopyrimidine-2,4(1*H*,3*H*)-diones

Pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (I)

m/e (I) 148(8), 147(100), 120(8), 119(25), 118(4), 93(9), 92(28), 91(6), 77(4), 76(4), 73·5(1), 66(3), 65(10), 64(10), 63(3), 53(3), 52(3), 51(4), 50(7), 41(4), 40(3), 39(6), 38(8), 37(6)

*m** 96·3 (147 → 119), 71·1 (119 → 92), 45·9 (92 → 65)

Pyrido[2,3-*d*]pyrimidin-4(3-$^2H_1$)-one

m/e (*I*) 149(10), 148(100), 147(38), 121(7), 120(25), 119(16), 93(22), 92(25), 91(7), 77(4), 76(4), 75(3), 73·5(2), 67(3), 66(4), 65(11), 64(14), 63(4), 53(4), 52(4), 51(5), 50(10), 49(4), 41(6), 40(4), 39(7), 38(14), 37(9)

*m** 97·5 (148 → 120), 96·3 (147 → 119), 72·1 (120 → 93), 71·1 (119 → 92), 70·5 (120 → 92), 45·9 (92 → 65), 37·5

Pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (II)

m/e (*I*) 164(8), 163(100), 121(4), 120(40), 119(2), 93(40), 92(32), 91(5), 67(3), 66(3), 65(10), 64(9), 52(3), 50(3), 41(3), 39(3), 38(8), 37(5)

*m** 88·4 (163 → 120)

1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XVI)

m/e (*I*) 192(11), 191(100), 171(4), 163(20), 162(25), 161(7), 134(5), 133(6), 107(5), 106(22), 105(5), 93(5), 81(8), 80(7), 79(83), 78(15), 77(5), 76(5), 66(5), 65(5), 64(8), 58(8), 53(5), 52(11), 51(13), 50(7), 44(22), 36(7)

*m** 139·2 (191 → 163), 84·0 (134 → 106), 59·0 (106 → 79), 34·2 (79 → 52)

Pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (VI; R = H)

m/e (*I*) 148(10), 147(100), 120(5), 119(76), 118(5), 104(5), 92(39), 91(15), 77(14), 76(11), 75(8), 65(19), 64(22), 52(11), 51(11), 50(11), 40(7), 39(11), 38(14), 37(9)

*m** 96·3 (147 → 119), 95·8, 71·1 (119 → 92), 45·9 (92 → 65), 47·4

Pyrido[3,2-*d*]pyrimidin-4(3-$^2H_1$)-one

m/e (*I*) 149(10), 148(100), 147(35), 121(4), 120(28), 119(21), 104(7), 93(17), 92(26), 91(8), 77(14), 76(7), 75(3), 67(4), 66(8), 65(23), 64(17), 63(4), 53(4), 52(7), 51(7), 50(11), 49(3), 42(4), 41(6), 40(10), 39(10), 38(23), 37(10)

*m** 97·5 (148 → 120), 96·3 (147 → 119), 72·1 (120 → 93), 71·2 (119 → 92)

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TABLE 1 (*Continued*)

2-Methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (VI; R = Me)

m/e (*I*) 162(10), 161(100), 160(8), 146(3), 133(22), 132(8), 120(4), 119(8), 118(14), 93(6), 92(14), 91(7), 79(3), 78(8), 77(8), 76(4), 65(7), 64(7), 51(4), 50(7), 43(5), 42(26), 41(6), 40(7), 39(5), 38(6), 37(3), 36(14)

*m** 132·1 (161 → 146), 131·2 (133 → 132), 109·9 (161 → 133), 75·6, 70·3 (120 → 92), 51·6

2-Phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (VI; R = Ph)

m/e (*I*) 224(14), 223(100), 222(14), 196(5), 195(29), 194(9), 180(5), 179(9), 161(6), 120(26), 106(6), 105(10), 104(15), 103(9), 93(3), 92(23), 91(5), 84(3), 76(5), 75(23), 74(8), 65(5), 64(4), 52(4), 51(9), 50(6), 44(20), 36(4)

*m** 170·4 (223 → 195), 144·3, 70·4 (120 → 92), 64·6 (223 → 120)

3-Hydroxy-2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (XI)

m/e (*I*) 178(11), 177(100), 162(12), 161(99), 160(10), 147(14), 146(7), 145(4), 144(4), 133(25), 132(11), 131(8), 120(7), 119(25), 118(21), 117(5), 107(3), 106(15), 105(5), 104(5), 103(4), 93(15), 92(24), 91(15), 79(11), 78(47), 77(19), 76(9), 65(14), 64(15), 59·5(4), 59(11), 53(6), 52(15), 51(12), 50(13), 45(10), 44(100), 43(20), 42(33), 41(17), 40(17), 39(14), 38(12), 37(7)

*m** 131·2 (133 → 132), 122·1 (172 → 147), 110 (161 → 133)

Pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (II)

m/e (*I*) 164(8), 163(100), 121(4), 120(43), 119(2), 93(7), 92(98), 91(7), 70(4), 66(12), 65(33), 64(15), 63(4), 53(4), 52(6), 51(4), 50(4), 44(10), 43(4), 41(11), 40(10), 39(10), 38(18), 37(6)

6-Methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

m/e (*I*) 178(9), 177(100), 135(3), 134(44), 133(3), 107(32), 106(36), 105(15), 80(3), 79(29), 78(13), 77(3), 76(3), 64(3), 53(6), 52(26), 51(11), 50(4), 39(6)

1,3-Dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XV)

m/e (*I*) 192(11), 191(100), 176(1), 163(1), 162(2), 135(8), 134(5), 107(3), 106(18), 105(6), 104(1), 91(2), 80(2), 79(10), 78(3), 77(1), 76(1), 66(1), 65(1), 64(2), 53(1), 52(5), 51(2), 50(1), 43(1), 42(3), 40(2), 39(2), 38(1)

*m** 139·1 (191 → 163), 104 (106 → 105), 94·0 (191 → 134), 83·9 (134 → 106), 59·0 (106 → 79)

1,3,6-Trimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

m/e (*I*) 206(14), 205(100), 177(3), 176(8), 162(2), 161(3), 149(4), 148(11), 121(7), 120(57), 119(22), 93(3), 92(4), 79(4), 78(3), 44(10)

*m** 152·8 (205 → 177), 118 (120 → 119), 97·3 (148 → 120)

Pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (I)

m/e (*I*) 148(12), 147(100), 146(8), 120(6), 119(18), 118(12), 117(6), 106(6), 105(4), 104(9), 103(6), 96(6), 93(12), 92(32), 91(12), 77(9), 76(6), 73·5(2), 66(6), 65(18), 64(18), 63(5), 53(6), 52(15), 51(15), 50(21), 49(6), 44(9), 43(4), 42(6), 41(6), 40(6), 39(9), 38(18), 37(12)

*m** 145 (147 → 146), 96·3 (147 → 119), 71·1 (119 → 92), 45·9 (92 → 65)

6,8-Dimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (VIII)

m/e (*I*) 176(10), 175(100), 174(5), 147(5), 146(5), 132(3), 120(10), 119(5), 106(4), 105(3), 79(7), 78(5), 52(8), 51(6), 42(6)

*m** 123·8 (175 → 147), 98 (147 → 120), 58·9 (106 → 79)

3-Methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (VII)

m/e (*I*) 162(13), 161(100), 160(13), 134(5), 133(22), 132(11), 131(3), 120(6), 105(12), 104(6), 103(6), 93(9), 92(5), 91(3), 80·5(3), 79(6), 78(5), 77(3), 76(5), 66(3), 65(5), 64(8), 52(3), 51(6), 50(12), 43(3), 42(31), 41(6)

3,6,8-Trimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (X)

m/e (*I*) 190(14), 189(100), 188(7), 176(3), 174(4), 161(4), 160(3), 148(3), 147(4), 146(4), 134(2), 120(6), 119(6), 79(4), 78(5), 64(4), 63(3), 52(6), 51(5), 42(27), 41(4), 39(3)

*m** 160·2 (189 → 174), 137·2 (189 → 161), 118 (120 → 119), 116 (189 → 148), 89·5 (161 → 118)

TABLE 1 (*Continued*)

2,6,8-Trimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (IX)

m/e (*I*) 190(12), 189(100), 188(8), 174(3), 161(2), 160(2), 149(2), 148(3), 147(5), 146(3), 133(2), 131(2), 121(2), 120(4), 119(6), 118(2), 107(2), 106(2), 105(3), 104(2), 93(2), 92(2), 80(2), 79(7), 78(5), 77(2), 76(2), 69(2), 66(2), 65(2), 64(4), 63(4), 62(2), 53(2), 52(7), 51(5), 50(3), 45(2), 44(4), 43(2), 42(18), 41(3), 39(2), 38(3), 36(7)

*m** 187 (189 → 188), 160·2 (189 → 174), 137·1 (189 → 161), 118 (120 → 119), 116 (189 → 148), 112·8 (189 → 146)

3-Hydroxy-2,6,8-trimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (XII)

m/e (*I*) 206(12), 205(90), 190(7), 189(45), 188(12), 175(5), 174(3), 161(3), 160(3), 159(3), 158(3), 148(12), 147(100), 146(7), 144(3), 121(3), 120(7), 119(13), 118(3), 106(3), 105(4), 104(3), 93(3), 92(6), 87(3), 79(8), 78(13), 77(7), 76(5), 73(3), 67(3), 66(3), 65(5), 64(15), 63(10), 62(3), 58(3), 53(3), 52(13), 51(13), 50(5), 45(3), 44(7), 43(5), 41(3), 40(4), 39(5), 38(3)

*m** 172·4 (205 → 189), 114·9 (188 → 147), 97·8, 96·3 (147 → 119), 62·3, 61·3, 33·2

Pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (II)

m/e (*I*) 164(11), 163(100), 147(4), 121(5), 120(43), 119(2), 94(2), 93(33), 92(12), 91(4), 82(25), 81(10), 80(25), 79(10), 67(2), 66(4), 65(13), 64(11), 63(2), 60(4), 52(5), 50(4), 45(2), 44(5), 43(5)

*m** 88·4 (163 → 120), 72·1 (120 → 93), 46·0 (92 → 65)

6,8-Dimethylpyrido[3,4-*d*]pyrimidine-2,4(*H*,3*H*)-dione (XIII)

m/e (*I*) 192(10), 191(100), 148(36), 121(7), 120(32), 119(28), 93(8), 92(4), 80(3), 79(32), 78(9), 77(3), 76(3), 66(4), 65(4), 63(3), 53(4), 52(17), 51(11), 50(5), 42(8), 39(3)

*m** 118 (120 → 119), 114·7 (191 → 148), 97·3 (148 → 120)

1,3-Dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XVII)

m/e (*I*) 192(12), 191(100), 163(5), 162(4), 161(3), 135(3), 134(8), 133(4), 107(7), 106(73), 105(18), 93(18), 91(3), 81(3), 80(3), 79(13), 78(8), 77(3), 76(3), 69(3), 66(4), 65(6), 64(14), 63(3), 56(3), 53(3), 52(7), 51(8), 50(7), 42(6), 38(8), 37(4)

*m** 104 (106 → 105), 94·1 (191 → 134), 83·9 (134 → 106), 58·9 (106 → 79)

1,3,6,8-Tetramethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XVIII)

m/e (*I*) 220(14), 219(100), 218(4), 205(3), 204(22), 191(3), 190(11), 189(7), 176(3), 175(8), 162(4), 161(3), 148(11), 147(23), 146(3), 135(2), 134(13), 133(11), 120(5), 119(14), 109·5(3), 107(4), 93(3), 92(6), 79(4), 78(10), 77(4), 72(5), 66(4), 65(5), 64(3), 63(3), 56(3), 52(7), 51(8), 50(3), 42(11), 41(3), 39(4)

*m** 190 (219 → 204), 164·9 (219 → 190), 132·8 (135 → 134), 123·5 (175 → 147), 120, 116, 111, 97, 96·3 (147 → 119)

3,6,8-Trimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XIV)

m/e (*I*) 206(11), 205(100), 191(5), 179(4), 178(7), 149(8), 148(63), 147(7), 121(8), 120(46), 119(26), 93(8), 92(5), 79(29), 78(9), 77(4), 76(4), 67(5), 66(5), 65(5), 64(7), 63(8), 52(18), 51(12), 50(5), 44(5), 42(9), 41(5), 39(5)

*m** 118 (120 → 119), 106·9 (205 → 148), 97·3 (148 → 120)

Pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (I)

m/e (*I*) 148(10), 147(100), 146(10), 120(7), 119(9), 118(9), 105(3), 104(2), 93(30), 92(80), 91(12), 77(9), 76(8), 75(7), 73·5(6), 68(6), 67(5), 66(9), 65(18), 64(21), 59(6), 53(15), 52(10), 51(6), 50(18), 44(8), 43(12), 41(6), 40(6), 38(12), 37(12)

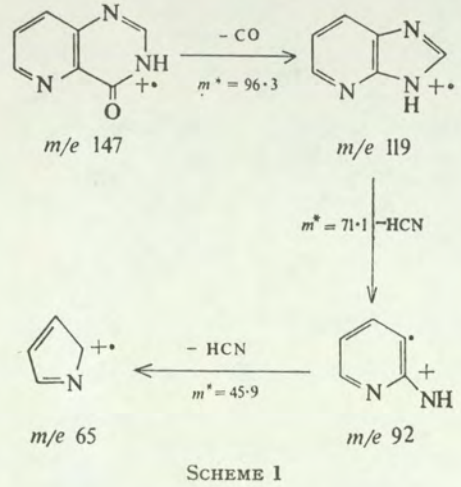
*m** 97·9 (147 → 120), 96·3 (147 → 119), 95·3 (146 → 118), 72 (120 → 93), 71 (119 → 92), 70, 46 (92 → 65), 45

Pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (II)

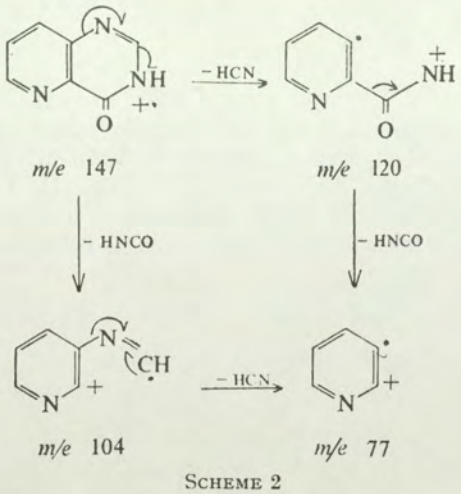
m/e (*I*) 164(29), 163(88), 162(6), 147(5), 145(4), 134(5), 121(20), 120(100), 119(12), 108(2), 107(4), 106(9), 94(14), 93(85), 92(18), 91(8), 80(5), 79(5), 77(4), 76(6), 70(11), 68(12), 66(10), 65(44), 64(32), 63(9), 61(3), 60(4), 59(3), 53(32), 52(35), 51(11), 50(70), 41(14), 40(13), 39(12), 38(36)

*m** 88·4 (163 → 120), 72·1 (120 → 93), 45·4 (93 → 65), 22·2 (65 → 38)

Four crystallisations of pyrido[3,2-*d*]pyrimidin-4(3*H*)-one from D_2O yielded a sample of pyrido[3,2-*d*]-pyrimidin-4(3-$^2H_1$)-one which, although it still contained *ca.* 30% of the non-deuteriated material, nevertheless gave a mass spectrum which confirmed the pathways suggested in Schemes 1 and 2 (*cf.* Table 1). The presence of a strong peak at *m/e* 93 in this spectrum which was absent in the 4(3*H*)-one showed that the proton attached to N-3 is not removed in the second stage of the principal fragmentation pathway (Scheme 1). Subsequent scrambling effects are observed in the loss of both DCN and HCN from this fragmentation ion to yield ions

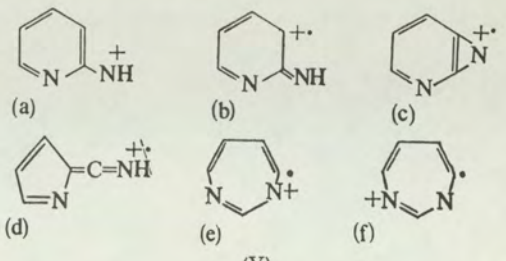


SCHEME 1



SCHEME 2

at *m/e* 65 and *m/e* 66. From this it could be suggested that diazatropylium radical ions, (Ve) and (Vf), more adequately represent the structure of the ion at *m/e* 92 in the spectrum of pyrido[3,2-*d*]pyrimidin-4(3*H*)-one than do formulae (Va)—(Vd) analogous to those previously drawn for similar fragmentation ions.[4,6] In view of the improbability of the existence of the odd-elecyron azatropylium ion derived from aniline,[7] however, such structures await a rigorous proof by means of labelling procedures.



(V)

The three other pyridopyrimidin-4(3*H*)-ones show fragmentation pathways initiated by the loss of H•, HCN, CO, or HNCO (*cf.* Table 1) which are generally substantiated by the appropriate metastable peaks and deuterium-labelling. An appreciable variation in the importance of the various possible modes of degradation, according to the position of the pyridine ring nitrogen atom, is observable. Thus, the loss of CO to yield fragmentation ions at *m/e* 119 becomes less important in the order [3,2-*d*] (76%), [2,3-*d*] (25%), [3,4-*d*] (18%), and [4,3-*d*] (9%) whereas the loss of H• to yield the even-electron ion at *m/e* 146 becomes more important in the same order (1·6%, 2·0%, 8%, and 10%). Pyrido-[4,3-*d*]pyrimidin-4(3*H*)-one shows the most complicated mass spectrum and its molecular-ion carries the lowest proportion of the ion current. This instability of pyrido[4,3-*d*]pyrimidin-4(3*H*)-one under electron impact parallels the higher susceptibility of the pyrido[4,3-*d*]-pyrimidine system to ring-opening reactions.[8]

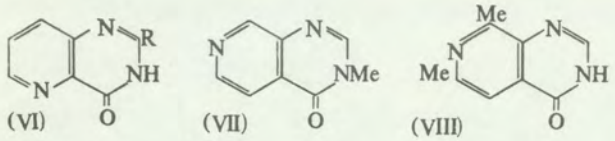
2-Methyl- (VI; R = Me) and 2-phenyl-pyrido[3,2-*d*]-pyrimidin-4(3*H*)-one (VI; R = Ph) are more stable to electron impact than pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (VI; R = H). The $(M - CO)^+$ ions showed intensities of 76, 22, and 29%, whereas the $(M - RCN)^+$ ions had intensities of 5, 4 and 26% for the compounds (VI; R = H, Me, and Ph) respectively. H• loss was also more important for these 2-substituted compounds. A study of the mass spectra of 3-methyl-(VII), 6,8-dimethyl-(VIII), 2,6,8-trimethyl-(IX), and 3,6,8-trimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (X) showed that an increased number of methyl substituents resulted in (*a*) an increased resistance to electron-induced fragmentation, (*b*) a decreased tendency for the molecular ion to lose CO, and (*c*) an increased proportion of the ion current carried by the $(M - H)^+$ ion. Thus the $(M - CO)^+$ ions for the compounds (VII), (VIII), (X), and (IX) had intensities of 22, 5, 4, and 2% respectively whereas the corresponding $(M - H)^+$ ions had intensities of 13, 5, 7, and 8%. Me• and MeCN loss from the molecular ion becomes significant (3—4%) for the trimethyl substituted compounds (IX) and (X) but in both these cases HCN loss is negligible.

[6] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967.

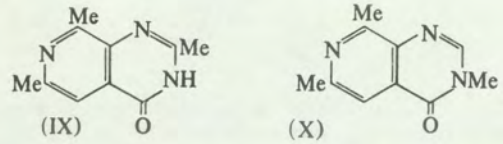
[7] A. V. Robertson, M. Marx, and C. Djerassi, *Chem. Comm.*, 1968, 414.

[8] W. J. Irwin and D. G. Wibberley, *Adv. Heterocyclic Chem.*, 1968, **10**, 149.

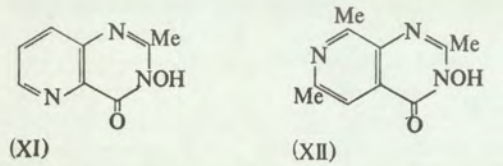
The mass spectra of the two cyclic hydroxamic acids (XI) and (XII) showed some similarities to each other. Initial losses of O, OH, and NO from the molecular ion occurred in both compounds. The molecular ion derived



(VI) (VII) (VIII)



(IX) (X)

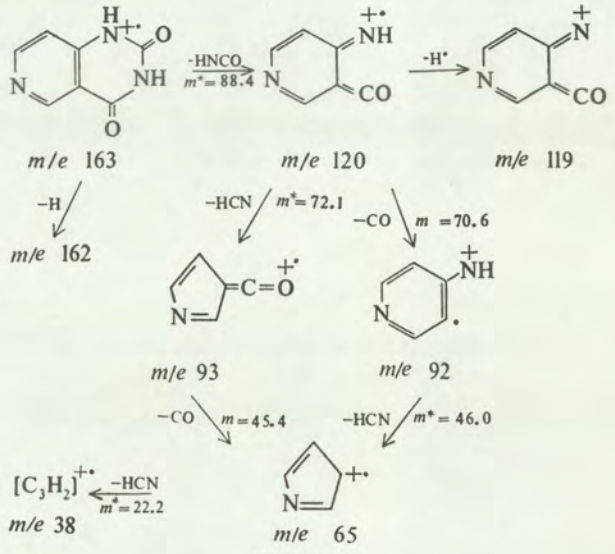


(XI) (XII)

from 3-hydroxy-2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one carried only *ca.* 10% of the ion current compared with *ca.* 40% carried by the molecular ion from 2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (VI; R = Me). 3-Hydroxy-2,6,8-trimethylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (XII) is similarly very much more susceptible to electron impact than 2,6,8-trimethylpyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (IX), the base peak in the spectrum of the former compound (XII) is the fragmentation ion $(M - OH - MeCN)^+$ at *m/e* 147 and not the molecular ion at *m/e* 205 (90%).

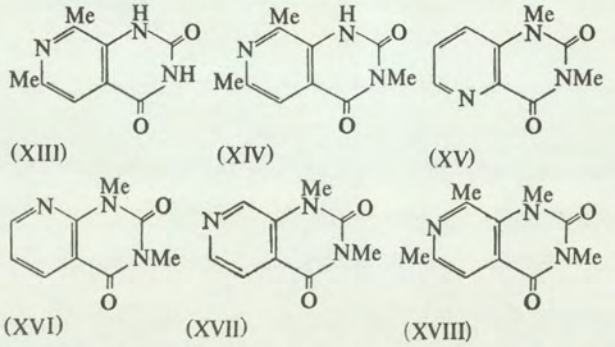
The pyridopyrimidine-2,4(1*H*,3*H*)-diones (II) were less stable to electron impact than the pyridopyrimidin-4(3*H*)-ones and their mass spectra showed strong resemblances to those of quinazoline-2,4(1*H*,3*H*)-dione and pteridine-2,4(1H,3*H*)-dione. Again it is the [4,3-*d*] series which fragments most easily and this is the only system in which the molecular ion is not the base peak. By far the most important initial loss, in all four compounds (II) is that of HNCO which previous authors have suggested occurs by a retro-Diels–Alder rearrangement for other fused pyrimidines.[6] The ion at *m/e* 120 formed by this loss of HNCO fragments further by loss of H·, HCN, or CO (*cf.* Scheme 3). The relative abundances of the fragmentation ions formed from these four isomers again vary with the position of the pyridine-ring N atom. Thus, the intensities of $(M - HNCO)^+$ ions, that is of the peaks at *m/e* 120 are 43, 40, 43, and 100% for the [3,2-*d*], [2,3-*d*], [3,4-*d*], and [4,3-*d*] systems respectively. The further loss of CO gives peaks of intensities 98, 32, 12, and 18% at *m/e* 92 whereas the loss of HCN gives peaks of intensities 7, 40, 33, and 85% at *m/e* 93. Small peaks are present at *m/e* 147 indicating O loss in the [4,3-*d*] and [3,4-*d*] series; a similar loss is quoted for quinazoline-2,4(1*H*,3*H*)-dione.[4]

The mass spectra of 8-methyl-substituted pyridopyrimidine-2,4(1*H*,3*H*)-diones are recorded in Table 1. The involvement of the 3-N atom in the retro-Diels–Alder rearrangements is clearly shown by the elimination of MeNCO from the molecular ion to form the fragmentation ion at *m/e* 148 (63%), and the absence of any appreciable elimination of HNCO in the mass spectrum of 3,6,8-trimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XIV). This trimethyl derivative (XIV) and 6,8-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XIII) show a fragmentation pathway very similar to that of pyrido[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (*cf.* Scheme 3). Compounds with a methyl substituent at



SCHEME 3

the 1-position, however, showed alternative fragmentation pathways and positional selectivity could again be observed. The three isomeric 1,3-dimethylpyridopyrimidine-2,4(1*H*,3*H*)-diones (XV)—(XVII), for example, had $(M - MeNCO)^+$ fragmentation ions at *m/e* 134 of intensities 5, 5, and 8% and $(M - CO)^+$ ions at



(XIII) (XIV) (XV)

(XVI) (XVII) (XVIII)

m/e 163 with intensities of 1, 20, and 5% respectively. The $(M - MeNCO - CO)^+$ fragmentation ions at *m/e* 106, on the other hand, showed intensities of 18, 22, and 73% respectively. The pyridinium ion $(C_5H_5N)^+$ at *m/e* 79 is an important ion in the spectra of these dimethyl derivatives. The introduction of four methyl groups produced considerable changes in the mode of

decomposition under electron impact. 1,3,6,8-Tetramethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XVIII) shows $(M - H)^+$ and $(M - MeNCO)^+$ fragmentation ions of low abundance (4%) and the principal initial decomposition is now the loss of a methyl radical to give the ion at *m/e* 204 (22%). Expulsion of MeNCO then yields the most abundant fragmentation ion in the spectrum (23%) at *m/e* 147. The loss of HCN from the $(M - MeNCO)^+$ ion in this tetramethyl derivative suggests that a rearrangement, possibly involving the incorporation of the 1-methyl group in a ring-expansion process, occurs with this ion.

EXPERIMENTAL

Mass spectra were determined on an A.E.I. MS9 instrument with an ionising voltage of 70 ev, trap current 100 μA, and accelerating voltage 8 kv. Samples were introduced through the heated-inlet system at 200°.

The pyrido[3,2-*d*]-, pyrido[3,4-*d*]- and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones and -pyrimidine-2,4(1*H*,3*H*)-diones were prepared by our previously reported methods.[1,9] Pyrido[2,3-*d*]pyrimidin-4(3*H*)-one and pyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione were prepared by the method of Robins and Hitchings.[10] 1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione was prepared by the method of McLean and Spring.[11] Pyrido[2,3-*d*]- and pyrido[3,2-*d*]-pyrimidin-4(3-$^2H_1$)-ones were prepared by four crystallisations of the corresponding -4(3*H*)-ones from D_2O. They were introduced into the mass spectrometer immediately following a sample of D_2O.

[8/1824 *Received, December 10th*, 1968]

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[10] R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2258.
[11] A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 1949, 2582.

Reductive Ring Cleavage of Fused Pyrimidin-4(3*H*)-ones

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Reductive Ring Cleavage of Fused Pyrimidin-4(3*H*)-ones

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Summary Fused pyrimidin-4(3*H*)-ones, particularly those with a 3-aryl substituent, readily undergo a ring-cleavage at the 2,3-position on treatment with lithium aluminium hydride.

PYRIMIDINES, quinazolines, pyridopyrimidines, pteridines, and purines are all susceptible to nucleophilic attack at the 2- and 4-positions of the pyrimidine ring. Consequently many of these compounds yield di- and tetra-hydro derivatives when treated with metal hydrides.[1] Fused pyrimidin-4(3*H*)-ones are also known to yield similar compounds,[2] although under certain forcing conditions ring-cleavage of quinazolines[3] and a quinazolinone[4] have been observed. We now report some results of our own studies into the reduction of fused pyrimidin-4(3*H*)-ones which indicate that ring-cleavage is a general reaction of these compounds,

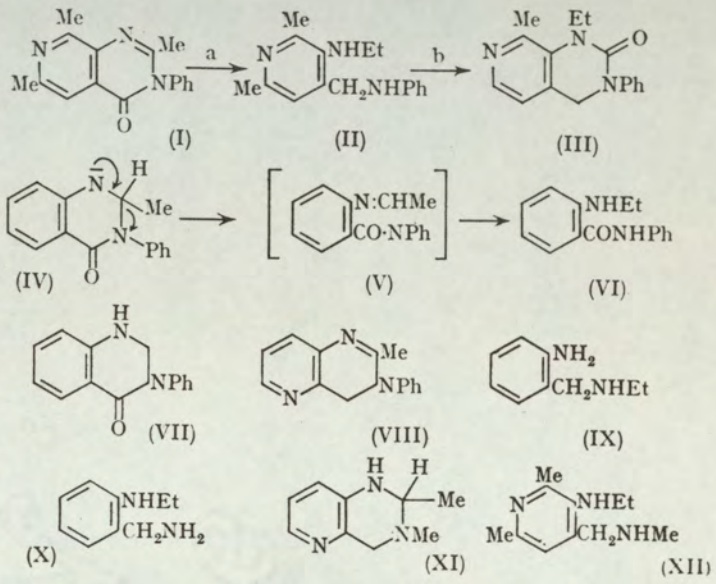
but that the ease and direction of the fission is dependent upon the substituents present in the pyrimidine ring, particularly at N(3).

Treatment of 2,6,8-trimethyl-3-phenylpyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (I) with excess lithium aluminium hydride for 1 hr. at room temperature yielded solely 4-anilinomethyl-2,6-dimethyl-3-ethylaminopyridine (II). The position of fission was proved by infrared (secondary amine absorptions), n.m.r. (presence of NHEt group), and mass spectra of the product. Chemical evidence was also obtained by the preparation of a dibenzoyl derivative, and finally by treatment with phosgene to yield again a pyridopyrimidine (III). 2-Methyl-3-phenylpyrido[3,2-*d*]-pyrimidin-4(3*H*)-one, 2-methyl-3-phenyl-quinazolin-4-(3*H*)-one, and 3-phenylquinazolin-4(3*H*)-one all underwent analogous ring-cleavage at the 2,3-position of the pyrimidine ring to yield the corresponding diamines.

The fused pyrimidin-4(3*H*)-ones have two sites which are susceptible to hydride attack; the endocyclic C=N and the exocyclic C=O. The complete specificity of the above ring-opening reactions indicates that in these examples the initial attack takes place at the C=N, probably producing an intermediate of type (IV) which then undergoes bond cleavage. Support for this view is obtained by the isolation of 2-ethylaminobenzanilide (VI) from a controlled reduction of 2-methyl-3-phenylquinazolin-4(3*H*)-one.

The main factor which controls the ring-cleavage appears to be the phenyl substituent at N(3), presumably by the stabilisation of anions such as (V). Thus, 1,2-dihydro-compounds (VII) and 3,4-dihydro-compounds (VIII) also ring-open in an analogous manner to yield the same diamines as obtained from the corresponding fused pyrimidin-4(3*H*)-ones.

Compounds with no substituent at N(3) also underwent specific ring-opening reactions. However, this occurred less readily than with the 3-phenyl compounds and the 1,2-bond was now the preferred position of cleavage. Thus, 2-methyl-quinazolin-4(3*H*)-one yielded 2-ethylamino-methylaniline (IX) (84%), and 2-aminomethyl-*N*-ethyl-aniline (X) (5%). 2-Methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one, 2-phenylquinazolin-4(3*H*)-one and quinazolin-4(3*H*)-one gave similar products. No doubt several factors are involved in determining the direction of ring-opening in these compounds and it seems likely that reduction of the carbonyl is important as this would be aided by the presence of an N(3) anion. The presence of 2-methyl-3,4-dihydroquinazoline from the mild reduction of 2-methyl-quinazolin-4(3*H*)-one lends weight to this view.



Reagents: (a) $LiAlH_4$; (b) $COCl_2$.

When methyl substituents are present at N(3) there is a marked reluctance for the compounds to undergo ring-cleavage and tetrahydro-derivatives (XI) can be isolated. Under forcing conditions the ring can be induced to open but whereas 2,3,6,8-tetramethylpyrido[3,4-*d*]pyrimidin-4-(3*H*)-one yields 3-ethylamino-2,6-dimethyl-4-methylamino-methylpyridine (XII) 2,3-dimethylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one gives a mixture of 1,2- and 2,3- ring-opened products.

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