PYRIDO[4,3-d]PYRIMIDINES

BY

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SUMMARY

The methods available for the synthesis of tetrahydro-, octahydro- and fully aromatic pyrido[4,3-d]pyrimidines are reviewed.

Three new routes for the syntheses of pyrido[4,3-d] pyrimidines are described.

Treatment of 4-aminonicotinic acid, or 4-acetamido-nicotinic acid with acetic anhydride yields 2-methyl-pyrido[4,3-d]-[1,3]-oxazin-4-one. 2-Methylpyrido-oxazine reacts readily with aliphatic and aromatic primary amines to yield directly 3-substituted 2-methylpyrido[4,3-d] pyrimidin-4(3H)-ones without the necessity for the isolation of the intermediate diamides.

Unsuccessful attempts to prepare 2-phenylpyrido [4,3-d]-[1,3]-oxazin-4-one are described. 4-Benzamido-nicotinic acid undergoes transacylation with acetic anhydride, to give in the first instance 4-acetamido-nicotinic acid, which is then cyclised to 2-methyl-pyrido[4,3-d]-oxazin-4-one. The possible reason for the transacylation is outlined.

2,3-Disubstituted pyrido[4,3-d]pyrimidin-4(3H)-ones are more conveniently prepared from ethyl 4-amidonicotinates. Ethyl 4-amidonicotinates are produced in excellent yields from ethyl 4-aminonicotinate and the appropriate acyl chloride in pyridine. Ethyl 4-amidonicotinates react with primary aliphatic amines under different conditions. The

product of the reaction of the 4-amidonicotinate with the amine is either a 2,3-disubstituted pyrido[4,3-d]pyrimidin-4(3H)-one or the diamide. The majority of the diamides are readily cyclised to the corresponding pyrido[4,3-d]pyrimidines by heat.

The mechanism for the cyclisation of ethyl 4-amidonicotinate to 2,3-disubstituted pyrido[4,3-d]pyrimidin-4(3H)-one is described.

Infrared spectra of ethyl 4-amidonicotinates, diamides and 2,3-disubstituted pyrido[4,3-d]pyrimidin-4(3H)-ones are discussed.

Nuclear magnetic resonance spectra of 2,3-disubstituted pyrido[4,3-d]pyrimidin-4(3H)-ones are described and analysed.

A new synthesis of pyrido[4,3-d]pyrimidines, from pyrimidines, has been developed. Treatment of 2-phenyl-4styrylpyrimidine-5-carboxylic acid with bromine in acetic acid yields 2,7-diphenylpyrano[4,3-d]pyrimidin-5-one, which is the first recorded example of the pyrano[4,3-d]pyrimidine ring system. 2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one reacts with primary aliphatic amines to give directly 6-substituted 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-ones. Unsuccessful attempts to prepare 2,7-diphenylpyrido[4,3-d]pyrimidine from 5-substituted 2,7-diphenylpyrido[4,3-d]pyrimidines are described. The preparation of 7-phenylpyrano[4,3-d]pyrimidin-2,5(3H)-dione

from 4-styrylpyrimidine-2(1H)-one-5-carboxylic acid and bromine is described. The product is less reactive towards amines than 2,7-diphenylpyrano[4,3-d]pyrimidine.

The fragmentation patterns in the mass spectra of a selected number of pyrido[4,3-d]pyrimidines are described.

The results of primary neuropharmacological and cardiovascular tests of a selected number of intermediate compounds and pyrido[4,3-d]pyrimidines are presented.

The author would like to thank his supervisor, Dr. D. G. Wibberley, for his help and encouragement during the course of this work, and the Pharmaceutical Society of Great Britain for the award of a Research Grant.

To my Parents

CONTENTS

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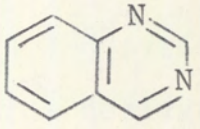
PART 1 INTRODUCTION

INTRODUCTION

The physical, chemical and biological studies of heterocylics have included quinazolines[1,2] (benzopyrimidines)(1) and pteridines[3] (tetrazanaphthalenes)(2). The pyrido-



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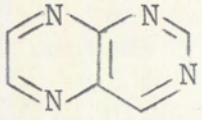

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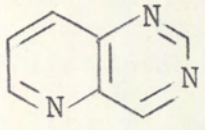
pyrimidines are the class of compounds which are closely related to quinazolines and pteridines. Four types of pyridopyrimidine (3-6) are known. The nomenclature and



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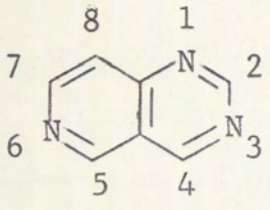
Pyrido[3,2-d] pyrimidine



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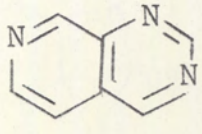

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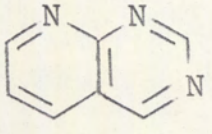


(6)

Pyrido[2,3-d] pyrimidine

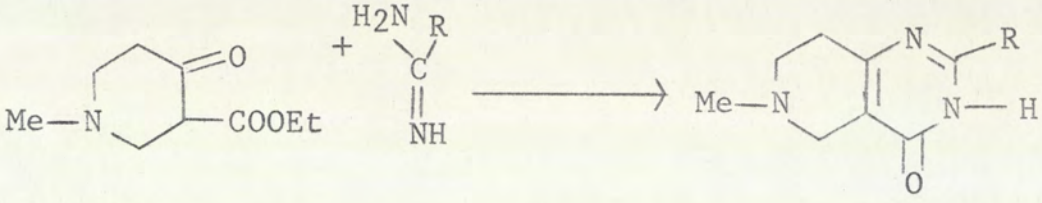
numbering of Chemical Abstracts is used.

The pyridopyrimidines are also alternatively named in the literature as 1,3,5-triazanaphthalene (3), 1,3,6-triazanaphthalene (4), 1,3,7-triazanaphthalene, or copazoline (5), and 1,3,8-triazanaphthalene (6).

A large proportion of investigation carried out on pyrido[4,3-d]pyrimidines has been of tetrahydro- and octahydro- derivatives. Only four fully aromatic pyrido[4,3-d]pyrimidines are known and their properties resemble those of quinazolines and pteridines in most respects.

(A) SYNTHESIS OF TETRAHYDROPYRIDO[4,3-d]PYRIMIDINES

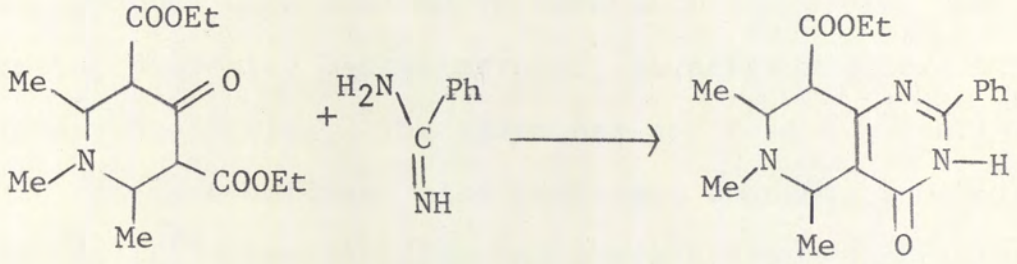
The first recorded pyrido[4,3-d]pyrimidine (8) was synthesised by Cook and Reed[4] during their investigation on the preparation of piperid-4-ones of potential analgesic activity. The condensation of ethyl or methyl 1-methylpiperid-4-one-3-carboxylate (7) with benzamidine (R=Ph)



(7) (8)

readily yielded 6-methyl-2-phenyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-4(3H)-one(8)(R=Ph.). Similar treatment of piperid-4-one carboxylate (7) with guanidine (R=NH_2.) gave

the 2-aminoderivative (8) ($R=NH_2$.). The condensation with urea required stronger conditions to yield 2-hydroxy-6-methyl-5,6,7,8-tetrahydropyrido [4,3-d] pyrimidin-4(3H)-one (8) (R=OH.). A similar condensation with S-methylisothiourea was not observed. The synthesis was also extended to the condensation of ethyl 1,2,6-trimethylpiperid-4-one 3,5-dicarboxylate (9) with benzamidine to give the trimethyl tetrahydrapyrido [4,3-d] pyrimidine (10). No reference was

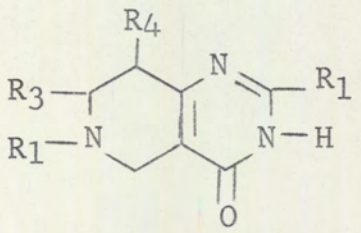


(9) (10)

made regarding the pharmacological activities of these tetrahydrapyrido[4,3-d]pyrimidines.

The diuretic and toxic properties of 2-amino-6-methyl-5,6,7,8-tetrahydropyrido [4,3-d] pyrimidin-4(3H)-one, (8) ($R=NH_2$), were investigated by Arman and his co-workers[5]. The compound was reported to possess moderate activities when compared with various pyrimidines.

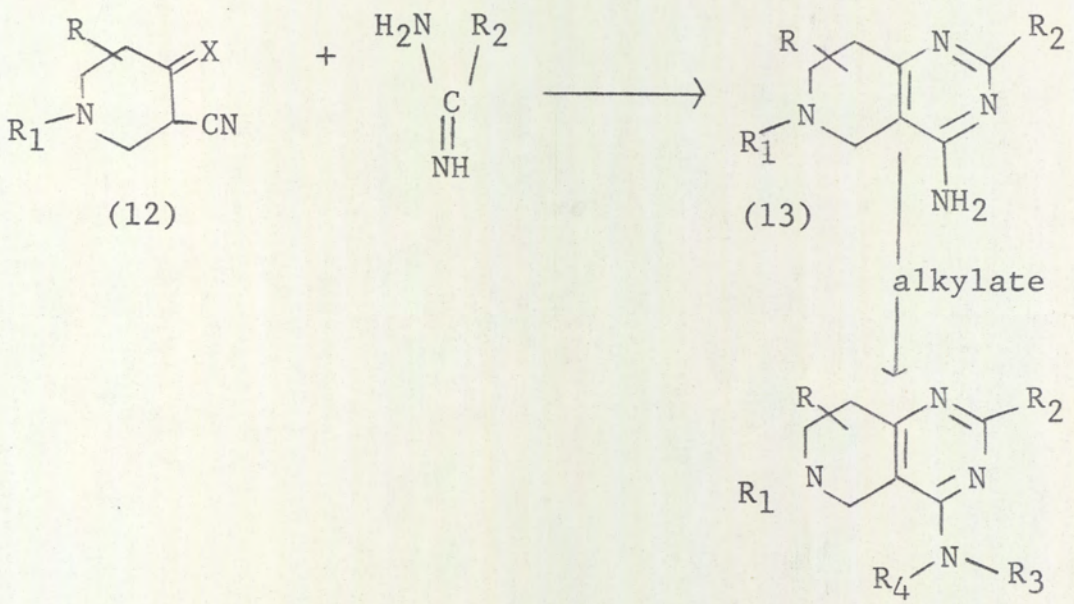
Tetrahydropyrido [4,3-d] pyrimidines of the type (11) and their non-toxic acid addition salts have been synthesised mainly by the above method, which involve condensing various substituted piperid-4-one 3-carboxylates with urea, thiourea, guanidine and the related amidines.[6 a,b] The compounds, thus



(11)

prepared were screened for pharmacodynamic properties. The compounds were claimed to have antiphlogestic, antipyretic, diuretic, bacteriostatic, sedative and coronary dilatory properties. The claim has not been substantiated.

The same amidines also underwent condensations with a series of 3-cyano-4-imino and 3-cyano-4-oxo-piperidines (12) (X=NH or O) to yield 4-amino-5,6,7,8-tetrahydro-

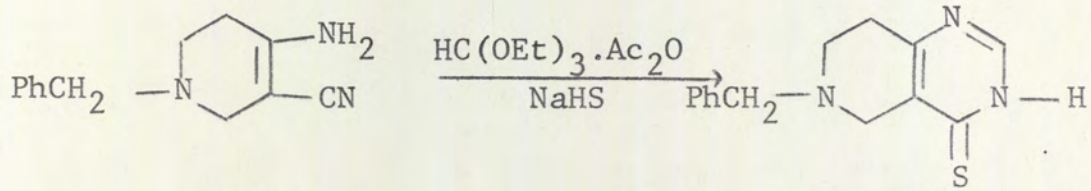


(12) (13) (14)

pyrido[4,3-d]pyrimidines[7] (13). The amino group at 4 position

could be alkylated to introduce various substitutents R_3 and R_4 (14). These compounds were claimed to possess pharmacodynamic properties of the same order as those reported for other tetrahydropyrido[4,3-d]pyrimidines (11).

Methods available for the preparation of fused pyrimidinethiones involve either laborious and inefficient multistage syntheses or drastic conditions. Taylor and co-workers,[8,9] however, have found that fused pyrimidinethiones may be prepared from o-aminonitriles, ethyl orthoformate and sodium hydrosulphide in one step reaction which proceeds in high yields and under mild conditions. Thus treatment of 4-amino-1-benzyl-3-cyano-Δ^3-piperidine (15) with ethyl orthoformate and acetic anhydride, followed by addition of sodium hydrosulphide yields 6-benzyl-5,6,7,8-



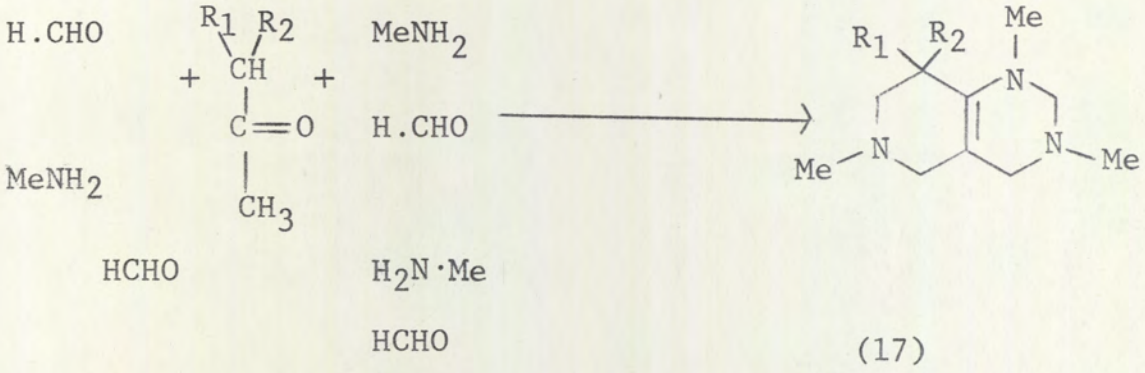
(15) (16)

tetrahydropyrido[4,3-d]pyrimidine-4(3H)-thione (16) via the intermediate ethoxymethylene amino derivative. Similar reactions of other aromatic and heterocylic o-aminonitriles with carbon disulphide in pyridine solution constitutes a facile one-step synthesis of fused pyrimidinedithiones.[10] Quinazolin-2,4,

(1H, 3H)-dithione is readily prepared by the treatment of o-aminobenzonitrile with carbon disulphide in pyridine.

(B) SYNTHESIS OF OCTAHYDROPYRIDO[4,3-d]PYRIMIDINES

An interesting method of synthesis of 8,8-diaryl -1,3,6,-trimethyl-1,2,3,4,5,6,7,8-octahydro pyrido[4,3-d] pyrimidine[11] (17) was reported in 1957. The reaction between methylamine, formaldehyde and a 1,1-diarylpropan-2-one in the presence of a basic catalyst yielded directly the



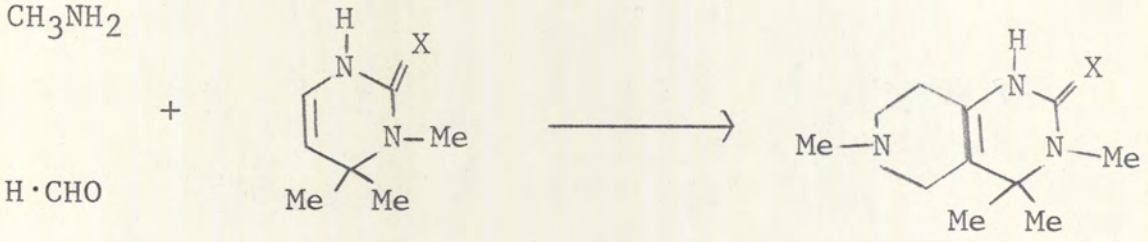
(17)

desired octahydropyridopyrimidine (17). The method is unique since it yields the pyridopyrimidine directly from the aliphatic starting materials. The compounds prepared by this route have been claimed to show antiarthritic activity in animals.

The octahydropyrido[4,3-d]pyrimidine dihydrochloride (17) (R_1=R_2=Ph)[12] has been claimed in addition to suppress

pneumonia produced in mice by Eschericha coli. The compound also suppressed pneumonia induced by the toxicity of Newcastle disease virus and delayed the onset of convulsions induced by influenza virus neurotoxin.

The Mannich reaction of 2-oxo and 2-thioxo-tetrahydropyrimidines (18) (X=O or S) has yielded the octahydro-



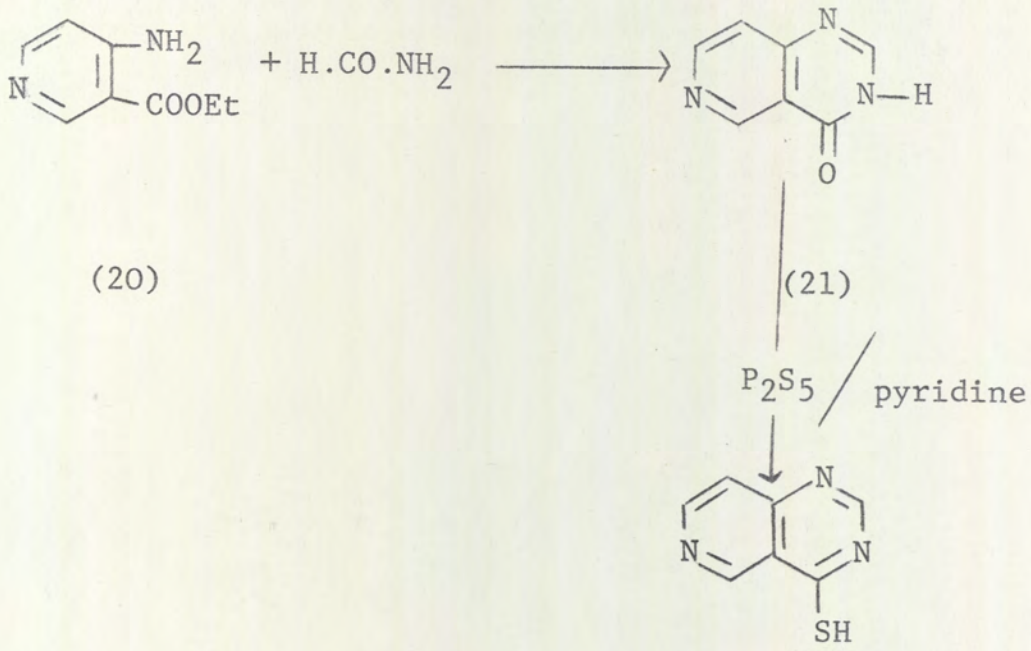
(18) (19)

pyrido[4,3-d]pyrimidin-2(1H)-one (19) (X=O) or -2(1H)-thione[13] (19) (X=S).

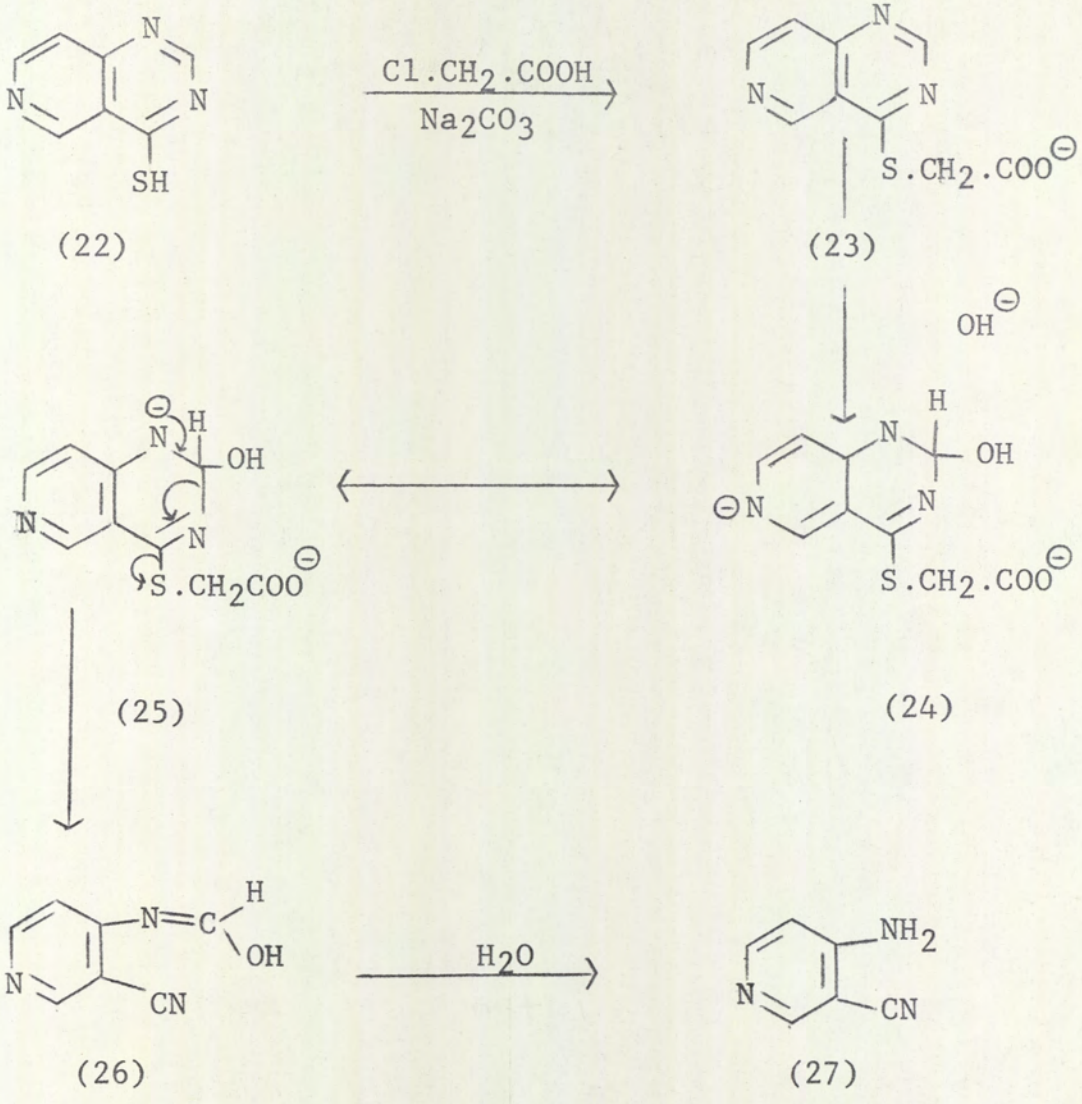
(C) SYNTHESIS OF PYRIDO[4,3-d]PYRIMIDINES

All the four fully aromatic pyrido[4,3-d]pryimidines reported in the literature have been synthesised from pyridines.

Taylor and his co-workers[14] had prepared pyrido[4,3-d]pyrimidin-4(3H)-one (21) to study the facile pyrimidine ring cleavage. Treatment of ethyl 4-aminonicotinate (20) with formamide gave pyrido[4,3-d]pyrimidin-4(3H)-one (21). The 4-oxo derivative (21) was converted into the 4-thioxo compound (22) via nucleophilic displacement of the acyloxy intermediate formed, with phosphorus pentasulphide.



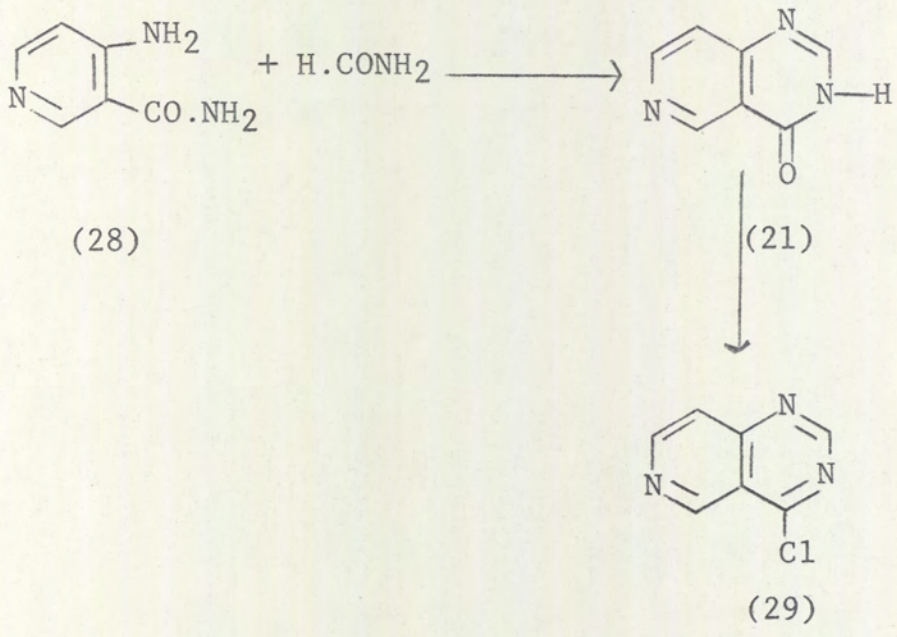
Like the other heterocylic systems containing a fused 4-substituted pyrimidine ring, 4-thiopyrido [4,3-d] pyrimidine (22) was cleaved by chloracetic acid and sodium bicarbonate to give 4-amino nicotinonitrile (27). The reaction apparently proceeded by initial formation of the expected 4-carboxymethylthiopyrido [4,3-d] pyrimidine (23) which then added hydroxide ion at C—2 to give a resonance-stabilised anion (24⟷25) which underwent an irreversible cleavage as shown to give the labile 4-formyl derivative (26). The end products isolated were 4-aminonicotinonitrile (27), unchanged starting material (22) and a small amount of pyrido [4,3-d] pyrimidin-4(3H)-one(21). Thus the degradation was facilitated by resonance activation of the 2-position by the 6-aza moiety



(22) (23) (24) (25) (26) (27)

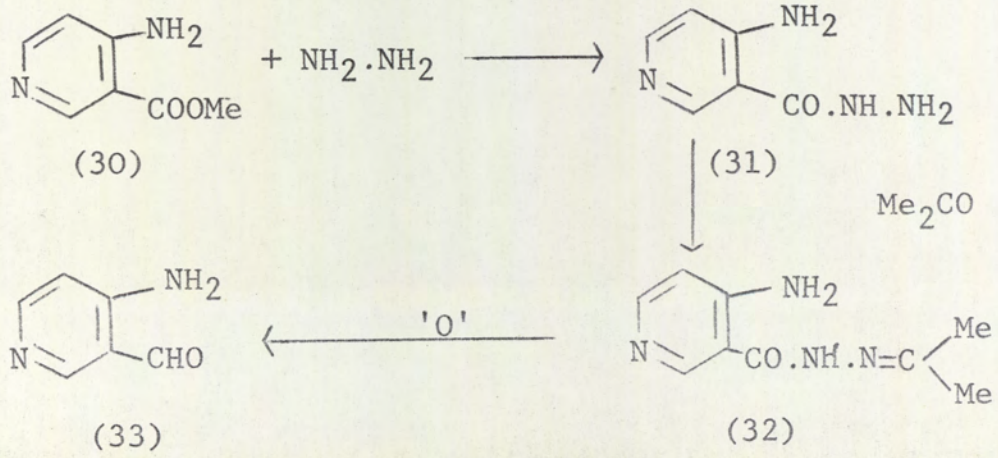
and the base. Similar resonance stabilised anion is not possible for pyrido[3,2-d]pyrimidin-4(3H)-thione and so was stable under these conditions.

Pyrido[4,3-d]pyrimidin-4(3H)-one (21) has been also prepared by Armarego[15] by the fusion of 4-aminonicotinamide (28) with formamide.

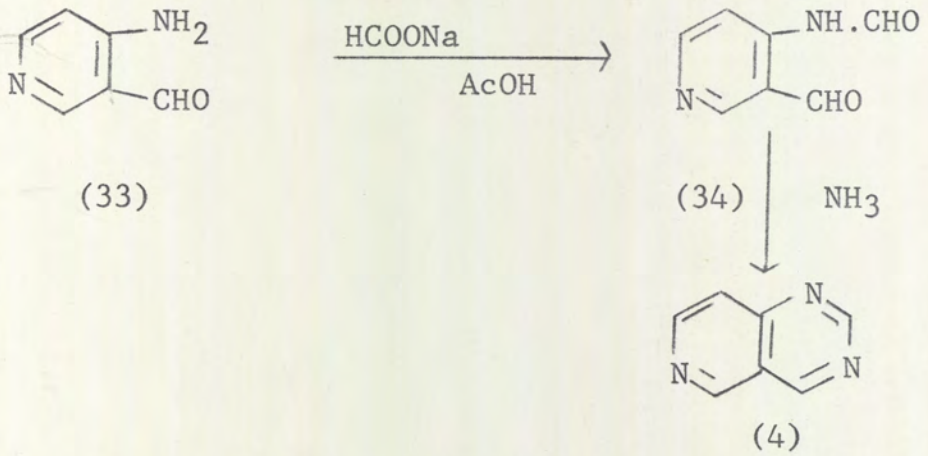


Pyrido [4,3-d] pyrimidin-4(3H)-one (21) was converted into 4-chloro derivative (29) by refluxing in phosphorus oxychloride.

The preparation of the parent compound (4) involved various stages starting from methyl 4-aminonicotinate.[15] (30). The ester (30) was converted into the isopropylidene derivative (32) via the hydrazide (31).



The oxidation of isopropylidene compound (32) yielded 4-aminonicotinaldehyde, (33) which was formylated to give 4-formamidonicotinaldehyde (34). Treatment of the formyl

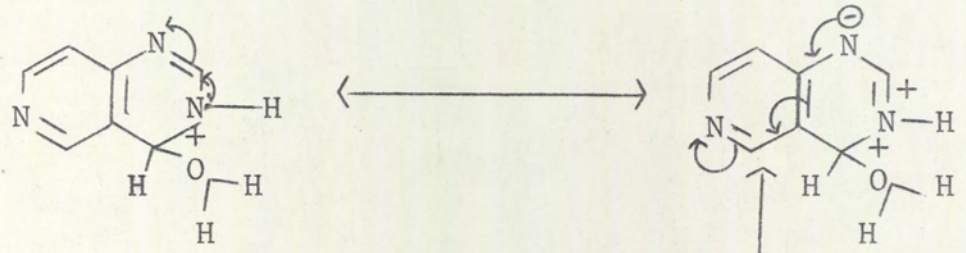


(4)

derivative (34) with ammonia in a bomb at 100° for two hours yielded pyrido[4,3-d]pyrimidine (4); it is a low melting point compound and is soluble in many non-polar solvents.

In common with other fused pyrimidines[2b, 3a] pyrido-pyrimidines may be expected to be susceptible to the nucleophilic addition of water across 3,4-bond. The phenomenon of covalent hydration across the 3,4-bond in pyridopyrimidines has been studied in detail by Armarego[15]. The neutral species were shown to be predominantly anhydrous. The ratios of the hydrated to the anhydrous forms in the [3,2-d], [3,4-d] and [2,3-d] series were 0.45×10^{-2}, 2.3×10^{-2} and 0.20×10^{-2} respectively. Neither this ratio nor the pK_a value for pyrido[4,3-d]pyrimidine (4) could be measured because the compound decomposed rapidly in acid

solution. The neutral species, even at about pH 7.1 showed small change in the ultra-violet spectrum after 3.5 hours (at 20°) and after 2 weeks at this pH the substance was completely converted into 4-aminonicotinaldehyde (33). The other three pyridOpyrimidines were very stable under the same conditions but they decomposed rapidly in N-sodium hydroxide.



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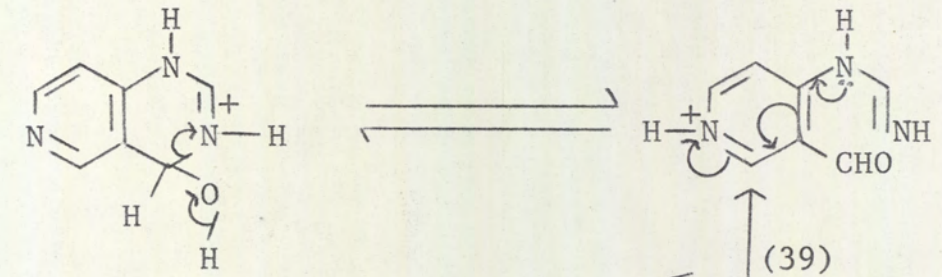

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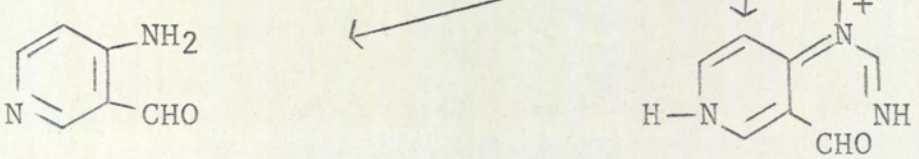


(33) (40)

The location of the nitrogen atom of the pyridine ring has a considerable bearing on the ease of formation and stability of the covalent hydrate. Pyrido[4,3-d]pyrimidine (4) is least stable because of the stabilisation of the hydrate with respect to the anhydrous compound (35 ⟷ 36 ⟷ 37) and ring chain tautomerism (38 ⇌ 39) favouring ring opening due to stabilisation of the amidine (39 ⟷ 40).

Like naphthalene, quinazoline and pteridine, pyrido[4,3-d]pyrimidine shows three $\pi \longrightarrow \pi^*$ transition bands at λ max 218, 263 and 285-293 and mμ respectively. Calculations have been made, first by a semi-empirical treatment due to Parrisier and Parr and to Pople[16] and then by a simplified version of this method[17] of the transition energies and intensities of the $\pi \longrightarrow \pi^*$ bands for pyrido[4,3-d]pyrimidine and various heterocylics. The results are in fair agreement with the experimentally determined value of Armarego[15]. Thus the calculated value of $\pi \longrightarrow \pi^*$ transition bands of pyrido[4,3-d]pyrimidine has been found as λ max 220, 279 and 295 mμ respectively.

PART 2 DISCUSSION

DISCUSSION

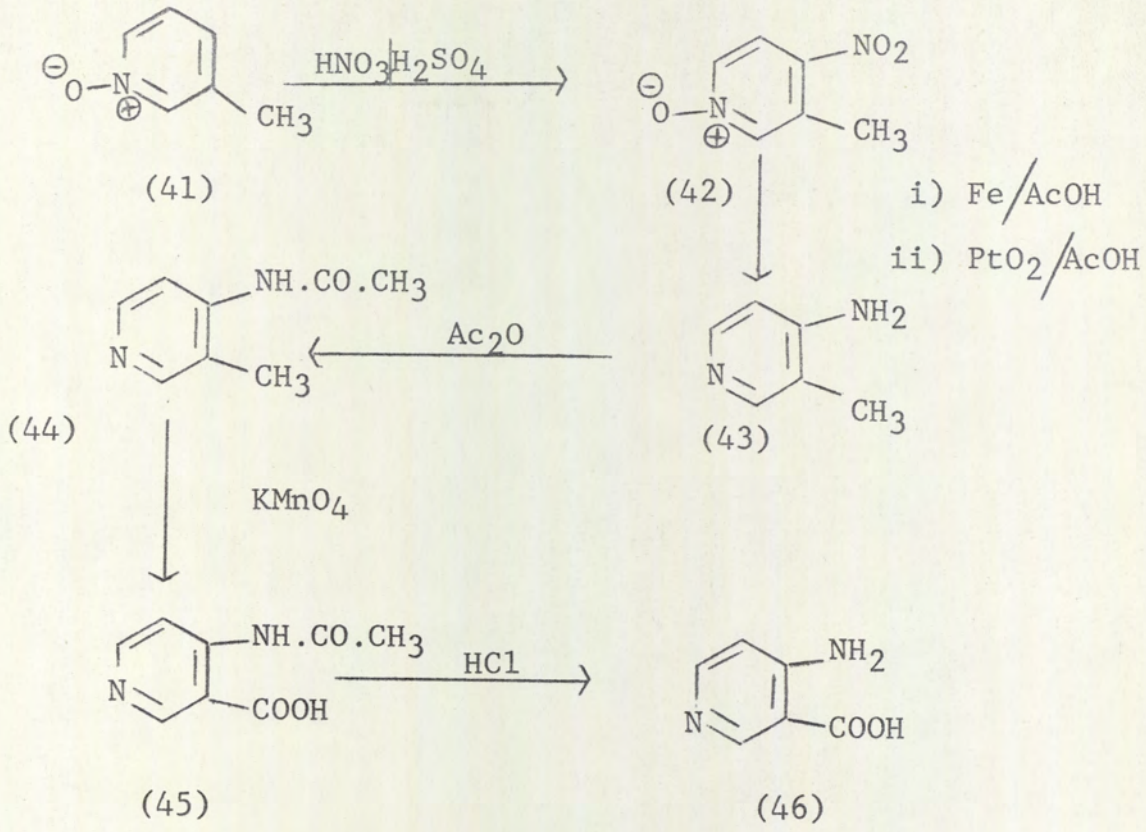
It has been shown in the introduction that only four fully aromatic pyrido[4,3-d]pyrimidines are known. The aims of the investigation reported in the thesis were first to develop new routes of syntheses of this ring system, then to examine the scope and limitation of each route and finally to study the physical, chemical and biological properties of the new compounds obtained.

(A) SYNTHESIS OF PYRIDO[4,3-d]PYRIMIDIN-4(3H)-ONES FROM PYRIDO[4,3-d]-[1,3]-OXAZIN-4-ONES

i) 4-Aminonicotinic acid

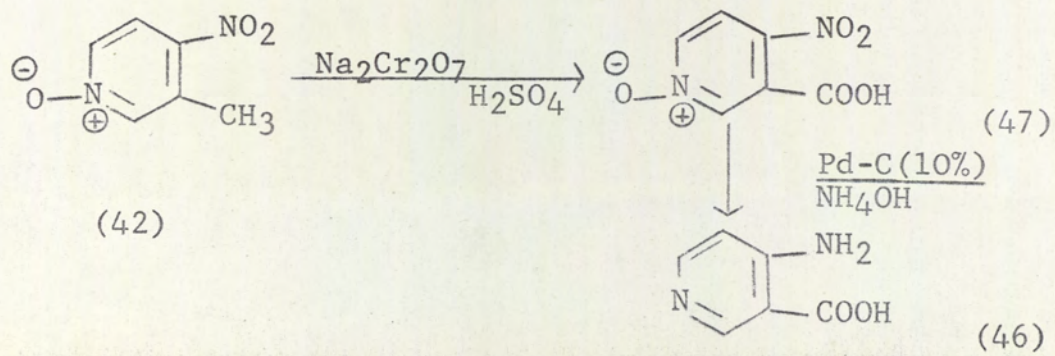
The key intermediate material in the synthesis of pyrido[4,3-d]-[1,3]-oxazin-4-ones was 4-aminonicotinic acid.

Two possible routes were available for the preparation of 4-aminonicotinic acid.(46). Armarego[15] had nitrated 3-picoline-1-oxide (41) to give 4-nitro-3-picoline-1-oxide (42). Reduction using iron and acetic acid gave 4-amino-3-picoline (43). The amine was acetylated (to protect the labile amino group) to give 4-acetamido-3-picoline (44). Oxidation with potassium permanagate gave 4-acetamidonicotinic acid (45). On hydrolysis the amido-acid gave the 4-amino-nicotinic acid (46).



4-Nitro-3-picoline-1-oxide (42) could also be reduced to 4-amino-3-picoline (43) using platinum oxide as a catalyst.

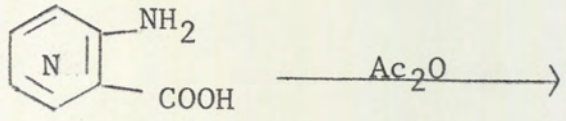
Hertz and Murty[18] had prepared 4-aminonicotinic acid (46) by the oxidation of 4-nitro-3-picoline-1-oxide (42) to 4-nitronicotinic acid-1-oxide[105] (47) and the subsequent reduction of the 4-nitronicotinic acid-1-oxide (47) to 4-aminonicotinic acid. (46)



Both the routes were investigated in the laboratory. It was found that Armarego's route to 4-aminonicotinic acid was laborious and the overall yield was very poor. Hertz and Murty's route to 4-aminonicotinic acid involved fewer stages, was convenient and the overall yield was good and the route was used in all the subsequent experiments.

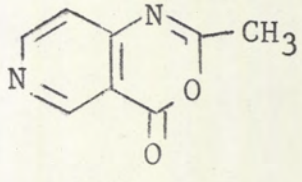
ii) Pyrido[4,3-d]-[1,3]-oxazin-4-ones

Littel and Allen[19] condensed the appropriate amino-pyridine carboxylic acids (48) with acetic anhydride to afford the corresponding 2-methylpyrido[1,3]-oxazin

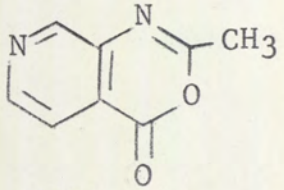


(48) (49)

-4-ones (49). They obtained by this method four series of 2-methylpyridooxazines; 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one (50); 2-methylpyrido[3,4-d]-[1,3]-oxazin-4-one (51); 2-methylpyrido[3,2-d]-[1,3]-oxazin-4-one (52); 2-methyl pyrido[2,3-d]-[1,3]-oxazin-4-one (53).



(50)



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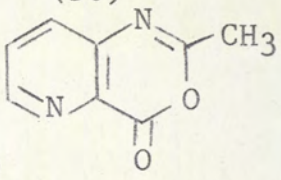

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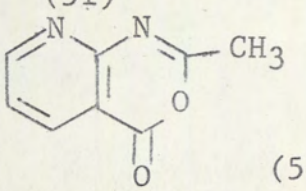
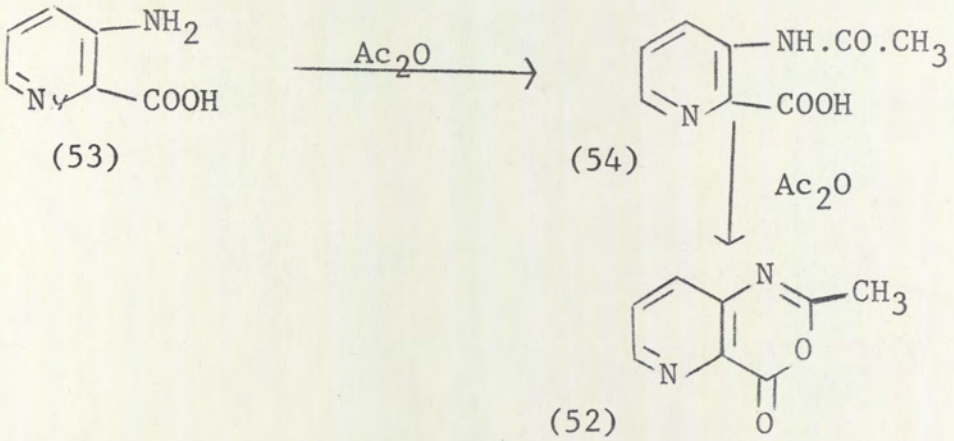


(53)

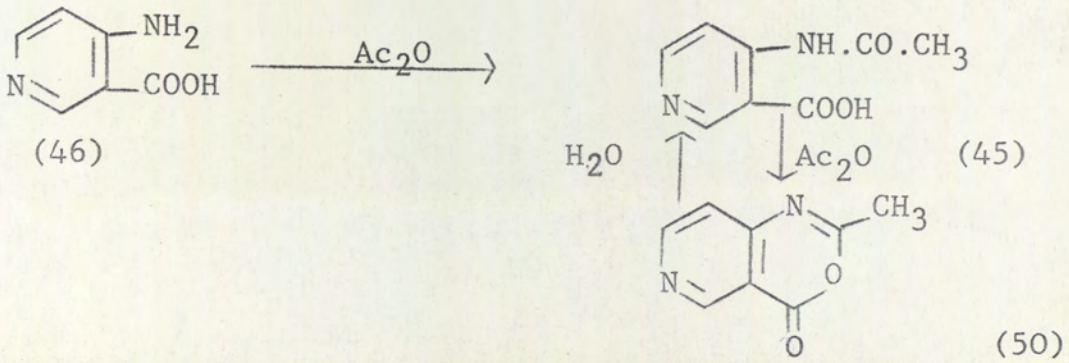
No reference was made to the intermediate acetamidopyridine carboxylic acids.

The preparations of pyrido[2,3-d]-[1,3]-oxazin-4-ones were also reported in 1965 by Dornow and Wille[20]. Irwin and Wibberley[21] had prepared 2-methylpyrido[3,2-d]-[1,3]-oxazin-4-one(52) from 3-aminopicolinic acid (53) or from 3-acetamidopicolinic acid (54).



(53) (54) (52)

Treatment of 4-aminonicotinic acid (46) or 4-acetamidonicotinic acid[22] (45) with acetic anhydride under the conditions employed by Littel and Allen[19] but with direct crystallisation of the crude product from ethyl acetate rather than the chromatographic separation yielded the 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one (50).



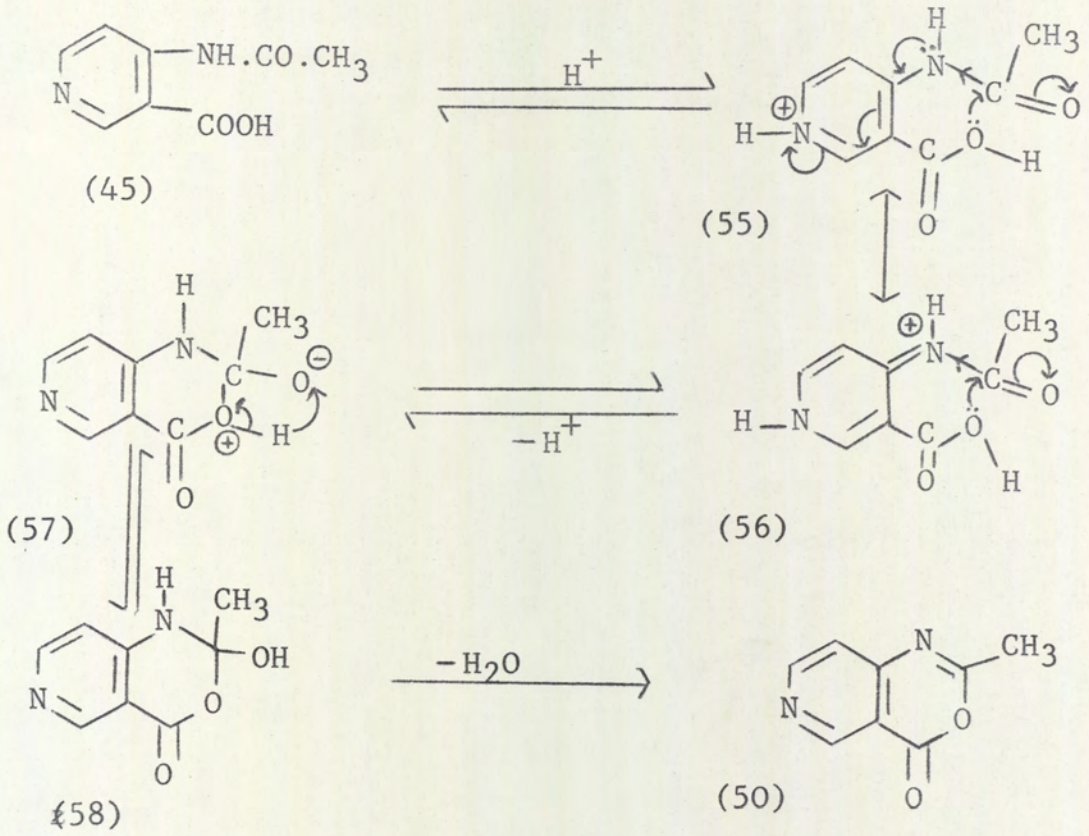
(46) (45) (50)

Littel and Allen did not quote the infra-red spectra nor the stabilities of the pyrido-oxazines.

The infra-red spectrum of the 2-methylpyrido-oxazine (50) in chloroform solution showed the high carbonyl stretching vibration expected of an unsaturated δ-lactone[23(a)] of this type. The stretching vibrations due to C=N and C-O were also assigned. The spectrum was closely similar to that of 2-methylpyrido[3,2-d]-oxazine[21] (52).

The 2-methylpyrido[4,3-d]-oxazine (50) was very unstable. On exposure to air for two hours or on stirring with water for ten minutes it was hydrolysed back to 4-acetamido-nicotinic acid (45). In the[3,2-d][21] series also 2-methyl-pyrido-oxazine has been shown to hydrolyse to the correspond-ing acetamido acid under similar conditions. Zentmeyer and Wagner[24] also reported about similar susceptibility to hydrolysis of 2-methylbenzoxazine analogue. The pyridooxazine (50) had there-fore to be used immediately after its isolation from the reaction mixture.

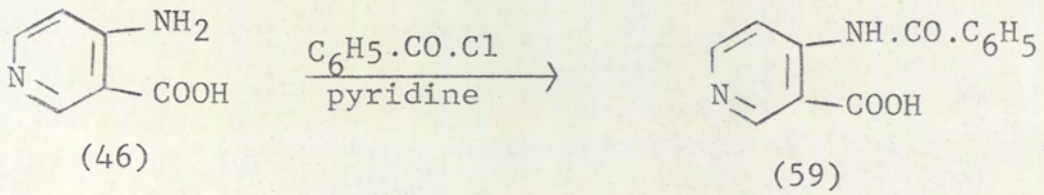
The cyclisation of 4-acetamidonicotinic acid (45) to the pyrido-oxazine (50) is probably enhanced by the presence of traces of acetic acid. The protonation of 4-acetamido-nicotinic acid (45) will occur at the ring N atom (by analogy with 4-aminopyridine[25(a)]) to give the protonated amine (55 ⟷ 56) in which the increased electron withdrawal from the acetamido carbonyl group will facilitate the nucleophilic attack by $\ddot{O}H$ of the carboxylic acid (55 and 56). Proton loss (55⟷56⇌57) and proton transfer(57⇌58)followed by loss



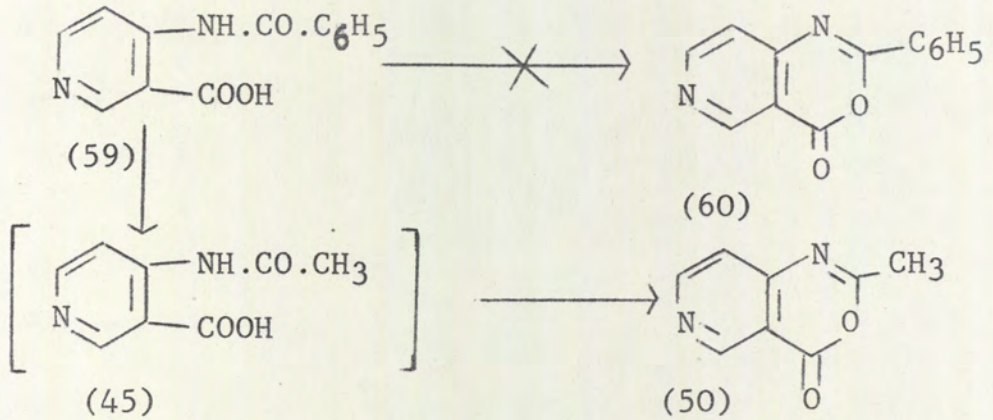
of water may give the pyrido-oxazine (50).

An attempt to prepare 2-phenyl-pyrido[4,3-d]-[1,3]-oxazin-4-one (60) was unsuccessful.

Using dry pyridine as the catalyst 4-aminonicotinic acid (46) could be benzoylated to give 4-benzamidonicotinic acid. (59)



By analogy with the [3,2-d] series[21], it was expected that 4-benzamidonicotinic acid (59) would yield 2-phenyl-pyrido[4,3-d]-[1,3]-oxazin-4-one (60). When the benzamido acid (59) was heated under reflux with acetic anhydride, however, 2-methyl pyrido[4,3-d]-[1,3]-oxazin-4-one (50) was the only product isolated. Transacylation to yield 4-acetamidonicotinic acid (45) must therefore have taken

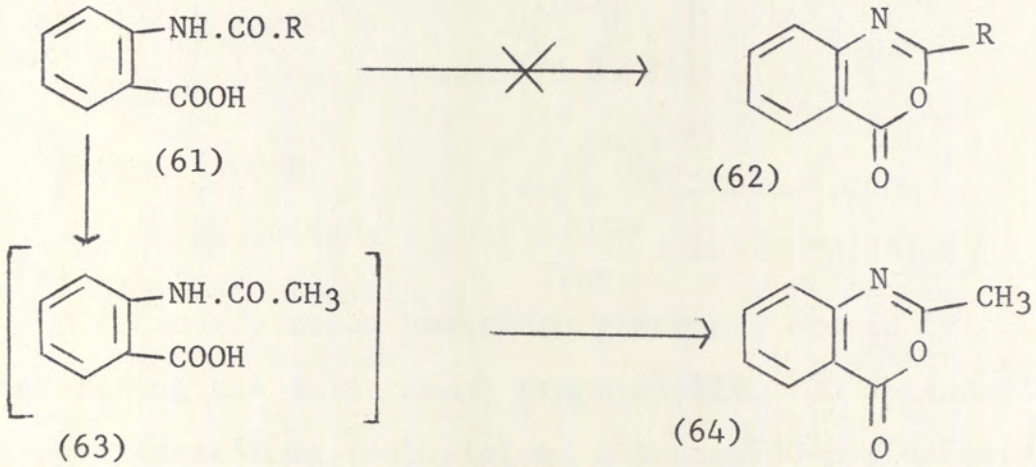


place intitially followed by dehydration to give 2-methyl-pyrido[4,3-d]-[1,3]-oxazin-4-one (50).

An attempt was made to cyclise 4-benzamidonicotinic acid (59) in the presence of benzoic anhydride. When three moles of benzoic anhydride were used for every mole of 4-benzamidonicotinic acid (59), the acid was recovered unchanged. If a large excess of benzoic anhydride (ten moles for one mole of benzamido acid) was employed, the 2-phenyl-pyridoxazine (60) was still not obtained. A mixture of benzoic acid, benzoic anhydride and 4-amidoacid were the

only products isolated. Direct heating of 4-benzamido-nicotinic acid gave only 4-aminonicotinic acid (46).

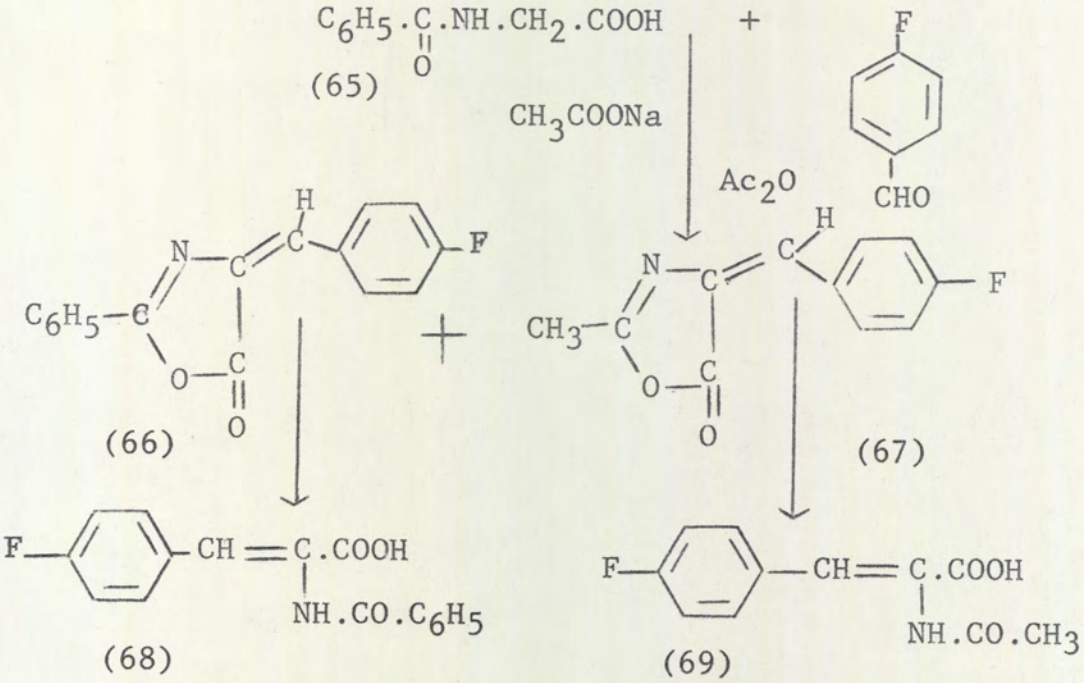
Examples of transacylation have been reported in the literature. Zentmyer and Wagner[24] found that the treatment of N-acylanthranilic acids (61) (R=3,4-dinitrophenyl or isovaleryl) with acetic anhydride in each case yielded 2-methylbenzoxazone (64) and not the expected 2-substituted benzoxazones (62) (R=3,5-dinitrophenyl or isovaleryl).



Transacylation to yield N-acetamidoanthranilic acid (63) must be the intitial stage followed by dehydration to give the 2-methylbenzoxazone (64).

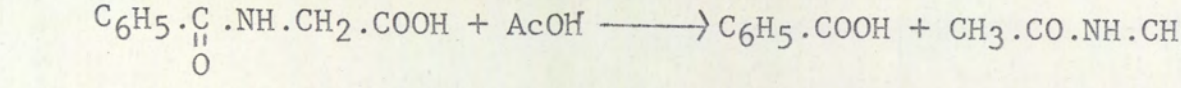
Benett and Niemman[26] had reported transacylation reactions involving replacement of benzoyl group by an acetyl group in several α-amino acids. Refluxing p-fluoro-benzaldehyde, hippuric acid (65) and acetic anhydride gave a mixture of two azlactones; 2-phenyl-4-(p-fluorobenzal-5(4H)

-oxazolone (66) and 2-methyl-4-(p-fluorobenzal)-5(4H)oxazolone (67).

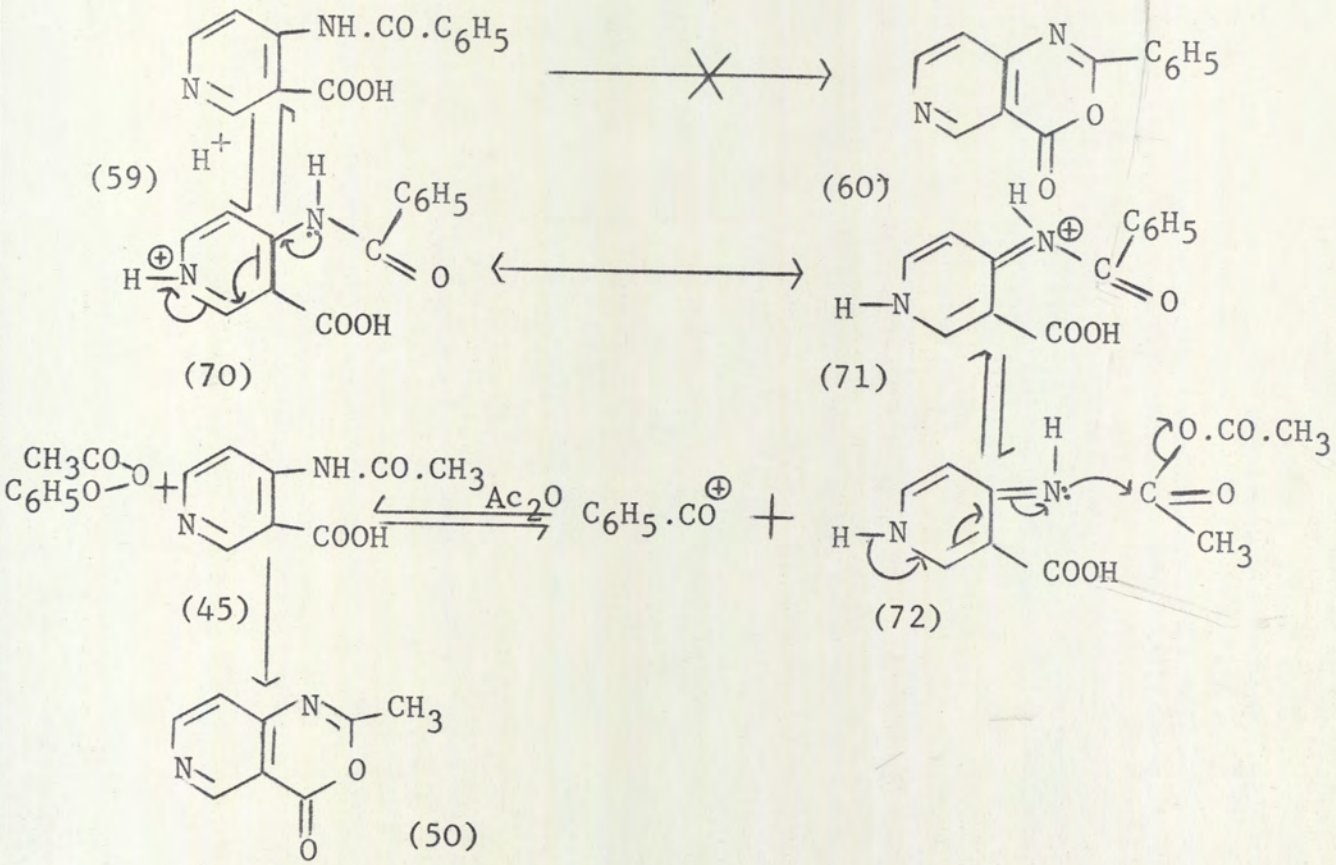


That transacylation had taken place was proved by separating the azlactones fractionally. On degradation 2-phenyloxazolone (66) yielded α-benzamido-p-fluorocinnamic acid (68), while the 2-methyloxazolone (67) yielded α-acetamido-p-fluorocinnamic acid (69).

Taschner and Kupryzewski[27] observed that a direct exchange of acyl groups in N-acylated amines, amino acids and peptides took place when refluxed with the organic acids. Thus on boiling hippuric acid (65) in presence of hydrogen bromide and acetic acid yielded benzoic acid and acetyl glycine (70).



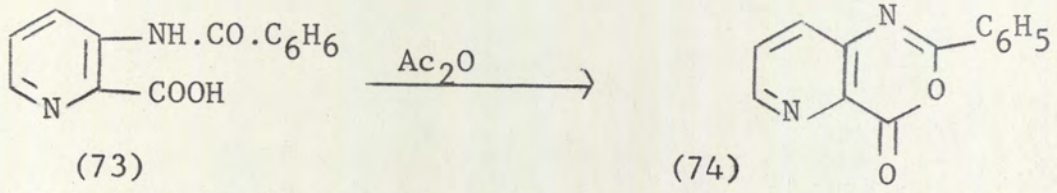
It is suggested that during the attempted cyclisation of 4-benzamidonicotinic acid (59) to 2-phenylpyridooxazine (60) two competitive reactions are capable of operation. These are cyclisation (59 ⟶ 60) which would be aided



by a reactive amide carbonyl and a nucleophilic $\ddot{O}H$, and transacylation (59 ⟶ 70 ⟷ 71 ⇌ 72 ⇌ 45) which would be aided by excess acetic anhydride and weakening of the N-CO bond.

The cyclisation of 4-acetamidonicotinic acid (45) to 2-methylpyridooxazine (50) proceeds more rapidly than expected for the benzamidonicotinic acid (59) because

of the unreactive nature of the $C_6H_5.CO.$ group compared to the $CH_3.CO.$ group. (It is known that aromatic acid chlorides are considerably less reactive than the aliphatic acid chlorides[28]). In the [3,2-d] series[21], however, 3-benzamidopicolinic acid (73) has been successfully converted into 2-phenyl pyrido[3,2-d]oxazin-4-one (74) in the presence of acetic anhydride. Therefore the reduced activity of the



(73) (74)

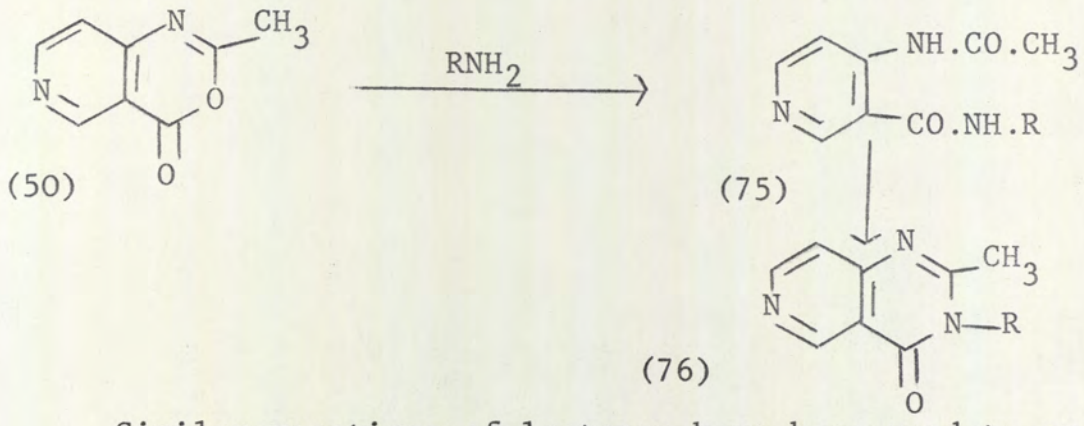
amide carbonyl is not the main cause of transacylation. The ease of transacylation is therefore probably related to the ease of protonation of this system (59 ⟶ 70 ⟷ 71) compared to the [3,2-d] system. This protonation polarises the N-C=O and facilitates splitting and subsequent transacylation (71 ⇌ 72 ⇌ 45). Once formed the cyclisation of 4-acetamidonicotinic acid (45) to 2-methylpyridooxazine (50) follows the path already suggested.

iii) 3-Substituted 2-methylpyrido[4,3-d]pyrimidin-4(3H)-ones

The scope of the pyridooxazine route was limited to the synthesis of 3-substituted-2-methylpyrido[4,3-d]pyrimidin-4(3H)-ones.

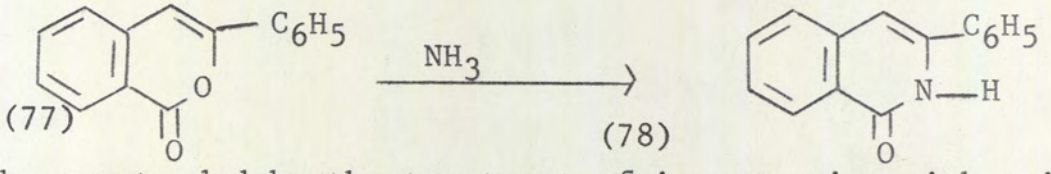
Treatment of 2-methyl pyrido[4,3-d]-oxazine (50) with

amines yield 4-acetamidonicotinamides (75) which may be cyclised by longer contact with amines or heat to give 3-substituted 2-methylpyrido[4,3-d] pyrimidin-4(3H)-ones (76).



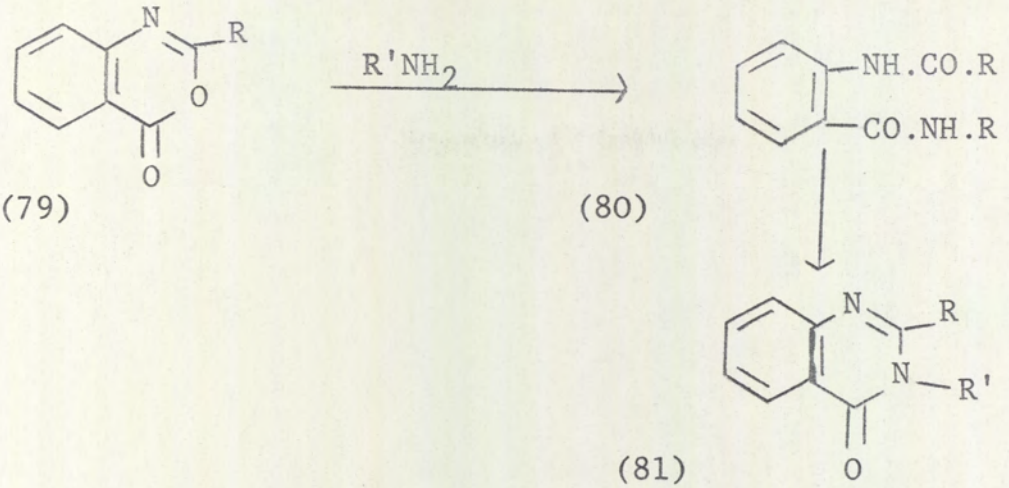
(50) (75) (76)

Similar reactions of lactones have been used to prepare other heterocylic compounds. Thus 3-phenylisocoumarin (77) has been converted into 3-phenylisocarbostyril (78) by the treatment of alcoholic ammonia.[29(a),(b)] The reaction has



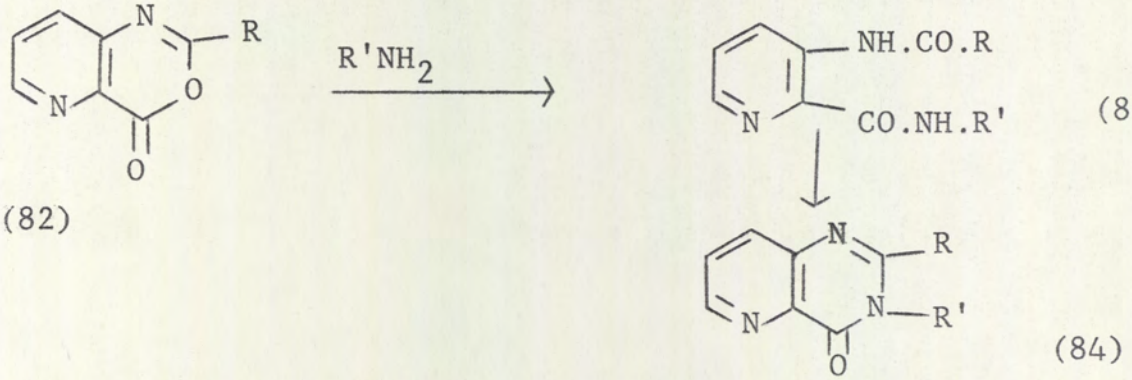
(77) (78)

been extended by the treatment of isocoumarins with primary amines to obtain a number of different isocarbostyrils.[30] Benzoxazones (79) react exothermically with ammonia and most primary amines to give good yields of 2,3-disubstituted quinazol-4(3H)-ones (81). Diamides (80) have been isolated in many reactions and are converted to quinazol-ones (81) under various reactions.[24,31] 2-methyl and 2-phenylpyrido [3,2-d] -oxazines (82) (R=CH_3 or C_6H_5) have been treated



(79) (80) (81)

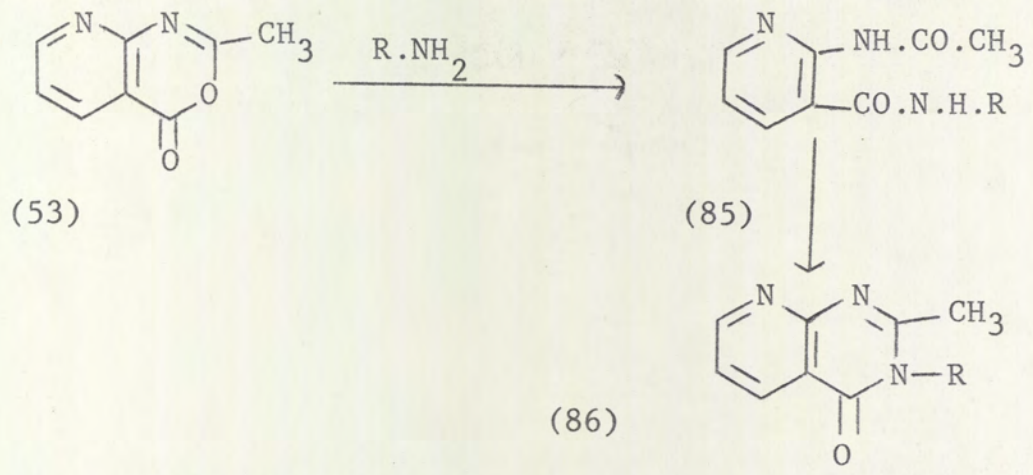
with primary aliphatic and aromatic amines to yield derivatives



(82) (83) (84)

of 3-acetamido and 3-benzamidopicolinamides (83) (R=CH_3 or C_6H_5), which are cyclised under various conditions to give two series of 2,3-disubstitutedpyrido[3,2-d]pyrimidin -4(3H)-ones[21] (84) (R=CH_3 or C_6H_5).

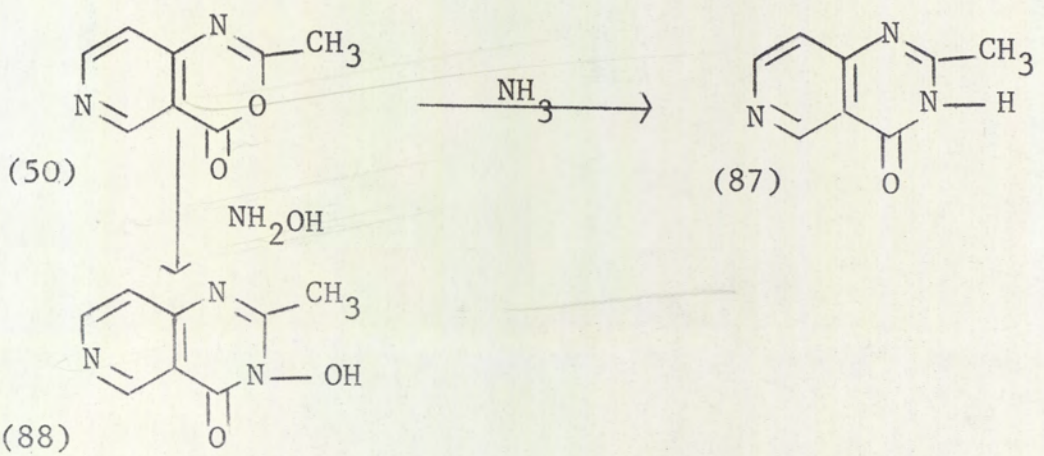
Similar treatment of 2-methylpyrido[2,3-d]-oxazine (53) with primary amines yielded a series of 3-substituted 2-methylpyrido[2,3-d]pyrimidin-4(3H)-ones (86), the cyclisation having proceeded through the intermediate diamides[32] (85).



(53) (85) (86)

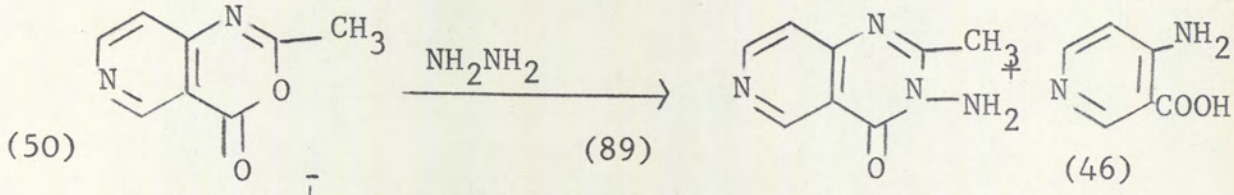
The lactones of this type react with amines because they possess electrophilic properties due to the presence of the double bond adjacent to the ring oxygen atom which nullifies the interaction of the oxygen lone-pair of electrons with the ring carbonyl group. This effect increases the reactivity of the carbonyl group.

The 2-methylpyrido [4,3-d]- oxazine (50) reacts with ammonia and hydroxylamine, at room temperature, to give in each case the corresponding pyridopyrimidine (87 and 88) without prior isolation of the intermediate diamides.

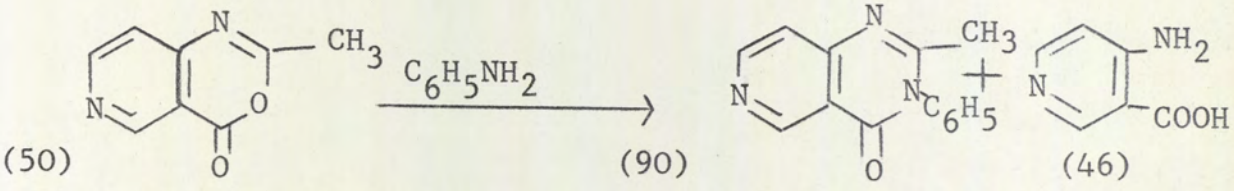


(50) (87) (88)

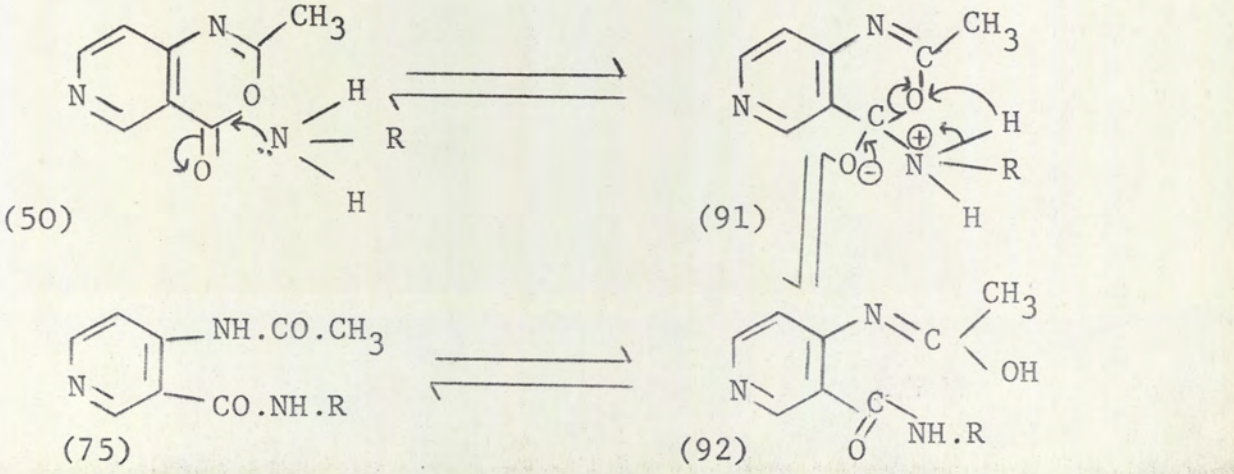
The pyridooxazine (50) also reacts with hydrazine at room temperature to give a mixture of 3-amino-2-methyl-pyrido[4,3-d]pyrimidin-4(3H)-one (89) and 4-aminonicotinic acid (46).



The pyridooxazine (50) does not react with aniline at room temperature but when fused at 190°, yields a mixture of 2-methyl-3-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (90) and 4-amino-nicotinic acid (46).



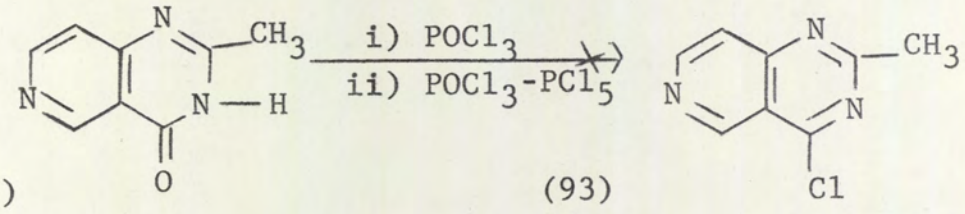
Intitial nucleophilic attack by the unshared electron pair of the nitrogen atom of the amines on the carbonyl carbon (50 ⇌ 91) followed by proton transfer (91 ⇌ 92) would be expected to give the intermediate 4-acetamido-nicotinamide (75).



The mechanistic path of the cyclisation of the diamides (75) to the pyridopyrimidines (76) has been suggested on p. 53

All of the four pyridopyrimidin-4(3H)-ones, thus prepared, showed strong C=O absorption in the region of 1700-1680 cm^{-1}.

Treatment of 2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (87) with phosporyl chloride or a mixture of phosphoryl chloride and phosphorus pentachloride did not yield the expected chlorocompound (93) nor the starting material (87). A charred brown product was isolated at the



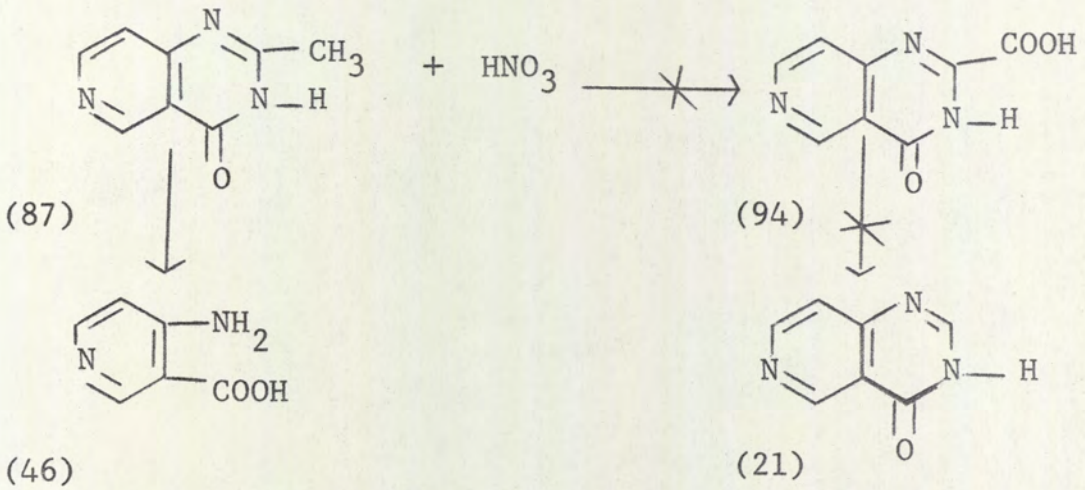
(87) (93)

end of reaction. This is in contrast to the [2,3-d] and [3,2-d] series,[33] where the reactions under similar conditions have yielded the chloro-compounds. 5-Nitro-4-quinazolone,[1a] however, does not react even in the presence of excess phosphorus pentachloride under a great variety of conditions. Similar difficulty has been encountered with 3,4-dihydroxypyrido[5,6-d]pyrimidine[1a] and in the pteridine series.[46]

An attempted condensation of 2-methyl pyrido [4,3-d]

pyrimidin-4(3H)-one (87) with benzaldehyde yielded a red oil, which could not be purified.

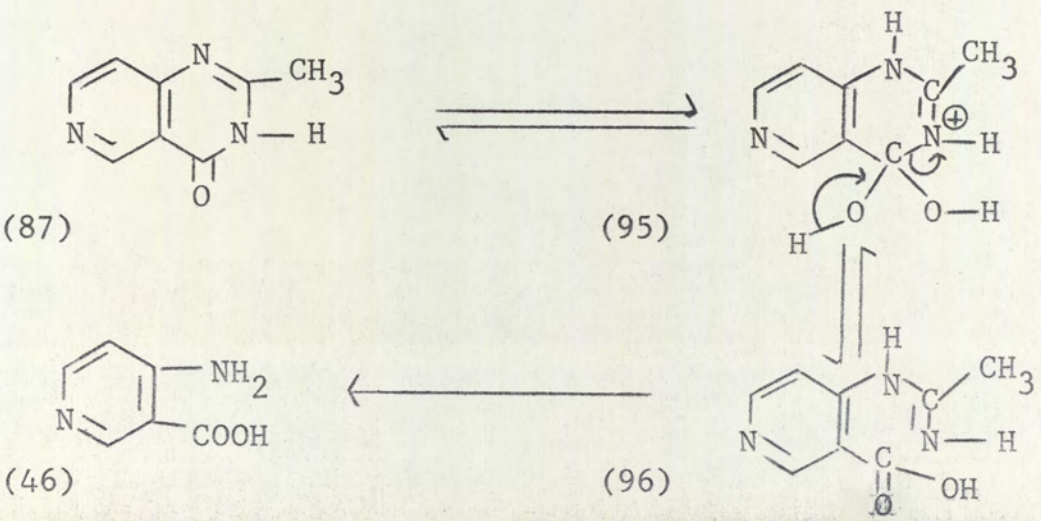
Treatment of 2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (87) with nitric acid gave 4-aminonicotinic acid (46) and not the carboxylic acid (94) or pyrido[4,3-d]pyrimidin-4(3H)-one (21). This contrasts with the [3,2-d] series[21]



(87) (94) (46) (21)

where 2-methylpyrido[3,2-d]pyrimidin-4(3H)-one has been oxidised and decarboxylated to give pyrido[3,2-d]pyrimidin-4(3H)-one.

Treatment of 2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (87) with dilute hydrochloric acid gives 4-aminonicotinic

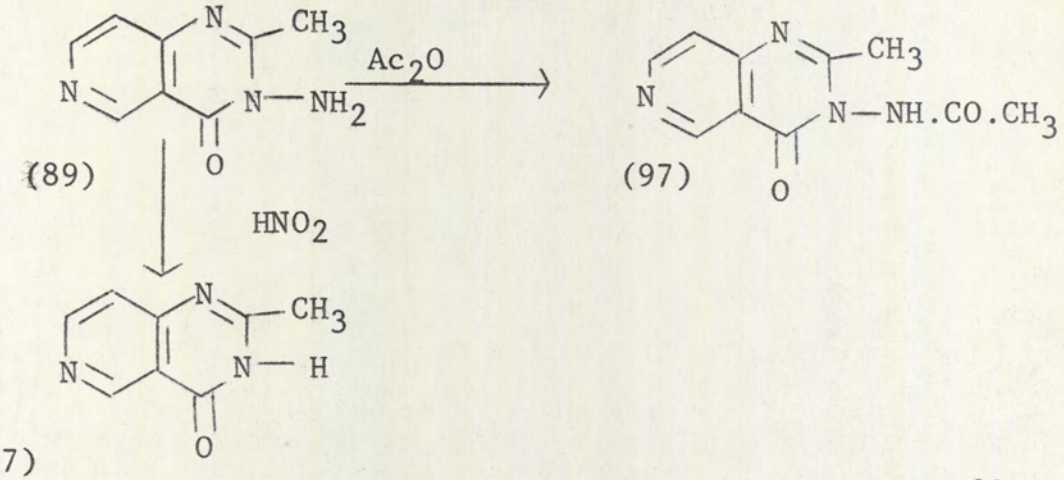


(87) (95) (96) (46)

acid (46). The first step may be opening of the ring (95) to give the amidine (96) which under the reaction condition must be hydrolysed to give 4-aminonicotinic acid (46).

Armarego[15] has commented on the particular susceptibility of the pyrido [4,3-d] pyrimidine (4) to covalent hydration causing the ring to open. It is suggested that the reactions of 2-methyl pyrido[4,3-d]pyrimidin-4(3H)-one failed because of a similar instability.

Treatment of 3-amino-2-methyl pyrido[4,3-d]pyrimidin-4(3H)-one (89) with acetic anhydride gave the acetyl derivative (97) and with nitrous acid gave 2-methyl-pyrido-[4,3-d]pyrimidin-4(3H)-one (87). Similar degradation with

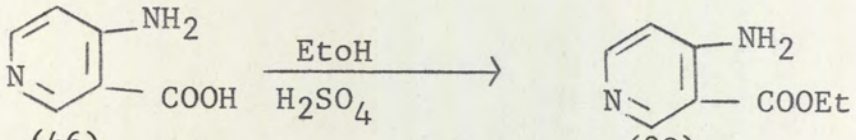


nitrous acid has been carried out in the [3,2-d] series[21] and in other heterocylic compounds.[34,35]

(B) SYNTHESIS OF PYRIDO[4,3-d]PYRIMIDIN-4-(3H)-ONES FROM ETHYL 4-AMIDONICOTINATES

i) Ethyl 4-aminonicotinate

Ethyl 4-aminonicotinate (20) was prepared using Taylor's condition[14] but with a longer reflux period to improve the yield. The rate of esterification is slow

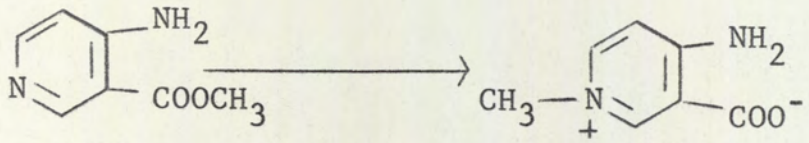


(46) (20)

probably because the amino group ortho to the acid group is sterically retarding the attack of the incoming alcohol molecule.[36] The amino group shows three absorption bands in the region of 3500-3200cm^{-1}. One at 3500cm^{-1} is due to asymmetric stretching mode; one at 3400cm^{-1} arises from the corresponding symmetrical mode. The peak at 3200cm^{-1} is probably a further split of the two NH_2 bands. The stretching vibration of C=O at 1695cm^{-1} and C-O at 1260cm^{-1} is characteristic of an aromatic amino ester.

Armarego[15] failed to obtain pyrido[4,3-d]pyrimidin-4-(3H)-one (21) from 4-aminonicotinic acid (46) and formamide. He also failed to condense methyl 4-aminonicotinate (30) with formamide. The pyrido-pyrimidin-4(3H)-one (21) was eventually obtained by treating 4-aminonicotinamide (29) with formamide. Taylor was successful in causing ethyl 4-aminonicotinate to react with formamide to yield pyrido

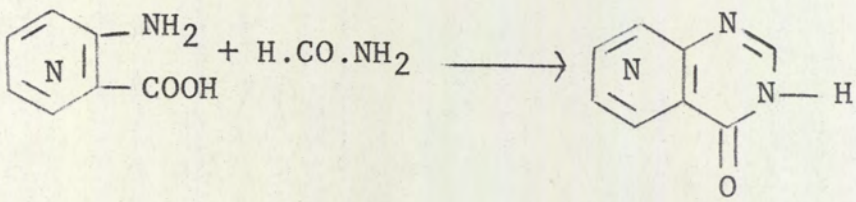
[4,3-d]pyrimidin-4(3H)-one (21). The present investigation confirms that Taylor's condition does yield pyrido[4,3-d] pyrimidin-4(3H)-one (21). A possible reason for Armarego's failure may be related to his use of methyl ester with a much higher melting point (173°) and therefore requiring stronger reaction conditions. Alternatively as Fox[37] has observed, methyl 4-aminonicotinate (97) may have been converted into betaine form (98) under the reaction condition and thus



(30) (98)

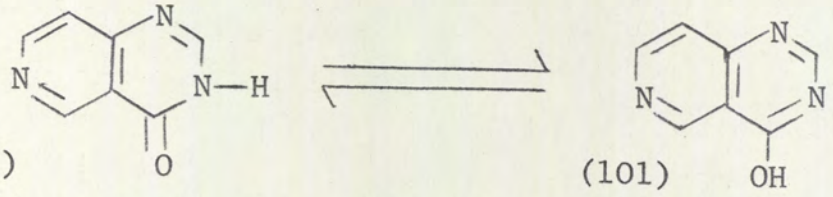
prevent the fusion.

The fusion is an extension of the von Niementowski reaction, whereby an anthranilic acid or its derivative is fused with an aliphatic amide to give quinazol-4-ones.[2(a)] Similar fusion of the appropriate amino pyridine carboxylic acids (99) and formamide have yielded the corresponding pyridopyrimidin-4(3H)-ones (100).[38,39,40,41]



(99) (100)

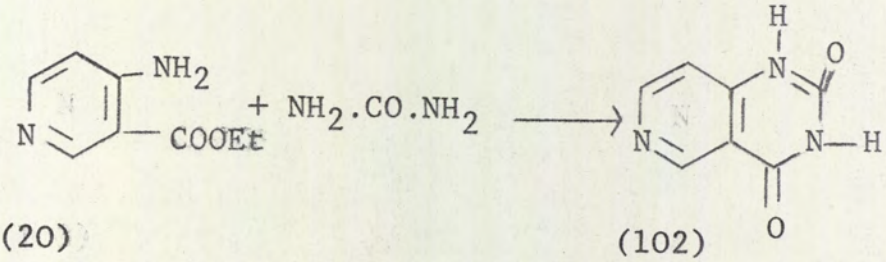
Pyrido[4,3-d]pyrimidin-4(3H)-one may be expected to show amide (21)$\rightleftharpoons$enol (101) tautomerism. The infra-red



(21) (101)

spectrum of the compound run in nujol shows a strong stretching vibration at 1695 cm^{-1} due to the ring C=O. This suggests the existance of principally the amide form in the solid state. Mason[42] has assigned a structure of quasi-o-quinonoid to pyrido[3,2-d]pyrimidin-4(3H)-one. No such definite assignment of the structure could be deduced for pyrido[4,3-d]pyrimidin-4(3H)-one.

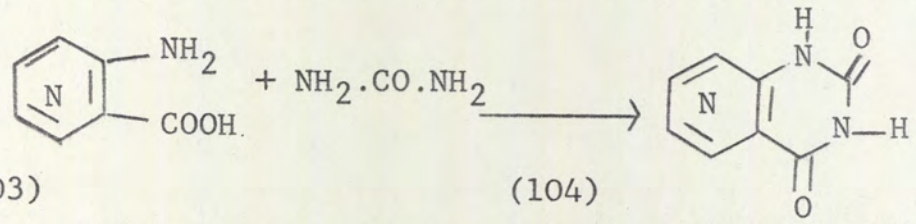
An attempt was made to fuse 4-aminonicotinic acid (46) and urea; the resulting pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102), however could not be purified sufficiently to give an analytical sample. The pyridopyrimidin-dione (102)



(20) (102)

was more conveniently prepared by fusing ethyl 4-aminonicotinate (20) and urea at 170° for one hour. Similar fusion of ortho amino carboxylic acids in other heterocylic series

have yielded the corresponding 2,4(1H,3H)-diones. Thus anthranilic acid and urea, when melted, together give quinazol-2,4(1H,3H)-dione.[43] Various aminopyridine carboxylic acids (103) have been fused with urea to obtain the corresponding pyridopyrimidin-2,4(1H,3H)-diones.[33,38,41,44]



(103) (104)

The infra-red spectrum of the pyridopyrimidin-2,4(1H,3H)-dione (102) showed a broad peak at 3200-2750cm^{-1} and so was assigned to the N-H band. A strong stretching vibration at 1700cm^{-1} was assigned to the ring C=O. Short and Thompson[45] have suggested that 2,4-dihydroxy pyrimidine probably exists mainly in diketonic form. On that basis pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102) may exist predominantly in the diamide form at least in the solid state.

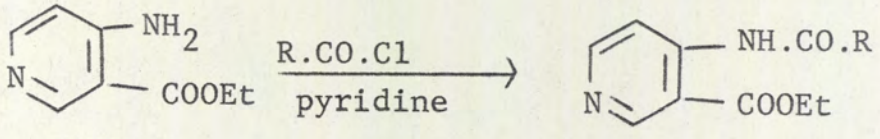
Attempts were made to convert pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102) into the 2,4-dichloro derivative using phosphorus oxychloride or a mixture of phosphorus pentachloride and phosphorus oxychloride. In each case a charred product was obtained. It is suggested that the pyrido[4,3-d]pyrimidine ring is unstable to halides of phosphorus and therefore decomposed. Similar instability to halides of phosphorus has been observed in the pteridine

ring system.[46] Boiling with phosphorus oxychloride destroyed 2-hydroxy,4-hydroxy and 2,4-dihydroxy pteridines.

In contrast to the [4,3-d] series, pyrido [2,3-d] pyrimidin-2,4(1H,3H)-dione[38] has been successfully transformed into the 2,4-dichloro derivative and into a variety of pyrido [2,3-d] pyrimidines with one or two functional groups in the pyrimidine moiety.

ii) Ethyl 4-Amidonicotinates

Treatment of ethyl 4-aminonicotinate (20) with acyl or aroyl chloride in pyridine gave ethyl 4-amidonicotinate

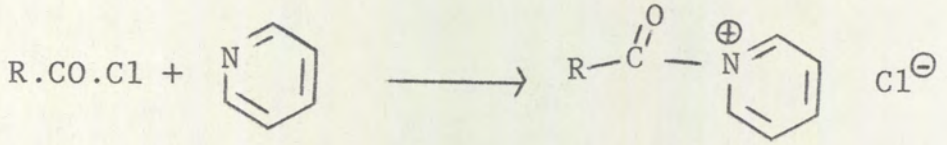


(20) (105)

(105). The method was successful with acetyl, benzoyl, 2-nitrobenzoyl, 4-methylbenzoyl (p-tolyl), 1-naphthoyl, 2-furoyl and nicotinoyl chlorides. Ethyl 4-acetamidonicotinate (105) ($R=CH_3$) was also prepared by the treatment of the aminoester (20) with acetic anhydride. Ethyl 4-benzamidonicotinate (105) ($R=C_6H_5$) was also prepared by the treatment of the aminoester (20) with benzoyl chloride in the presence of aqueous sodium hydroxide.

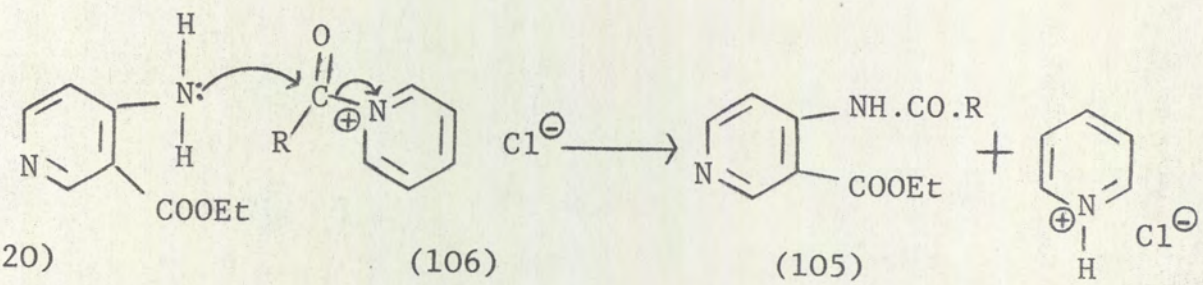
The conversion of amines into amides by treatment with acyl chlorides in pyridine are reactions of preparative

value which have been long in use. Pyridine is preferred as a basic catalyst compared to aqueous sodium hydroxide, since it forms the unstable quaternary salt (106), with



(106)

a labile $R.CO^{+}$ group. Nucleophilic attack by the lone pair of the nitrogen of the amine (20) on the acylpyridinium cation (106) with fission of the N-C bond of the acyl-pyridinium salt may be expected to give the desired

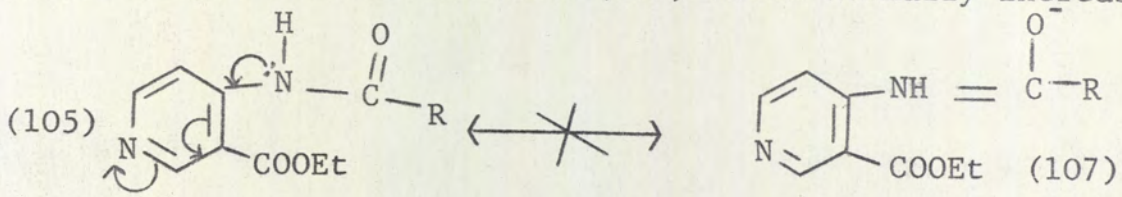


(20) (106) (105)

amidoester (105).

The infra-red spectra of all the amidonicotinates were determined as dilute chloroform solutions. The three peaks of the amino group in ethyl 4-aminonicotinate were replaced by a sharp single N-H peak at about 3200cm.$^{-1}$ Such a single stretching mode is expected of a secondary amide. Two absorption bands can be theoretically expected in the range of 1720-1640cm^{-1}; one for the ester (C=O) at a higher frequency and the other for the amide I combination band (C=O) at a slightly lower frequency. All the 4-amido-

nicotinates (105), however, showed only one strong broad peak at about 1700cm^{-1}. This peak was assigned to both the ester (C=O) and the amide I combination band (C=O). The frequency of amide I has been raised by about 40cm^{-1} above the normal amide region.[23(b)] The mesomeric shift towards the ring nitrogen atom (105) will decrease the contribution of the single bond contributor (107) which normally increases

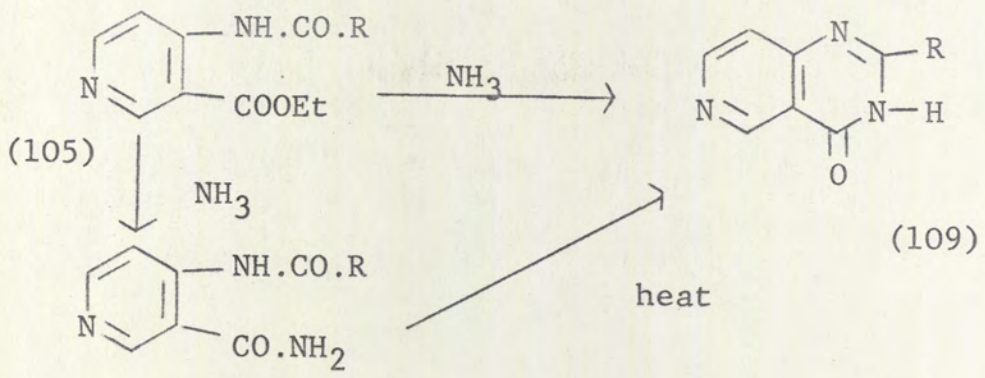


the bond length and hence decreases C=O bond absorption in amides. As expected in the secondary amide series, all of the amidonicotinates exhibited the strong amide band II at about 1510cm^{-1}. The amidonicotinates also showed amide III band at 1300cm^{-1}, which appeared as sharp peaks but of weaker intensity compared to amide I and amide II bands.

The amidonicotinate (105) (R=2-nitrophenyl) showed two strong absorption bands at 1540 and 1350cm^{-1}, characteristic of the asymmetric and symmetric valence vibration of the NO_2 group.

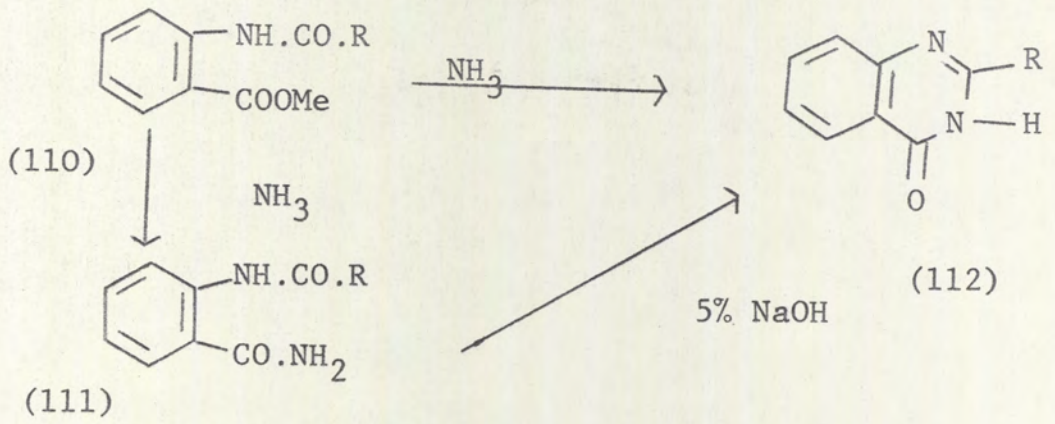
iii) 2,3-Disubstituted Pyrido[4,3-d]pyrimidin-4(3H)-ones

When ethyl 4-amidonicotinate (105) was treated with ammonia, the diamide (108) or the pyridopyrimidine (109)



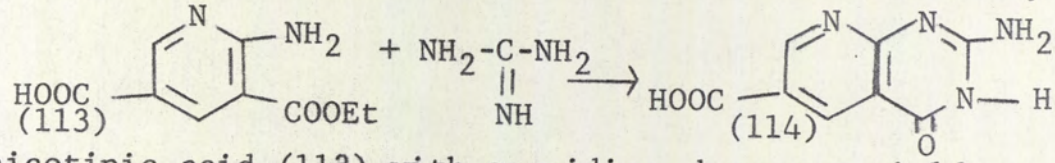
was isolated from the reaction mixture in good yield. The amidonicotinates (105) (R=methyl, 2-furyl, 3-pyridyl) were directly converted into the pyridopyrimidines (109) without isolable intermediate diamides (108). The pyridopyrimidine (109) ($R=CH_3$)was also prepared via the pyridooxazine route (p. 27). The bulk of the remaining amidonicotinates (105) (R=phenyl, 2-nitrophenyl, 4-methylphenyl and 1-naphthyl) gave the diamides (108) as the sole product.

Conversion of an ester into an amide is a well established typical reaction of an ester. The ammonolysis of methyl phenyl acetate in methanol has been quantitatively studied by Betts and Hammett.[47] Similar quantitative studies of the conversion of an ester into an amide by ammonia or amines have been carried by other workers as well.[48,49] Methyl N-arolyanthranilates (110) have been readily converted into amides (111) by the action of ammonia.[50] In some instances



the diamides (111) are partially converted into the corresponding quinazol-ones (112). The diamides (111) are completely converted into quinazolones (112) by heating with 5% aqueous sodium hydroxide.

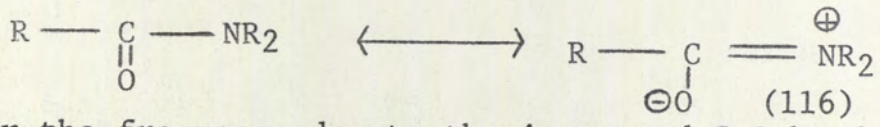
A parallel reaction of amidopyridine esters with ammonia has not been reported so far in the other system of pyridopyrimidines. The reaction of 6-amino-5-ethoxycarbonyl



nicotinic acid (113) with guanidine, however, yields 2-aminopyrido[2,3-d]pyrimidin-4(3H)-one-6-carboxylic acid[51] (114).

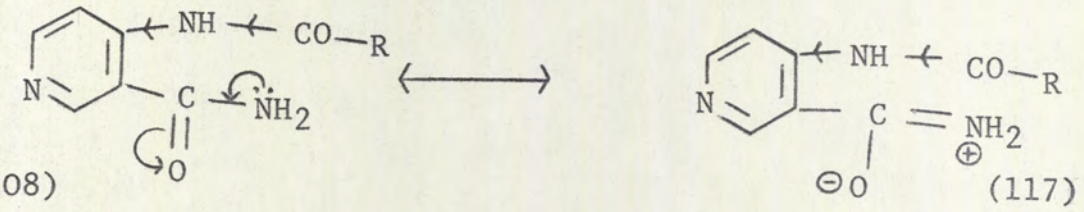
The single N-H peak of the amido nicotinates (105) was replaced in the diamides (108) by two N-H stretching modes at about 3300cm.$^{-1}$ Two separate amide I band were

present in the region of 1700-1640cm.$^{-1}$ [In the diamide (108) (R=phenyl) only one N-H peak and only one amide band I were present; with the diamide (108) (R=1-naphthyl), three amide I band were observed.] In amides, the carbonyl frequency is influenced not only by the electronegative reactivities of the substituents but also by the combination of canonical forms such as (115) and (116) which in all cases will tend



(115) (116) 23(c)

to lower the frequency due to the increased C-O bond length. The extent to which this mesomeric effect operates depends upon the availability of the lone pair of electrons for multiple bond formation. In the present series of the diamides (108) prepared, the functional group -NH.CO.R is



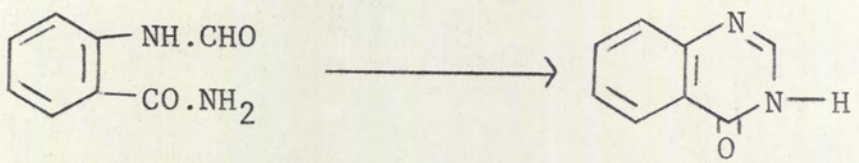
(108) (117)

responsible for the higher frequency amide I band, while the lower frequency absorption represents the functional group -CO.NH_2. This is because the mesomeric effect (108 ⟷ 117) increases the C-O bond length of the functional group -CO.NH_2 compared to the -NH.CO.R group and so lowers the absorption frequency. The diamides

exhibited amide II band at about 1520cm^{-1} as sharp but less intense peaks than that reported for the isomeric 3-amidopicolinamides.[21]

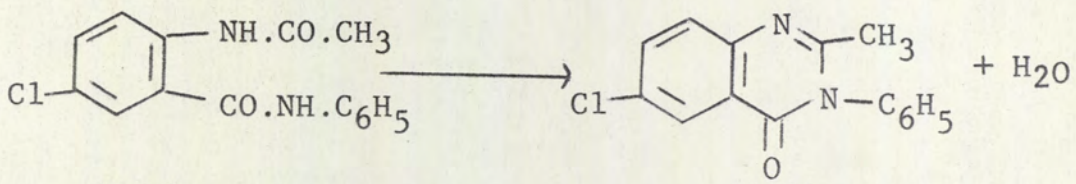
The diamides (108) (R=phenyl, 2-nitrophenyl, 4-methylphenyl, 1-naphthyl) were cyclised to the pyrido-pyrimidines (109) by heat at their melting point for a period of 15 to 30 minutes. The melt was extracted with boiling acetic acid and concentrated to give the desired pyrido-pyrimidine.

Cyclisation of diamides of this type by heat is a method of wide applicability and has been successfully used in the synthesis of 4-quinazolones and other pyrido pyrimidin-4(3H)-ones series.[21] Thus formyl anthranilamide (118) easily yields 4-quinazolone (119).[1(b)] N-acetyl anthranilamide



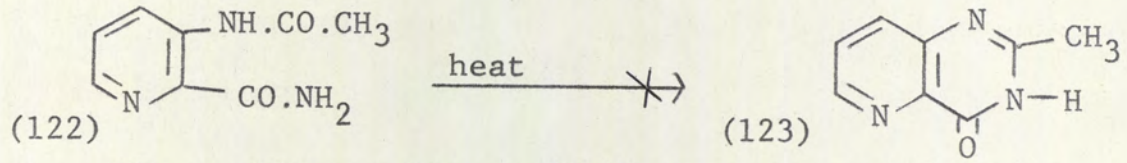
(118) (119)

(120) is cyclised by heating at the melting point for several hours to give 6-chloro-2-methyl-3-phenyl-4-quinazolone.(121)



(120) (121)

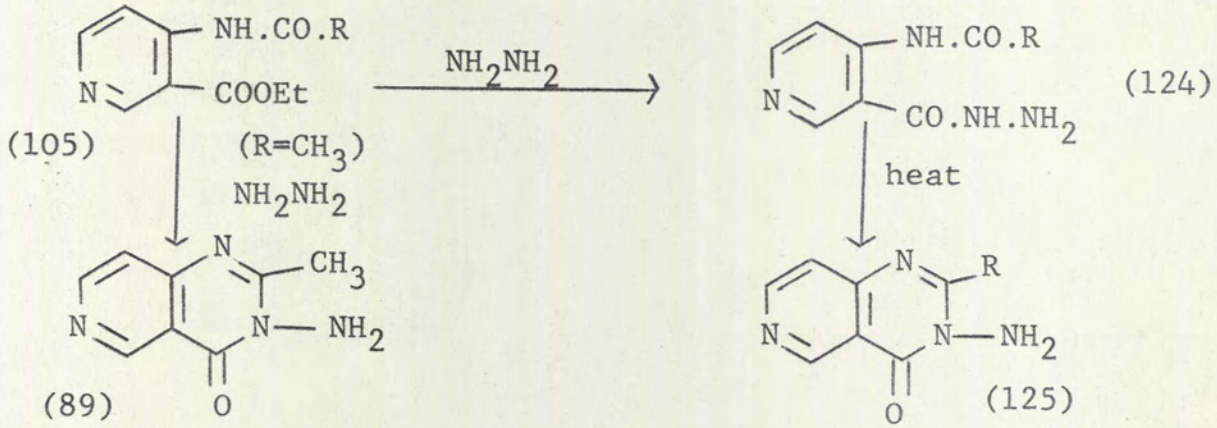
In contrast to the [4,3-d] series, in the [3,2-d] series, 3-acetamidopicolinamide[21] (122) could not be cyclised (123) by heat alone.



(122) (123)

The pyridopyrimidines (109) were characterised by the strong stretching absorption at about 1700cm^{-1}, representing the ring C=O. The pyridopyrimidine (109)(R=4-methylphenyl) showed the N-H stretching mode at 3150cm.$^{-1}$

Treatment of ethyl 4-amidonicotinate (105) with hydrazine in ethanol yielded either the pyridopyrimidine (125) or the hydrazide (124). The amidonicotinate (105)

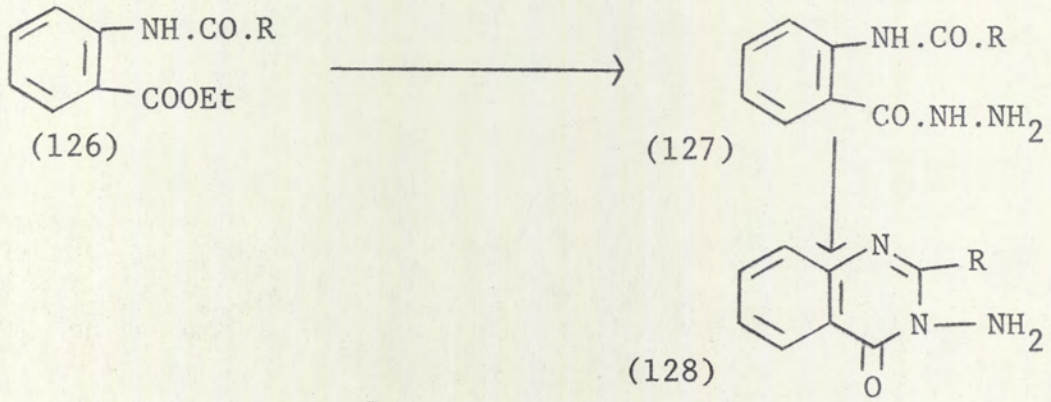


(105) (89) (124) (125)

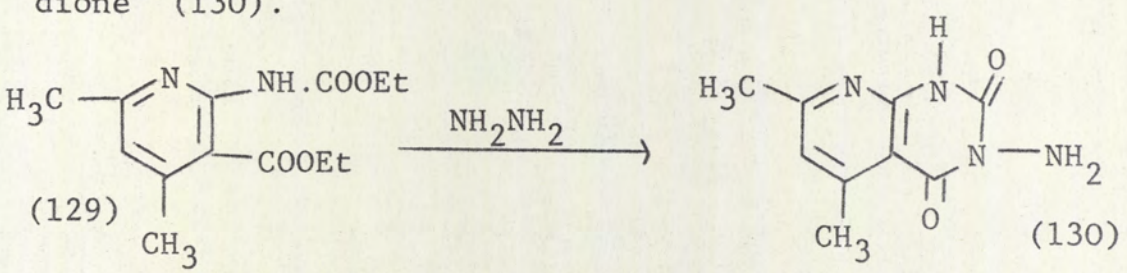
(R = CH_3) gave directly 3-amino-2-methylpyrido[4,3-d] pyrimidin-4(3H)-one (89), which was also prepared via the pyridooxazine route (p.28). The bulk of the remaining amidonicotinates (105) (R=phenyl, 2-nitrophenyl, 4-methylphenyl, 1-naphthyl, 2-furyl and 3-pyridyl) gave hydrazides (124)

as the only products.

In the quinazolone series, o-aroyl anthranilates (126) have been treated with hydrazine to give the hydrazides (127), which are cyclised to quinazol-ones (128).[94]



In the pyrido [2,3-d] pyrimidine series, the carbamate (129) has been condensed with hydrazine hydrate to give 3-amino -5,7-dimethylpyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione[20] (130).



All the hydrazides (124) showed characteristic absorption bands in the infra-red spectra. The single amido N-H peak of the amidonicotinate was replaced by two N-H stretching modes, at about 3300cm.$^{-1}$ The peaks were often broad and less sharp compared to the amidonicotinate N-H

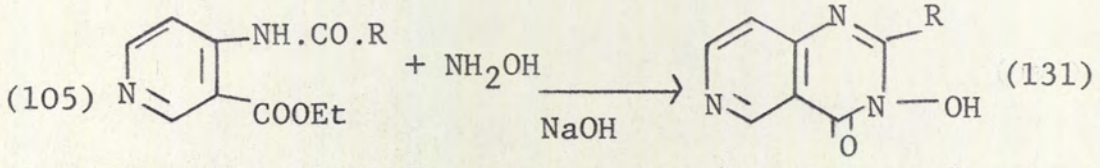
peak and were assigned to the primary amide -CO.NH.NH_2 and the secondary amide - NH.CO.R. The single C=O peak of the amidoester was replaced by two amide I band in the range of 1700-1640cm^{-1} except in the amide (124) (R=1-naphthyl) which showed three bands in this region . The amide I band at higher frequency was assigned to the secondary amide (NH.CO.R) functional group, while the lower frequency band was assigned to the primary amide (-CO.NH.NH_2) I band (cf.p41) The hydrazides (124) showed amide II band at about 1520$cm.^{-1}$

The hydrazides (124) were cyclised to the pyrido-pyrimidines (125) by heating at the melting points. All the 3-aminopyridopyrimidines (125) (R=phenyl, 2-nitrophenyl, 4-methylphenyl, 1-naphthyl and 2-furyl) were prepared by this general method. 4-nicotinamidohydrazide (124) (R=3-pyridyl) could not be cyclised by heat. The hydrazide (124), (R= 3-pyridyl) decomposed at the melting point. Phosphoryl chloride and concentrated sulphuric acid also failed to cyclise the hydrazide. The 3-aminopyridopyrimidines (125) had lower melting points than the corresponding hydrazides (124). In the [3,2-d] series,[21] 3-acetamidopicoline hydrazide has been successfully cyclised by heat alone.

The 3-aminopyridopyrimidines (125) showed two characteristic absorption bands; the primary amine (NH_2) showed two N-H stretching modes at about 3200$cm.^{-1}$ The N-H peaks

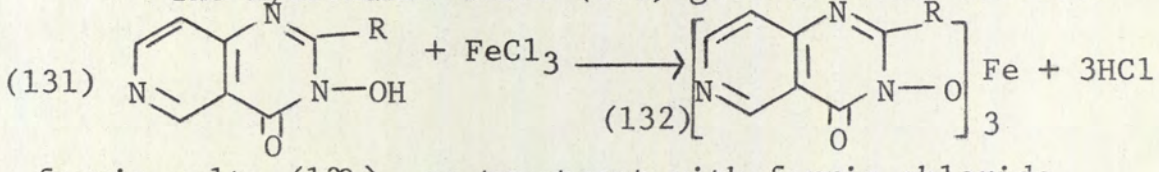
were stronger and more intense than those observed for the intermediate hydrazides. The two amide I bands of the hydrazides were replaced in the cyclic compounds by a sharp single peak at about 1700cm^{-1}, assigned to the ring C=O.

Treatment of 4-amidonicotinate (105) with hydroxylamine in aqueous sodium hydroxide yielded the cyclic



hydroxamic acid (131), without isolable intermediate acyclic hydroxamic acid. Six cyclic hydroxamic acids (131) (R= methyl, phenyl, 4-methylphenyl, 1-naphthyl, 2-furyl and 3-pyridyl) were prepared in this manner. The cyclic hydroxamic acid (131) (R=methyl) was also prepared from the pyridooxazine route (cf.p. 27).

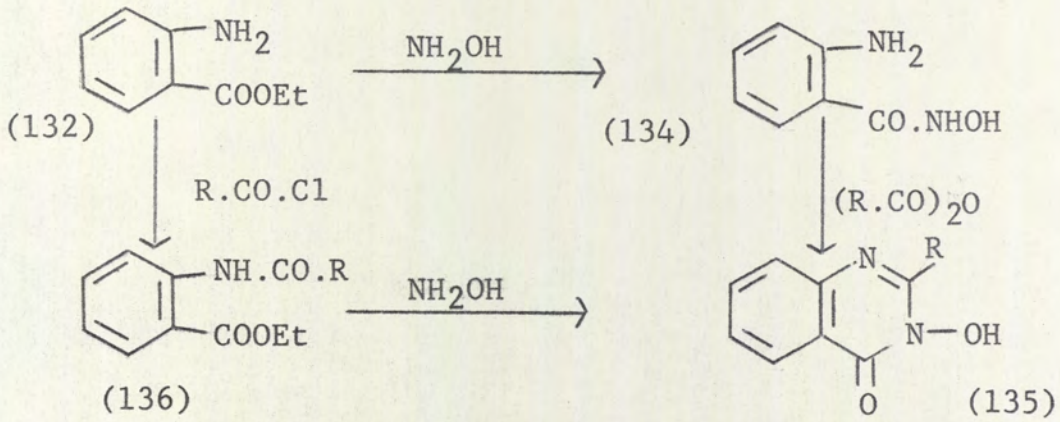
The hydroxamic acids (131) gave red wine coloured



ferric salts (132), on treatment with ferric chloride.

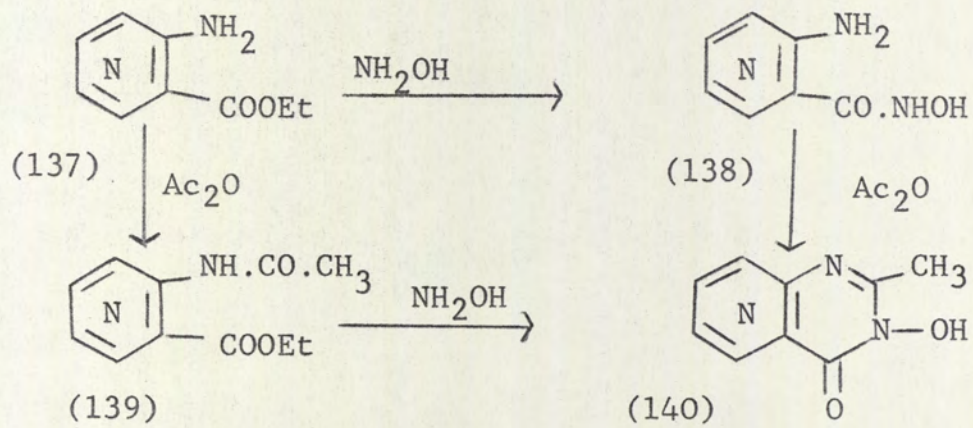
The amidonicotinate (105) (R=2-nitrophenyl) failed to give the cyclic hydroxamic acid (131) (R=2-nitrophenyl)on treatment with the hydroxylamine solution. A dark brown oil was the only product isolated from the reaction mixture. It could not be purified.

Cyclic hydroxamic acids of the quinazoline series have been synthesised by two routes from the esters of anthranilic acids.[52,53] Thus ethyl o-amino anthranilates (133) with hydroxylamine gives o-aminobenzhydroxamic acid (134),



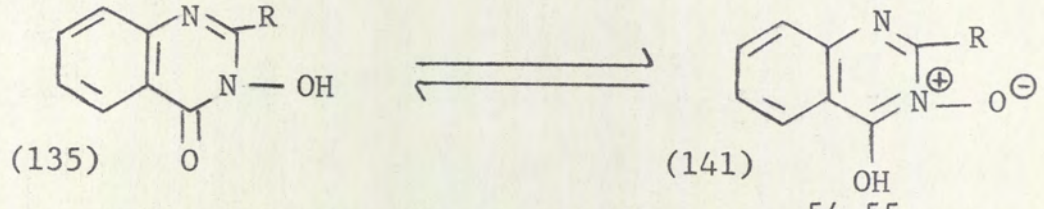
which with anhydride gives the cyclic hydroxamic acid (135). Alternatively the treatment of methyl o-acetamidobenzoate (136) with hydroxylamine gives the cyclic hydroxamic acid (135).

In the [2,3-d] and [3,2-d] series,[53] the cyclic hydroxamic acids (140) have been prepared by the action of acetic



anhydride on aminohydroxamic acids (138) or by the action of hydroxylamine on the amido ester (139).

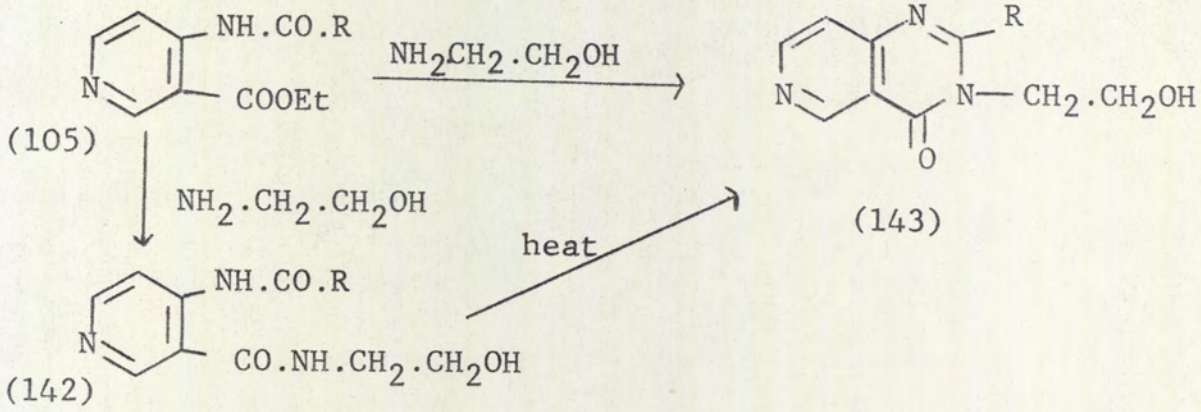
Tautomerism (135 ⇌ 141) is possible in cyclic



hydroxamic acids, but the physical evidence[54,55] indicates that in most solutions and all solids the hydroxamic acids exist in the ketoform.

The cyclic hydroxamic acids (131) in pyrido [4,3-d] pyrimidine series showed strong ring C=O absorption in the range of 1700cm.$^{-1}$ The hydroxamic acids (131) (R=methyl, 4-methylphenyl and 1-naphthyl) showed broad O-H stretching band at 2700-2300cm,$^{-1}$

When a solution of ethyl 4-acetamido-nicotinate (105) (R=methyl), ethanolamine and ethanol was heated under reflux, 3-(2'-hydroxyl)-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one



(143) (R=methyl) was obtained in good yield. Similar treatment of ethyl 4-benzamidonicotinate (105) (R=phenyl)

and ethyl 4-1'-naphthylamidonicotinate (105) (R=1-naphthyl) yielded only the diamides (142) (R=phenyl or 1-naphthyl) as the main products.

The diamides (142) showed two N-H peaks, characteristic of the secondary amides. As in all the other diamides, two secondary amide I band were present. The absorption band at higher frequency was strong and intense and assigned to the functional group (-NH.CO.R). The absorption band at lower frequency was weak and assigned to the functional group ($-NH.CH_2.CH_2.OH$) (cf.p.41). The amide·II band was present at about $1520cm.^{-1}$

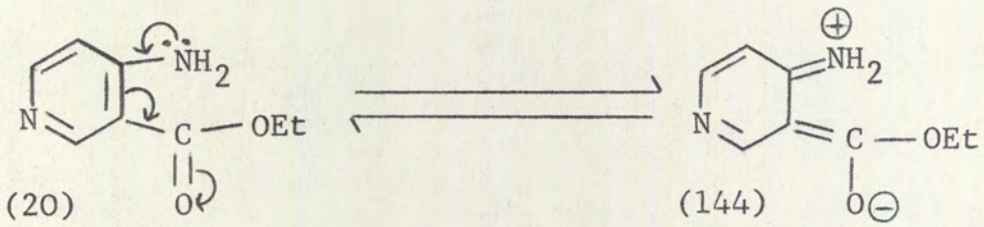
The diamide (142) (R=phenyl) was cyclised to the pyridopyrimidine (143) (R=phenyl) by heating. The pyridopyrimidines (143) (R=methyl and phenyl) showed sharp O-H absorption at about $3200cm^{-1}$ and the stretching vibration of the ring C=O at about $1700cm.^{-1}$

Ethanolamine has not been employed in the synthesis of quinazolones or other pyridopyrimidin-ones.

The diamides (108) (124) (R=2-nitrophenyl) and the pyridopyrimidines (109) (125) (R=2-nitrophenyl) showed in addition two strong absorption bands at about $1540cm^{-1}$ and $1350cm^{-1}$, characteristic of an asymmetric and symmetric valence vibration of the NO_2 group.

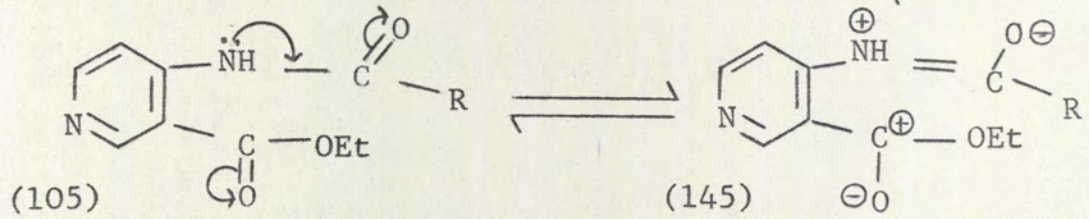
iv) Mechanism of the cyclisiation of Ethyl 4-amidonicotinates to pyrido[4,3-d]pyrimidin-4(3H)-ones

Ethyl 4-amidonicotinates (105) are much more reactive towards amines than either ethyl or methyl 4-aminonicotinate. The conversion of methyl 4-aminonicotinate into 4-aminonicotinamide requires a pressure of 100 atmospheres of nitrogen and raised temperature.[15] The reaction of 4-amido-



(20) (144)

nicotinates with amines proceed under much milder conditions. The mesomeric effect (20 ⇌ 144) in the aminoester reduces the electrophilicity of the ester carbonyl. In 4-amido-nicotinates, however, the mesomeric shift (105 ⇌ 145)

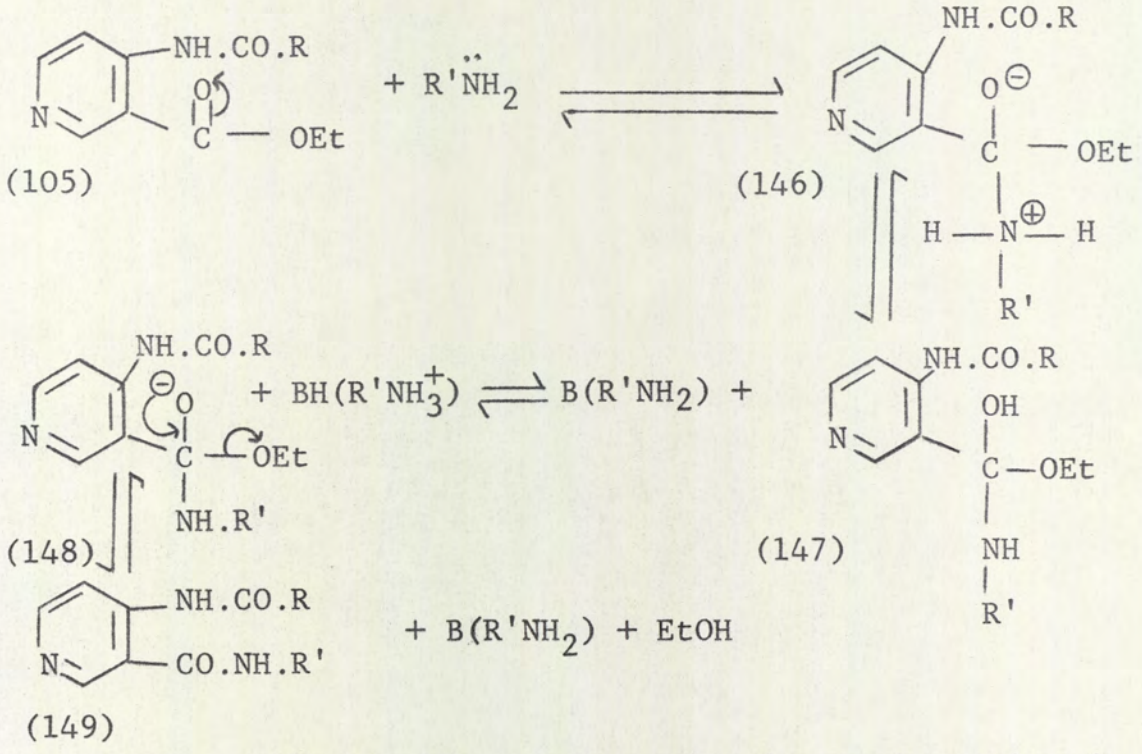


(105) (145)

is more probable because of the functional group (-CO.R) and so makes the ester carbonyl much more electron deficient and therefore highly vulnerable to nucleophilic attack.

Treatment of 4-amidonicotinates (105) with amines ($R'NH_2$; R=H, NH_2, OH and $CH_2.CH_2.OH$) give in the first instance the diamides (149). The conversion to the 4-amido-

nicotinamide (149) is probably base catalysed. The possible path of the reaction may be summarised as:



The addition of an amine molecule to the carbonyl function of the ester (105) gives the intermediate (146) which can exist by proton transfer in the form (147). The intermediate (146) or (147) yields proton to the base (146 or 147 ⇌ 148). The final step (148 ⇌ 149) is the removal of the alkoxide ion enhanced by the protonated base. Thus the catalytic function of the excess base is to assist the departure of the alkoxy group.

Amidonicotinates react readily with the primary aliphatic amines but the primary aromatic amines eg.aniline

Amine	pK_b	Ref
ethanolamine	4.56	56
ammonium hydroxide	4.74	56
hydrazine hydrate	5.52	56
hydroxylamine	7.97	56
aniline	9.42	56
3-aminopyridine*	11.50	57

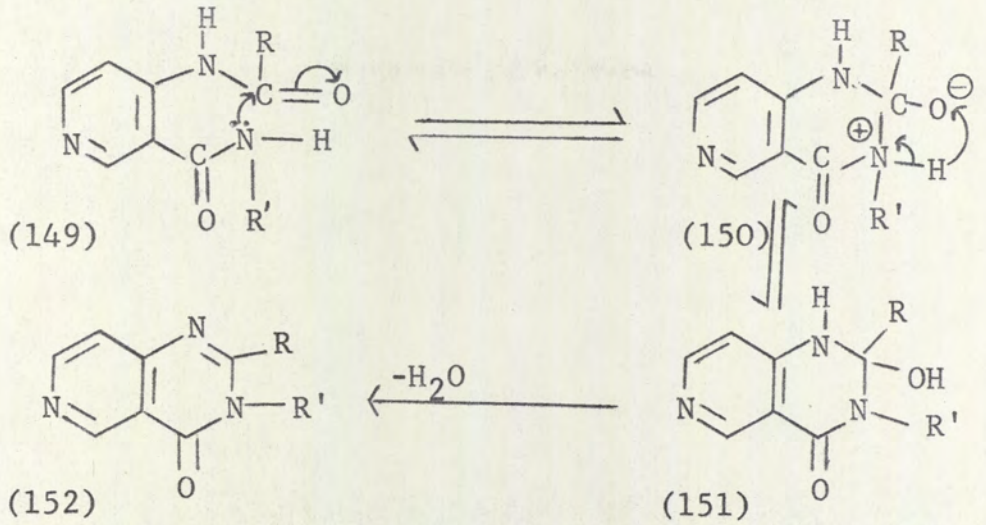
Table I

[*pK_b value refers to 3-NH_2 group and <u>not</u> the ring nitrogen (obtained by analogy with m-nitro aniline with pK_b of 11.50).]

and 3-aminopyridine fail to react under all the different conditions. The initial step of conversion of ester into amide involves the nucleophilic attack by the amine nitrogen. The stronger the base, the stronger will be the nucleophilic reagent and so easier will be the intitial nucleophilic addition. The table I shows that aniline and 3-aminopyridine are the weakest bases. Thus their failure to react with the ester may be expected. The reactivity of the hydroxylamine is enhanced by the presence of an external basic catalyst (sodium hydroxide).

The cyclisation of the diamides (149) is suggested

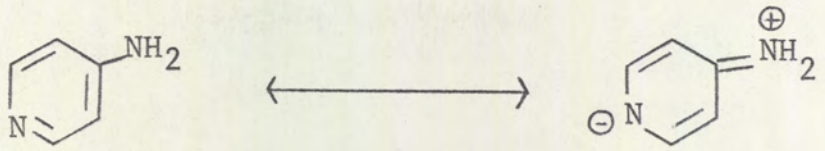
to occur as follows:-



The initial step is the nucleophilic attack of the lone pair of the nitrogen of the nicotinamido group (-CO.NH.R') (149) on the carbonyl carbon of the amide group (-NH.CO.R) to give the intermediate (150). The next step is the proton transfer (150 $\rightleftharpoons$ 151) to give 2-hydroxy 2-substituted pyrido[4,3-d]pyrimidin-4(1H,3H)-one (151). The final step is the elimination of water (152 $\longrightarrow$ 153). Similar routes have been postulated in the [3,2-d] series[21].

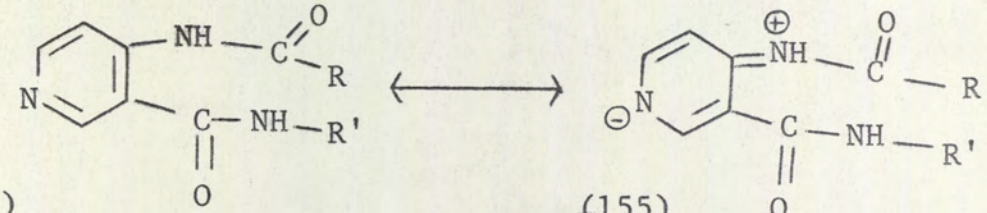
The nucleophilic attack of the nitrogen of the nicotinamido group on the carbonyl carbon of the 4-amido group is in general the rate determining step in the cyclisation to the pyridopyrimidine. Factors increasing the electrophilicity of the attacked carbonyl group and also the factors increasing the nucleophilicity of the attacking nitrogen should therefore favour the reaction.

The infra-red and dipole measurement have shown that the primary amine of 4-amino pyridine is a resonance hybrid of the uncharged (153) and the charged forms[25(b)] (154).



(153) (154)

This effect reduces the electron density on the exocylic nitrogen of the amine. By this analogy, the electron



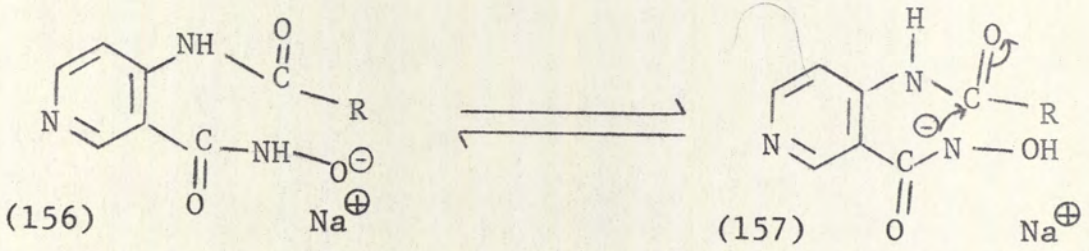
(149) (155)

density on an exocylic 4-amidonitrogen atom (and hence on the adjacent carbonyl carbon) may be expected to be lower because of the possible uncharged (149) and charged (155) resonance form. Thus the electrophilicity of the attacked carbonyl is increased. Such resonance forms cannot exist for 3-amidopicolinamide (83). This accounts for the easier cyclisation in the [4,3-d] series compared with the [3,2-d] series.[21]

The cyclisation in the [4,3-d] series is, however, also dependent to a certain extent on other factors such as the nature of substituent R, the substituent R' and the

reaction conditions (in particular, the reaction time, the temperature and the pH). Thus the treatment of 4-amidonicotinate (105) [R=methyl (3days); phenyl (4 weeks); 2-furyl (2 weeks); 3-pyridyl (2 weeks)] with ammonia give directly the pyridopyrimidines (109) without isolable intermediate diamides (108). The amidonicotinate (105) (R=phenyl), however, when allowed to react with ammonia for a shorter period (3 days) yields only the diamide (108) (R=phenyl). The amidonicotinates (105) (R=methyl, phenyl or 1-naphthyl) do not react with ethanolamine at room temperature but the reaction proceeds smoothly under reflux.

Treatment of 4-amidonicotinate (105) with hydroxylamine to give directly the cyclic hydroxamic acids (131) is almost certainly enhanced by the presence of sodium hydroxide in the reaction mixture. Sodium hydroxide gives rise to the conjugate base (156) or its tautomeric form (157), anion, which readily initiates the nucleophilic attack.



(156) (157)

Treatment of 4-amidonicotinate (105) (R=methyl) with various amines yield only the pyridopyrimidines without isolable diamides. This indicates that the methyl group must be very reactive and thus enhances the cyclisation

of the intermediate diamides.

The diamide (124) (R=3-pyridyl) failed to cyclise under all the different conditions employed.

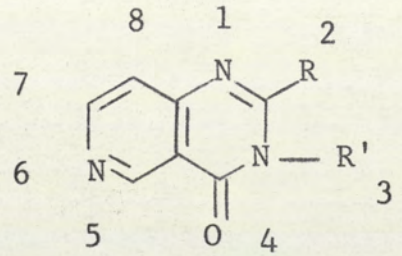
v) Nuclear Magnetic Resonance Spectra of Pyrido[4,3-d]pyrimidin-4(3H)-ones

The pyrido[4,3-d]pyrimidines were insoluble in the more commonly used non-polar solvents. The n.m.r. spectra, were therefore studied in trifluoroacetic acid, which dissolved the solute sufficiently enough to give a satisfactory spectrum. In this solvent, however, protons attached to 'O' and 'N' atoms do not show up due to protonation.

The table (2) records the appearance of protons in pyridine ring and of protons and substituents in pyrimidine ring.

Nuclear magnetic resonance spectra of pyrido[4,3-d]pyrimidin-4(3H)-ones in trifluoroacetic acid

(152)



Chemical shifts (τvalues) and coupling constants (J in c/sec in parentheses).

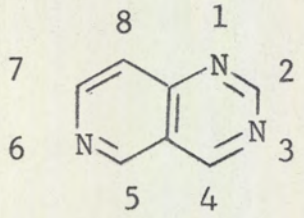
Table 2

R	R'	Protons in pyridine ring 5-H	7-H	8-H	Protons and substituents in pyrimidine ring
H	H	0.11s	0.8d(7)	1.48d(7)	0.81s(2-H)
Me	H	0.15s	0.8d(7)	1.47d(7)	6.94s(2-CH_3)
Me	OH	0.14s	0.92d(7)	1.48d(7)	6.92s(2-CH_3)
Me	$[CH_2]_2OH$	0.17s	0.87d(7)	1.52d(7)	6.78s(2-CH_3), 5.08s (3-CH_2.CH_2OH)
Me	NH_2	0.15s	0.85d(7)	1.55d(7)	6.8s(2-CH_3)
Me	NH.CO.CH_3	0.21s	0.95d(7)	1.58d(7)	7.2s(NH.CO.CH_3),7.41s(CH_3)

R	R'	Protons in pyridine ring 5-H	7-H	8-H	Protons and substituents in pyrimidine ring
OH	H	0.48s	1.14d(7)	2.06d(7)	None
Ph	H	0.17s	0.89d(7)	1.5d(7)	1.6-2.35m(2-$C_6\underline{H}_5$)
Ph	OH	0.11s	0.92d(7)	1.52d(7)	1.71-1.97 and 2.15-2.50m (2-$C_6\underline{H}_5$)
Ph	NH_2	0.1s	0.91d(7)	1.52d(7)	1.85-2.48m(2-$C_6\underline{H}_5$)
4-Me-C_6H_4	H	0.18s	0.88d(7)	1.48d(7)	1.78d(8) and 2.40d(8) (A_2B_2 split of Me.$C_6\underline{H}_4$), 7.41s($C\underline{H}_3$)
4-Me.C_6H_4	OH	0.15	0.95d(7)	1.58d(7)	1.92d(8) and 2.45d(8) (A_2B_2 split of Me.$C_6\underline{H}_4$), 7.46s ($C\underline{H}_3$)
4-Me.C_6H_4	NH_2	0.09s	0.8d(7)	1.47d(7)	1.98d(8) and 2.4d(8) (A_2B_2 split of Me.$C_6\underline{H}_4$), 7.42s($C\underline{H}_3$)
2-NO_2.C_6H_4	H	0.1s	0.92d(7)	1.55d(7)	1.5-1.65m(1 proton) and 1.9-2.1 (3 protons) ($NO_2.C_6\underline{H}_4$)
2-NO_2.C_6H_4	NH_2	0.18s	0.95d(7)	1.51d(7)	1.4-1.6m (1 proton) and 1.9-2.2 (3 protons) ($NO_2.C_6\underline{H}_4$)

Footnote: s - singlet; d - doublet; m - multiplet.

The n.m.r. spectrum of the parent compound has been determined in deuterochloroform and acetone.[58] The Chemical shift (τ) and coupling constants (J) have been assigned as follows:-



(4)

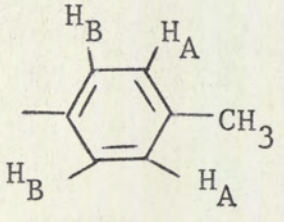
	H-2	H-4	H-5	H-7	H-8	$J_{4,8}$	$J_{5,8}$	$J_{7,8}$
$CDCl_3$	0.46	0.38	0.53	1.00	2.08	0.7	0.8	5.8
Me_2CO	0.49	0.19	0.40	1.00	2.12	0.7	0.8	5.8

The signal of the H-2 proton of pyrido[4,3-d]pyrimidin -4(3H)-one (152) (R=H, R'=H) absorbed at a higher field than the H-2 proton of the parent compound. τ values for H-2 proton of 4-hydroxy pyrimidine in different solvents has been quoted as: D_2O, 1.63; 2.13N D_2SO_4 0.74; 1.4 NaOD 1.78.[59] The H-2 proton of quinazoline (DMSO) shows up at τ 0.59.[60] The H-2 proton of pteridine ($CHCl_3$) gives a signal at τ 0.35.[61] All of these examples indicate that in addition to the chemical structure of the compounds the solvent-solute interaction makes major modification in the shift of an individual proton.

The replacement of the H-2 proton by a methyl group gives a singlet at 6.94 τ. The n.m.r. spectra of pyridopyrimidines

become more complex as the methyl group is replaced by phenyl and other aromatic functions. Thus 2-phenyl and 2-2'-nitrophenyl substituents in the pyrido [4,3-d] pyrimidines showed a broad peak or a split multiplet in the expected range for aromatic compounds. The nitro group of the pyridopyrimidines (152) (R=2'-nitrophenyl, R'=H or NH_2) did not cause any noticeable down field shifts of protons of the pyridine ring. In the heterocylic compounds the electron donating groups such as OMe, OH and Me are expected to cause greater upfield shifts, whereas the electron attracting nitro groups are expected to cause downfield shifts.[60]

The introduction of 4-methylphenyl substituents at 2-position in the pyridopyrimidines (152) (R=4-Me-C_6H_4; R'=H,NH_2 or OH) gave rise to a pair of doublets in addition to the expected singlet of the methyl group. The spectra of



(158)

these pyridopyrimidines were characterised as exhibiting an A_2B_2 system[62(a)] (158) in which the four spin coupled

nuclei give two chemical shifts each common to two of the nuclei (thus $\tau = 1.8$ and $\tau = 2.4$) and each of the muclei (at $\tau = 1.8$) is then coupled to the same extent to each of those (at $\tau = 2.4$,) the coupling constant (J) being 8 c/sec. The magnitude of the coupling constants fall within the expected range (6-10 c/sec) of ortho protons of benzenoid compounds.[63]

The presence of naphthyl, furyl and pyridyl substituents at the 2-position in the pyridopyrimidines gave extremely complex n.m.r. spectra, in which it was difficult to assign the position of an individual proton. Thus the pyrido-pyrimidine (152) (R=1-naphthyl, R'=H) gave a complex splitting pattern in the range of τ 1.6-2.5 (in dimethyl sulphoxide) and a similar complex pattern at about τ 1.4-2.4 (in trifluoroacetic acid). The pyridopyrimidine (152) (R=2-furyl, R'=OH) gave a signal of three fine split doublets (with J=2 c/sec) at τ 2.9-3.2 and a series of sharp singlets and doublets in the range of τ 0.0-2.0 (trifluoroacetic acid). The pyridopyrimidine (152) (R=3-pyridyl, R'=H) gave a resonant complex signal in the range of τ 0.00-1.6 (trifluoroacetic acid).

The absorption peak of the pyrido-pyrimidine (152) (R=methyl, R'=$C\underline{H}_2.C\underline{H}_2.OH$) at τ 5.0 8 showed up as a broad singlet. Ideally an A_2B_2 system may be expected for the

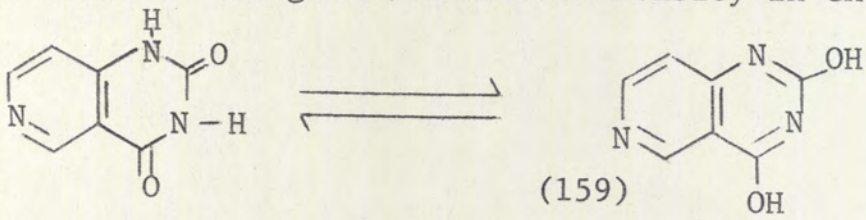
$-CH_2.CH_2-$ functional group and so two doublets should have appeared. The presence of acidic solvent probably protonates the alcohol 'OH' group and thus makes the two pairs of protons magnetically and chemically equivalent with $J_A=J_B=0$, thus accounting for the appearance of a singlet only.

The n.m.r. signals of protons at 5,7 and 8 position of the pyridine ring demonstrated the π deficient character of the ring. The lowest down-field signal was assigned to 5-H proton. The two adjacent protons at 7 and 8 positions were seen as two doublets. This splitting pattern of 7-H and 8-H was an example of simple two spin AB system[62(b)] with a spin constant $J_{AB}=7$ c/sec. This simple first order splitting patterns of the protons of the pyridine ring was repeated in all the 2- and 3-disubstituted compounds examined, with very similar chemical shift positions in most cases. The coupling constant of two adjacent protons of pyridine in $CDCl_3$ has been quoted as $J_{2,3}=5.5$ c/sec.[64]

The absorption peaks for 5-H, 7-H and 8-H were not observed in the pyridopyrimidines (152) (R=1-naphthyl, 2-furyl and 3-pyridyl) since the absorption signals of these protons coincided with the chemical shifts of these functional groups.

The protons of pyridine ring of pyrido[4,3-d]

pyrimidin-(1H,3H)-2,4-dione (102) resonated at a much higher field compared to the protons of pyridine ring of the other pyrido[4,3-d]pyrimidines (cf. table 2). This is attributed to the greater electron density in the



(102) (159)

pyridine ring (102 ⇌ 159) compared with the parent compound.

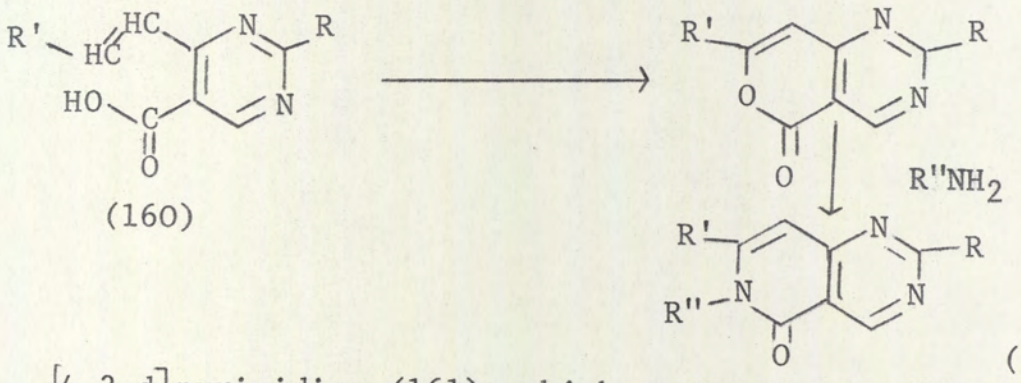
N.m.r. spectra of quinazoline or of other series of pyridopyrimidines in trifluoroacetic acetic acid have not been so far reported. N.m.r. spectrum of pyrido[2,3-d] pyrimidin-(1H,3H,8H)-2,4,7-trione has been determined in dimethyl sulphoxide.[65]

(C) SYNTHESIS OF PYRIDO[4,3-d] PYRIMIDINES FROM PYRIMIDINES

All the four pyrido[4,3-d]pyrimidines reported in the literature were prepared from pyridines and had the substituents in the pyrimidine ring. It was, therefore, decided to develop a route of synthesis of pyrido[4,3-d] pyrimidines from pyrimidines, with the possibilities of substituents in the pyridine ring.

The route envisaged for such a synthesis was based on a possible cyclisation of an appropriate styrylpyrimidine carboxylic acid (160) (R=H, C_6H_5, OH or such similar

substituent)(R= phenyl or substituted phenyl) to pyrano



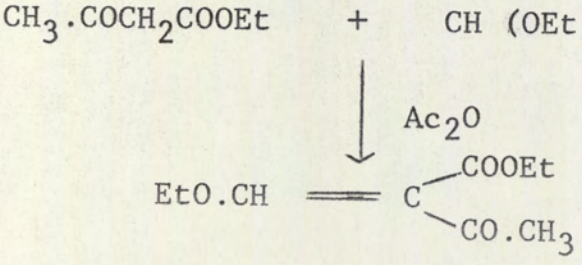
(160) (161) (162)

[4,3-d]pyrimidine (161), which on treatment with amines might be expected to give the desired pyrido[4,3-d] pyrimidines (162).

A literature search showed that two suitable starting materials, ethyl 4-methyl 2-phenyl pyrimidine-5-carboxylate (164) and 5-ethoxycarbonyl-4-methylpyrimidin-2(1H)-one (208) were known.

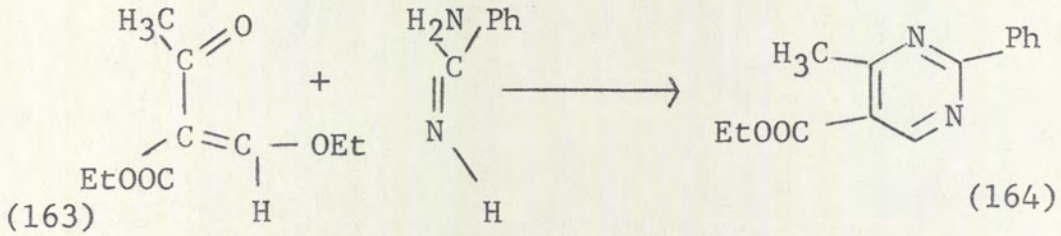
i) 2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one

Treatment of ethyl acetoacetate with ethyl orthoformate in the presence of acetic anhydride gave ethyl ethoxymethyleneacetoacetate[66] (163).



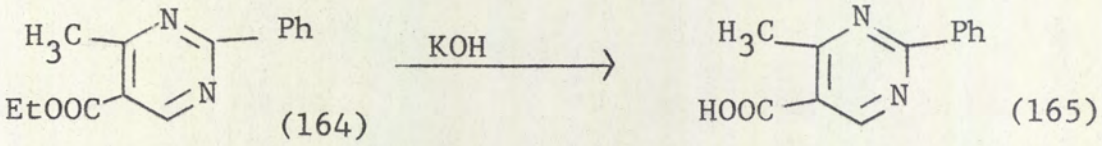
(163)

When ethyl ethoxymethyleneacetoacetate (163) was treated with benzamidine, ethyl 4-methyl 2-phenylpyrimidine -5-carboxylate (164) was isolated in good yield from the reaction mixture.[67] The condensation was catalysed by the base.



(163) (164)

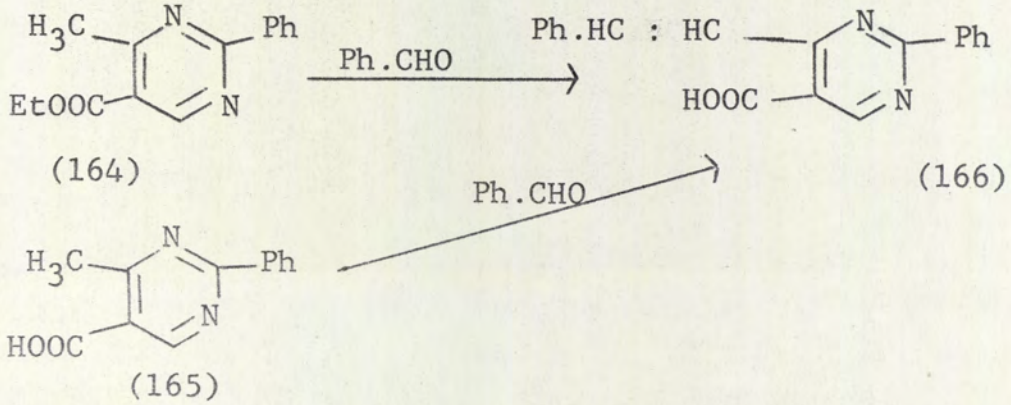
The pyrimidine ester was hydrolysed to the corresponding carboxylic acid (165). The formation of the carboxylic acid was characterised by the absence of C_2H_5



(164) (165)

peaks in the n.m.r. spectrum and the shift of the carbonyl C=O band to lower frequency in the infra-red spectrum.

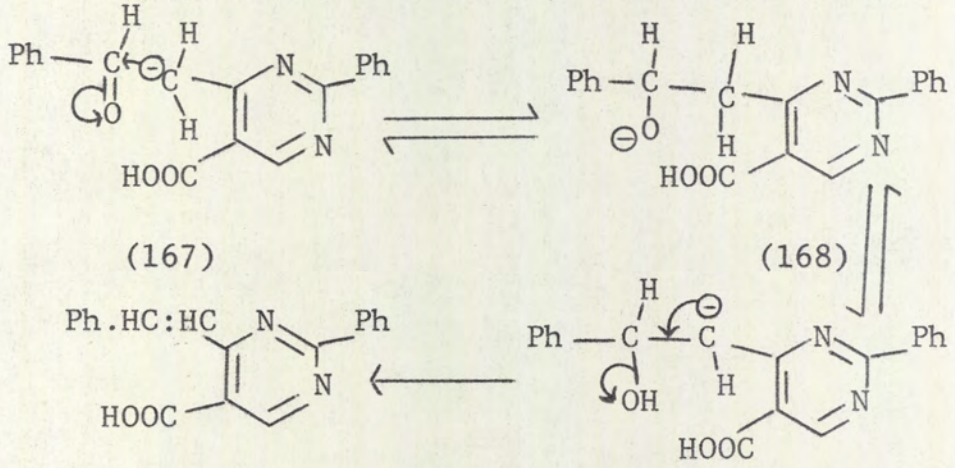
When the pyrimidine ester (164) or the pyrimidine carboxylic acid (165) was condensed with benzaldehyde, 2-phenyl-4-styrylpyrimidine-5-carboxylic acid (166) was the only product isolated from the reaction mixture.



(164) (166) (165)

The infrared spectrum showed C=O absorption band and α C=C conjugated ethylenic band. The singlet due to CH_3 was replaced in the n.m.r. spectrum by a complex multiplet of 10 protons of two phenyl groups. The ethylenic protons could not be clearly assigned because of the close and similar chemical shifts to that of the aromatic protons.

The condensation of pyrimidine carboxylic acid with benzaldehyde is probably base catalysed. It is suggested that the pyrimidine nucleus by the virtue of the nitrogen



(167) (168)

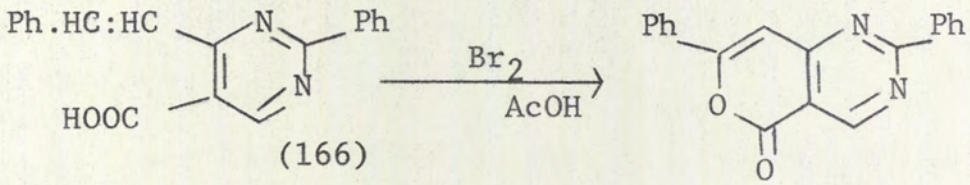
(166) (169)

atom, is acting as a basic centre to produce an anion (167), which carries out a nucleophilic attack on the carbonyl carbon of the aldehyde (167 $\rightleftharpoons$ 168). Proton transfer (168 $\rightleftharpoons$ 169) and the displacement of hydroxyl ion (OH^-) would then yield the styrylpyrimidine carboxylic acid.

The reactive nature of alkyl group α to a ring N in

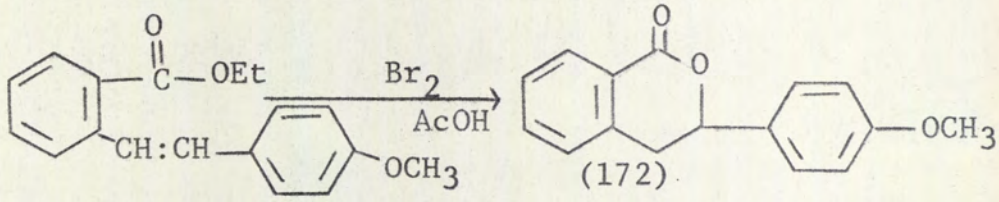
pyrimidine and other π-deficient compounds are well known.[68] Similar condensation of 2-methyl-nicotinic acids with aromatic aldehydes have yielded not only the styrylnicotinic acids, but also other products, depending on the reaction conditions.[69,70,71]

2-phenyl-4-styrylpyrimidine-5-carboxylic acid (166) was converted into 2,7-diphenylpyrano [4,3-d] pyrimidin-5-one (170) by refluxing the styrylpyrimidine acid with bromine and acetic acid.



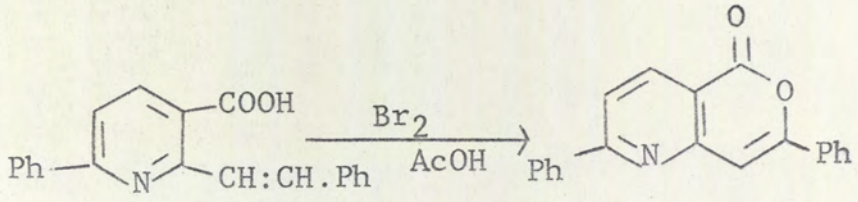
(166) (170)

This type of pyrano [4,3-d] pyrimidine may be considered as a pyrimidine analogue of an isocoumarin. Thus heating sodium 2-4'-methoxy styrylbenzoate (171) with bromine in acetic acid gives 2-4'-methoxyphenyl isocoumarin[72] (172). Similar treatment of 2-styrylnicotinic acid (173) with



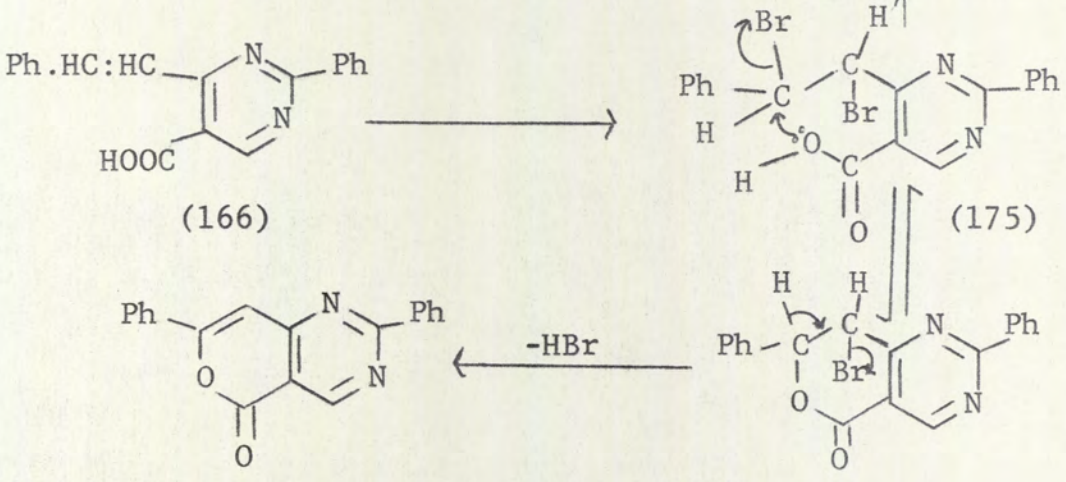
(171) (172)

bromine in acetic acid gives 5-oxo-7-phenylpyrano [4,3-b] pyridine[71] (174).



(173) (174)

The first stage of cyclisation must be the trans addition of bromine across the ethylenic double bond[73] to give the dibromo compound (175). The nucleophilic attack by lone pair of oxygen electrons and a simultaneous displacement of Br^- and H^+ would then yield the cyclic bromo compound (176). The final step is the loss of a second HBr



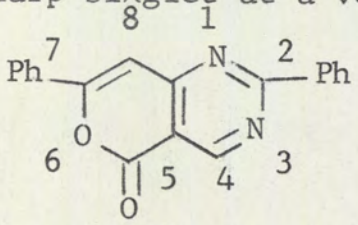
molecule (176 ⟶ 170). Thus bromination and dehydrobromination have taken place in the same operation.

2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one is the first recorded example of the pyrano[4,3-d]pyrimidine ring system. The pyranopyrimidine was insoluble in the common non-polar solvents. The compound was unaffected by water and air.

The infra-red spectrum showed the carbonyl peak at 1740cm^{-1} in the expected region for α,β unsaturated lactones. β-amino-α,β unsaturated esters[74] absorb at 1730cm^{-1}. The

carbonyl absorption band also resembles that shown by 2- and 4-hydroxyethyl-nicotinic lactones[75,76] and pyrano [4,3-b] pyridines.[71] The higher frequency shift is attributed to the ring strain caused by the fusion of lactone to the pyrimidine ring. A slightly weaker absorption was observed at 1620cm^{-1} due to the conjugated double bond.

The n.m.r. spectrum of the pyrano [4,3-d] pyrimidine (170) showed a sharp singlet at a very low field and was assigned

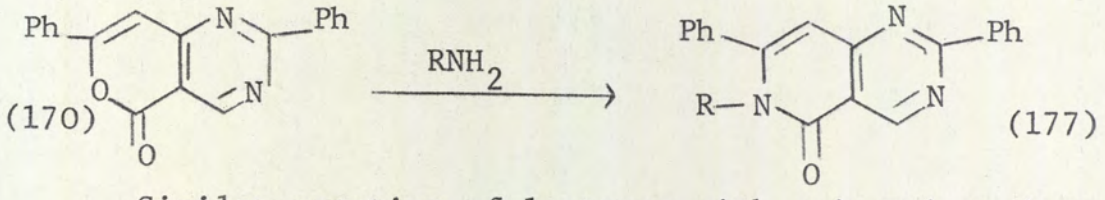


(170)

to 4-H proton. The two phenyl substituents at 2 and 7 positions gave a split multiplet. The olefinic proton at 8-H was unassignable since its chemical shift value coincided with the phenyl substituents.

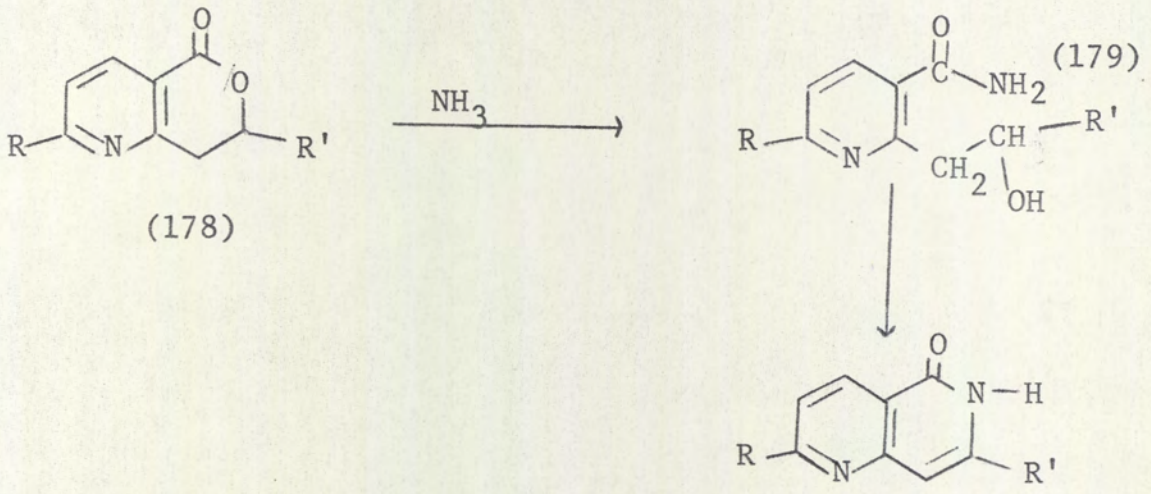
ii) 6-Substituted-2,7-diphenylpyrido [4,3-d] pyrimidin-5(6H)-ones

Treatment of 2,7-diphenylpyrano [4,3-d] pyrimidine (170) with ammonia, hydroxylamine and hydrazine at room temperature, yielded in each case directly 6-substituted 2,7-diphenyl-pyrido [4,3-d] pyrimidin-5(6H)-ones (177) (R=H, OH and NH_2)



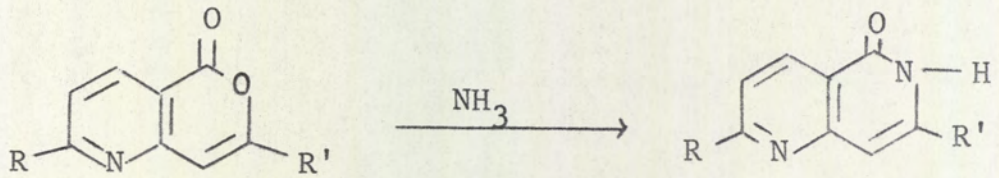
Similar reaction of lactones with amines have been used to prepare other heterocylic compounds. 2-2'-Hydroxy-ethyl nicotinic lactone (178) reacts with ammonia, to give

in the first instance 2-2'-hydroxyethyl nicotinamide (179) which by oxidation and concurrent cyclisation then gives



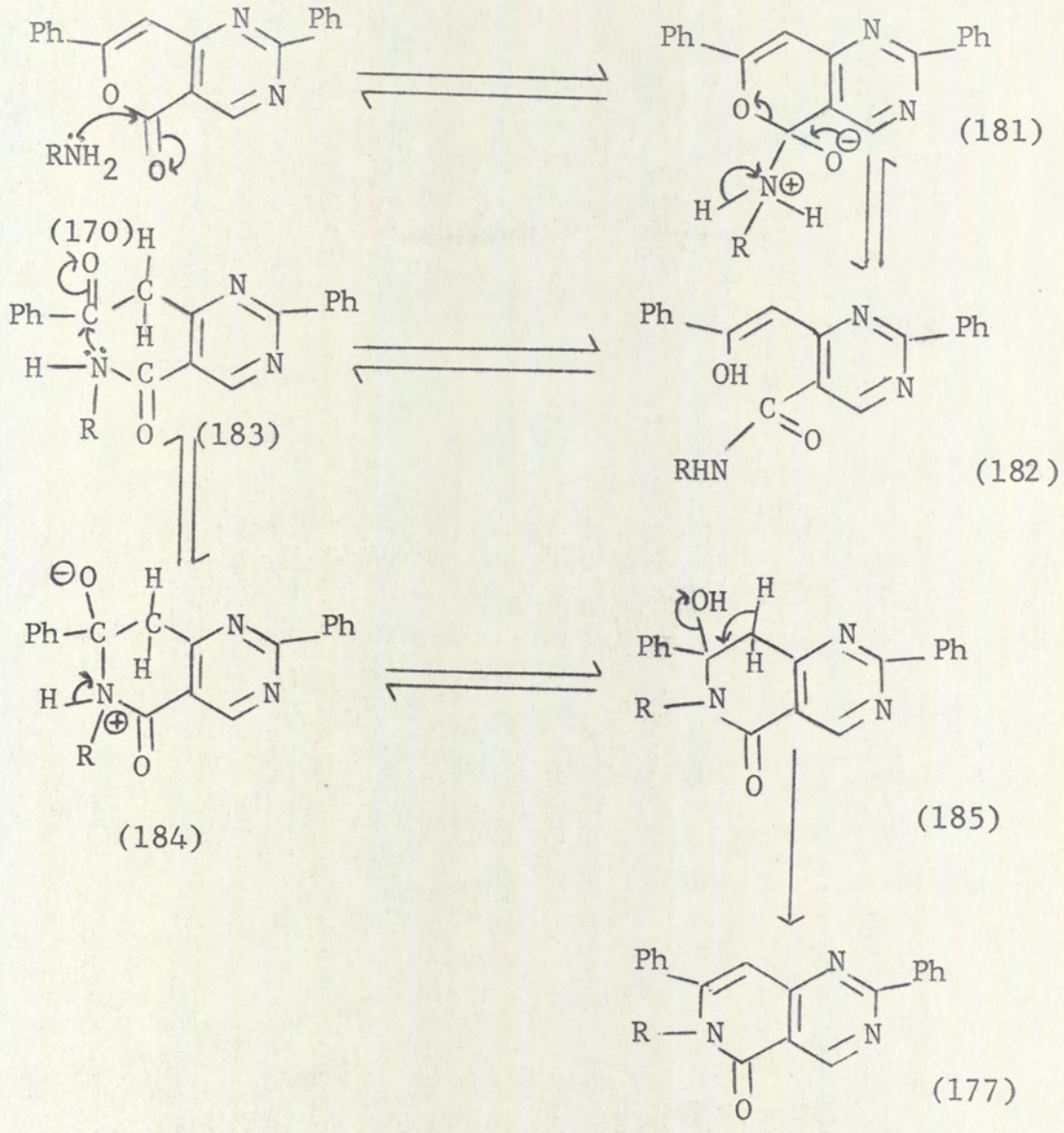
(178) (179) (180)

5,6-dihydro-5-oxo-1,6-naphthyridine[75] (180). Pyrano [4,3-b] pyridines (181) react with ammonia to give directly 5,6-dihydro-5-oxo-1,6-naphthyridines[71] (180).



(181) (180)

The probable path of conversion of pyrano [4,3-d] pyrimidine (170) into pyrido [4,3-d] pyrimidine (177) is similar to that of pyrido-oxazine (cf.p.28) and may be summarised as follows:-

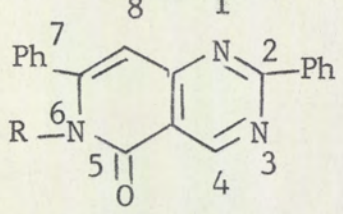


The reaction condition employed was such that the intermediate keto-amide (183) could not be isolated.

The infra-red spectra of the pyrido pyrimidines (177) showed the C=O stretching vibrations in the range of 1680-1660cm^{-1} - lower than those observed for 2,3-disubstituted pyrido[4,3-d]pyrimidin -4(3H)-ones. The conjugated double

bond absorbed at about 1620cm.$^{-1}$ In addition the pyrido-pyrimidines showed absorption bands due to NH, NH_2 and OH functional groups respectively.

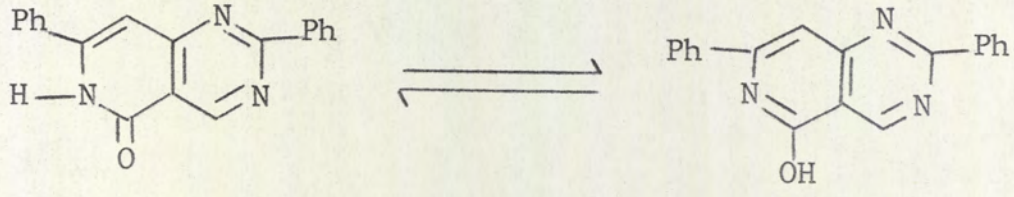
The n.m.r. spectra of all the three pyridopyrimidines were very similar. Thus all of them showed the 4-H singlet



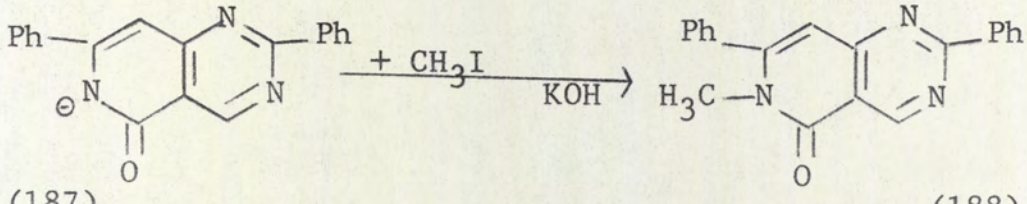
(177)

at a very low field. The phenyl protons resonated as a split multiplet. The 8-H proton was seen as a singlet at about τ2.7.

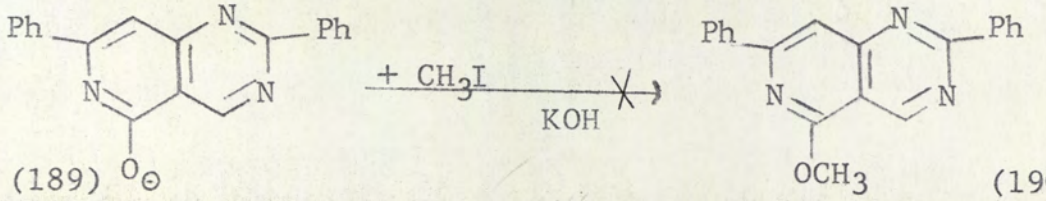
Treatment of 2,7-diphenylpyrido[4,3-d]pyrimidin-5-(6H)-one (177) (R=H) with methyl iodide could be expected to give either N-methyl derivative (188) or the oxygenated ether derivative (190) because of the two possible tautomeric



(177) (186)



(187) (188)

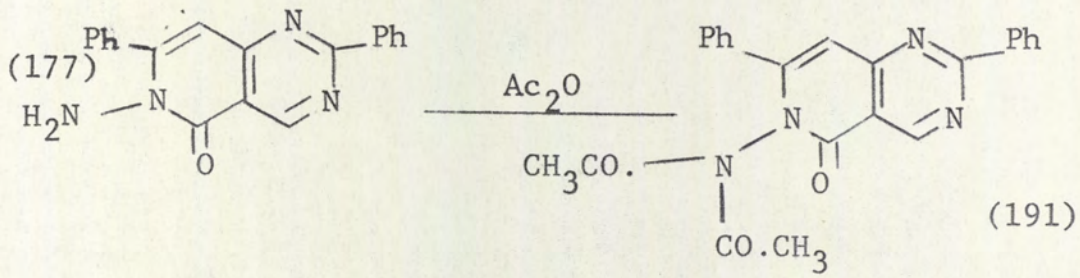


(189) (190)

forms (177 $\rightleftharpoons$ 186).

The infra-red spectrum showed a strong carbonyl absorption at 1645cm.$^{-1}$ suggesting that N-methyl derivative had formed. Bogert and Seil[77] have also suggested that alkylation by alcohol, alkali and methyl iodide should give invariably the N-methyl derivatives. N-alkylations have been widely carried out on various heterocylic compounds. Thus methylation of uracil has yielded the dimethyl derivative.[78] The alkylation of quinazolones have been carried out by Morley and Simpson.[79]

6-Amino 2,7-diphenylpyrido[4,3-d]pyrimidin-5-(6H)-one (177) ($R=NH_2$) reacted readily with excess acetic anhydride



(191)

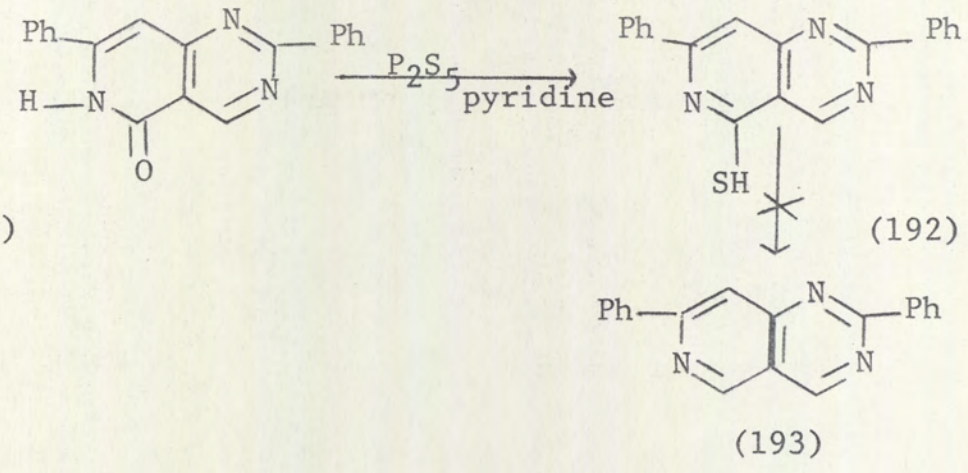
to give the diacetyl derivative (191) and not the monoacetyl derivative indicating that the amino group must be very reactive.

6-Amino-2,7-diphenylpyrido[4,3-d]pyrimidine (177) ($R=NH_2$) was readily degraded by nitrous acid to 2,7-diphenylpyrido[4,3-d]pyrimidine (177) (R=H). Similar degradation was also successful with 3-amino 2-methyl pyridopyrimidine. (cf.p.31).

iii) Attempted preparation of 2,7-diphenylpyrido[4,3-d] pyrimidine

The heterocylic parent compounds are often prepared by indirect methods from the corresponding hydroxy, chloro, thio or hydrazino substituted compounds. The circumstances under which a hydroxy group can be directly replaced by hydrogen are variable and generally rather difficult.[80(a)] The conversion of hydroxy compounds into chloro, thio or hydrazino derivatives and the subsequent replacement by hydrogen offer an easier alternative to obtain the parent compounds. It was the author's intention to use such an approach to attempt to prepare 2,7-diphenylpyrido[4,3-d] pyrimidine (193) from 2,7-diphenylpyrido[4,3-d]pyrimidin -5(6H)-one (177) (R=H).

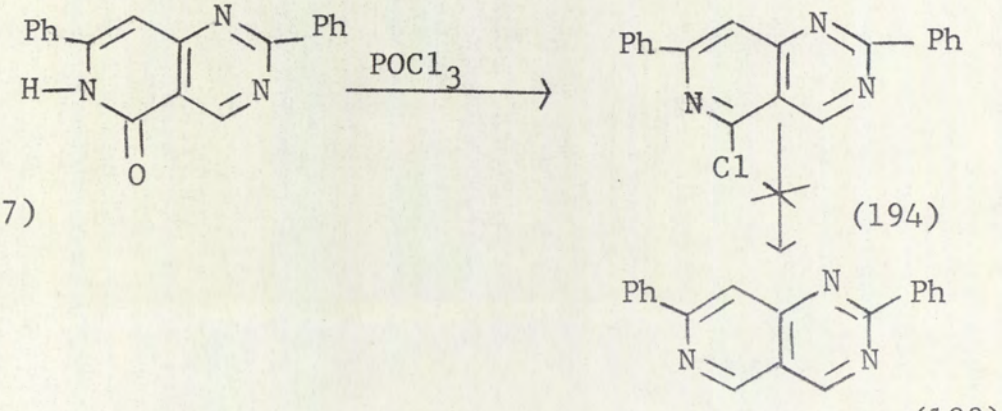
The reaction of 2,7-diphenylpyrido[4,3-d]pyrimidin -5(6H)-one with phosphorus pentasulphide in pyridine after a long reflux period, yielded 2,7-diphenyl-5-thiopyrido [4,3-d] pyrimidine (192).



(177) (192) (193)

Treatment of 5-thiopyridopyrimidine (192) with Raney nickel in ethanol, cellosolve or dioxane gave back the unchanged 5-thiopyridopyrimidine (192). Dethiolations have been successfully carried in other heterocylic compounds under similar conditions.[81,82,83] Failure may be attributed to the grade of Raney nickel employed or the low solubility of the thiocompound in the solvents used.

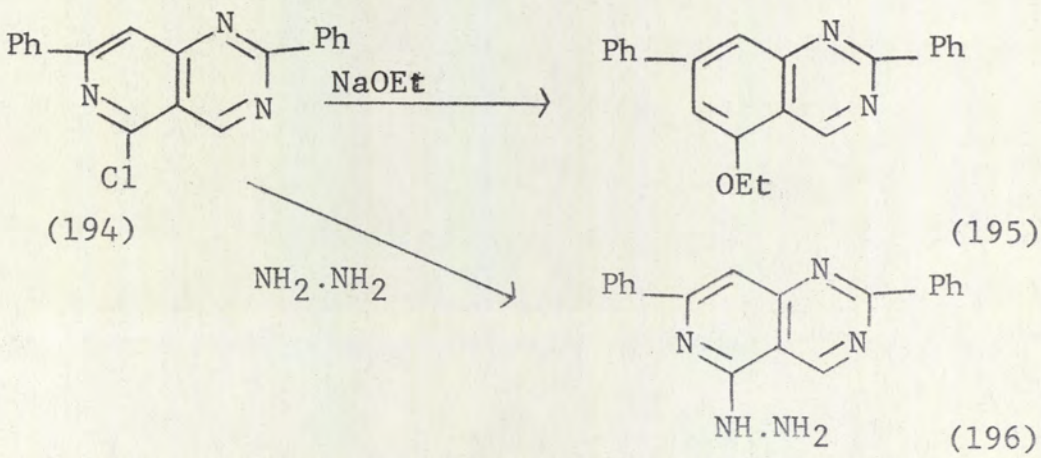
When 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one was treated with phosphoryl chloride, the corresponding 5-chloro 2,7diphenylpyrido[4,3-d]pyrimidine (194) was obtained in good yield.



(177) (194) (193)

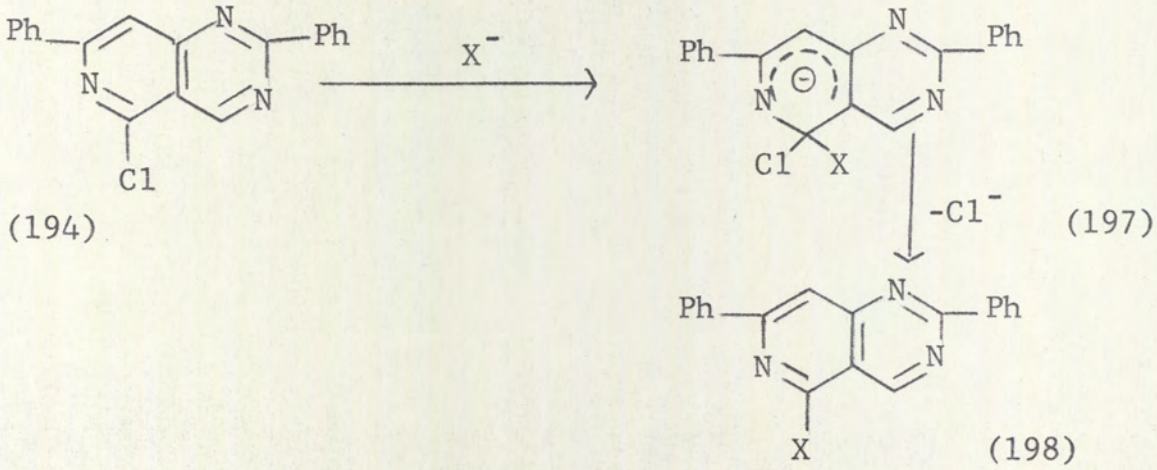
An attempted hydrogenation using palladium-calcium carbonate as the catalyst and different solvents such as ethanol, benzene or cellosolve failed to give the desired pyrido[4,3-d]pyrimidine (193). In each case the 5-chloro compound (194) was recovered. This is in contrast to the ease of dehalogenations observed in other heterocylic compounds. Thus 2-chloro, 2,4-dichloro or 2,4,6-trichloro-pyrimidines have been readily dehalogenated.[80(b)] Tin and hydrochloric acid also failed to dehalogenate the chloro-compound. Dimethyl sulphoxide has been successfully employed to debrominate and dechlorinate organic compounds.[84,85,86] The treatment of 5-chlorocompound with sodium and dimethyl sulphoxide however, failed to yield the pyridopyrimidine (193).

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine (194) was reactive to displacement by anionic reagents, which may be expected because of the halogen atom ortho to the ring nitrogen. Thus treatment of the 5-chloro compound with sodium ethoxide gave the ethoxy derivative (195) and reflux with hydrazine yielded the hydrazino compound (196).



(194) (195) (196)

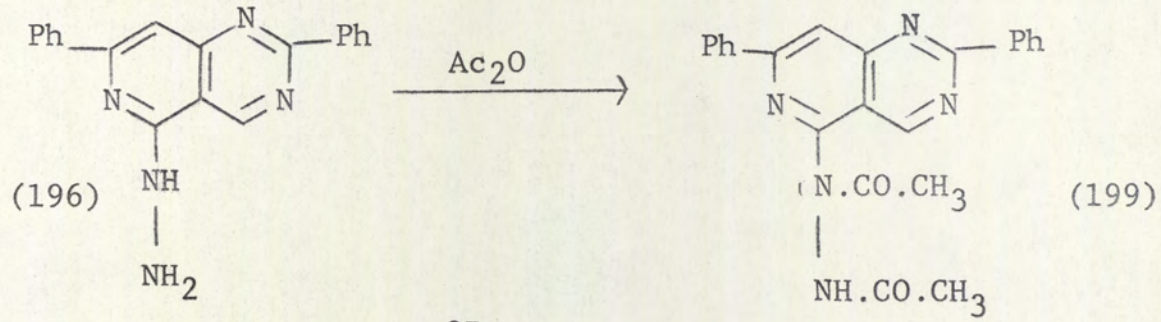
The probable path of these nucleophilic displacements involve an initial attack by X ($X=\bar{N}H.NH_2$ or $\bar{O}Et$) to



(194) (197) (198)

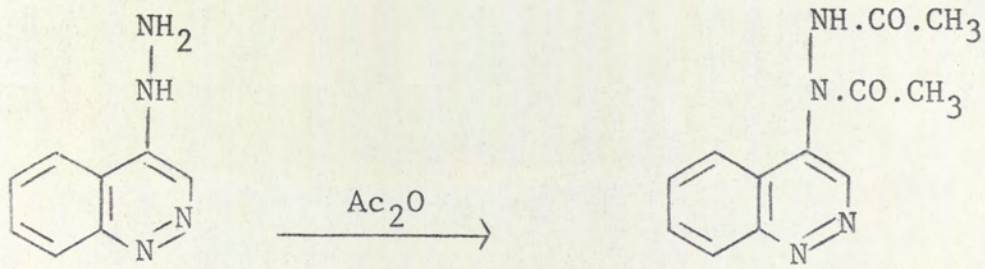
give the intermediate sigma complex (197) which by the expulsion of the halide ion yields the 5-substituted pyrido [4,3-d] pyrimidine (198).

The hydrazino compound (196) reacted readily with excess acetic anhydride to give the diacetyl derivative (199). 4-cinnolyl hydrazine (200) has been similarly reported to give



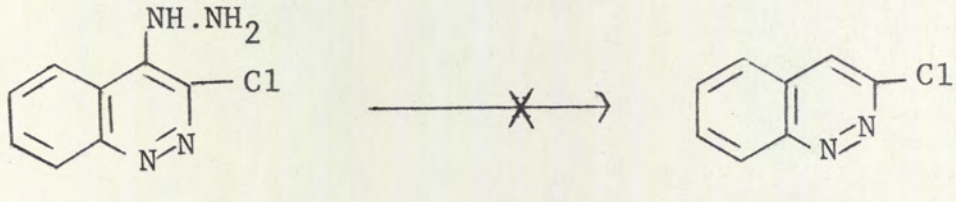
(196) (199)

the diacetyl derivative[87] (201).



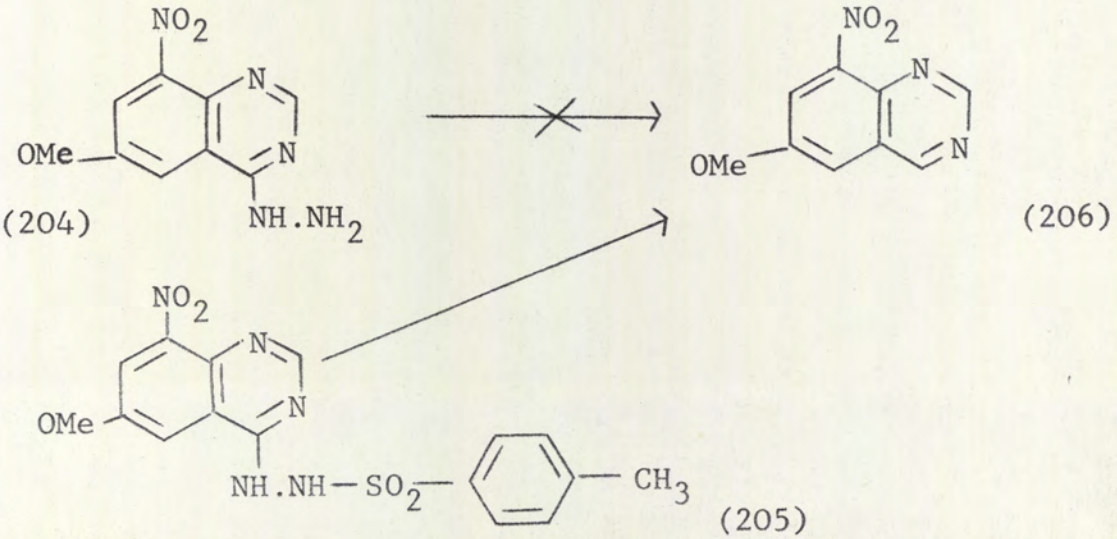
(200) (201)

Hydrazino - heterocylic compounds have been oxidised to the parent compounds with copper and silver salts.[88,89] Treatment of 5-hydrazinopyrido[4,3-d]pyrimidine (193) with copper sulphate in alkaline, neutral or acidic medium failed to oxidise it to pyrido[4,3-d]pyrimidine (193). The hydrazino compound, when refluxed with silver acetate yielded charred products. 3-chloro 4-cinnolyl hydrazine (202) has failed to yield 3-chlorocinnoline[87] (203).



(202) (203)

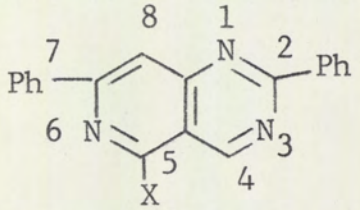
4-Hydrazino-6-methoxy-8-nitroquinazoline (204) failed to oxidise even on treatment with stronger reagents such as Fehling solution or ferric cyanide. The conversion of hydrazino-quinazoline (204) to the toluene sulphonyl derivative (205) and subsequent oxidation gave a very poor yield of 6-methoxy 8-nitroquinazoline[90] (206).



Albert and Catterell[91] have found that oxidative reactions of copper sulphate with hydrazino heterocylics depend on the number of nitrogen atoms in the ring as well.

All of the 5-substituted pyrido[4,3-d]pyrimidines (198) (X=SH, Cl, $NH.NH_2$ and OEt) showed very similar n.m.r. spectra.

(198)



Thus protons for 4-H and 8-H were assigned, as were the phenyl protons at 2- and 7-positions. 4-H proton of the hydrazino compound (198) ($X=NH.NH_2$) or of the diacetyl derivative (199) were not observed.

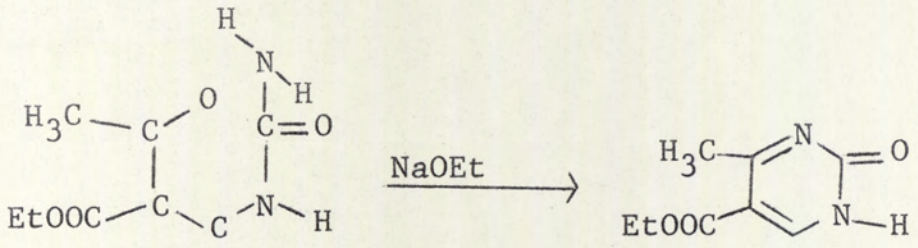
iv) 7-Phenylpyrano[4,3-d]pyrimidin-2,5(3H)-dione

Treatment of ethyl acetoacetate with urea in the presence of ethyl orthoformate yielded ethyl 2-ureido methylene acetoacetate[92] (207).

$$NH_2.CO.NH_2 + CH_3CO.CH_2COOEt \longrightarrow NH_2.CO.NH.CH=C(COOEt)(CO.CH_3)$$

(207)

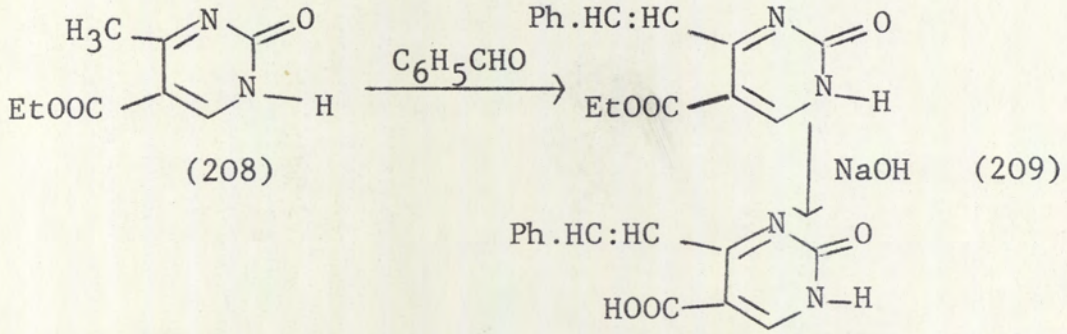
The ureido ester (207) was cyclised to 5-ethoxy carbonyl-4-methylpyrimidin-2(1H)-one (208) in the presence of sodium ethoxide.[93] The infra-red spectrum showed the



(207) (208)

N-H absorption band characteristic of a typical cyclic amide structure. The higher carbonyl absorption band was assigned to the ester function, while the lower frequency band represented the ring carbonyl.

The pyrimidine (208) condensed readily with benzaldehyde to give the styryl ester (209). Hydrolysis of the styryl

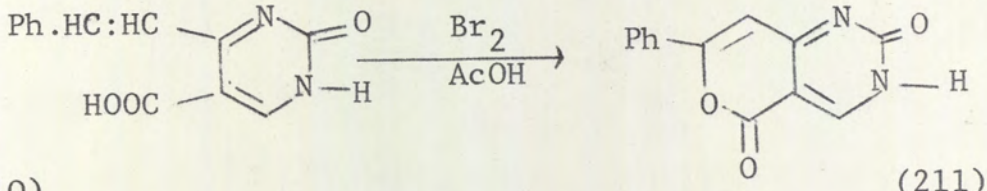


(208) (209) (210)

ester (209) yielded the corresponding acid (210). The carbonyl group of the acid and the ring absorbed at the same frequency.

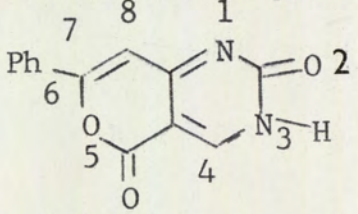
Treatment of the styrylpyrimidine acid (210) with

bromine in acetic acid yielded 7-phenylpyrano[4,3-d] pyrimidin-2,5(3H)-dione (211). The pyranopyrimidin-dione



(210) (211)

(211) showed the high lactone carbonyl absorption (1750cm^{-1}), while the pyrimidine ring carbonyl absorbed at a lower frequency (1690cm^{-1}). The characteristic absorptions due to N-H and conjugated 'C=C' were also present in the infra-red spectrum. The n.m.r. spectrum showed the 4-H proton at a very low field (τ 0.49) and a multiplet due to the protons of phenyl (C_6H_5) substituent at 7-position. An additional



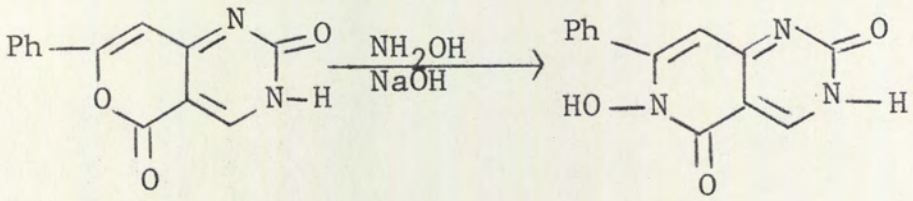
(211)

feature of the spectrum was the signal of 8-H proton, which showed as a singlet (τ 2.6) at a higher field compared to 8-H proton of 2,7-diphenylpyrano[4,3-d]pyrimidin-5-one (170).

v) 6-Substituted 7-phenylpyrido[4,3-d] pyrimidin-2,5(3H,6H)-diones

The pyrano[4,3-d]pyrimidin-dione (211) was an un-reactive compound compared to 2,7-diphenylpyranopyrimidine. It failed to react with ammonia. With hydroxylamine, the pyranopyrimidine-dione (211) did yield the cylic hydroxamic

acid (212). The reaction was probably base catalysed. The carbonyl function of the 2-position absorbed at a

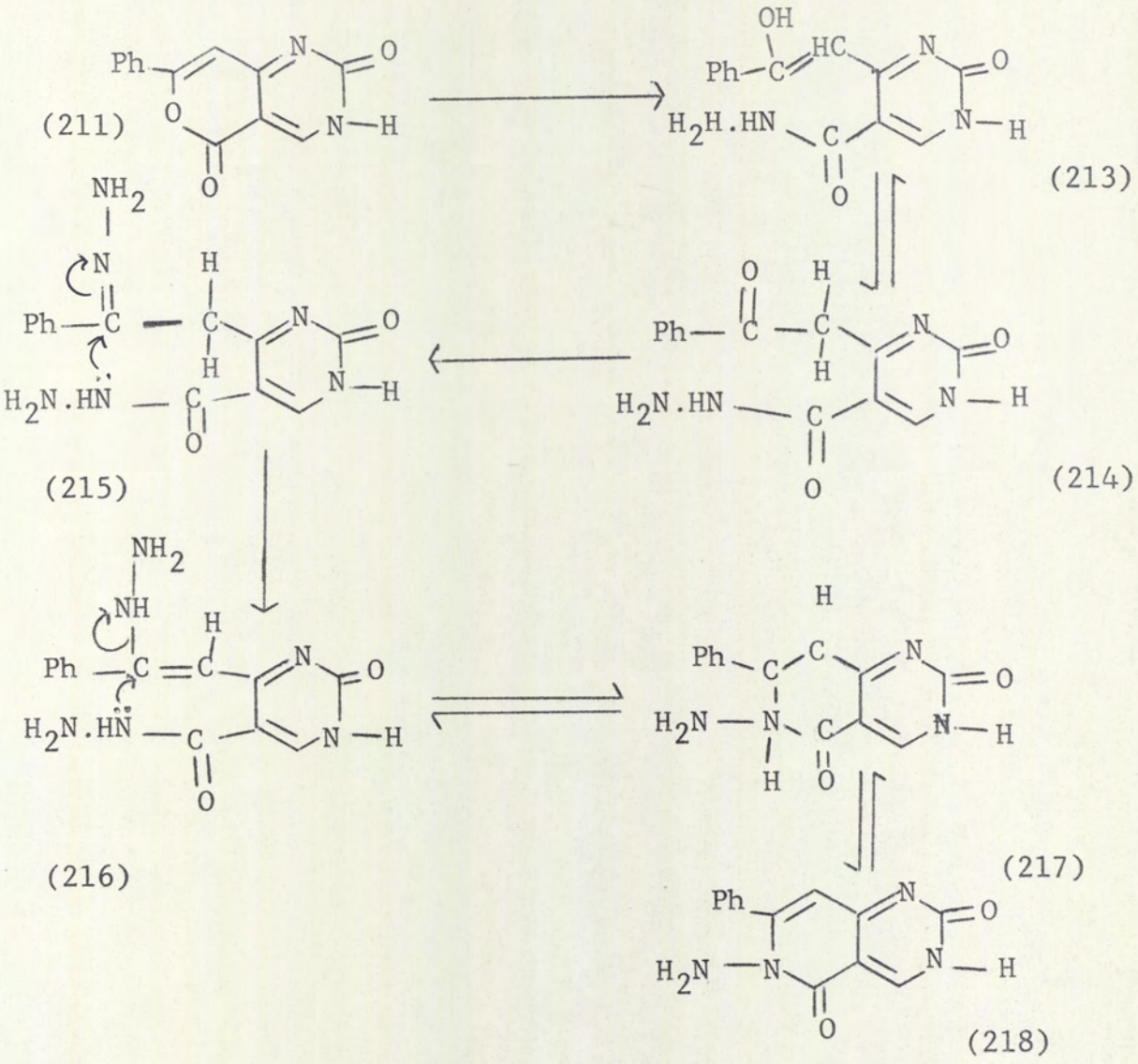


(211) (212)

higher region compared to the 5-carbonyl functional group. The n.m.r. spectrum showed the expected signals for 4-H (singlet), 7-C_6H_5 (multiplet) and 8-H (singlet) respectively.

Treatment of pyranopyrimidindione (211) with hydrazine gave the product whose structure could not be determined with certainty.

The analytical figures agreed with the structure (215 or 216) (M=286). The mass spectrum gave the molecular weight (M=254) which agreed with the structure (218). It is suggested that initially pyranopyrimidindione (211) reacts with hydrazine to give the hydrazide (213 or 214), which further reacts with the excess hydrazine to give the hydrazone (215). Under the electron impact a molecule of hydrazine is so readily lost (216 ⟶ 217 ⟶ 218) that the parent peak at 286 does not show up in the mass spectrum. When the hydrazone (215 or 216) was heated in an open tube



(211) (213) (214) (215) (216) (217) (218)

for half a minute hydrazine vapour evolved very readily. The residual gummy product, could not be, however, induced to solidify nor could it be purified.

The n.m.r. spectrum had to be run in trifluoroacetic acid, but no distinction could be made between formulae (215) or (216) and (218).

The infra-red spectrum gave a peak for N-H and a

broad peak in the carbonyl region. It did not, however, aid in the elucidation of the structure.

An attempted preparation of an acetyl derivative yielded a mixture of products, which could not be separated or purified.

D. MASS SPECTRA OF PYRIDO[4,3-d]PYRIMIDINES

Mass spectra of a selected number of pyrido[4,3-d] pyrimidines were determined and their fragmentation patterns studied. The parent molecular ion peaks were present in all the pyridopyrimidines and a number of them also exhibited m/2e peaks. The presence of metastable (m*) peaks in certain compounds helped to confirm the degradation patterns. The peaks due to the fragments N_2, NH_3, H_2O, CO and CHO, formed as a result of various breakdown pathways were present in most of the spectra. It must be emphasised that the various intermediate formulae, postulated below are speculative. The formulae represent only one form of the intermediate fragment ions. Several alternative structures of the fragment ions are possible. A detailed study probably using deuterium isotopes is needed before the fragment structures can be confirmed.

All pyrido[4,3-d]pyrimidines fragment initially via the pyrimidine ring. Only the major breakdown paths have

been discussed. The spectra indicate several minor decompositions as well.

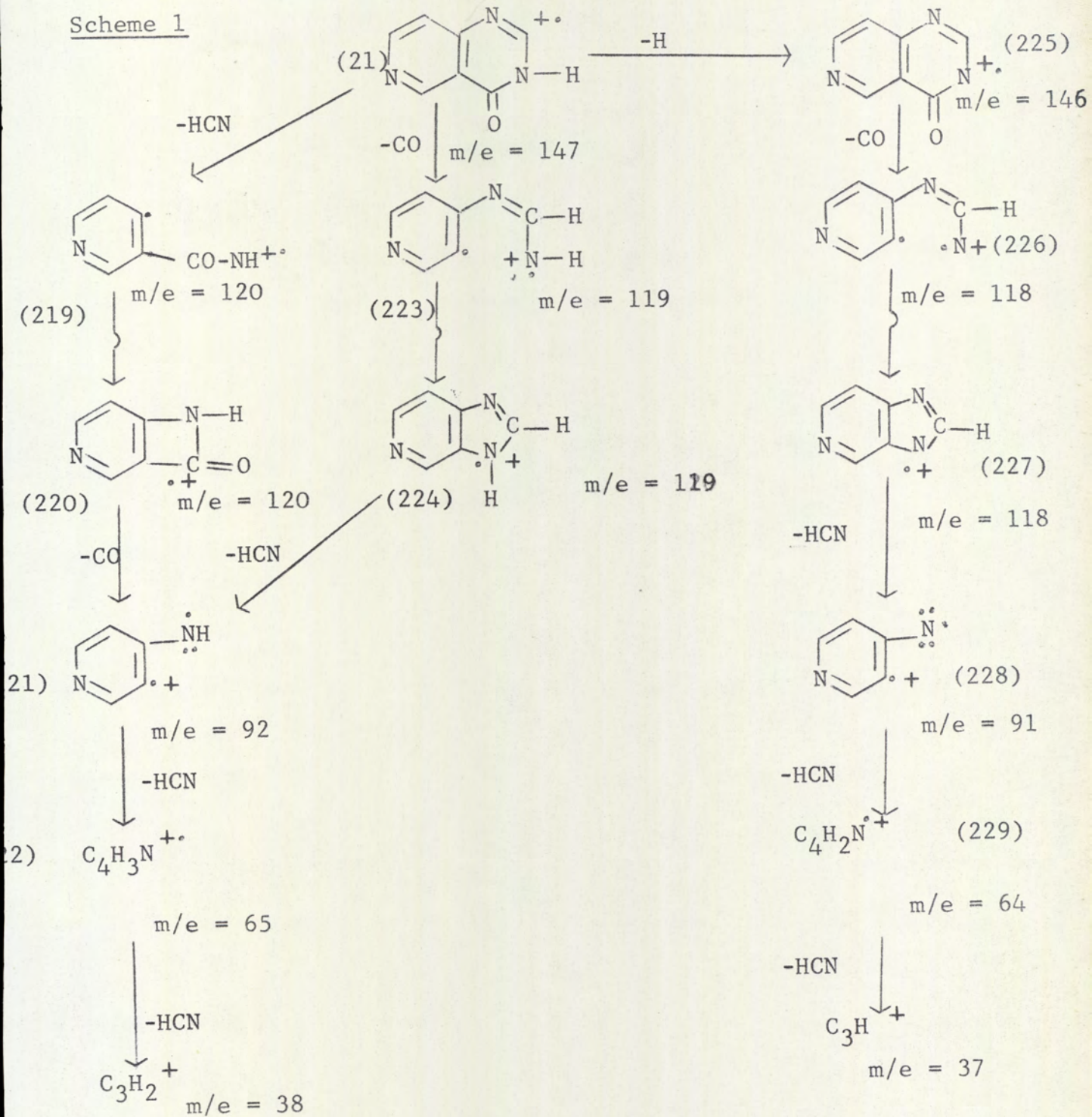
The primary breakdown patterns of 2,3-disubstituted pyridopyrimidines depend mainly on the functional groups in the 2- and 3-positions.

The possible path of breakdown of pyrido[4,3-d] pyrimidin-4(3H)-one (21) has been outlined in the scheme 1. The parent ion (21) looses HCN to give the fragment of mass m/e=120 (219), which by rearrangement may exist as a four membered ring attached to the pyridine ring (220). The loss of HCN from pyrimidine[95], itself, has given, an intermediate fragment which can exist as a four membered cylic ring as well.

The parent ion (21) can alternatively loose a molecule of CO to give the fragment of mass m/e=119 (223), which by rearrangement can exist as a purine type structure (224). The purine ion looses two molecules of HCN to give a structure of mass m/e=65 (224 $\longrightarrow$ 221 $\longrightarrow$ 222). This dissociation path is analogus to 2-, 4- and 8-hydroxy quinazolines,[96] where the initial loss of CO has been suggested to give a purine type of structure as well. In these quinazoline compounds, the loss of CO is also

Fragmentation Pattern of Pyrido[4,3-d]pyrimidin-4-(3H)-one

Scheme 1



Footnote: The arrow ⟶ indicates that the rearrangement is suggested without evidence.

accompanied by the loss of 2 molecules of HCN.

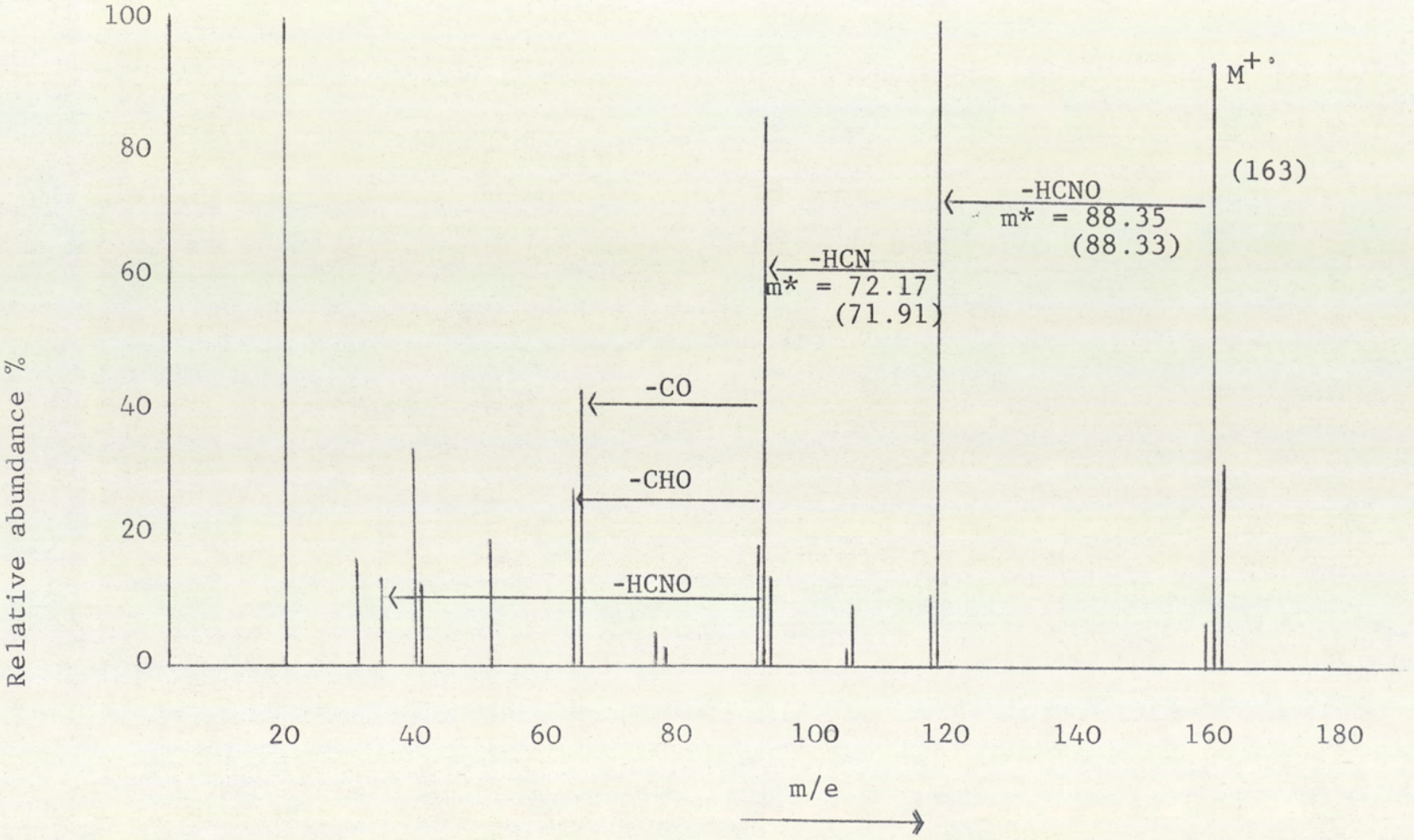
All of the hydroxy quinazolines[96] give important (M-1) peaks, not involving the exchangable protons, followed by a loss of CO. Similar loss seems to be taking place in the pyrido[4,3-d]pyrimidin-4(3H)-one, as outlined in the scheme (1).

The initial fragmentation of uracil[95,97] seems to be a retro-Diels-Alder decomposition with the expulsion of neutral HNCO. Quinazol-2,4(1H,3H)-dione[96] and pteri-2,4(1H,3H)-dione[98] also eliminate HNCO in the intitial stage. By analogy with these compounds pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102) may be also expected to eject HNCO in the first stage of decomposition. This indeed was the case, as outlined in figure (1) and substantiated by the metastable (m*) peak at m/e = 88.35. The actual location of HCNO molecule loss from the pyrimidine ring could not be assigned with certainty.

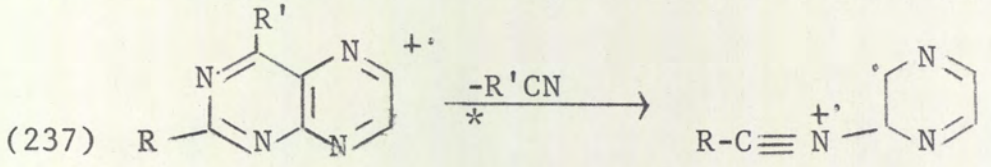
Two paths are suggested for the breakdown of 3-amino 2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (89) (scheme 2). The molecular ion (89) can eliminate NH (230), followed by loss of HNCO to give the ion of m/e = 118 (231) in the open chain form or in the cyclic form (232) by rearrangement. The initial loss of NH is analogus to the initial loss of 'O' observed in the mass spectra of various aromatic N-OH

Mass spectrum of pyrido[4,3-d]pyrimidin-(1H,3H)-2,4-dione

Figure 1

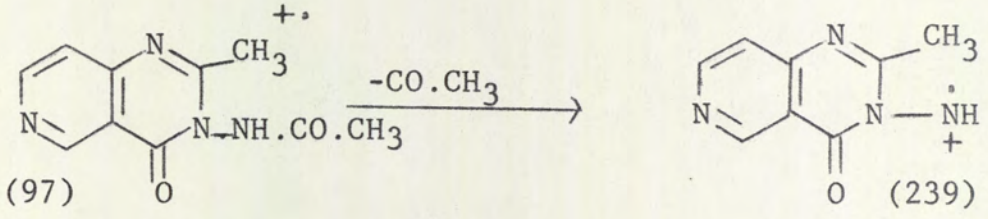


type compounds. Thus benzophenone oxime shows an initial loss of oxygenatom.[99] The open chain structure (231) is



(237) (238)

comparable to the intermediate ion (238) present in the pteridines (237) degradation patterns.[98] Alternatively an initial loss of H and CO or CHO may yield an ion of m/e = 147, (234 or cylic 235 form) which by a subsequent loss of H and N_2 can give the ion of m/e = 118 (231). The acetyl derivative (97) decomposes initially with a loss of $CO.CH_3$ or CH_3 followed by CO to give the ion of m/e = 175 (239). The further degradation of this ion can then follow the same



(97) (239)

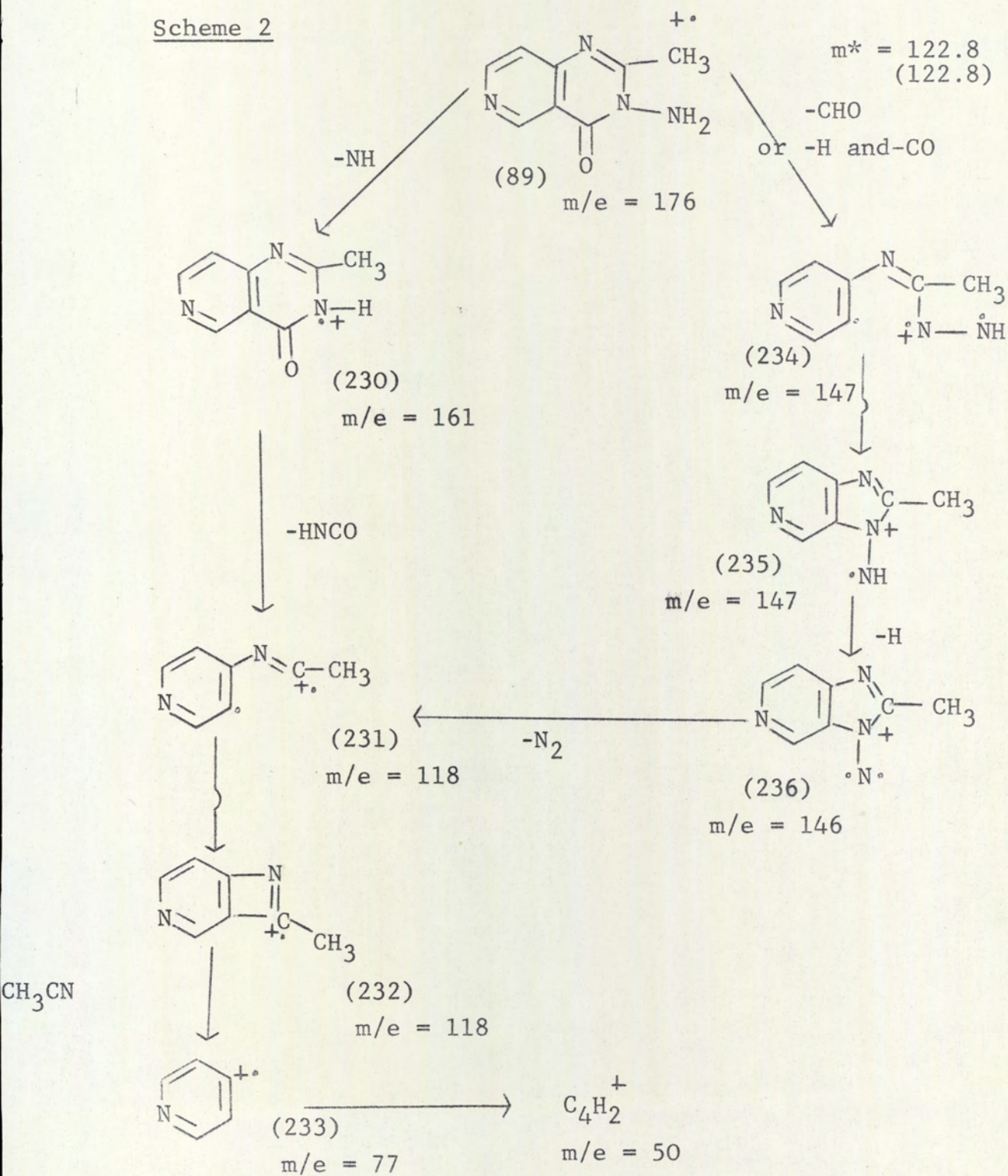
pathway as the amino derivative (89).

The degradation behaviour of 3-amino 2-phenylpyrido [4,3-d]pyrimidin-4(3H)-one (125) (R=phenyl) is almost the same as that for the 2-methylderivative, (scheme 2), benzonitrile (C_6H_5CN) being eliminated in this case instead of methylcyanide ($CH_3.CN$).

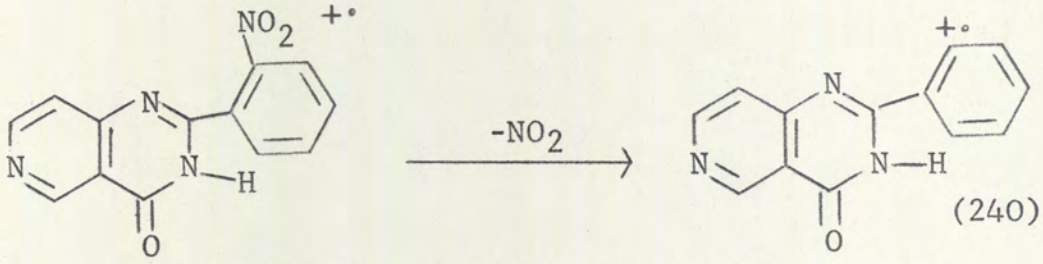
The mass spectrum of 2-2'-nitrophenylpyrido[4,3-d] pyrimidin-4(3H)-one (109) (R=2-nitrophenyl) exhibits a

Fragmentation Pattern of 3-Amino-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one

Scheme 2

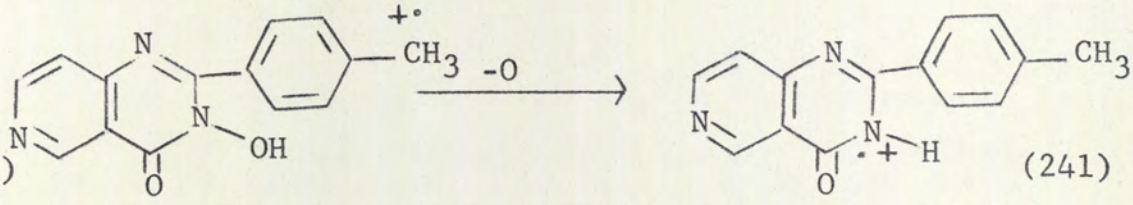


fairly strong peak at m/e = 222 (240) due to the loss of NO_2 group. This is followed by the loss of C_6H_5CN to give

(109)  (240)

the peak at m/e = 120 (219 or 220). Some peaks are also observed at m/e = 140,136,135 and 133, which could not be assigned. These peaks seem to have arisen due to some form of rearrangement brought about by the NO_2 substituent. In certain nitro compounds an initial loss of (M-O), (M-NO) and ($M-NO_2$) have been observed.[100] The spectrum of nitrophenyl-pyrido-pyrimidine (109) does not however show any loss due to (M-O) or(M-NO).

The degradation of 3-hydroxy 2-4'-methylphenylpyrido [4,3-d]pyrimidin-4(3H)-one (131) (R=4-methylphenyl) starts with a loss of 'O' (241) followed by the loss of 4-methyl benzonitrile ($CH_3.C_6H_4.CN$) to give the peak of m/e = 120

(131)  (241)

(219 or 220). The spectrum is complicated after the loss of 'O', since various minor fragmentations also take place.

The parent ion of 2-2'furylpyrido[4,3-d]pyrimidin

-4(3H)-one (109) (R=2-furyl) can primarily breakdown in six different ways. The most probable path however, as suggested by the relative intensity is the loss of 2-cyanofuryl radical ($C_4H_3O.CN$) to give the ion peak at m/e=120 (219 or 220). The peak at m/e = 93 indicates that cyanofuryl ion is a stable ion. The parent molecular ion (109) (R=2-furyl) can initially eliminate CO, H, C_4H_3O and HCNO as well.

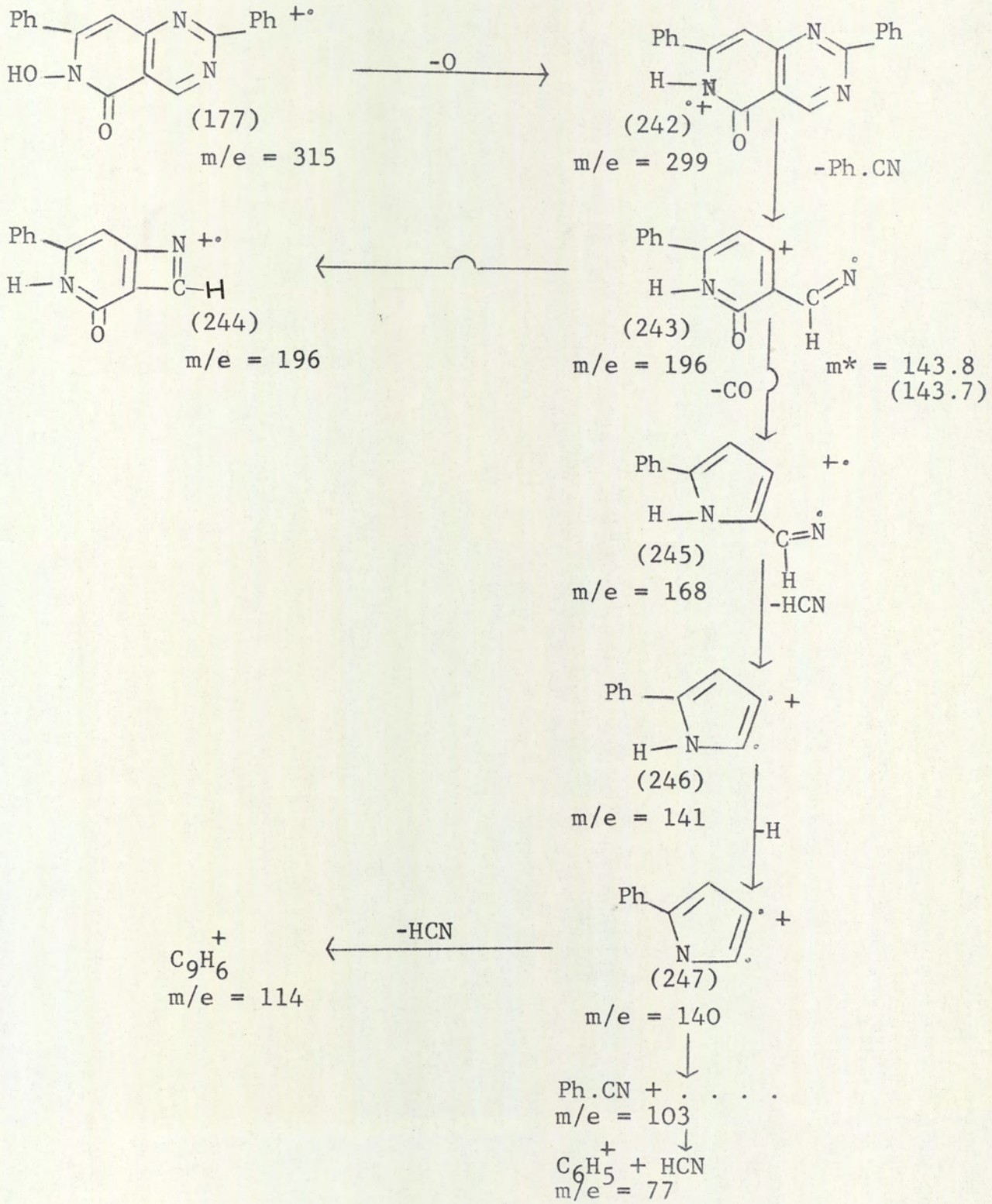
The mass spectrum of 2-3'-pyridyl pyrido[4,3-d] pyrimidin-4(3H)-one (109) (R=3-pyridyl) is simple, since it shows a direct loss or 4-cyanopyridine ($4\text{-}CN.C_6H_5N$) from the parent ion to give the peak at m/e = 120 (219 or 220).

The mass spectra of 6- and 5-substituted pyrido[4,3-d] pyrimidines are characterised by the presence of the benzo-nitrile ($C_6H_5.CN$) fragment at m/e = 103. The fragment decomposed further with a loss of CN, HCN or H_2CN to give the ionised benzyne radicals at m/e = 77, 76 and 75 respectively. The benzyne ions degrade still further to give the peaks at m/e = 65,63,52,51,50 and 39 - typical of many aromatic compounds. [101a]

The degradation pattern of 6-hydroxy 2,7-diphenyl-pyrido[4,3-d]pyrimidin-5(6H)-one (177) (R=OH) is outlined in the scheme 3. The initial loss of 'O' (242) is followed by

Scheme 3 Fragmentation Pattern of

6-Hydroxy 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one



the elimination of benzonitrile (C_6H_5CN) to give the ion of m/e = 196 (243). The structure of this ion (243) is represented as an open chain, though it may exist by re-arrangement in cylic form (244), as well. The loss of CO from the ion (243 or 244) gives pyrrole type cation (245). The initial loss of CO from the isomeric hydroxy pyridines have been suggested to yield pyrrole ions.[101(f)][102] The elimination of CO from 2-hydroxy 3,4-dimethyl quinoline[101(b)] has been proposed to yield a pyrrole type cylic structure.

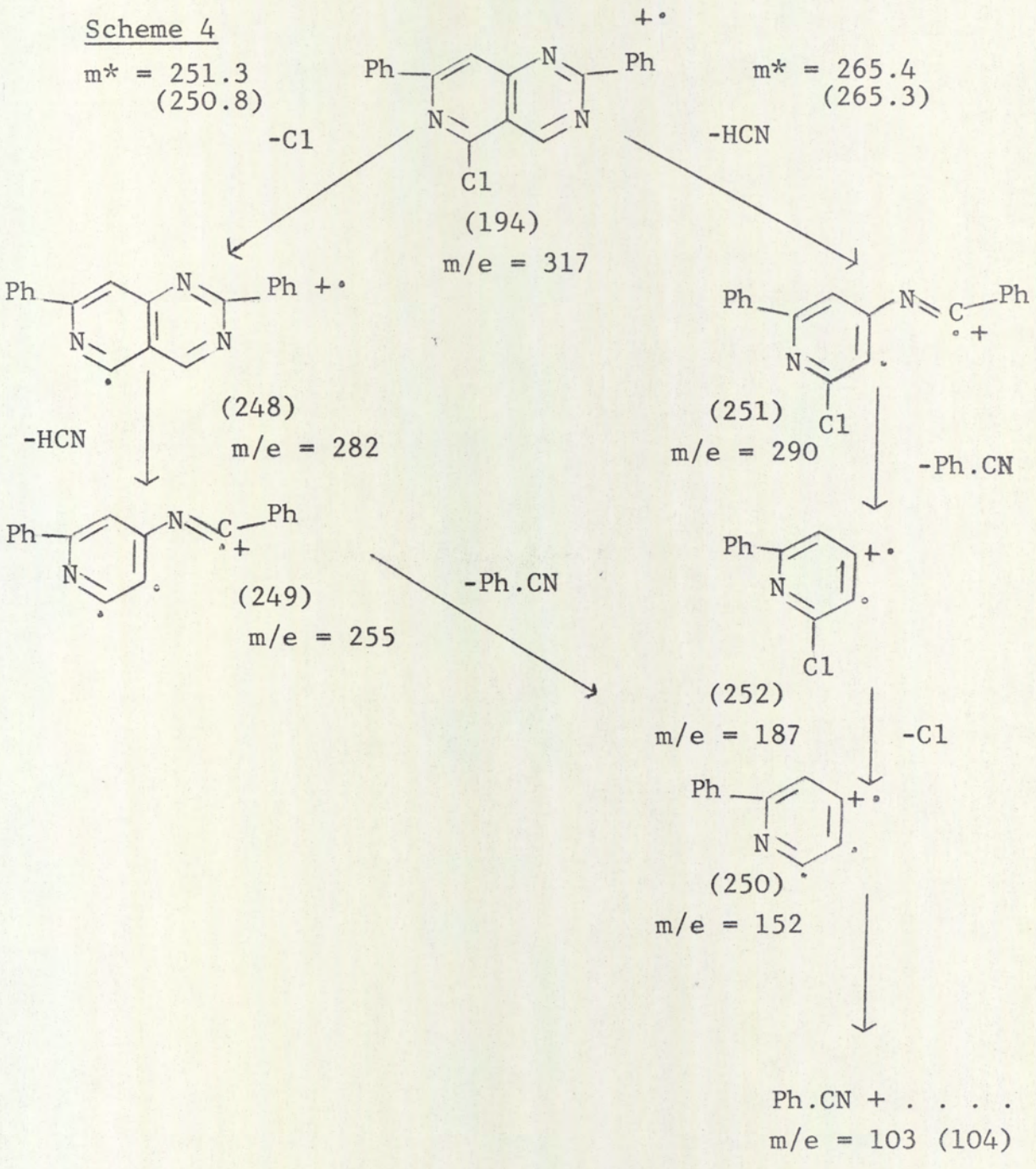
The degradation behaviour of the remaining pyrido-pyrimidin-5(6H)-ones follow mainly the path proposed for the 6-hydroxy compound (177) (R=OH). Thus 2,7-diphenylpyrido [4,3-d]pyrimidin-5(6H)-one (177) (R=H) and 6-methyl 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (188) loose initially C_6H_5CN followed by loss of CO and HCN, while 6-amino 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177) ($R=NH_2$) looses C_6H_5-CN followed by loss of CHO and HCN. All these resulting fragments decompose further to yield a strong ion peak at m/e = 140 (247).

The spectrum of 5-chloro 2,7-diphenylpyrido[4,3-d] pyrimidine (194) shows, besides the molecular ion peak (194) (m/e = 317), a very pronounced peak at m/e = 282 (248) (cf. scheme 4) due to the loss of Cl ion. This is followed by cleavage of HCN (249) and C_6H_5.CN to yield a stable pyridinium ion at m/e = 152 (250). Alternatively it can lose HCN, C_6H_5CN and Cl (as shown in scheme 4). The initial loss of a

Fragmentation Pattern of

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine

Scheme 4



halogen atom is a salient feature of aromatic halogenated compounds as well. Thus p-chloro isopropyl benzene,[103] 2-chloroquinoline[101(c)] and chloroquinazolines[96] all show an initial loss of the halogen atom.

The breakdown patterns of the remaining 5-substituted pyrido[4,3-d]pyrimidines show the same characteristic behaviour as the 5-chloro derivative. Thus 2,7-diphenyl-5-thiopyrido[4,3-d]pyrimidine (192) cleaves with a loss of SH, followed elimination of C_6H_5CN and HCN to give the phenyl pyridinium ion of m/e = 152 (250). It can also loose C_6H_5-CN, SH and HCN, respectively to yield again the ion at m/e = 152 (250). Though thiophenols and aromatic thiols[101(d)] often lose H initially from the SH group, no such loss could be observed in the present investigation.

The mass spectrum of 5-ethoxy 2,7-diphenylpyrido[4,3-d]pyrimidine (195) shows that the ether group OC_2H_5 fragments in various ways to give eventually the ion peak at m/e = 282 (248). Thus the initial loss due to H, CH_3, CHO, C_2H_4 OC_2H_4, C_2H_5 and OC_2H_5 are all assigned to the peaks in the spectrum. The ion then looses C_6H_5-CN and HCN to give the peak at m/e = 152 (250). Alternatively the parent ion can loose C_6H_5CN, HCN and OC_2H_5 respectively. 8-methoxy quinoline, 8-methoxy furoquinoline[104] and various alkoxy quinazolines[96] also fragment initially with the loss of alkoxy groups, decomposing in different ways.

The main fragmentation path of 5-hydrazinopyrido[4,3-d] pyrimidine (196) involves a stepwise loss of $NH.NH_2$, C_6H_5CN and HCN respectively.

PART 3 EXPERIMENTAL

EXPERIMENTAL

Infrared spectra were determined unless otherwise stated in chloroform solution on a Unicam S.P.200 spectrophotometer. Major peaks only are recorded except when assignment of a minor peak was obvious.

Nuclear magnetic spectra were determined unless otherwise stated in trifluoroacetic acid solution (with tetramethyl silane as an internal standard) on a Varian A60A 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 constants in c./sec.

Mass spectra were determined on an A.E.I. MS9 spectrometer. 'M' signifies molecular weight.

Melting points are uncorrected. Sublimation and reaction temperatures are those of an external silicone bath.

Compounds obtained by more than one route were deemed identical when their melting points were undepressed and their infrared spectra and n.m.r. spectra superimposable.

A. SYNTHESIS OF PYRIDO[4,3-d]PYRIMIDIN-4(3H)-ONES FROM PYRIDO[4,3-d]-[1,3]-OXAZIN-4-ONES.

i) 4-Aminonicotinic Acid.

4-Nitro-3-Picoline-1-Oxide (42)

Liquified 3-picoline-1-oxide (41) (85 g.) was added to sulphuric acid (310 ml., d1.84), cooled to 5°. Fuming nitric acid (240 ml., d1.5) was added gradually with shaking and the mixture refluxed for 2.5 hours.

The mixture was poured into crushed ice (1kg.) and neutralised with sodium carbonate (680g.). After allowing to stand overnight, the yellow precipitate was collected and the filtrate extracted with chloroform (600 ml.). The yellow precipitate was extracted twice with boiling chloroform (200 ml.) and the extracts combined. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallised from acetone (1000 ml.) to give yellow needles (70 g., 58%), of the nitro compound, m.p. 133-135°. Armarego[15] quotes a yield of 64% and m.p. 131-134°.

ν_{max}: 1610, 1530 and 1350 (NO_2), 1310, 1260, 1090 cm^{-1}.

4-Amino-3-Picoline (43)

a) 4-Nitro-3-Picoline-1-oxide(6.25 g.) in glacial acetic acid (125 ml.) was heated under reflux and iron filings (18.75 g.) added gradually and cautiously. After the addition, the reaction was allowed to proceed another 2 hours. Acetic acid was distilled off and the residue poured

into water (200 ml.). After adjusting the pH to 10-11 with sodium hydroxide (40%), the product was shaken with chloroform (300 ml.) and the emulsion thus formed was filtered through Kieselguhr, the chloroform separated from the filtrate and the aqueous layer saturated with sodium chloride and extracted further with chloroform. The dried ($MgSO_4$) extract gave 4-amino-3-picoline (2.3 g., 53%), m.p. 104-106°. (lit.[15] 60-70%; m.p. 107-109°).

ν_{max}: 3490, 3400, 3310 and 3190 (N-H), 1640 (C=N), 1510, 1340, 880, 840 cm^{-1}.

b) 4-Nitro-3-picoline-1-oxide (1.4 g.), glacial acetic acid (14 ml.) and platinum oxide (0.14 g.) were placed in a hydrogenator and the mixture shaken at room temperature until the uptake of hydrogen had ceased (4 hours). The solution was filtered (Kieselguhr) and evaporated to dryness to give a reddish brown oil. The oil was poured into water (15 ml.) and after basification with sodium hydroxide (40%), was extracted with chloroform (3 x 50 ml.). The dried ($MgSO_4$) extract yielded 4-amino-3-picoline as light yellow needles (0.7 g., 72%). The infrared spectrum and melting points were similar to that prepared by method (a).

4-Nitronicotinic Acid-1-Oxide (47)

4-Nitro-3-picoline-1-oxide (10 g.) was added slowly, with stirring to sulphuric acid (35 ml., d1.84) in an ice

bath. The resulting solution was then added dropwise to a solution of sodium dichromate (24 g.) in sulphuric acid (35 ml., dl.84) which had been cooled to 0^{o}. During the addition the temperature was maintained at $20\text{-}30^{o}$. The temperature of the reaction mixture was raised to $45\text{-}55^{o}$ and maintained for 6 hours. The mixture was poured into crushed ice (250 g.) and left overnight in a cool place. The resulting precipitate was collected and washed with excess ice water. The product was dissolved in dilute ammonia and precipitated by adding dilute hydrochloric acid to give 4-nitro nicotinic acid-1-oxide (7.9 g., 65%), m.p. $168\text{-}170^{o}$ (decomp.)

Badger and Rao[105] quote 69% yield; m.p. 172^{o} (decomp.). ν_{max} (Nujol): 2650-2500 (O-H), 1670 (C=O), 1560 and 1380 (NO_2), 1270 (C-O), 1200, 1080, 960, 855, 760 cm^{-2}.

4-Aminonicotinic Acid (46)

a) Oxidation of 4-Acetamido-3-Picoline (44)

4-Amino-3-picoline (3.5 g.) was refluxed with acetic anhydride (10.5 ml.) for 0.5 hour. Excess acetic anhydride was distilled off to give a reddish oil. The oil was triturated with aqueous methanol to give 4-acetamido-3-picoline, (2.5 g. 50%), m.p. $152\text{-}154^{o}$.

Armarego[15] quotes 72% yield. No reference is made to the m.p.

ν_{max}: 3400 and 3200 (N-H), 1695 (amide I), 1580, 1510 (amide II) 1450, 1295, 845cm^{-1}.

4-Acetamido-3-picoline (2 g.), water (300 ml) and

powdered potassium permanganate (6 g.) at 75° for 6 hours, yielded 4-acetamido nicotinic acid (1.1 g., 45%), m.p. 242-245° (decomp.) (lit[22] 255° (decomp.)).

ν_{max} (Nujol): 3300-2600 (O-H), 1705 (C=O) 1660 (amide I), 1510 (amide II), 1240, 850cm.$^{-1}$.

4-Acetamidonicotinic acid (1.6 g.), concentrated hydrochloric acid by Armarego's method gave 4-aminonicotinic acid , m.p. 336-337° (decomp.), lit.[15] 55%, 335-336° (decomp.)

ν_{max} (Nujol): 3325 and 3200 (N-H), 2750-2550, (bonded O-H), 1690 (C=O), 860, 840cm.$^{-1}$.

b) Reduction of 4-Nitronicotinic Acid-1-Oxide.

4-Nitronicotinic acid-1-oxide (10 g.) was suspended in water (100 ml.) and ammonia solution (d0.88) added for the acid to go into solution (pH 9.0). Palladium-charcoal (10%,5 g.) was added and the mixture hydrogenated until the uptake of hydrogen had ceased (3 days). The solution was filtered (Kieselguhr) and concentrated to give 4-aminonicotinic acid (5 g., 67%) m.p. 336-337° (decomp.) alone and on admixture with a sample from (a).

ii) Pyrido[4,3-d]-[1,3]-oxazin-4-ones

2-Methylpyrido[4,3-d]-[1,3]-oxazin-4-ones

a) 4-Acetamidonicotinic acid (0.4 g.) and acetic anhydride (10 ml.) were refluxed for 2 hours. Excess solvent was distilled off and the residue crystallised from ethylacetate to give 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one (0.23 g., 64%) as light yellow needles, m.p. 158-159°, (lit.[19] 70%,

156-159°)

ν_{max}: 1780 ('vinyl ester type' C=O), 1650 (C=N), 1250 (C-O), 1000, 860 $cm.^{-2}$.

b) 4-Aminonicotinic acid (0.4 g.) and acetic anhydride (10 ml.) under similar condition yielded the same pyrido-oxazine (0.3 g., 64%).

Hydrolysis back to 4-acetamidonicotinic acid occurred on i) stirring the methylpryido-oxazine with water for 10 min. ii) on exposure to air for 2 hours.

Attempted Preparation of 2-Phenylpyrido[4,3-d]-[1,3]-oxazin-4-one (60)

4-Benzamidonicotinic acid (59)

4-Aminonicotinic acid (0.5 g.), pyridine (1 ml.) and benzoyl chloride (0.5 ml.) were refluxed at 120° for 0.5 hours. The mixture was poured into water (20 ml.) and 4-benzamidonicotinic acid (0.54 g., 62%) collected. The benzamido-acid was purified by dissolving in formic acid and precipitated adding water, to yield a white powder, m.p. 299-300° (decomp.).

Found: C, 64.3; H, 4.2; N, 11.8. $C_{13}H_{10}N_2O_3$ requires C, 64.5; H, 4.1; N, 11.6%.

ν_{max} (Nujol): 3150 (N-H), 1700 (acid C=O), 1645 (amide I), 1515 (amide II), 1270 (C-O), 825 cm^{-1}.

4-Benzamidonicotinic acid (0.4 g.) and acetic anhydride (10 ml.) were refluxed together for 2 hours. Excess solvent

was removed and the residue (0.2 g., 74%) crystallised from ethyl acetate. The product, thus obtained, was identified as 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one because of i) m.p. 158-159°, alone and on admixture with genuine 2-methylpyrido-oxazine, ii) similar infrared spectrum, iii) hydrolysis of the product to give 4-acetamidonicotinic acid, iv) treatment with ammonia to give 2-methylpyrido [4,3-d]pyrimidine-4(3H)-one.

4-Benzamidonicotinic acid (0.4 g.,1 mol.) and benzoic anhydride (1.2 g., 3 mol.) were refluxed together for 3 hours. The mixture was cooled and washed with excess ether to give back the unchanged amido-acid (0.35 g., 88%).

4-Benzamidonicotinic acid (0.4 g., 1 mol.) and benzoic anhydride (3.7 g., 10 mol.) were refluxed together for 3 hours. The mixture was cooled and washed with excess ether to give back the unchanged amido-acid (0.25 g., 62%).

4-Benzamidonicotinic acid (0.4 g.) was heated in an open tube at 250° for 2 hours. The residue (0.21 g., 92%) was identified as 4-aminonicotinic acid.

iii) 3-Substituted 2-Methylpyrido[4,3-d]pyrimidin-4(3H)-ones.

2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one. (4-Hydroxy-2-methylpyrido[4,3-d]pyrimidine). (87)

(a) 2-Methylpyrido[4,3-d]-[1,3]-oxazin-4-one (0.4 g.) was

added to ammonia (5 ml., d0.88) and the suspension of the precipiated amide stirred until the solution was complete (10 hours). The solution was evaporated to give the pyrido-pyrimidine (0.38 g., 95%). The pyridopyrimidine was sublimed at 250°/4mm. and crystallised from acetic acid to give colourless needles, m.p. 309-310° (decomp.).

Found: C, 59.8; H, 4.2; N, 26.1. $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%.

ν_{max}(Nujol): 1700 (C=O), 1600, 1505, 1300, 1180, 900 $cm.^{-1}$.

(b) Ethyl 4-acetamidonicotinate (0.5 g.) and absolute ethanol (20 ml.) were cooled to 0° and saturated with ammonia. The reaction mixture was maintained at room temperature for 3 days. The solvent was evaporated to give the same pyrido-pyrimidine (0.34 g., 89%) as by method (a).

(c) A solution of 3-amino-2-methylpyrido[4,3-d]pyrimidin 4(3H)-one (0.1 g.) in 2N-hydrochloric acid (3 ml.) and ethanol (5 ml.) was treated with sodium nitrite (0.3 g.) in water (1 ml.). The mixture was stirred at room temperature for 30 minutes neutralised with sodium hydroxide, evaporated to dryness and extracted with ethanol. Concentration of the extract yielded the same pyrido[4,3-d]pyrimidine (0.05 g., 55%) as by method (a).

Attempted Condensation of 2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one with benzaldehyde.

2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one (0.5 g.), benzaldehyde (5 ml.) and piperidine (5 drops) were refluxed at 160° for 3 hours. The dark red mixture was evaporated to yield a red oil (0.4 g.). All attempts to solidify the oil failed and the oil decomposed on attempted distillation. The nature of the oil could not be established. It was not investigated further.

Oxidation of 2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one with Fuming Nitric Acid

2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one (0.5 g.) and fuming nitric acid (5 ml., d1.5), were refluxed on water bath for 4 hours. The solution was evaporated to dryness and the residue was crystallised from water to give 4-aminonicotinic acid, (0.25 g., 60%).

Ring Opening and Hydrolysis of 2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one.

2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one (0.5 g.) and dilute hydrochloric acid (5 ml.) were refluxed for 1 hour. The solution was cooled and the pH adjusted to 7. The precipitate (0.3 g., 71%) was identified as 4-aminonicotinic acid.

Attempted Preparation 4-Chloro-2-methylpyrido[4,3-d]pyrimidine (93).

2-Methylpyrido[4,3-d]pyrimidin-4(3H)-one, (1 g.) and phosphoryl chloride (10 ml.) were refluxed together for 2 hours. The mixture was cooled and poured into ice water to yield a dark decomposed product (0.7 g.)

Similar treatment of 2-methylpyrido⁀pyrimidine with a mixture of phosphoryl chloride and phosphorus pentachloride again yielded a decomposed product.

3-Hydroxy-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (88)

(a) Hydroxylamine hydrochloride (0.28 g.) was added to a solution of sodium (0.07 g.) in ethanol (10 ml.). The precipitated sodium chloride was removed and 2-methylpyrido [4,3-d]-[1,3]-oxazin-4-one (0.32 g.) added to the filtrate. The mixture was stirred for 28 hours and the precipitated pyrido-pyrimidine (0.2 g., 57%) collected. The pyrido-pyrimidine was sublimed at 165°/2mm. and crystallised from acetic acid to give colourless needles, m.p. 244-247° (decomp.). Found: C, 54.1; H, 3.8; N, 23.9. $C_8H_7N_3O_2$ requires C, 54.2; H, 4.0; N, 23.7%.

ν_{max} (Nujol): 2600-2300 (O-H), 1695 (C=O), 1620, 1590, 1260, 1200, 1160, 940, 795 $cm.^{-1}$.

The product was a cylic hydroxamic acid and gave red wine colour with alcoholic ferric chloride.

(b) Ethyl 4-acetamidonicotinate (1.4 g.), ethanol (5 ml.) and hydroxylamine solution (8.4 ml.) (p.128) were allowed to stand at room temperature. After 1 hour a thick yellow paste had formed. The mixture was evaporated to dryness after 24 hours and water (5 ml.) added to the residue. The solution was acidified with acetic acid to give the cyclic hydroxamic acid (0.75 g., 63%), similar to that prepared by method (a).

3-Amino-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (89)

(a) The 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one (1.5 g.) hydrazine hydrate (4.5 ml.) and ethanol (25 ml.) were stirred for 24 hours. The suspension was filtered and the filtrate concentrated to yield the pyridopyrimidine (0.8 g., 50%). Crystallisation from ethanol gave colourless prisms, m.p. 167-168°.

Found: C, 53.95; H, 4.2; N, 31.3. M.176. $C_8H_8N_4O$ requires C, 54.55; H, 4.5; N, 31.8%. M.176.

ν_{max} (Nujol): 3300 and 3175 (N-H), 1680 (C=O), 1640, 1390, 1210, 1060, 850 $cm.^{-1}$.

The insoluble product (0.2 g., 15%) before filtration was identified as 4-aminonicotinic acid.

(b) Ethyl 4-acetamidonicotinate (1.5 g.), hydrazine hydrate (3 ml.) and ethanol (5 ml.) were stirred at room temperature. A thick yellow suspension had resulted after a few minutes. The suspension was filtered after 4½ days to

give the same pyrido⌒pyrimidine (0.97 g., 77%) as by method (a).

3-Acetamido-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (97)

3-Amino-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (0.5 g.) was refluxed with acetic anhydride (5 ml.) for 2 hours. Excess anhydride was distilled off and the residue triturated with ethanol to give the acetamidopyridopyrimidine (0.5 g., 81%). The pyridopyrimidine was crystallised from ethanol to give colourless needles, m.p. 142-144°.

Found: C, 55.9; H, 5.25; N, 24.85. M.218. $C_{10}H_{10}N_4O_2$ requires C, 55.0; H, 4.6; N, 25.7. M.218.

ν_{max} (Nujol): 3410 (N-H), 1730 and 1700 (C=O), 1600, 1560, 1320, 1280, 1030, 960, 870, 800, 725 $cm.^{-1}$.

2-Methyl-3-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (90)

The 2-methylpyrido[4,3-d]-[1,3]-oxazin-4-one (0.16 g.) and aniline (0.25 ml.) were heated together in an open tube at 190° for 0.75 hours. The melt was extracted with boiling benzene and filtered while hot. Concentration of the extract gave the pyridopyrimidine (0.08 g., 34%). The pyridopyrimidine was sublimed at 170°/2.5mm. and crystallised from acetic acid, m.p. 200-202°.

Found: C, 70.9; H, 4.7; N, 18.0. $C_{14}H_{11}N_3O$ requires C, 70.9; H, 4.7; N, 17.7%.

ν_{max}: 1695 (C=O), 1610, 1595, 1395, 1360, 1300, 900$cm.^{-1}$,

τ: ($CDCl_3$): 0.12s (5-H); 1.0d, J=7(8-H); 2.3-2.8 m(3-C_6H_5 and 7-H); 7.7s(2-CH_3).

The residue insoluble in benzene was 4-aminonicotinic acid (0.1 g., 74%).

The pyridooxazine was recovered unchanged when stirred with aniline and ethanol at room temperature for 48 hours.

B. SYNTHESIS OF PYRIDO[4,3-d]PYRIMIDIN-4(3H)-ONES FROM ETHYL 4-AMIDONICOTINATES

i) Ethyl 4-Aminonicotinate (20)

4-Aminonicotinic acid (1.2 g.), absolute ethanol (18 ml.) and sulphuric acid (1.35 ml., d1.84) were refluxed for 4 days. Excess alcohol was evaporated and the residue poured into ice water (20 g.). The mixture was basified with ammonia (d0.88) and extracted with chloroform (3 x 20 ml.). The dried ($MgSO_4$) extract on evaporation gave the crude ester, (1.1 g., 76%). Crystallisation from petroleum ether (b.p. 60-80°) yielded brown crystals, m.p. 106-107° (lit.[14] 72%, m.p.100-105°). ν_{max}: 3500, 3400 and 3200 (N-H), 1695 (C=O), 1625, 1310, 1260 (C-O), 1195, 1105, 830cm^{-1}.

Pyrido[4,3-d]pyrimidin-4(3H)-one (21)

Ethyl 4-aminonicotinate (2.4 g.) and formamide (4.5 ml.) were maintained at 180° for 5 hours. The dark red melt was boiled with water (100 ml.) and charcoal (1 g.) for 10 minutes. The mixture was filtered (Kieseleghur) while

hot and the filtrate concentrated to give the pyrido-pyrimidine (0.85 g.), 40%). Crystallisation from acetic acid gave colourless prisms, m.p. 290-291° (decomp.), lit[14], 61%, 280° (decomp.) .

Found: C, 57.3; H, 4.0; N, 28.9. M.147. Calc. for $C_7H_5N_3O$ C, 57.1; H, 3.4; N, 28.6%. M.147.

ν_{max}: (Nujol): 1690 (C=O), 1600, 1310, 1260, (C-O), 1180, 920, 860, 840, 800cm.$^{-1}$.

Pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102)

a) Ethyl 4-aminonicotinate (0.8 g.) and urea (0.3 g.) were fused at 170° for 1 hour. The brown melt was triturated with alcohol to yield the pyridopyrimidine (0.35 g., 44%). The pyridopyrimidine was purified by dissolving in dilute ammonia and precipitated by adding dilute hydrochloric acid. The m.p. was above 360°.

Found: C, 51.5; H, 3.2; N, 26.0. M.163. $C_7H_5N_3O_2$ requires C, 51.6; H, 3.1; N, 25.8%. M.163.

ν_{max} (Nujol): 3200-2750 (N-H and O-H), 1705 (C=O), 1620, 1300, 1050, 790, 690 cm.$^{-1}$.

b) 4-Aminonicotinic acid (0.8 g.) and urea (0.3 g.) were fused at 170° for 1 hour. The brown melt was triturated with alcohol to yield the same pyridopyrimidine (0.3 g., 31%) as prepared by method (a). The compound, however, could not be purified sufficiently enough to yield an analytical sample

Attempted Preparation of 2,4-Dichloropyrido[4,3-d]pyrimidine

Pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (0.5 g.), phosphorus oxychloride (7.5 ml.) and triethylamine (1 ml.) were refluxed for 5 hours. Excess solvent was distilled off and the residue poured into ice water to give a charred product (0.4 g.)

Similar treatment of pyridopyrimidin-dione with phosphoryl chloride and phosphorus pentachloride, still gave the charred product.

Attempted Preparation of 2-Hydroxypyrido[4,3-d]pyrimidin-4(3H)-thione

Ethyl 4-aminonicotinate (0.32 g.) and thiourea (0.16 g.) were fused at 160° for 1 hour. The brown melt was triturated with ethanol and the precipitate (0.2 g., 75%) collected. It was identified as 4-aminonicotinic acid.

ii) Ethyl 4-Amidonicotinates

General Procedure For The Preparation Of Ethyl 4-Amidonicotinates

Ethyl 4-aminonicotinate, the appropriate acyl chloride and pyridine were refluxed for a period of 20-60 minutes. The reaction mixture was cooled and poured into water (10 ml.) and the amido-ester was collected and crystallised from the appropriate solvent.

Ethyl 4-Acetamidonicotinate (105) ($R=CH_3$)

a) Treatment of Ethyl 4-aminonicotinate (1 g.) acetyl chloride (1 ml.) and pyridine (3 ml.) for 20 minutes yielded the amido-ester as an oil. The oil was extracted with chloroform (3 x 10 ml.). Evaporation of the dried ($MgSO_4$) extract yielded the low melting point ester (0.69 g., 55%). Crystallisation from petroleum ether (b.p. 100-120°) gave light brown crystals, m.p. 109°-110°.

Found: C, 57.6; H, 5.9; N, 13.3. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.5%.

ν_{max}: 3300 (N-H), 1705-1695 (ester C=O and amide I), 1590 1510 (amide II), 1380, 1300 (amide III), 1240, 1100, 850cm.$^{-1}$.

b) Ethyl 4-aminonicotinate (1 g.) and acetic anhydride (10 ml.) were refluxed for 30 minutes. Excess solvent was removed and the residue triturated with petroleum ether to yield the same amidoester (0.4 g., 64%) as prepared by method (a)

Ethyl 4-Benzamidonicotinate (105) (R=Ph)

a) Ethyl 4-aminonicotinate (0.16 g.), benzoyl chloride (0.3 ml.) and pyridine (1 ml.), for 1 hour yielded the amido-ester (0.19 g., 72%). Crystallisation from ethanol gave colourless needles, m.p. 143-144°.

Found: C, 66.9; H, 5.2; N, 10.3. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4%.

ν_{max}: 300 (N-H), 1690 (ester C=O and amide I), 1590, 1510

(amide II), 1300 (amide III), 1260, 1120, 710cm.$^{-1}$.

b) Ethyl 4-aminonicotinate (0.5 g.), benzoyl chloride (1.25 ml.) and sodium hydroxide (10%, 3.5 ml.) were shaken vigorously for 15 minutes. The suspension was filtered and washed with excess cold ethanol to give the same amido-ester (0.5 g., 62%) as prepared by method (a).

Ethyl 4-2'-nitrobenzamidonicotinate (105) (R=2-$NO_2.C_6H_4$)

Ethyl 4-aminonicotinate (0.16 g.), 2-nitrobenzoyl chloride (0.18 g.) and pyridine (2 ml.) for 30 minutes yielded the amido-ester (0.21 g., 69%). Crystallisation from ethanol gave colourless needles, m.p. 128-129°.

Found: C, 57.2; H, 3.9; N, 13.2. $C_{15}H_{13}N_3O_5$ requires C, 57.2; H, 4.1%, N, 13.3%.

ν_{max}: 3250 (N-H), 1710 (ester C=O and amide I), 1595, 1540 and 1350 (NO_2), 1510 (amide II), 1300 (amide III), 1140, 1120, 1050, 860, 650 cm.$^{-1}$.

Ethyl 4-4'-Methylbenzamidonicotinate (105) (R=4-MeC_6H_4)

Ethyl 4-aminonicotinate (0.16 g.), 4-methylbenzoyl chloride (p-tolyl chloride) (0.3 g.) and pyridine (2 ml.), for 1 hour yielded the amido-ester (0.245 g., 89%). Crystallisation from ethanol gave colourless needles, m.p.151-152°.

Found: C, 67.6; H, 5.6; N, 10.0. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.7; N, 9.9%.

ν_{max}:3250 (N-H), 1690 (ester C=O and amide I), 1580, 1505

(amide II), 1300 (amide III), 1260, 1180, 1110cm.$^{-1}$.

Ethyl 4-1'-Naphthylamidonicotinate (105) (R=1-Naphthyl)

Ethyl 4-aminonicotinate (0.16 g.), 1-naphthoyl chloride (0.2 g.) and pyridine (2 ml.), for 45 minutes yielded the amido-ester (0.24 g., 80%). Crystallisation from ethanol gave colourless needles, m.p. 149-140°.

Found: C, 72.4; H, 5.3; N, 8.9. $C_{19}H_{16}N_2O_3$ requires C, 72.6; H, 5.1; N, 8.9%.

ν_{max}: 3300 (N-H), 1690 (ester C=O and amide I), 1580, 1505 (amide II), 1420, 1300 (amide III), 1240, 1130, 1110cm.$^{-1}$.

Ethyl 4-2'-Furylamidonicotinate (105) (R=2-Furyl)

Ethyl 4-aminonicotinate (0.16 g.), furoyl chloride (0.13 g.) and pyridine (2 ml.), for 45 minutes yielded the amido-ester (0.24 g., 94%). Crystallisation from ethanol gave colourless needles, m.p. 179-180°.

Found: C, 59.9; H, 4.7; N, 10.9. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.7; N, 10.8%.

ν_{max}: 3300 (N-H), 1695 (ester C=O and amide I), 1580, 1510 (amide II), 1420, 1380, 1300 (amide III), 1100, 1020, 980cm.$^{-1}$.

Ethyl 4-Nicotinamidonicotinate (105) (R=3-Pyridyl)

Ethyl 4-aminonicotinate (0.16 g.), nicotinyl chloride hydrochloride (0.17 g.) and pyridine (1.5 ml.) for 35 minutes yielded the amido-ester (0.17 g., 67%). Crystallisation from

ethanol gave colourless needles m.p. 148-149°.

Found: C, 62.1; H, 4.6; N, 15.4. $C_{14}H_{13}N_3O_3$ requires C, 62.2; H, 4.5; N, 15.5.

ν_{max}: 3250 (N-H), 1685 (ester C=O and amide I), 1580, 1505, (amide II), 1420, 1370, 1300 (amide III), 1270, 1120, 1020cm.$^{-1}$.

iii) 2,3-Disubstituted Pyrido[4,3-d]pyrimidin-4(3H)-ones.

4-Amidonicotinamides (108)

General Procedure For The Preparation of 4-Amidonicotinamides

Ethyl 4-amidonicotinate in absolute ethanol (20 ml.) was cooled to 0°C. and saturated with ammonia. The reaction mixture in a stoppered flask, was left at room temperature for the stated time (4-24 days). The solution or the suspension was evaporated to dryness and the residue washed with chloroform (to remove any unchanged amido-ester) to yeild the diamides.

4-Benzamidonicotinamide (108; R=Ph)

Ethyl 4-benzamidonicotinate (0.5 g.) after 3 days yielded the diamide (0.4 g., 90%). Crystallisation from ethanol gave colourless needles, m.p. 216-218°.

Found: C, 65.8; H, 4.5; N, 17.5. $C_{13}H_{11}N_3O_2$ requires C, 64.7; H, 4.6; N, 17.4%.

ν_{max} (Nujol): 3310 (N-H), 1695 (amide I), 1600, 1505 (amide II) 1260, 840 and 640 cm.$^{-1}$.

4-2'-Nitrobenzamidonicotinamide (108) (R=2.NO_2.C_6H_4)

Ethyl 4-2'-nitrobenzamidonicotinate (0.55 g.) after 7 days, yielded the diamide (0.42 g., 85%). The diamide was purified by dissolving in acetic acid and precipitated by adding water. The m.p. was 249-251°.

Found: C, 54.4; H, 3.6; N, 19.5. $C_{13}H_{10}N_4O_4$ requires C, 54.5; H, 3.5; N, 19.6%.

ν_{max} (Nujol): 3420 and 3200 (N-H), 1695 and 1670 (amide I), 1620, 1590, 1540 and 1355 (NO_2), 1510 (amide II), 1320, 1260, 850, 800, 720cm.$^{-1}$.

4-4'Methylbenzamidonicotinamide (108) (R=4-Me.C_6H_4)

Ethyl 4-4'-methylbenzamidonicotinate (1 g.), after 24 days, yielded the diamide (0.85 g., 94%). Crystallisation from acetic acid gave colourless needles, m.p. 271-273°.

Found: C, 65.8; H, 5.3; N, 16.3. $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.4%.

ν_{max} (Nujol): 3250 and 3075 (N-H), 1680 and 1640 (amide I), 1580, 1505 (amide II), 1320, 1260, 1180, 1085, 835, 740cm.$^{-1}$.

4-1'-Naphthylamidonicotinamide (108) (R=1-Naphthyl)

Ethyl 4-1'-naphthylamidonicotinate (1.5 g.), after 4 days, yielded the diamide (1.23 g., 90%). The diamide was purified by dissolving in cellosolve and precipitated by adding water. The m.p. was 240-242°.

Found: C, 69.9; H, 4.7; N, 13.8. $C_{17}H_{13}N_3O_2$ requires C, 70.1;

H, 4.5; N, 14.4%.

ν_{max} (Nujol): 3450 and 3150 (N-H), 1690, 1670 and 1640 (amide I), 1580, 1505 (amide II), 1310, 1280, 1050, 830, 800, 760cm.$^{-1}$

2-Substituted Pyrido[4,3-d]pyrimidin-4(3H)-ones (109)

General Procedure For The Preparation Of 2-Substituted Pyrido[4,3-d]pyrimidin-4(3H)-ones From Ethyl 4-Amidonicotinates

Ethyl 4-amidonicotinate in absolute ethanol (20 ml.) was cooled to 0°C and saturated with ammonia. The reaction mixture, in a stoppered flask was left at room temperature for the stated time (14-28 days). The solution or the suspension was evoporated to dryness and the residue washed with chloroform to give the pyridopyrimidine.

2-Phenylpyrido[4,3-d]pyrimidin-4(3H)-one (109) (R=Ph)

Ethyl 4-benzamidonicotinate (0. 5 g.) after 28 days, yielded the pyridopyrimidine (0.35 g., 85%). Crystallisation from acetic acid gave colourless needles, m.p. 284-286°. Found: C, 70.0; H, 4.2; N, 19.0. $C_{13}H_9N_3O$ requires C, 69.9; H, 4.1; N, 18.8%.

ν_{max} (Nujol): 1700 (C=O), 1600, 1560, 1505, 1300, 1170, 860, 780, 700cm.$^{-1}$.

2-2'-Furylpyrido[4,3-d]pyrimidin-4(3H)-one (109) (R=2-Furyl)

Ethyl 4-2'-furylamidonicotinate (1.5 g.), after 14 days yielded the pyridopyrimidine (1.2 g., 99%). Crystal-

lisation from celloslve gave light pink needles, m.p. 335-337° (decomp.).

Found: C, 62.2; H, 3.7; N, 19.9. M213. $C_{11}H_7N_3O_2$ requires C, 62.0; H, 3.3; N, 19.7%. M213.

ν_{max} (Nujol): 1700 (C=O), 1600, 1505, 1310, 1180, 1020, 910, 855 and 750cm.$^{-1}$.

2-3'-Pyridylpyrido[4,3-d]pyrimidine-4(3H)-one (109)(R=3-Pyridyl)

Ethyl 4-amidonicotinate (1.5 g.), after 14 days yielded the pyridopyrimidine (.25 g., 100%). Crystallisation from celloslove gave colourless needles, m.p.304-306° (decomp.)

Found: C, 64.4; H, 3.2; N, 25.2. M223. $C_{12}H_8N_4O$ requires C, 64.6; H, 3.2; N, 25.1%. M223.

ν_{max} (Nujol): 1715 (C=O), 1600, 1505, 1320, 1180, 1030, 860, 720, 700cm.$^{-1}$.

General Procedure For The Preparation Of 2-Substituted Pyrido[4,3-d]pyrimidin-4(3H)-ones From 4-Amidonicotinamides

The diamide was heated at the stated temperature for the stated time. The brown melt obtained was extracted with boiling acetic acid and the extract concentrated to yield the pyridopyrimidine

2-Phenylpyrido[4,3-d]pyrimidin-4(3H)-one (109) (R=Ph)

4-Benzamidonicotinamide (0.5 g.), at 218° for 15 minutes yielded the pyridopyrimidine (0.31 g., 67%).

Crystallisation from acetic acid (charcoal) gave the same pyridopyrimidine as prepared on p. 118

Attempted Conversion of 3-Amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (125)(R=Ph) into 2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (109)(R=Ph)

3-Amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (0.1 g), hydrochloric acid (2N, 3 ml.) and ethanol (5 ml.) was treated with sodium nitrite (0. 3 g.) in water (1 ml.). The mixture was stirred at room temperature for 30 minutes and the precipitate (0.06 g.,60%) collected. It was identified as 3-amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one.

2-2'-Nitrophenylpyrido[4,3-d]pyrimidin-4(3H)-one (109) (R=2-NO_2.C_6H_4)

4-2'-Nitrobenzamidonicotinamide (0.9 g.), at 235°, for 20 minutes yielded the pyridopyrimidine (0.77 g., 92%). Crystallisation from acetic acid (charcoal) gave colourless needles, m.p. 275-277°.

Found: C, 58.0; H, 2.9; N, 20.9. M268. $C_{13}H_8N_4O_3$ requires C, 58.2; H, 3.0; N, 20.9%. M268.

ν_{max} (Nujol): 1700 (C=O), 1600, 1535 and 1360 (NO_2), 1180,880 860, 780, 720cm.$^{-1}$.

2-4'-Methylphenylpyrido[4,3-d]pyrimidin-4(3H)-one (109)

(R=4-$CH_3.C_6H_4$)

4-4'-Methylbenzamidonicotinamide (0.4 g.) at 255° for 20 minutes yielded the pyridopyrimidine (0.31 g., 83%). Crystallisation from acetic acid (charcoal) gave colourless needles, m.p. 296-299°.

Found: C, 70.8; H, 4.6; N, 17.7. $C_{14}H_{11}N_3O$ requires C, 70.9; H, 4.7; N, 17.7%.

ν_{max} (Nujol): 3150 (N-H), 1680 (C=O), 1600, 1560, 1300, 1180, 1030, 940, 880, 840, 800, 730cm.$^{-1}$.

2-1'-Naphthylpyrido[4,3-d]pyrimidin-4(3H)-one (109) (R=1-Naphthyl)

4-1'-Naphthylamidonicotinamide (0.55 g.) at 240° for 30 minutes yielded the pyridopyrimidine (0.46 g., 89%). Crystallisation from aceticacid (charcoal) gave colourless needles, m.p. 326-327°.

Found: C, 74.6; H, 4.2; N, 15.6. $C_{17}H_{11}N_3O$ requires C, 74.7; H, 4.1; N, 15.4.

ν_{max} (Nujol): 1700 (C=O), 1600, 1510, 1420, 1310, 1170, 880, 860, 810, 780cm.$^{-1}$.

4-Amidonicotinic acid hydrazide (124)

General Procedure For The Preparation Of 4-Amidonicotinic acid hydrazide

A mixture of the 4-amidonicotinate, hydrazine hydrate and ethanol, was stirred at room temperature for the stated time. The suspension was filtered and washed with excess chloroform

(to remove any unchanged amido-ester) to yield the hydrazide.

4-Benzamidonicotinic acid hydrazide (124) (R=Ph)

Ethyl 4-benzamidonicotinate (0.5 g.), hydrazine hydrate (1.2 ml.) and ethanol (4 ml.) after 24 hours, yielded the hydrazide (0. 39 g., 83%). Crystallisation from ethanol gave colourless needles, m.p. 229-231°.

Found: C, 60.7; H, 4.8; N, 22.1. $C_{13}H_{12}N_4O_2$ requires C, 60.9; H, 4.7; N, 21.9%.

ν_{max} (Nujol): 3200 and 3125 (N-H), 1700 and 1640 (amide I), 1590, 1520 (amide II), 1350, 1260, 1230, 1000, 850, 690cm.$^{-1}$.

4-2'-Nitrobenzamidonicotinic acid hydrazide (124)

(R=2-NO_2.C_6H_4)

Ethyl 4-2'-nitrobenzamidonicotinate (2 g.), hydrazine hydrate (6 ml.) and ethanol (7 ml.), after 14 hours, yielded the hydrazide (1.58 g., 83%). Crystallisation from ethanol gave colourless needles, m.p. 239-241°.

Found: C, 51.5; H, 3.8; N, 23.7. $C_{13}H_{11}N_5O_4$ requires C, 51.8; H, 3.7; N, 23.3%.

ν_{max} (Nujol): 3275 and 3100 (N-H), 1685 and 1655 (amide I), 1590, 1540, and 1340 (NO_2), 1505 (amide II), 1310, 1220, 1060, 970, 850, 730cm.$^{-1}$.

4-4'-Methylbenzamidonicotinic acid hydrazide (124)

(R=4-$CH_3.C_6H_4$)

Ethyl 4-4'-methylbenzamidonicotinate (1.7 g.), hydrazine hydrate (5 ml.) and ethanol (10 ml.), after 16 hours, yielded the hydrazide (1.55 g., 96%). Crystallisation from cellosolve gave colourless crystals, m.p. 234-236°.

Found: C, 62.4; H, 5.2; N, 20.5. $C_{14}H_{14}N_4O_2$ requires C, 62.2; H, 5.2; N, 20.7.

ν_{max} (Nujol): 3200 and 3075 (N-H), 1685 and 1640 (amide I), 1595, 1520 (amide II), 1260, 1190, 1000, 855, 740cm.$^{-1}$.

4-1'-Naphthylamidonicotinic acid hydrazide (124)(R=1-Naphthyl)

Ethyl 4-1'-naphthylamidonicotinate (1.5 g.), hydrazine hydrate (4.5 ml.) and ethanol (8 ml.), after 14 hours, yielded the hydrazide (1.3 g., 91%). Crystallisation from ethanol gave colourless prisms, m.p. 239-240°.

Found: C, 66.5; H, 4.8;, N, 18.2. $C_{17}H_{14}N_4O_2$ requires C, 66.7; H, 4.6; N, 18.3%.

ν_{max} (Nujol): 3325 and 3150 (N-H), 1695 and 1650 (amide I), 1580, 1520 (amide II), 1350, 1280, 1250, 1130, 850, 790, 770, 720cm.$^{-1}$.

4-2'-Furylamidonicotinic acid hydrazide (124) (R=2-Furyl)

Ethyl 4-2'-furylamidonicotinate (0.85 g.), hydrazine hydrate (3 ml.) and ethanol (5 ml.), after 12 hours, yielded the hydrazide (0.76 g., 95%). Crystallisation from cellosolve

gave light pink needles, m.p. 231-233°.

Found: C, 53.6; H, 4.3; N, 22.7. $C_{11}H_{10}N_4O_3$ requires C, 53.6; H, 4.1; N, 22.8%.

ν_{max} (Nujol): 3250 and 3125 (N-H), 1700 and 1640 (amide I), 1590, 1520 (amide II), 1350, 1210, 1180, 1000, 880, 860, 760cm.$^{-1}$.

4-Nicotinamidonicotinic acid hydrazide (124)(R=3-Pyridyl)

Ethyl 4-nicotinamidonicotinate (1.5 g.) hydrazine hydrate (4.5 ml.) and ethanol (15 ml.), after 16 hours, yielded the hydrazide (1.3 g., 92%). Crystallisation from Cellosolve gave colourless needles, m.p. 222-224° (decomp.).

Found: C, 56.2; H, 4.4; N, 27.1. M257. $C_{12}H_{11}N_5O_2$ requires C, 56.0; H,4.3; N, 27.2%. M257.

ν_{max} (Nujol): 3200 and 3100 (N-H),1700 and 1600 (amide I), 1600, 1520 (amide II), 1320, 1280, 1230, 1060, 850, 720cm.$^{-1}$.

3-Amino 2-Substituted pyrido[4,3-d]pyrimidin-4(3H)-ones (125)

General Procedure For the Preparation Of 3-Amino 2-Substituted pyrido[4,3-d]pyrimidin-4(3H)-ones from 4-Amido-nicotinic Acid Hydrazide

The acid hydrazide was heated at the stated temperature for the stated time. The brown melt was triturated with ethanol to yield the pyridopyrimidine.

3-Amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (125)(R=Ph)

4-Benzamidonicotinic acid hydrazide (0.5 g.), at 210°, for 30 minutes, yielded the pyriodpyrimidine (0.37 g., 80%). Crystallisation from ethanol (charcoal) gave colourless needles, m.p. 192-194°.

Found: C, 65.4; H, 4.4; N, 23.5. M238. $C_{13}H_{10}N_4O$ requires C, 65.5; H, 4.2; N, 23.5%. M238

ν_{max} (Nujol): 3275 and 3125 (N-H), 1695 (C=O), 1640, 1600, 1550, 1300, 1170, 870, 800, 770, 690cm.$^{-1}$.

3-Amino-2-2'-nitrophenylpyrido[4,3-d]pyrimidin-4(3H)-one (125)(R=2-$NO_2.C_6H_4$)

4-2'-Nitrobenzamidonicotinic acid hydrazide (0.9 g.) at 220° for 45 minutes, yielded the pyridopyrimidine (0.71 g., 83%). Crystallisation from ethanol (charcoal) gave colourless needles, m.p. 221-223°.

Found: C, 55.1; H, 3.5; N, 24.6. $C_{13}H_9N_5O_3$ requires C, 55.1; H, 3.2; N, 24.7.

ν_{max} (Nujol): 3300 and 3175 (N-H), 1700 (C=O), 1600, 1560, 1535 and 1360 (NO_2), 1230, 1150, 850, 800cm.$^{-1}$.

3-Amino-2-4'methylphenylpyrido[4,3-d]pyrimidin-4(3H)-one (125)(R=4-$CH_3.C_6H_4$)

4-4'-Methylbenzamidonicotinic acid hydrazide (1.2 g.), at 230° for 15 minutes yielded the pyridopyrimidine (0.92 g., 82%). Crystallisation from ethanol gave colourless prisms, m.p. 161-162°.

Found: C 66.7; H, 5.0; N, 22.1. $C_{14}H_{12}N_4O$ requires C, 66.7; H, 4.8; N, 22.2%.

ν_{max} (Nujol): 3275 and 3150 (N-H), 1695 (C=O), 1600, 1560, 1520, 1180, 920, 820, 800, 730cm.$^{-1}$.

3-Amino-2-1'-naphthylpyrido[4,3-d]pyrimidin-4(3H)-one (125) (R=1-Naphthyl)

4-1'-Naphthylamidonicotinic acid hydrazide (0.5 g.) at 220°, for 25 minutes, yielded the pyridopyrimidine (0.43 g., 91%). Crystallisation from ethanol (charcoal) gave colourless needles, m.p. 206-208°.

Found: C, 70.8; H, 4.3; N, 19.3. $C_{17}H_{12}N_4O$ requires C, 70.8; H, 4.2; N, 19.4%.

ν_{max} (Nujol): 3300 and 3250 (N-H), 1680 (C=O), 1600, 1230, 1190, 990, 950, 910, 850, 800, 760cm.$^{-1}$.

3-Amino-2-2'-furylpyrido[4,3-d]pyrimidin-4(3H)-one (125) (R=2-Furyl)

4-2'-Furylamidonicotinic acid hydrazide (0.5 g.), at 230° for 20 minutes yielded the pyridopyrimidine (0.185 g.,

40%). Crystallisation from ethanol (charcoal) gave light pink needles, m.p.234-235°.

Found: C, 58.0; H, 3.8; N, 24.5. $C_{11}H_8N_4O_2$ requires C, 57.8; H, 3.5; N, 24.6%.

ν_{max} (Nujol): 3250 and 3125 (N-H), 1690 (C=O), 1605, 1580, 1530, 1260, 1230, 1180, 1145, 1020, 980, 920, 850, 800, 700cm.$^{-1}$.

Attempted Preparation of 3-Amino-2-3'-Pyridylpyrido[4,3-d] pyrimidin-4(3H)-one (125) (R=3-Pyridyl).

4-Nicotinicamidonicotinic acid hydrazide failed to cyclise under the following conditions:-

i) Stirring for 4 weeks in excess hydrazine.

ii) Heating at 200° for 15 minutes.

iii) Heating at 220° for 10 minutes decomposed the hydrazide.

iv) Heating in the presence of phosphoryl chloride for 2 days.

v) Heating in the presence of polyphosphoric acid for 2 days.

vi) Heating in the presence of concentrated sulphuric acid.

3-Hydroxy 2-Substituted pyrido[4,3-d]pyrimidin-4(3H)-ones (131)

General Procedure For The Preparation Of 3-Hydroxy 2-Substituted pyrido[4,3-d]pyrimidin-4(3H)-ones From Ethyl 4-Amidonicotinate

The 4-amidonicotinate was set aside at the room temperature for the stated time with hydroxylamine solution in aqueous ethanol (5 ml.). The pasty suspension obtained was evaporated to dryness and dissolved in a minimum quantity of water. The resulting solution was acidified with glacial acetic acid to yield the cyclichydroxamic acid. Purification was achieved by sublimation under reduced pressure below the m.p. of the pyridopyrimidine and crystallisation from the appropriate solvent.

Hydroxylamine hydrochloride (1.39 g.) in water (2 ml.) was added to sodium hydroxide solution (20%, 8 ml.) to give the desired hydroxylamine solution.[52]

All the cyclichydroxamic acids gave red wine colour with alcoholic ferric chloride.

3-Hydroxy-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (131)(R=Ph)

Ethyl 4-benzamidonicotinate (0.8 g.) and hydroxylamine solution (5 ml.), after 48 hours, yielded the cyclichyroxamic acid (0.62 g., 88%). Sublimation at 190°/0.3mm. and crystallisation from ethanol gave fine feathery needles, m.p. 260-262° (decomp.)

Found: C, 65.3; H, 3.9; N, 17.3. $C_{13}H_9N_3O_2$ requires C, 65.3;

H, 3.8; N, 17.5%.

ν_{max} (Nujol): 1695 (C=O), 1610, 1210, 1160, 940, 860, 680cm.$^{-1}$.

Attempted Preparation of 3-Hydroxy-2-2'-nitrophenyl pyrido[4,3-d] pyrimidin-4(3H)-one (131)(R=2-NO_2.C_6H_4)

Ethyl 4-2'-nitrobenzamidonicotinate (1.5 g.) and hydroxylamine solution (9.2 ml.) failed to yeild the cyclic hydroxamic acid even after 1 week. A brown oil was the only product isolated. The oil could not be induced to solidify using various solvents. A suitable derivative could not be prepared. The oil decomposed on attempted distillation. It did not give positive test for cyclic hydroxamic acid. It was not investigated further.

3-Hydroxy-2-4'-methylphenylpyrido[4,3-d]pyrimidin-4(3H)-one (131) (R=4-CH_3.C_6H_4)

Ethyl 4-4'-methylbenzamidonicotinate (0.84 g.) and hydroxylamine solution (5.5 ml.), after 48 hours, yielded the cyclic hydroxamic acid (0.69 g., 93%). Sublimation at 240°/4mm. and crystallisation from ethanol gave light yellow needles, m.p. 279-281° (decomp.)

Found: C 66.4; H, 4.4; N, 16.7. M253. $C_{14}H_{11}N_3O_2$ requires C, 66.5; H, 4.4; N, 16.6%. M253.

ν_{max} (Nujol): 2600-2400 (O-H), 1700 (C=O), 1610, 1560, 1310, 1200, 1180, 930, 860, 820, 790, 740cm.$^{-1}$.

3-Hydroxy-2-1'-naphthylpyrido[4,3-d]pyrimidin-4(3H)-one (131) (R=1-Naphthyl)

Ethyl 4-1'-naphthylamidonicotinate (1 g.) and hydroxylamine solution (6 ml.), after 12 hours, yielded the cyclic hydroxamic acid (0.65 g., 72%). Sublimation at 235°/3.4mm. and crystallisation from acetic acid gave yellow needles, m.p. 258-262° (decomp.)

Found: C, 70.5; H, 3.9; N, 14.6. $C_{17}H_{11}N_3O_2$ requires C, 70.6; H, 3.8; N, 14.5.

ν_{max} (Nujol): 2700-2550 (O-H), 1700 (C=O), 1605, 1525, 1305, 1170, 920, 740cm.$^{-1}$.

2-2'-Furyl-3-hydroxypyrido[4,3-d]pyrimidin-4(3H)-one (131) (R=2-Furyl)

Ethyl 4-2'-furylamidonicotinate (1 g.) and hydroxylamine solution (6 ml.), after 48 hours, yielded the cyclic hydroxamic acid (0.54 g., 61%). Sublimation at 255°/2mm. and crystallistion from cellosolve gave fine yellow needles, m.p. 319-321° (decomp).

Found: C57.9; H, 3.2; N, 18.4. $C_{11}H_7N_3O_3$ requires C, 57.7; H, 3.1; N, 18.3%.

ν_{max} (Nujol): 1705 (C=O), 1620, 1590, 1540, 1320, 1185, 1020, 860, 760cm.$^{-1}$.

3-Hydroxy-2-3'-pyridylpyrido[4,3-d]pyrimidin-4(3H)-one (131) (R=3-Pyridyl)

Ethyl 4-nicotinamidonicotinate (1 g.) and hydroxylamine solution (6 ml.), after 48 hours, yielded the cyclic hydroxamic acid (0.68 g., 77%). Sublimation at 255°/9mm. and crystallisation from cellosolve gave light yellow needles, m.p. 292-294° (decomp.)

Found: C, 59.8; H, 3.3; N, 23.2. $C_{12}H_8N_4O_2$ requires C, 60.0; H, 3.4; N, 23.3%.

ν_{max} (Nujol): 1680 (C=O), 1600, 1545, 1305, 1040, 920, 860, 790, 700cm.$^{-1}$.

3-(2'-Hydroxyethyl)-2-substituted pyrido[4,3-d]pyrimidin-4(3H)-ones (143)

3-(2'-Hydroxylethyl)-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (143)(R=CH_3)

Ethyl 4-acetamidonicotinate (1.5 g.), ethanol amine (0.5 ml.) and ethanol (10 ml.) were refluxed together. After 4 days, more ethanolamine (1 ml.) was added and the reflux continued for another 2 days. The solution was evaporated to dryness to give a semisolid mass. The mass was triturated with acetone to give the pyridopyrimidine (1.09 g., 74%). Crystallisation from ethanol gave colourless shiny needles, m.p. 171-172°.

Found: C, 58.5; H, 5.5; N, 20.8. $C_{10}H_{11}N_3O_2$ requires

C, 58.5; H, 5.4; N, 20.5%.

ν_{max} (Nujol): 3200-3100 (O-H), 1680 (C=O), 1610, 1350, 1280, 1205, 1150, 1080, 1030, 880, 810, 650cm.$^{-1}$.

4-Benzamido-N(2-hydroxyethyl)-nicotinamide (142) (R=Ph)

Ethyl 4-benzamidonicotinate (1.62 g.), ethanolamine (0.72 ml.) and ethanol (25 ml.) were refluxed together for 24 hours. The mixture was evaporated to dryness. The residue was washed with chloroform to give the diamide (1.37 g., 80%). Crystallisation from ethanol gave colourless needles, m.p. 214-215°.

Found: C, 63.1; H, 5.4; N, 14.5. $C_{15}H_{15}N_3O_3$ requires C, 63.2; H, 5.4; N, 14.7%.

ν_{max} (Nujol): 3300 and 3150 (N-H and O-H), 1685 and 1650 (amide I), 1595, 1520 (amide II), 1300, 1260, 1050, 1030, 700cm.$^{-1}$.

3-(2'-Hydroxyethyl)-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (143)(R=Ph)

4-Benzamido-N-(2-hydroxyethyl)-nicotinamide (0.5 g.) was heated at 230° for 20 minutes. The brown melt was triturated with ethanol to yield the pyridopyrimidine (0.26 g., 55%). Crystallisation from ethanol (charcoal) gave colourless needles, m.p. 173-174°.

Found: C, 67.3; H, 5.0; N, 15.7. $C_{15}H_{13}N_3O_2$ requires C, 67.4; H, 4.9; N, 15.7%.

ν_{max} (Nujol): 3250-3150 (O-H), 1680 (C=O), 1600, 1560, 1340, 1160, 1080, 1020, 850, 700cm.$^{-1}$.

4-1'-Naphthylamido-N-(2-hydroxyethyl)-nicotinamide (142) (R=1-Naphthyl)

Ethyl 4-1'-naphthylamidonicotinate (0.8 g.), ethanolamine (2.4 ml.) and ethanol (20 ml.) were refluxed together for 3 days. The solution was evaporated to dryness and the oily residue triturated with chloroform to yield the diamide (0.27 g., 33%). Crystallisation from ethanol gave colourless needles, m.p. 203-204°.

Found: C 68.2; H, 5.1; N, 12.5. $C_{19}H_{17}N_3O_3$ requires C, 68.2; H, 5.1; N, 12.5%.

ν_{max} (Nujol): 3450 and 3220 (N-H and O-H), 1680 and 1660 (amide I), 1580, 1510 (amide II), 1320, 1220, 1130, 1060, 900, 850, 820, 780cm.$^{-1}$.

Attempted Reaction Of Ethyl 4-Acetamidonicotinate With Aniline

a) Ethyl 4-acetamidonicotinate (1 g.), aniline (1 ml.) and ethanol (20 ml.) were refluxed together for 14 days. The reaction mixture was evaporated to dryness to give back the starting material (0.8 g., 80%).

b) Ethyl 4-acetamidonicotinate (0.5 g.) and aniline (0.5 ml.) were heated in an open tube at 160° for 30 minutes. The mixture was cooled to yield back the amidoester.

N.m.r. spectra of pyrido[4,3-d]pyrimidin-4(3H)-ones are reported on p.57 and p.58.

(C) SYNTHESIS OF PYRIDO[4,3-d] PYRIMIDINE FORM PYRIMIDINES

i) 2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one

Ethylethoxymethylene acetoacetate (163)

Ethyl acetoacetate (13 g.), acetic anhydride (20.4 g.) and ethyl orthoformate (14.8 g.) were refluxed together at 140° for 40 minutes. Excess acetic anhydride and ethanol were distilled off. The residual oil was transferred into vacuum distillation apparatus and the fraction collection at 110-120°/27in. (8 g, 43%) (lit[66] 10 g., 140-160°/17in.)

Ethyl 4-methyl 2-phenylpyrimidine-5-carboxylate (164)

To a mixture of ethyl ethoxymethylene acetoacetate (3.7 g.) and benzamidine hydrochloride (3.2 g.) was added a solution of sodium ethoxide [prepared from sodium (0.5 g.), absolute alcohol (20 ml.)]. The mixture was refluxed on a water bath for 1 hour and filtered while hot. Cooling the filtrate yeilded the pyrimidine (1.8 g., 38%), m.p. 94-96° (lit[67] 2.3 g., m.p. 99-100°).

ν_{max} (Nujol): 1720 (C=O), 1595, 1565, 1540, 1430, 1280, 1220, 1170, 1100, 1080, 770, 740, 690cm.$^{-1}$.

τ : 0.41 s(6-H), 1.4m and 2.2m(2-C_6H_5), 5.3q J=7.5 (5-$COOCH_2.CH_3$), 6.7s(4-CH_3), 7.98t, J=7(5-$COOCH_2.CH_3$)

4-Methyl 2-phenylpyrimidine-5-carboxylic acid (165)

Ethyl 4-methyl-2-phenylpyrimidine-5-carboxylate (5 g.), ethanol (50 ml.), potassium hydroxide (1.4 g.) and water

(10 ml.) were refluxed together for 4 hours. The mixture was evaporated to dryness and the residue dissolved in water (10 ml.). On acidification with dilute hydrochloric acid the carboxylic acid precipitated, yield (3.5 g., 62%) m.p. 245-247°(decomp.). (lit[67] 4 g., m.p. 243°).

ν_{max} (Nujol): 3100-2700 (O-H), 1700 (C=O), 1580, 1540, 1430, 1295, 1260 (C-O), 1180, 1105, 925, 780, 740, 720, 690cm.$^{-1}$.

τ : 0.37 s(6-H), 1.5m and 2.2m (2-C_6H_5), 6.68 s(4-CH_3)

2-Phenyl-4-Styrylpyrimidine-5-carboxylic acid (166)

a) 4-Methyl-2-phenylpyrimidine-5-carboxylic acid (0.6 g.) and benzaldehyde (1.2 g.) were refluxed at 180° for 4 hours. The resulting oil was triturated with ether to give the styryl-pyrimidine (0.6 g., 71%). Crystallisation from ethanol gave yellow needles m.p. 228-231°.

Found: C, 75.4; H, 4.5; N, 9.1. M302. $C_{19}H_{14}N_2O_2$ requires C, 75.5; H, 4.7; N, 9.3%. M302.

ν_{max}(Nujol): 3100-2800 (O-H), 1695 (C=O), 1625 (conjugated -CH:CH-), 1595, 1580, 1530, 1420, 1260 (C-O), 1180, 1105, 970, 950, 780, 750, 730, 685cm.$^{-1}$.

b) Ethyl 4-methyl-2-phenylpyrimidine-5-carboxylate (0.5 g.) and benzaldehyde (1 g.) were refluxed at 180° for 3 hours. The reaction mixture was cooled and triturated with ether to give the same styrylpyrimidine carboxylic acid (0.35 g.) as prepared by method (a).

2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one (170)

2-Phenyl-4-styrylpyrimidine-5-carboxylic acid (1.5 g.), bromine (1.8 g.) and acetic acid (25 ml.) were refluxed at 135° for 10 hours. The reaction mixture was cooled and poured into water (20 ml.) to yield the pyranopyrimidine (1 g., 67%). Crystallisation from cellosolve gave light pink needles, m.p. 216-218°.

Found: C, 75.95; H, 4.3; N, 9.5. M300. $C_{19}H_{12}N_2O_2$ requires C, 76.0; H, 4.0; N, 9.3%. M300.

ν_{max} (Nujol): 1740 ('vinyl ester type' C=O), 1620 (-C=C-), 1580, 1400, 1260, 1230, 1160, 1050, 930, 840, 770, 690cm.$^{-1}$

τ : 0.28 s(4-H), 1·4 - 2·3 m(2-C_6H_5, 7-C_6H_5, 8-H).

ii) 6-Substituted 2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-ones. (177)

2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177)(R=H)

a) 2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one (0.5 g.) was suspended in absolute ethanol (30 ml.) and the mixture cooled to 0°. The mixture was saturated with ammonia and the stoppered flask left at room temperature for 5 days. The mixture was evaporated to dryness to yeild the pyridopyrimidine (0.45 g., 90%). Crystallisation from cellosolve gave yellow prisms, m.p. 346-348° (decomp.).

Found: C, 76.15; H, 4.5; N, 14.15. M299. $C_{19}H_{13}N_3O$ requires C, 76.25; H, 4.4; N, 14.0%. M299.

ν_{max}(Nujol): 3190 (N-H), 1670 (C=O), 1625 (-C=C-), 1590, 1570·

1400, 845, 770, 730, 690 $cm.^{-1}$.

τ : 0.08 s(4-H), 1.5m and 2.2m (2-C_6H_5, 7-C_6H_5), 2.45 s(8-H).

b) To a suspension of 6-amino-2,7-diphenyl pyrido[4,3-d] pyrimidin-5(6H)-one (0.1 g.), in hydrochloric acid (2N, 3 ml.) and ethanol (5 ml.), was added a solution of sodium nitrite (0.3g) in water (10 ml.) . The mixture was stirred for 45 minutes at room temperature and the suspension poured into water. The precipitate (0.06 g., 63%), obtained was identified as 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one, similar to that prepared by method (a).

6-Hydroxy 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177) (R=OH)

To a suspension of 2,7-diphenylpyrano[4,3-d] pyrimidine (0.3 g.) in aqueous ethanol (5 ml.) was added the hydroxylamine solution (1.8 ml.). (p.128). A red clear solution had formed after 5 minutes followed by the formation of a thick paste. The paste was left at room temperature for 2 days and evaporated to dryness. The residue was dissolved in water (4 ml.) and acidified with acetic acid to yield the cyclic hydroxamic acid (0.18 g., 57%). Crystallisation from ethanol gave light yellow needles, m.p. 244-246°.

Found: C, 72.3; H, 4.4; N, 13.2 M315. $C_{19}H_{13}N_3O_2$ requires C, 72.4; H, 4.2; N, 13.3%. M315.

ν_{max} (Nujol): 3150 (O-H), 1650 (C=O), 1605 (-C=C-), 1550, 1260, 1200, 850$cm.^{-1}$.

τ : −0.15 s(4-H), 1.65m and 2.3m(2-C_6H_5, 7-C_6H_5, 8-H)2.6 s (8-H)

The pyridopyrimidine gave a red wine colour with alcoholic ferric chloride.

6-Amino-2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177) (R=NH_2)

2,7-Diphenylpyrano[4,3-d]pyrimidine (0.7 g.), hydrazine hydrate (2 ml.) and ethanol (5 ml.) were stirred for 4 days at room temperature. The resulting suspension was filtered to yield the pyridopyrimidine (0.5 g., 68%). Crystallisation from ethanol gave yellow needles, m.p. 207-208°.

Found: C, 72.5; H, 4.6; N, 18.0. M314.115610. $C_{19}H_{14}N_4O$ requires C, 72.6; H, 4.5; N, 17.8%. M314.116754.

ν_{max} (Nujol): 3300 and 3200 (N-H), 1660 (C=O), 1605 (-C=C-), 1595, 1565, 1415, 1260, 1140, 1020, 840, 780, 690cm^{-1}.

τ : -0.1 s(4-H), 1.5m and 2.25m (2-C_6H_5, 7-C_6H_5), 2.75s (8-H).

6-Diacetylamino-2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (191)

6-Amino-2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (0.4 g.) and acetic anhydride (5 ml.) were refluxed for 1 hour. Excess acetic anhydride was distilled off and the gummy residue triturated with ethanol to give the diacetyl pyridopyrimidine (0.35 g., 69%). Crystallisation from ethanol gave colourless needles, m.p. 177-179°.

Found: C, 69.25; H, 4.5; N, 14.0. M398. $C_{23}H_{18}N_4O_3$ requires C, 69.4; H, 4.55; N, 14.1. M398.

ν_{max} (Nujol): 1735 (acetyl C=O), 1700 (ring C=O), 1620 (-C=C-), 1595, 1565, 1405, 1245, 1205, 1180, 1030, 970, 840, 775, 695cm.$^{-1}$

6-Methyl 2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (188)

2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (0.73 g.), potassium hydroxide (1.2 g.), water (9 ml.), methanol (24 ml.) and methyl iodide (3 ml.) were refluxed together for 24 hours. The reaction mixture was cooled and the precipitate collected. The product was extracted with boiling ethanol and filtered while hot. Concentration of the filtrate yielded the N-methyl-pyridopyrimidine (0.6 g., 78%). Crystallisation from ethanol or cellosolve gave colourless needles, m.p. 188-190°. The insoluble residue (0.1 g.) during the filtration was the unchanged starting material.

Found: C, 76.8; H, 4.9; N, 13.6. M314. $C_{20}H_{15}N_3O$ requires C, 76.7; H, 4.8; N, 13.4. M314

ν_{max} (Nujol): 1640 (C=O), 1600, 1595, 1560, 1540, 1400, 1265, 1020, 840, 780, 695 cm.$^{-1}$.

τ : -0.1 s(4-H), 1.6m and 2.35m(2-C_6H_5, 7-C_6H_5), 2.8 s(8-H), 6.3 s(6-N-CH_3).

iii) Attempted preparation of 2,7-diphenylpyrido[4,3-d]pyrimidine (193)

2,7-Diphenyl-5-thiopyrido[4,3-d]pyrimidine (192)

2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (0.37 g.), phosphorus pentasulphide (o.6 g.) and dry pyridine (3 ml.) were refluxed together for 24 hours. The brown viscous mixture was cooled and poured into crushed ice (20 g.) to yield the thiopyridipyrimidine (0.25 g., 64%). Crystallisation from cellosolve gave green crystals, m.p. 296-298°.

Found: C, 72.4; H, 4.3; N, 13.2; S 10.05. M315

$C_{19}H_{13}N_3S$ requires C, 72.35, H, 4.15, N, 13.3, S, 10.2%. M315.

ν_{max} (Nujol): 1630, 1565, 1220, 1160, 1080, 1020, 890, 845, 770, 710, 700cm.$^{-1}$

τ : 0.5 s(4-H), 1.7m and 2.25m (2-C_6H_5, 7-C_6H_5), 2.47 s(8-H).

2,7-Diphenyl-5-thiopyrido[4,3-d]pyrimidine (0.45 g.), concentrated hydrochloric acid (0.2 ml.), Raney nickel (0.9 g.) and ethanol were refluxed for 4 hours. The mixture was evoporated to dryness. The residue was extracted with cellosolve (3 x 10 ml.) and filtered while hot (Kieselghur). Concentration of the extract gave back the unchanged thiopyrido pyrimidine (0. 35 g., 93%).

The thiocompound was also recovered unchanged when refluxed with Raney nickel in cellosolve or dioxane.

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine (194)

2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (0.5 g.) and phosphoryl chloride (5 ml.) were refluxed together for 6 hours. Excess phosphoryl chloride was distilled off and the residue poured into crushed ice (50 g.). The mixture was neutralised with sodium carbonate and then extracted with chloroform (3 x 50 ml.). The dried ($MgSo_4$) extract on distillation yielded the chloropyridopyrimidine (0. 5 g., 94%). Crystallisation from cellosolve gave buff shiny needles, m.p. 186-188°.

Found: C, 71.6; H, 4.0; N, 13.0; Cl, 11.0. M317. $C_{19}H_{12}N_3Cl$ requires C, 71.8; H, 3.8; N, 13.2; Cl, 11.15. M317.

ν_{max} (Nujol): 1595, 1550, 1345, 1250, 1160, 1020, 970, 880, 860, 770, 695 $cm.^{-1}$.

τ : 0.45 s(4-H), 1.9m and 2.7m(2-C_6H_5, 7-C_6H_5), 2.9 s(8-H).

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine was recovered unchanged when i) hydrogenated using palladium-calciumcarbonate (5%) and benzene, ethanol, chloroform or cellosolve as solvent ii) refluxed with Raney-nickel and ethanol iii) refluxed with tin and hydrochloric acid iv) sodium and dimethylsulphoxide (under reflux).

5-Hydrazino-2,7-diphenylpyrido[4,3-d]pyrimidine (196)

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine (1 g.)

and hydrazine hydrate (20 ml.) were refluxed for 1 hour. The reaction mixture was cooled and the suspension collected to yield the hydrazinopyridopyrimidine (0.7 g., 71%). Crystallisation from cellosolve gave red crystals, m.p. 245-247° (decomp.)

Found: C, 72.8; H, 5.0; N, 22.15. M313. $C_{19}H_{15}N_5$ requires C, 72.8; H, 4.8; N, 22.35%. M313.

ν_{max} (Nujol): 3300 (N-H), 1600, 1570, 1530, 1430, 1350, 1020, 965, 850, 780, 740, 695cm.$^{-1}$.

τ : 1.9m-2.3m(2-C_6H_5, 7-C_6H_5), 2.65 s(8-H).

5-Hydrazino 2,7-diphenylpyrido[4,3-d]pyrimidine was recovered unchanged when i) refluxed with copper sulphate ii) refluxed with copper sulphate and acetic acid iii) refluxed with copper sulphate and sodium hydroxide.

When 5-hydrazino pyridopyrimidine was refluxed in silver acetate and acetic acid, a charred mass was obtained.

5-(1',2'-Diacetyl) hydrazinopyrido[4,3-d]pyrimidine (199)

5-Hydrazino 2,7-diphenylpyrido[4,3-d]pyrimdine (1 g.) and acetic anhydride (15 ml.) were refluxed together for 2 hours. Excess acetic anhydride was distilled off and the residue triturated with ethanol to give the diacetyl derivative (0.9 g., 71%). Crystallisation from cellosolve gave white needles, m.p. 269-271°.

Found: C, 69.5; H, 5.0; N, 17.5. M397. $C_{23}H_{19}N_5O_2$ requires

C, 69.5; H, 4.7; N, 17.6%. M397,

ν_{max} (Nujol): 3300 (N-H), 1695 (C=O), 1605, 1585, 1260, 780, 695cm.$^{-1}$.

τ : 2.1m(2-$C_6\underline{H}_5$, 7-$C_6\underline{H}_5$), 2.3 s(8-$\underline{H}$), 7.65s and 7.75s (1',2'-di-CO.$C\underline{H}_3$).

5-Ethoxy 2,7-Diphenylpyrido[4,3-d]pyrimidine (195)

5-Chloro-2,7-diphenylpyrido[4,3-d]pyrimidine (0.5 g.), sodium (0.07 g.) and absolute ethanol (5 ml.) were refluxed for 1 hour. The mixture was cooled and the yellow precipitate collected. The product was extracted with boiling ethanol (3 x 5 ml.) and filtered while hot. Concentration of the filtrate yielded the ethoxy derivative (0.32 g., 62%). Crystallisation from ethanol gave light pink needles, m.p. 128-129°.

Found: C, 77.1; H, 5.4; N, 12.95. M327. $C_{21}H_{17}N_3O$ requires C, 77.0; H, 5.2; N, 12.8. M327.

ν_{max}: 1620 (-C=C-), 1580, 1405, 1340, 1270, 1170, 1140, 1050, 1020, 940, 870, 780, 695cm.$^{-1}$.

τ : ($CDCl_3$): 0.6 s(4-$\underline{H}$), 1.7m, 1.9m and 2.5m (2-$C_6\underline{H}_5$, 7-C_6H_5), 2.2 s(8-H), 5.35q J=7 (5-$OC\underline{H}_2CH_3$), 8.5t J=7 (5-$OCH_2.C\underline{H}_3$).

iv) 7-Phenylpyrano [4,3-d] pyrimidin-2,5(3H)-dione

Ethyl 2-ureidomethylene acetoacetate (207)

Urea (3 g.), ethyl acetate (7 g.) and ethyl orthoformate (8.1 g.) were refluxed together for 12 hours. The reaction mixture was cooled to yield the ureidoester (4 g., 37%) as light yellow crystals, m.p. 191° (lit[92], 5 g., m.p. 195°).

5-Ethoxycarbonyl-4-methylpyrimidin-2(1H)-one (208)

To Ethyl 2-ureidomethylene acetoacetate (2 g.) in absolute ethanol (30 ml.) was added a solution of sodium ethoxide [sodium (0.3 g.) in absolute ethanol (10 ml.)] and the mixture refluxed together to give a jelly like precipitate. Ethanol was distilled off under vacuum and the residue treated with water (20 ml.). The mixture was acidified with glacial acetic acid to give the pyrimidine (1.1 g., 60%), m.p. 255-256° (lit[93], 1.4 g., m.p. 257°).

ν_{max} (Nujol): 3100 (N-H), 1760 (ester C=O), 1720 (ring C=O), 1590, 1280 (C-O), 1215, 1105, 1020, 940, 800, 660cm.$^{-1}$

τ : 0.6 s(6-H), 5.4q, J=7.5(5-COOC$\underline{H}_2$.CH_3), 6.8 s(4-C$\underline{H}_3$), 8.7t, J=7.5(5-COOCH_2.C$\underline{H}_3$).

5-Ethoxycarbonyl-4-styrylpyrimidin-2(1H)-one (209)

5-Ethoxycarbonyl-4-methylpyrimidin-2(1H)-one (3.7 g.) and benzaldehyde (10 g.) were refluxed at 180° for 4½ hours. The reaction mixture was cooled and triturated with excess ether to yield the styrylpyrimidine (3 g., 55%). Crystal-

lisation from acetic acid gave yellow crystals, m.p. 184-186°. (lit,[93] 2.3 g., m.p. 187°).

ν_{max} (Nujol): 3100 (N-H), 1710 (ester C=O), 1690 (ring C=O), 1650 (conjugated C=C), 1600, 1540, 1420, 1280, 1260 (C-O), 1225, 1190, 1100, 800, 700cm.$^{-1}$.

τ : 0.7 s(6-H), 1.51 s(4-C$\underline{H}$:C$\underline{H}$.C_6H_5), 2.2m(4-CH:CH.$C_6\underline{H}_5$), 5.4q, J=7.5(5-COOC$\underline{H}_2$.CH_3), 8.6t, J=7.5(5-COOCH_2.C$\underline{H}_3$).

4-Styrylpyrimidin-2(1H)-one-5-carboxylic acid (210)

5-Ethoxycarbonyl-4-styrylpyrimidin-2(1H)-one (0.5 g.) and sodiumhydroxide (10%, 7.5 ml.) were refluxed together for 1 hour. The solution was cooled and acidified with dilute sulphuric aicd to yield the pyrimidine carboxylic acid (0.4 g., 90%). The acid was purified by dissolving in dilute ammonia and precipitating adding dilute hydrochloric acid, m.p. 276-278° (decomp.).

Found: C, 64.35; H, 4.4; N, 11.7. M242. $C_{13}H_{10}N_2O_3$ requires C, 64.5; H, 4.2; N, 11.6%. M242.

ν_{max} (Nujol): 3100 (N-H and O-H), 1705 (ring C=O and acid C=O), 1645 (conjugated -C=C-), 1600, 1540, 1500, 1400, 1280, 1250, (C-O), 1100, 980, 805, 700cm.$^{-1}$.

τ : 0.68 s(6-$\underline{H}$), 1.52 s(4-C$\underline{H}$:C$\underline{H}$-C_6H_5), 2.35m(4-CH:CH.$C_6\underline{H}_5$).

7-Phenylpyrano[4,3-d]pyrimidin-2,5(3H)-dione. (211)

4-Styrylpyrimidin-2(1H)-one-5-carboxylic acid (3 g.), bromine (1.1 ml.) and acetic acid (30 ml.) were refluxed together

12 hours. The reaction mixture was cooled to yeild the pyranopyrimidine (2.6 g., 88%). It was purified initially by boiling in water, ether and ethanol. Further purification was achieved by dissolving in dilute ammonia and precipitating by the addition of dilute hydrochloric acid, m.p. above 360° (decomp.).

Found: C, 64.8; H, 3.5; N, 12.3. M240.050722. $C_{13}H_8N_2O_3$ requires, C, 65.0; H, 3.3; N, 11.7%. M240.053487.

ν_{max} (Nujol): 3020 (N-H), 1750 (vinyl ester type C=O), 1690 (ring C=O), 1630 (conjugated -C=C-), 1595, 1330, 1230, 1060, 940, 800, 770, 680cm.$^{-1}$.

τ : 0.49 s(4-H), 1.9m and 2.3m(7-C_6H_5), 2.6 s(8-H).

v) 6-Substituted 7-phenylpyrido[4,3-d]pyrimidin-2,5(3H,6H)-diones

6-Hydroxy-7-phenylpyrido[4,3-d]pyrimidin-2,5(3H,6H)-dione (212)

To a suspension of 7-phenylpyranopyrimidin-dione (1 g.) in ethanol (8 ml.) was added the hydroxyl amine solution (6 ml.) (p.128). The mixture changed to clear yellow solution . After an hour a thick paste had formed. The paste was allowed to stand at room temperature for 3 days and then evaporated to dryness. The residue was dissolved in water (10 ml.) and acidified with acetic acid to yield the cyclic hydroxamic acid (0.8 g., 75%). The hydroxamic acid was purified by dissolving in formic acid and precipitating with water, m.p. above 360°.

Found: C, 61.0; H, 4.0; N, 16.4. M255. $C_{13}H_9N_3O_3$ requires C, 61.2; H, 3.6; N, 16.4%. M255.

ν_{max} (Nujol): 3180 (N-H and O-H), 1680 (C=O at 2 position), 1640 (C=O at 5 position), 1260, 1220, 1200, 1165, 900, 800, 770, 710, 680cm.$^{-1}$.

τ : 0.33s (4-H), 2.25m(7-C_6H_5), 3.14s (8-H)

The pyridopyrimidine gave a red wine colour with alcoholic ferric chloride.

Attempted Preparation of 7-phenylpyrido[4,3-d]pyrimidin-2,5(3H,6H)-dione

a) The pyranopyrimidin-dione (0.5 g.) and ammonia solution (3 ml; 0.881) were stirred for 5 weeks at room temperature.

b) The pyranopyrimidin-dione (0.2 g.) was suspended in absolute ethanol (20 ml.) and the mixture saturated with ammonia at 0°. The mixture was left in a stoppered flask at room temperature for 5 weeks.

In each case the pyranopyrimidin-dione was recovered unchanged.

(Attempted) Preparation of 6-Amino-7-phenylpyrido[4,3-d]pyrimidon-2,5(3H,6H)-dione (218)

The pyranopyrimidin-dione (1 g.) and hydrazine hydrate (15 ml.) in ethanol (5 ml.) were stirred at room temperature, for 5 weeks. The suspension was filtered off. The product (0.8 g.) was purified by boiling in water, ether, ethanol and

cellosolve, m.p. 337° (decomp.).

Found: C, 54.7; H, 5.2; N, 28.7. If hydrazide: (215 or 216, p.83), $C_{13}H_{14}N_6O_2$ requires C, 54.5; H, 4.9; N, 29.3%.

If pyridopyrimidine (218) (p.83),

Found: M254. $C_{13}H_{10}N_4O_2$ requires M254.

ν_{max} (Nujol): 3400, 3250, 3200 and 3150 (N-H), 1700 and 1660 (C=O), 1605, 1300, 1220, 1020, 850, 755, 710, 695cm.$^{-1}$

τ : (if pyridopyrimidine) (218); 0.4 s(4-H) 2·35 m(7-C_6H_5), 3.3s (8-H).

When the product was heated in an open tube for 30 seconds, hydrazine evolved very rapidly. The residual gummy product could not be, however, induced to solidify nor could it be purified.

An attempted acylation gave a mixture of products, which could not be separated.

D. MASS SPECTRAL TABLE*

The most intense peak was taken as 100%. The relative intensity peak I% (relative abundance) was then measured and calculated based on the most intense peak. All the peaks above relative abundance of 2% are recorded.

m/e = mass/charge ratio

indicates metastable peak (m); values in parentheses indicate theoretical value of metastable peaks, obtained for m/e at higher mass (m) degrading to m/e at lower mass (m_2)

$$(m^* = \frac{m_2^2}{m_1})$$

4-Nicotinamidonicotinic acid hydrazide (124)(R=3-Pyridyl)

m/e	258	257	239	238	227	226	225	224	223	210	177
I%	2	5	5	6	15	100	7	6	5	5	3
m/e	91	79	78	77	76	66	65	64	59	57	53
I%	2	9	85	6	5	5	4	6	16	2	6
m/e	52	51	50	44	43	42	41	40	39	33	32
I%	10	45	23	4	4	5	4	4	8	3	5
m/e	31	28	27	18							
I%	18	17	15	87							

Pyrido[4,3-d]pyrimidin-4(3H)-one (21)

m/e	148	147	146	120	119	118	105	104	103	93	92
I%	15	100	15	14	14	14	3	2	2	30	80
m/e	91	77	76	75	73.5	68	67	66	65	64	59
I%	12	9	8	7	5	6	5	9	18	21	6

m/e	53	52	51	50	44	43	41	40	38	37	28
I%	15	10	6	18	8	12	6	6	12	12	21

m/e	18
I%	85

Pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione (102)

		(m_1)						(m_2)			
m/e	164	163	162	147	145	134	121	120	119	108	107
I%	29	88	6	5	4	5	20	100	12	2	4

			(m_2)				(88.33)	(m_1)			
m/e	106	105	94	93	92	91	88.35*	80	79	77	76
I%	9	2	14	85	18	8	4	5	5	4	6

		(71.91)									
m/e	75	72.17*	70	68	66	65	64	63	61	60	59
I%	3	4	11	12	10	44	32	9	3	4	3

m/e	53	52	51	50	43	41	40	39	38	29	18
I%	32	35	11	20	14	14	13	12	36	18	100

m/e	17	16
I%	18	8

3-Amino 2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (89)

		(m_1)					(m_2)				(122.8)
m/e	177	176	175	161	149	148	147	146	135	133	122.8 *
I%	9	100	2	6	6	55	4	8	7	2	4

m/e	123	121	120	119	118	117	107	106	105	104	103
I%	2	4	2	6	7	2	5	4	4	3	2

m/e	93	92	91	79	78	77	76	64	63	62	56
I%	4	5	3	4	14	7	4	4	7	2	3

m/e	53	52	51	50	44	43	42	41	40	31	38
I%	5	4	6	24	6	4	8	7	5	4	3

m/e	37	28	27	18
I%	2	14	30	85

3-Acetamido-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one (97)

								(m_1)			(m_2)
m/e	219	218	204	203	202	201	177	176	161	148	147
I%	4	34	4	24	5	25	12	**100**	2	4	28
		(122.8)									
m/e	135	122.7*	120	119	118	106	105	104	92	91	79
I%	2	2	2	3	9	2	3	2	2	3	2
m/e	78	77	76	65	64	53	52	51	50	43	42
I%	10	8	4	2	5	2	2	3	22	88	6
m/e	41	40	31	29	28	18					
I%	6	3	3	5	10	15					

3-Amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one (125)(R=Ph)

		(m_1)				(m_2)(183.5)					
m/e	239	238	237	223	210	209	183.7*	183	182	181	179
I%	9	60	31	3	13	**100**	2	9	4	13	5
m/e	121	120	119	105	104	103	94	78	77	76	64
I%	4	11	3	5	18	19	4	18	**100**	20	18
m/e	53	52	51	50	39	28	27	18	17		
I%	9	6	27	58	78	7	8	65	20		

2-2'-Nitrophenylpyrido[4,3-d]pyrimidin-4(3H)-one (109)(R=$NO_2.C_6H_4$)

m/e	270	269	268	239	237	223	222	192	183	176	170
I%	2	6	32	11	10	4	10	3	4	8	3
m/e	168	167	141	140	139	136	135	134	133	132	121
I%	4	3	5	17	4	11	10	7	27	3	5
m/e	120	119	118	105	104	103	102	93	92	91	90
I%	**100**	11	12	12	18	21	24	24	14	26	10
m/e	89	88	79	78	77	76	75	74	65	66	65
I%	4	3	4	19	15	51	19	7	6	8	17
m/e	64	63	62	54	53	52	51	50	46	43	42
I%	63	14	4	7	20	19	25	44	6	7	7
m/e	41	40	39	31	37	30	28	18			
I%	8	7	21	12	7	8	9	63			

3-Hydroxy 2-4'-methylphenylpyrido[4,3-d]pyrimidin-4(3H)-one

(131)(R=4-$CH_3.C_6H_4$)

m/e	254	253	252	239	238	237	236	224	223	211	210
I%	3	23	2	2	11	33	3	6	27	2	5
									(m_1)		
m/e	209	196	195	194	182	167	146	121	120	119	118
I%	4	3	4	3	2	2	2	9	100	9	4
								(m_2)			
m/e	117	116	115	105	103	96	93	92	91	90	89
I%	20	12	11	3	5	2	18	6	18	13	10
						(70.53)					
m/e	79	78	77	76	75	70.35*	66	65	64	63	62
I%	2	6	7	6	3	2	3	18	18	9	2
m/e	53	52	51	50	44	41	40	39	38	37	28
I%	7	6	10	18	2	3	4	13	6	3	4
m/e	27	26	18	17							
I%	3	2	6	5							

2-2'-Furylpyrido[4,3 d]pyrimidin-4(3H)-one (109)(R=2-Furyl)

m/e	214	213	212	186	185	184	170	158	157	156	155
I%	14	100	16	7	11	5	3	7	14	5	4
m/e	146	142	141	131	130	129	121	120	119	118	108
I%	5	3	3	5	7	3	2	13	5	6	3
m/e	107	105	104	103	102	95	94	93	92	91	79
I%	5	7	9	29	7	16	38	22	13	12	14
m/e	78	77	76	75	68	67	66	65	64	63	59
I%	13	34	36	14	7	4	11	16	43	5	7
m/e	53	52	51	50	41	40	39	38	37	31	29
I%	16	17	9	32	4	11	60	22	14	16	7
m/e	28	27	26	18	17						
I%	10	5	4	32	7						

2-3'-Pyridylpyrido[4,3-d]pyrimidin-4(3H)-one (109)(R=3-Pyridyl)

m/e	224	223	221	198	154	146	142	121	120	119	118
I%	2	16	2	2	2	4	2	10	**100**	2	3
m/e	106	105	104	103	93	92	91	79	78	77	76
I%	2	13	3	2	11	3	3	2	6	4	3
m/e	66	65	64	53	52	51	50	40	39	28	18
I%	2	3	6	4	4	6	6	2	2	3	18
m/e	17										
I%	14										

2-Phenyl-4-Styrylpyrimidine-5-Carboxylic acid (166)

m/e	304	303	302	301	274	273	259	258	257	256	255
I%	3	21	**100**	21	2	6	3	21	72	3	3
m/e	230	225	220	200	199	197	179	157	156	155	154
I%	5	2	2	5	15	5	4	3	23	36	8
m/e	153	152	130	128	127	126	116	115	105	104	103
I%	4	3	4	13	23	9	3	9	18	23	24
m/e	102	101	91	89	78	77	76	75	63	53	52
I%	9	4	3	3	6	27	12	4	5	9	11
m/e	51	50	44	39	28	18					
I%	14	5	2	4	6	17					

2,7-Diphenylpyrano[4,3-d]pyrimidin-5-one (170)

m/e	301	300	277	271	269	244	223	217	197	169	167
I%	25	**100**	5	21	4	3	15	3	5	6	5
m/e	150	142	141	140	122	114	108	105	104	103	102
I%	4	4	20	6	5	4	4	5	40	4	4
m/e	97	94	83	81	78	77	65	51	50	44	41
I%	3	3	3	3	35	15	21	28	7	5	6
m/e	39	32	31	29	28	27	18	17			
I%	5	8	6	7	40	7	**100**	95			

2,7-Diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177) (R=H)

m/e	301	300	299	272	271	242	215	198	197	196	195
I%	95	**100**	6	3	3	3	12	2	90	**100**	3
m/e	169	168	167	154	153	149	142	141	140	139	129
I%	8	80	7	2	6	3	3	12	20	2	2
m/e	128	126	115	114	105	104	103	102	77	66	65
I%	2	2	2	5	10	70	6	5	4	4	3
m/e	53	52	51	50	42	41	38	31	29	28	18
I%	3	11	5	2	7	8	7	5	2	4	7
m/e	17										
I%	5										

6-Hydroxy 2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177)

(R=OH)

											(m_1)
m/e	316	315	301	300	299	298	272	271	223	197	196
I%	2	4	3	19	53	24	2	2	4	14	**100**
					(m_2)						(143.7)
m/e	195	182	170	169	168	167	154	153	152	149	143.8*
I%	3	2	6	24	8	2	5	4	7	5	2
m/e	142	141	140	139	129	128	127	126	116	115	114
I%	2	10	19	6	4	6	4	5	5	4	13
m/e	113	105	104	103	102	92	91	90	89	88	87
I%	7	9	**100**	24	3	5	6	4	11	5	4
m/e	78	77	76	75	74	66	65	64	63	62	53
I%	8	50	25	10	5	17	12	19	10	5	32
m/e	52	51	50	44	39	38	37	28	27	23	18
I%	12	36	16	8	12	8	6	8	6	6	29
m/e	17										
I%	60										

6-Amino-2,7diphenylpyrido[4,3-d]pyrimidin-5(6H)-one (177)(R=NH_2)

m/e	316	315	314	302	301	300	299	287	286	285	256
I%	6	36	100	3	2	9	6	6	12	30	6

m/e	255	254	253	211	198	197	182	181	180	179	178
I%	9	10	6	6	9	6	3	6	12	2	3
m/e	177	168	167	166	165	157	156	155	154	153	152
I%	2	2	3	3	2	12	15	30	21	15	9
m/e	142	141	140	139	129	128	127	126	116	115	114
I%	6	7	24	12	5	24	30	24	18	6	5
m/e	128	126	115	114	105	104	103	102	77	66	65
I%	2	2	2	5	10	70	6	5	4	4	3
m/e	53	52	51	50	42	41	38	31	29	28	18
I%	3	11	5	5	7	8	7	5	2	4	7
m/e	17										
I%	5										

6-Diacetylamino-2,7-diphenylpyrido[4,3-d]pyrimidin-5(6H)-one

(191)

m/e	399	398	357	356	355	341	340	339	315	314	313
I%	2	6	2	11	2	7	11	**100**	28	**100**	89
m/e	312	301	300	299	288	287	286	285	272	196	153
I%	10	2	9	3	2	3	13	2	2	7	6
m/e	140	129	128	127	105	104	103	102	**78**	77	76
I%	3	4	6	9	2	12	11	6	3	15	8
m/e	75	65	64	63	53	52	51	50	43	42	39
I%	3	3	4	5	**12**	7	9	3	22	4	5
m/e	28	18									
I%	12	83									

6-Methyl 2,7-diphenylpyrido[4,3-d]pyrimidim-5(6H)-one (188)

m/e	315	314	313	287	286	242	211	210	209	192	183
I%	2	16	**100**	3	2	3	7	36	5	2	2
m/e	182	181	180	179	168	167	157	154	153	152	151
I%	7	11	3	4	3	2	4	4	11	7	9
m/e	141	140	139	130	129	128	127	126	125	119	118
I%	4	7	3	2	3	7	10	7	2	6	55

m/e	117	116	115	114	113	106	105	104	103	102	101
I%	4	5	5	5	4	3	8	13	13	5	2
m/e	92	91	90	89	88	79	78	77	76	65	64
I%	2	10	3	4	2	2	6	33	5	2	7
m/e	63	53	52	51	39	28	27	18			
I%	2	23	7	4	2	4	4	17			

2,7-Diphenyl-5-thiopyrido[4,3-d]pyrimidine (192)

m/e	317	316	315	283	282	280	254	231	220	214	213
I%	12	24	**100**	7	22	24	2	2	6	4	6
m/e	212	211	181	179	178	176	168	164	159	158	153
I%	8	4	7	2	2	3	3	3	2	7	3
m/e	152	150	145	132	104	103	97	93	85	83	77
I%	6	7	3	4	6	7	3	3	5	2	6
m/e	76	72	71	70	69	59	58	57	56	55	52
I%	3	3	6	5	54	7	6	12	3	5	2
m/e	51	50	45	44	43	42	41	38	36	32	31
I%	3	5	4	7	7	2	4	16	55	5	8
m/e	29	28	27	18	17						
I%	7	6	5	**100**	**100**						

5-Chloro 2,7-Diphenylpyrido[4,3-d]pyrimidine (194)

				(m_1)				(m_2)			(m_2)
m/e	320	319	318	317	316	292	291	290	289	283	282
I%	10	51	37	**100**	12	3	3	7	3	3	7
		(265.3)			(250.8)						
m/e	281	265.4*	255	254	251.3*	214	190	188	187	179	178
I%	3	2	5	4	2	3	9	3	25	5	5
m/e	160	159	158	153	152	151	129	127	125	124	114
I%	5	4	14	9	51	9	12	7	5	5	7
m/e	104	103	102	101	86	84	78	77	76	75	74
I%	22	**100**	9	5	10	56	5	52	26	14	5
m/e	63	59	52	51	50	39	31	28	27	18	17
I%	9	8	9	26	12	9	10	9	8	35	9

5-Hydrazino-2,7-diphenylpyrido[4,3-d]pyrimidine (196)

m/e	316	315	314	313	299	298	297	296	295	285	284
I%	2	3	**100**	4	2	4	2	2	3	5	11
m/e	283	282	259	258	257	212	211	210	209	195	194
I%	28	12	2	3	2	2	11	76	2	5	6
m/e	193	183	181	180	179	168	167	166	165	157	155
I%	12	2	3	11	25	2	3	6	4	4	3
m/e	154	153	152	151	141	140	139	129	128	127	126
I%	11	16	18	4	2	7	4	4	9	9	8
m/e	125	115	105	104	103	102	101	97	91	90	89
I%	3	2	4	38	27	9	3	2	4	5	3
m/e	85	83	78	77	76	72	71	65	64	63	59
I%	4	2	2	20	4	2	6	5	6	3	6
m/e	57	53	52	51	45	43	41	32	31	29	28
I%	6	2	4	3	6	4	2	2	18	5	4
m/e	27	18									
I%	3	4									

5-(1',2'-Diacetyl)hydrazinopyrido[4,3-d]pyrimidine (199)

m/e	398	397	357	356	355	354	340	339	338	337	314
I%	2	5	2	14	36	2	2	2	7	17	5
m/e	313	312	385	284	283	282	211	210	195	183	182
I%	26	50	5	12	14	7	2	17	2	5	10
m/e	179	169	155	154	153	152	149	142	141	140	129
I%	19	2	4	5	10	12	10	7	5	4	7
m/e	128	114	113	112	104	103	102	99	98	97	85
I%	9	10	5	9	22	14	7	19	6	17	50
m/e	84	83	82	78	77	76	72	71	70	69	63
I%	12	22	7	5	32	10	10	72	16	24	7
m/e	59	58	57	56	55	52	51	50	45	44	43
I%	21	7	**100**	17	29	7	14	5	14	7	**100**
m/e	42	41	39	31	29	28	27	18	17		
I%	7	26	7	30	15	14	12	**100**	25		

5-Ethoxy 2,7-Diphenylpyrido[4,3-d]pyrimidine (195)

m/e	329	328	327	326	314	313	312	300	299	298	284
I%	2	16	54	5	2	21	**100**	13	54	7	11
m/e	283	282	273	270	269	224	197	196	195	180	179
I%	37	14	3	2	2	11	11	65	4	11	15
m/e	170	169	168	154	153	152	149	141	140	139	128
I%	3	13	7	2	5	5	7	4	9	4	2
m/e	105	104	103	102	77	76	55	51	50	39	28
I%	2	13	4	6	6	10	18	3	4	6	7
m/e	18										
I%	82										

4-Styrylpyrimidin-2(1H)-one-5-carboxylic acid (210)

m/e	243	242	241	210	197	196	195	185	169	157	154
I% j	19	77	62	15	46	10	38	15	15	15	14
m/e	149	140	137	136	128	127	121	115	112	108	105
I%	93	7	7	**100**	14	15	12	31	25	31	31
m/e	104	103	102	101	91	80	78	77	76	75	63
I%	15	18	16	6	23	30	28	77	24	20	23
m/e	57	56	55	54	53	52	51	50	44	41	39
I%	37	18	21	8	22	32	52	28	38	48	42
m/e	28	27	26	18	17						
I%	30	23	14	**100**	56						

7-Phenylpyrano[4,3-d]pyrimidin-2,5(3H)-dione (211)

m/e	242	241	240	239	238	213	212	211	210	194	186
I%	2	17	**100**	23	4	7	26	33	2	2	6
m/e	185	184	163	162	158	157	142	141	140	136	135
I%	8	2	2	12	4	4	2	3	2	3	7
m/e	129	128	106	105	104	102	96	92	78	77	76
I%	6	4	6	23	2	5	5	3	6	30	3
m/e	68	53	52	51	50	28	18				
I%	10	5	4	11	4	4	6				

6-Hydroxy-7-phenylpyrido[4,3-d]pyrimidin-2,5(3H,6H)-dione (212)

m/e	257	256	255	241	240	239	238	213	212	211	210
I%	2	3	33	10	17	**100**	23	10	50	47	23
m/e	186	185	184	183	182	169	168	167	157	156	155
I%	13	10	17	8	7	15	18	20	9	8	23
m/e	149	141	140	138	130	129	128	127	124	118	117
I%	36	15	18	10	10	16	23	13	15	13	12
m/e	108	105	104	103	102	101	96	95	94	93	92
I%	16	16	16	10	26	10	21	13	11	12	12
m/e	91	90	84	82	80	79	78	77	76	75	71
I%	10	11	15	18	21	21	21	79	21	16	23
m/e	70	69	67	66	65	57	56	55	54	53	52
I%	16	33	23	18	20	36	17	29	10	24	26
m/e	51	50	45	44	43	42	41	40	39	29	28
I%	49	26	13	13	48	21	59	13	34	66	45
m/e	27	18	17	16							
I%	33	**100**	**100**	75							

6-Amino-7-phenylpyrido[4,3-d]pyrimidin-2,5(3H,6H)-dione (?) (218)

m/e	255	254	253	240	239	238	227	226	214	213	212
I%	14	**62**	69	2	14	2	5	12	9	7	5
m/e	202	184	183	182	171	170	155	154	143	142	141
I%	9	7	6	7	7	6	9	10	7	11	9
m/e	137	132	131	130	129	128	127	116	115	114	109
I%	12	5	9	6	14	12	7	9	14	11	21
m/e	105	104	103	102	101	96	95	94	93	92	91
I%	9	21	25	27	9	7	8	7	4	2	5
m/e	89	88	80	78	77	76	75	74	68	67	66
I%	11	4	11	14	**100**	26	18	14	18	27	14
m/e	65	64	63	62	54	53	52	51	50	44	41
I%	18	17	18	12	4	21	42	91	37	9	14
m/e	40	39	38	37	30	29	28	18			
I%	23	37	16	9	8	16	51	49			

*Mass Spectra of the compounds were run in the Chemistry Dept.

(E) PHARMACOLOGICAL SCREENING RESULTS*:

A selected number of diamides (149) (table I) and pyrido[4,3-d] pyrimidines (152) (table II) were subjected to general pharmacological screening tests in intact mice, dogs and guinea pigs. In particular the compounds were tested for effects on smooth muscles, central nervous system and cardiovascular system. The compounds were also screened as antibacterial agents.

Diamides Screened For Pharmacological Activities

(149)

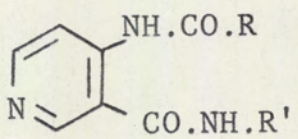
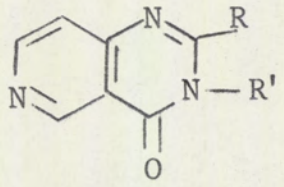


Table I

Compound No.	R	R'
1	C_6H_5	H.
2	C_6H_5	NH_2.
3	C_6H_5	$CH_2.CH_2.OH$
4	3-Pyridyl	NH_2.

Pyrido[4,3-d]pyrimidines Screened For Pharmacological Activities



(152)

Table II

Compound No.	R	R'
1.	CH_3	H.
2.	CH_3	OH.
3.	CH_3	$CH_2.CH_2.OH$.
4.	$2\text{-}NO_2\text{-}C_6H_4$	H.
5.	$4\text{-}CH_3\text{-}C_6H_4$	NH_2
6.	2-Furyl	H.
7.	3-Pyridyl	H.
8.	3-Pyridyl	OH.

a)Anti-bacterial Activity

None of the compound tested showed any significant antimicrobial activity.

b)Effect on smooth muscle:

A dose of 10 mg./kg. of the compound was given to an anaesthetised guinea-pig via intra peritoneal route and the antispasmodic effect obtained was compared with those obtained with acetylcholine, 5-hydroxy-tryptophan, Bradykinin and Histamine. None of the compound thus screened exhibited any

significant antispasmodic effect.

c)Effect on central nervous system

An oral dose of 100 mg./kg. of the compound was given to the mouse and the effects such as behaviour, body temperature, anti-maximal electro-shock, leptazol convulsions, tail clip, phenylquinone induced writhing, recorded. Mice were also injected with 100 mg./kgm. of the compound by the subcutaneous route and the animal subjected to hot plate experiment. The effect on central adrenergic receptor and central cholinergic mechanism was also noted by giving an oral dose of 50 mg./kgm. to mice.

The diamides (149) ($R=C_6H_5$, $R'=H.$, $R=C_6H_5$, $R'=CH_2.CH_2.OH$) and the pyridopyrimidines (152) ($R=CH_3$, $R'=OH$; $R=CH_3$, $R'=CH_2.CH_2.OH$; $R=4\text{-}CH_3\text{-}C_6H_4$, $R'=NH_2$) were devoid of any significant effect on central nervous system.

The pyridopyrimidine (152) ($R=2\text{-}NO_2\text{-}C_6H_4$, $R'=H$) showed moderate activity in a phenyl-quinone induced writhing test. The compound also showed a slight depression on the central adrenergic receptor and effected slightly the behaviour of the mouse.

4-Benzamidonicotinic acid hydrazide (149) ($R=C_6H_5$, $R'=NH_2$) was inactive in most of the central nervous system tests except in the body temperature test, when a hyperthermia of 1.5^{o} C was observed.

The pyridopyrimidine (152) (R=CH_3, R'=H) showed a moderate phenylquinone induced writhing effect and a slight depression in the central adrenergic receptor.

The pyridopyrimidine (152) (R=3-pyridyl, R'=H) exhibited a marked activity in the phenyl-quinone writhing test. A moderate depression in the central adrenergic receptor and a moderate hyperthermia were also noted.

The compounds, 4-nicotinamidonicotinic acid hydrazide (149) (R=3-pyridyl, R'=NH_2) and 3-hydroxy-2-(3-pyridyl)-pyrido [4,3-d] pyrimidin-4(3H)-one (152) (R=3-pyridyl, R'=OH), similarly exhibited a moderate activity in the phenylquinone writhing test.

2-2'-Furylpyrido[4,3-d]pyrimidin-4(3H)-one (152) (R=2-furyl, R'=H) produced a moderate hyperthermia, about half that of Imipramine.

d)Effect on cardio-vascular system

The cardio-vascular tests were carried out by injecting the compound at a dose of 10 mg./kg. intravenously in the anaesthetised dog. All the compounds thus injected, showed a variable fall of 15 mm.-42 mm. in the blood pressure. The pyridopyrimidine (152) (R=3-pyridyl, R'=H) showed a slight reduction in the heart rate, while the pyridopyrimidine (R=CH_3, R'=H) showed a slight increase in the heart rate. The pyridopyrimidine (152 (R=2-furyl, R'=H) exhibited an increased

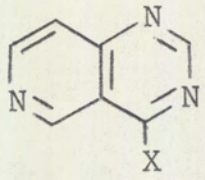
depth in the respiration. The pyridopyrimidine (152) ($R=CH_3$, $R'=OH$) exhibited a slight reduction in the carotid occlusion reflexes.

The range of compounds prepared and their pharmacological effects could not at this stage form the basis of a detailed discussion of structure activity relationship.

*The Biological testings of the compounds were carried out by Allen and Hanburys Limited, Ware, Hertfordshire.

PART 4 APPENDIX

(A) KNOWN PYRIDO[4,3-d]PYRIMIDINES



Compound	X	References
1. Pyrido[4,3-d]pyrimidine	H	15.
2. 4-Chloropyrido[4,3-d]pyrimidine	Cl	15.
3. 4-Hydroxypyrido[4,3-d]pyrimidine	OH	14,15.
4. 4-Thiopyrido[4,3-d]pyrimidine	SH	14.

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(C) NEW COMPOUND FORMULA INDEX

C	H	N	O	Cl	S		
19	12	3	-	1	-	5-Chloro-2,7diphenylpyrido[4,3-d] pyrimidine	141
19	13	3	1	-	-	2,7-Diphenylpyrido[4,3-d]pyrimidin -5(5H)-one	136
19	13	3	-	-	1	2,7-Diphenyl-5-thiopyrido-[4,3-d] pyrimidine	140
19	13	3	2	-	-	6-Hydroxy 2,7-diphenylpyrido-[4,3-d] pyrimidin-5(6H)-one	137
19	14	2	2	-	-	2-Phenyl-4-styrylpyrimidine-5- carboxylic acid	135
19	14	4	1	-	-	6-Amino-2,7-diphenylpyrido[4,3-d] pyrimidin-5(6H)-one	138
19	15	5	-	-	-	5-Hydrazino-2,7-diphenylpyrido [4,3-d] pyrimidine	141
19	16	2	3	-	-	Ethyl-4-1'-Naphthylamidonicotinate .	115
19	17	3	3	-	-	4-(1'Naphthylamido-N-(2-hydroxyethyl) -nicotinamide	133
20	15	3	1	-	-	6-Methyl 2,7-diphenylpyrido[4,3-d] pyrimidin-5(6H)-one	139
21	17	3	1	-	-	5-Ethoxy 2,7-diphenylpyrido[4,3-d] pyrimidine	143
23	18	4	3	-	-	6-Diacetylamido-2,7-diphenylpyrido [4,3-d] pyrimid-5(6H)-one	138
23	19	5	2	-	-	5-(1'-2'-Diacetyl)hydrazino pyrido [4,3-d] pyrimidine	142

*Correct mol.wt. from mass spectrum. Incorrect microanalysis

The Synthesis of Pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones from 4-Aminonicotinic Acid

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The Synthesis of Pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones from 4-Aminonicotinic Acid

By A. G. Ismail and D. G. Wibberley, Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham 4

Treatment of either a pyrido[4,3-*d*][1,3]oxazin-4-one or an ethyl 4-amidonicotinate with amines yields a 4-amidonicotinamide which may be cyclised by longer contact with the amine, or by heat, to give a pyrido[4,3-*d*]-pyrimidin-4(3*H*)-one. Some typical infrared and nuclear magnetic resonance spectra are discussed.

OVER two hundred tetrahydro- and octahydro-pyrido-[4,3-*d*]pyrimidines [1] have been synthesised as potential diuretic, antirheumatic, and bacteriostatic drugs, but only four fully aromatic pyrido[4,3-*d*]pyrimidines [2,3] are known. The parent compound has been prepared [3] by treatment of 4-formamidopyridine-3-aldehyde with methanolic ammonia at 100° and pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (VI; $R^1 = R^2 = H$) (4-hydroxypyrido[4,3-*d*]-pyrimidine) by heating either ethyl 4-aminonicotinate [2] or 4-aminonicotinamide [3] with formamide. The 4-hydroxy-compound has been converted into the 4-chloro- [2,3] and the 4-mercapto-pyrido[4,3-*d*]pyrimidine.[2] A restricting factor in the synthesis of this ring system is the length of any route to suitable intermediates bearing either the pyridine or pyrimidine rings. For example 4-amino-nicotinaldehyde, which is potentially the most versatile starting material for the preparation of 1-, 2-, or 3-substituted derivatives, has been prepared in seven stages from a commercially available compound.[3]

4-Aminonicotinic acid (I), the starting material for two routes which we investigated, was best prepared from 3-methyl-4-nitropyridine 1-oxide by oxidation to 4-nitronicotinic acid 1-oxide [4] followed by catalytic reduction.[5] We have previously demonstrated that pyrido-[3,2-*d*][1,3]oxazin-4-ones may be converted into pyrido-[3,2-*d*]pyrimidin-4(3*H*)-ones by treatment with amines. The parallel reaction of 2-methylpyrido[4,3-*d*][1,3]oxazin-4-one (II; $R^1 = Me$) with ammonia, hydroxylamine, or aniline has now been shown to yield the corresponding pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones (VI; $R^1 = Me$). The method was not as successful as that in the [3,2-*d*]-series, however, owing to the rapid hydrolysis of the pyrido-oxazine (II; $R^1 = Me$) by moisture. A further limitation was that in the attempted preparation of the pyrido-oxazine (II; $R^1 = Ph$), by the action of acetic anhydride on 4-benzamidonicotinic acid, the 2-methyl-pyrido-oxazine (II; $R^1 = Me$) was produced.

[1] F. Hoffmann-La Roche and Co., B.P. 776,335 (*Chem. Abs.*, 1957, **51**, 18,015); J. T. Plati and W. Wenner, U.S.P. 2,802,826 (*Chem. Abs.*, 1958, **52**, 3874); G. Ohnacker, U.S.P. 3,186,991 (*Chem. Abs.*, 1965, **63**, 4312); G. Ohnacker, U.S.P. 3,248,395 (*Chem. Abs.*, 1966, **65**, 3888.

[2] E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Amer. Chem. Soc.*, 1960, **82**, 6058.

[3] W. L. F. Armarego, *J. Chem. Soc.*, 1962, 4094.

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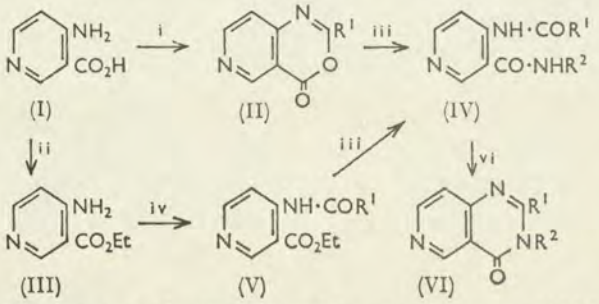
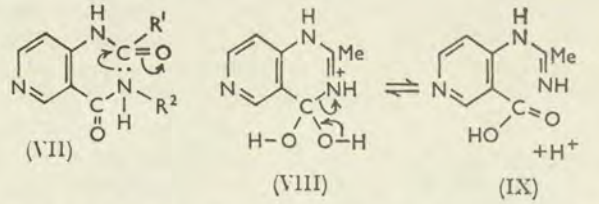
The di-amides (IV) are isolable intermediates in reactions of this type [6] and in view of the above difficulties we investigated the alternative route (I) ⟶ (III) ⟶ (V) ⟶ (IV) to these compounds. 4-Amidonicotinates (V) were produced in excellent yields from the amino-ester (III) and the appropriate acyl chloride in pyridine. Treatment of these amido-esters (V) with amines then yielded the required 4-amidonicotinamides (IV). Certain



Reagents: i, Ac_2O; ii, EtOH–H_2SO_4; iii, R^2NH_2; iv, R^1COCl; v, heat or R^1NH_2.

of these di-amides cyclised to the pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones (VI) simply by prolonged contact with the amine. Hydroxylamine, for example, gave cyclic hydroxamic acids (VI; $R^2 = OH$) directly with six different 4-amidonicotinates (cf. Table 4) and ethyl 4-acetamidonicotinate gave the pyrido[4,3-*d*]pyrimidines (VI; $R^1 = Me$) directly with ammonia, hydroxylamine, and ethanolamine. The bulk of the remaining 4-amido-nicotinates investigated yielded the 4-amidonicotin-amides (IV) on treatment with amines.

We suggest, by analogy with the [3,2-*d*]-series that the nucleophilic attack (VII) of the nitrogen of the nicotin-amido-group on the carbonyl carbon of the 4-amido group is, in general, the rate-determining step in the cyclisation to the pyrido[4,3-*d*]pyrimidines (VI).



Factors increasing the electrophilicity of the attacked carbonyl group should therefore favour the reaction. This accounts for the easier cyclisations observed in the current investigation compared with the [3-2-*d*]-series, since the electron density on an exocyclic 4-amido-nitrogen atom (and hence on the adjacent carbonyl carbon) is lower than that on a 3-amido-nitrogen atom.[7] Some evidence of a dual mechanism, however, is provided by the fact that ease of cyclisation was not always directly related to the electron-withdrawing properties of the group R^1 (cf. Table 4).

The structure of the products from the action of the amines on either the pyrido-oxazine or the amido-nicotinates was most rapidly determined from their infrared spectra. The 4-amidonicotinates (V) were all soluble in chloroform and in this solvent showed a single N–H stretching absorption at 3300—3250 cm.$^{-1}$, a single, but often broad, band in the region 1710—1685 cm.$^{-1}$ (amide I and ester C=O), and another strong band at 1510—1505 cm.$^{-1}$ (amide II). The infrared spectra of the di-amides (IV) (Nujol) showed the two N–H bands in the region 3450—3050 cm.$^{-1}$, two separate amide I bands in the region 1700—1640 cm.$^{-1}$, and a single amide II band near 1520 cm.$^{-1}$, sharper, and less intense than that previously found for the isomeric 3-amidopicolin-amides. All the pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones gave a strong carbonyl band at about 1695 cm.$^{-1}$ and those with a group other than hydrogen or amino in the 3-position showed no N–H or amide absorption.

The n.m.r. spectra of a selection of the pyrido-pyrimidines (VI) in trifluoroacetic acid demonstrated the π-deficient character of the ring at the 5-, 7-, and 2-positions. In pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (VI; $R^1 = R^2 = H$), for example, the 5-proton gave a singlet at τ 0·11 and the 2-proton a singlet at 0·81; the doublets of the AB system of the 7- and 8-protons occurred at 0·8 and 1·48, respectively. This simple first order splitting pattern of the protons of the pyridine ring was repeated in all the 2- and 3-substituted compounds examined, with very closely similar chemical shift positions in many cases (cf. Table 1).

Previous workers [2,3] have commented on the particular instability of the [4,3-*d*]-ring-system and Armarego [3] has shown that the parent compound commences ring opening to 4-aminopyridine-3-aldehyde after only 3 minutes at pH 2·07. We believe that our attempts to effect reactions of the substituents in the pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones failed because of a similar instability. Thus 3-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one could not be converted into the 4-chloro-compound under conditions successful with isomeric systems.[8] 3-Amino-2-phenylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (VI; $R^1 = Ph$, $R^2 = NH_2$) did not yield the pyridopyrimidine (VI; $R^1 = Ph$, $R^2 = H$) on treatment with nitrous acid, and attempted condensation of 2-methylpyrido[4,3-*d*]-pyrimidin-4(3*H*)-one with benzaldehyde failed. 4-Aminonicotinic acid was isolated both in the attempted oxidation of this same compound (VI; $R^1 = Me$, $R^2 = H$) and in several attempted cyclisations of the di-amides (IV). Ring opening (VIII) and hydrolysis, presumably of the amidine (IX), to 4-aminonicotinic acid was rapidly accomplished by warming the pyridopyrimidine (VI; $R^1 = Me$, $R^2 = H$) with dilute hydrochloric acid.

EXPERIMENTAL

Infrared spectra were determined with a Unicam SP 200 spectrophotometer and n.m.r. spectra with a Varian A-60A

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[7] A. Albert in 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York and London, 1963, vol. I, p. 31.

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TABLE 1

Nuclear magnetic resonance spectra[a] of pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones (VI) in trifluoroacetic acid; chemical shifts (τ values) and coupling constants (J. in c./sec. in parentheses)

		Protons in pyridine ring			
R^1	R^2	5-H	7-H	8-H	Protons and substituents in pyrimidine ring
H	H	0·11s	0·8d (7)	1·48d (7)	0·81s (2-*H*)
Me	H	0·15s	0·8d (7)	1·47d (7)	6·94s (2-CH_3)
Me	OH	0·14s	0·92d (7)	1·48d (7)	6·92s (2-CH_3)
Me	$[CH_2]_2OH$	0·17s	0·87d (7)	1·52d (7)	6·78s (2-CH_3), 5·08s (3-CH_2CH_2OH)
OH	H	0·48s	1·14d (7)	2·06d (7)	None
Ph	H	0·17s	0·89d (7)	1·5d (7)	1·6—2·35m (2-C$_6H_5$)
Ph	OH	0·11s	0·92d (7)	1·52d (7)	1·71—1·97m and 2·15—2·50m (2-C$_6H_5$)
Ph	NH_2	0·1s	0·91d (7)	1·52d (7)	1·85—2·48m (2-C$_6H_5$)
4-Me·C_6H_4	H	0·18s	0·88d (7)	1·48d (7)	1·78d (8) and 2·40d (8) (A_2B_2 split of Me·C$_6H_4$), 7·41s (CH_3)
4-Me·C_6H_4	OH	0·15s	0·95d (7)	1·58d (7)	1·92d (8) and 2·45d (8) (A_2B_2 split of Me·C$_6H_4$), 7·46s (CH_3)
4-Me·C_6H_4	NH_2	0·09s	0·8d (7)	1·47d (7)	1·98d (8) and 2·4d (8) (A_2B_2 split of Me·C$_6H_4$), 7·42s (CH_3)
2-NO_2·C_6H_4	H	0·52s	1·35d (7)	2·0d (7)	1·9—2·1m (1 proton) and 2·33—2·57m (3 protons) (NO_2·C$_6H_4$)
2-NO_2·C_6H_4	NH_2	0·61s	1·32d (7)	2·05d (7)	1·9—2·2m (1 proton) and 2·4—2·9m (3 protons) (NO_2·C$_6H_4$)

[a] Measured at 60 Mc./sec. s = Singlet, d = doublet, m = multiplet.

TABLE 2

4-Amidonicotinates (V)

	Reaction time	Yield		$\nu_{max.}$ in $CHCl_3$ (cm.$^{-1}$)				Found (%)				Required (%)		
R^1	(min.)	(%)	M. p.	N–H	Ester and amide I	Amide II	Others	C	H	N	Formula	C	H	N
Me	20	55	109—110°	3300	1705—1695	1510		57·6	5·9	13·3	$C_{10}H_{12}N_2O_3$	57·7	5·8	13·5
Ph	60	72	143—144	3300	1690	1510		66·9	5·2	10·3	$C_{15}H_{14}N_2O_3$	66·7	5·2	10·4
2-NO_2·C_6H_4	60	69	128—129	3250	1710	1510	1540 and 1355 (NO_2)	57·2	3·9	13·2	$C_{15}H_{13}N_3O_5$	57·2	4·1	13·3
4-Me·C_6H_4 ...	60	89	151—152	3250	1690	1505		67·6	5·6	10·0	$C_{16}H_{16}N_2O_3$	67·6	5·7	9·9
1-Naphthyl	45	80	149—150	3300	1690	1505		72·4	5·3	8·9	$C_{19}H_{16}N_2O_3$	72·6	5·1	8·9
2-Furyl	45	94	179—180	3300	1690	1510		59·9	4·7	10·9	$C_{13}H_{12}N_2O_4$	60·0	4·7	10·8
3-Pyridyl ...	35	67	148—149	3250	1685	1510		62·1	4·6	15·4	$C_{14}H_{13}N_3O_3$	62·2	4·5	15·5

TABLE 3

4-Amidonicotinamides (IV)

					$\nu_{max.}$ in Nujol (cm.$^{-1}$)				Found (%)				Required (%)		
R^1	R^2	Reaction conditions	Yield (%)	M. p.	N–H	Amide I	Amide II	Others	C	H	N	Formula	C	H	N
2-NO_2·C_6H_4	H	7 days, 20°	85	249—251°	3420 3200	1695 1670	1510	1540 and 1355 (NO_2)	54·4	3·6	19·5	$C_{13}H_{10}N_4O_4$	54·5	3·5	19·6
4-Me·C_6H_4	H	24 ,, 20	94	271—273	3250 3075	1680 1640	1505		65·8	5·3	16·3	$C_{14}H_{13}N_3O_2$	65·9	5·1	16·5
1-Naphthyl	H	4 ,, 20	90	240—241	3450 3150	1690 1670 1640	1510		69·9	4·7	13·8	$C_{17}H_{13}N_3O_2$	70·1	4·5	14·4
Me	NH_2	4 ,, 20	73	167—168	3300 3175	1680 1640			49·7	5 1	28·9	$C_8H_{10}N_4O_2$	49·5	5·2	28·8
Ph	NH_2	1 ,, 20	83	279—281	3200 3125	1700 1640	1520		60·7	4·8	22·1	$C_{13}H_{12}N_4O_2$	60·9	4·7	21·9
2-NO_2·C_6H_4	NH_2	14 hr., 20	83	239—241	3275 3100	1685 1655	1505	1540 and 1340 (NO_2)	51·5	3·8	23·7	$C_{13}H_{11}N_5O_4$	51·8	3·7	23·3
4-Me·C_6H_4	NH_2	16 hr., 20	96	234—236	3200 3075	1685 1640	1520		62·4	5·2	20·5	$C_{14}H_{14}N_4O_2$	62·2	5·2	20·7
1-Naphthyl	NH_2	14 ,, 20	91	239—240	3325 3150	1695 1650	1520		66·5	4·8	18·2	$C_{17}H_{14}N_4O_2$	66·7	4·6	18·3
2-Furyl	NH_2	12 ,, 20	95	231—233	3250 3125	1700 1640	1520		53·6	4·3	22·7	$C_{11}H_{10}N_4O_3$	53·6	4·1	22·8
3-Pyridyl	NH_2	16 ,, 20	92	222—224	3200 3100	1700 1660	1520		56·2	4·4	27·1	$C_{12}H_{11}N_5O_2$	56·0	4·3	27·2
Ph	$[CH_2]_2OH$	1 day, 78	80	214—215	3300 3150	1685 1650	1520		63·1	5·4	14·5	$C_{15}H_{15}N_3O_3$	63·2	5·3	14·7
1-Naphthyl	$[CH_2]_2OH$	3 days, 78	33	203—204	3450	1680	1510		68·2	5·1	12·5	$C_{19}H_{17}N_3O_3$	68·1	5·1	12·5

TABLE 4

Pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones (VI)

R¹	R²	Reaction conditions	Yield (%)	M. p.	$\nu_{max.}$ in Nujol (cm.⁻¹) Ring C=O	Others	Found (%) C	H	N	Formula	Required (%) C	H	N
Me	H[a]	NH_3 3 days, 20°	89	309—310°	1695	1505 (amide II)	59·8	4·2	26·1	$C_8H_7N_3O$	59·6	4·4	26·1
2-Furyl	H	NH_3 14 ,, 20°	99	335—337	1700	1505 (amide II)	62·2	3·7	19·9	$C_{11}H_7N_3O_2$	62·0	3·3	19·7
3-Pyridyl	H	NH_3 14 ,, 20°	100	304—306	1715	1505 (amide II)	64·4	3·2	25·2	$C_{12}H_8N_4O$	64·6	3·2	25·1
Phenyl	H	Fusion 15 min., 220°	67	284—286	1700	1505 (amide II)	70·0	4·2	19·0	$C_{13}H_9N_3O$	69·9	4·1	18·8
2-NO_2·C_6H_4	H	Fusion 20 ,, 235°	92	275—277	1700, 1690	1535, 1360 (NO_2) 1505 (amide II)	58·0	2·9	20·9	$C_{13}H_8N_4O_3$	58·2	3·0	20·9
4-Me_2·C_6H_4	H	Fusion 20 ,, 255°	83	296—299	1680	3150 (N–H) 1520 (amide II)	70·8	4·6	17·7	$C_{14}H_{11}N_3O$	70·9	4·7	17·7
1-Naphthyl	H	Fusion 30 ,, 240°	89	326—327	1700	1510 (amide II)	74·6	4·2	15·6	$C_{17}H_{11}N_3O$	74·7	4·1	15·4
Me	OH[a,b]	NH_2OH 24 hr., 20°	63	244—247	1695	2600—2300 (O–H)	54·1	3·8	23·9	$C_8H_7N_3O_2$	54·2	4·0	23·7
Ph	OH	NH_2OH 48 ,, 20°	88	260—262	1695		65·3	3·9	17·3	$C_{13}H_9N_3O_2$	65·3	3·8	17·5
4-Me_2·C_6H_4	OH	NH_2OH 48 ,, 20°	93	279—281	1700	2600—2400 (O–H)	66·4	4·4	16·7	$C_{14}H_{11}N_3O_2$	66·5	4·4	16·6
1-Naphthyl	OH	NH_2OH 12 ,, 20°	72	258—262	1700	2700—2550 (O–H)	70·5	3·9	14·6	$C_{17}H_{11}N_3O_2$	70·6	3·8	14·5
2-Furyl	OH	NH_2OH 48 ,, 20°	61	319—321	1705		57·9	3·2	18·4	$C_{11}H_7N_3O_3$	57·7	3·1	18·3
3-Pyridyl	OH	NH_2OH 48 ,, 20°	77	292—294	1680		59·8	3·3	23·2	$C_{12}H_8N_4O_2$	60·0	3·4	23·3
Ph	NH_2	Fusion 30 min., 210°	80	192—194	1695	3275 and 3125 (N–H)	65·4	4·4	23·5	$C_{13}H_{10}N_4O$	65·5	4·2	23·5
2-NO_2·C_6H_4	NH_2	Fusion 45 ,, 220°	83	221—223	1700	3300 and 3175 (N–H) 1535 and 1360 (NO_2)	55·1	3·5	24·6	$C_{13}H_9N_5O_3$	55·1	3·2	24·7
4-Me_2·C_6H_4	NH_2	Fusion 15 ,, 230°	82	161—162	1695	3275 and 3150 (N–H)	66·7	5·0	22·1	$C_{14}H_{12}N_4O$	66·7	4·8	22·2
1-Naphthyl	NH_2	Fusion 25 ,, 220°	91	206—208	1680	3300 and 3250 (N–H)	70·8	4·3	19·3	$C_{17}H_{12}N_4O$	70·8	4·2	19·4
2-Furyl	NH_2	Fusion 20 ,, 230°	40	234—235	1690	3250 and 3125 (N–H)	58·0	3·8	24·5	$C_{11}H_8N_4O_2$	57·8	3·5	24·6
Me	$[CH_2]_2OH$	$NH_2[CH_2]_2OH$ 6 days, 78°	74	171—172	1680	3200—3100 (O–H)	58·5	5·5	20·8	$C_{10}H_{11}N_3O_2$	58·5	5·4	20·5
Ph	$[CH_2]_2OH$	Fusion 20 min., 230°	55	173—174	1680	3250—3150 (O–H)	67·3	5·0	15·7	$C_{15}H_{13}N_3O_2$	67·4	4·9	15 7
H	H[c]		40	289—290	1690	1525 (amide II)	57·3	4·0	28·8	$C_7H_5N_3O$	57·1	3·4	28·6
OH	H[d]		44	360	1710—1700	3200—2750 (N–H and O–H)	51·5	3·2	26·0	$C_7H_5N_3O_2$	51·6	3·1	25·8

[a] Identical with products prepared from the pyrido-oxazine (II; R¹ = Me). [b] All 3-OH compounds gave a wine-red colour with $FeCl_3$. [c] By method of E. C. Taylor R. J. Knopf, Y. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Amer. Chem. Soc.*, 1960, **82**, 6058. [d] By fusion of ethyl 4-aminonicotinate (0·8 g.) with urea (0·3 g.) for 1 hr. at 170°.

spectrometer, with tetramethylsilane as an internal standard. Compounds obtained by more than one route were deemed identical when their mixed m. p. was undepressed and their infrared spectra were superimposable. Quoted fusion temperatures are those of an external silicone bath.

4-Aminonicotinic acid (I), m. p. 336—337° (decomp.), $\nu_{max.}$ (Nujol) 3325 and 3200 (N–H), 2750—2550 (bonded O–H), and 1690—1680 (acid C=O), was prepared by way of 4-nitronicotinic acid 1-oxide.[4,5]

Ethyl 4-aminonicotinate (III), m. p. 106—107°, $\nu_{max.}$ ($CHCl_3$) 3500, 3400, and 3200 (N–H), and 1695 (ester C=O) was prepared by the method of Taylor *et al.*[2] but with a reflux time of 4 days.

Ethyl 4-Acetamidonicotinate (V; R^1 = Me).—(*a*) Ethyl 4-aminonicotinate (1·0 g.), acetyl chloride (1·0 ml.), and pyridine (3·0 ml.) were heated together under reflux for 20 min. The mixture was cooled and diluted with water, and the *amido-ester* was collected and crystallised from light petroleum (b. p. 100—120°). For physical constants of this, and other 4-amidonicotinates prepared by a similar method, but crystallised from ethanol, see Table 2.

(*b*) Ethyl 4-aminonicotinate (1·0 g.) and acetic anhydride (10 ml.) were heated together under reflux for 1 hr. The excess of anhydride was removed under reduced pressure, and the residue was triturated with light petroleum (b. p. 100—120°) to yield the amido-ester.

4-Benzamidonicotinic Acid.—Treatment of 4-aminonicotinic acid with benzoyl chloride and pyridine under the conditions described above for the 4-acetamido-ester yielded the *amido-acid* (62%), m. p. 299—300° (Found: C, 64·3; H, 4·2; N, 11·8. $C_{13}H_{10}N_2O_3$ requires C, 64·5; H, 4·1; N, 11·6%), $\nu_{max.}$ (Nujol) 3150 (N–H), 1700 (acid C=O), 1645 (amide I), and 1515 (amide II) $cm.^{-1}$.

2-Methylpyrido[4,3-d][1,3]*oxazin-4-one* (II; R^1 = Me).—(*a*) Treatment of 4-aminonicotinic acid with acetic anhydride under the conditions described by Littel and Allen,[9] but with direct crystallisation of the crude product from ethyl acetate rather than the chromatographic separation, yielded the pyrido-oxazine (64%), m. p. 158—159°, $\nu_{max.}$ ($CHCl_3$), 1780 ('vinyl ester type' C=O), 1650 (C=N), and 1250 (C–O) $cm.^{-1}$.

(*b*) Similar treatment of both 4-acetamidonicotinic acid [10] and 4-benzamidonicotinic acid gave the same pyridoxazine (II; R^1 = Me). Hydrolysis back to 4-acetamidonicotinic acid occurred when the pyridoxazine was stirred with water for 10 min. or exposed to the air for a few hours.

2-Methylpyrido[4,3-d]*pyrimidin-4*(3H)*-one*(*4-Hydroxy-2-methylpyrido*[4,3-d]*pyrimidine* (VI; R^1 = Me, R^2 = H).—2-Methylpyrido[4,3-*d*][1,3]oxazin-4-one (0·4 g.) was added to ammonia (5·0 ml.; *d* 0·88) and the suspension of the precipitated amide was stirred until solution was complete (10 hr.). The solution was evaporated to yield the *pyrido-pyrimidine* (0·38 g., 77%), m. p. 308—310° (from acetic acid), identical with a sample prepared by the action of ammonia on ethyl 4-acetamidonicotinate (cf. Table 4 for analysis and $\nu_{max.}$).

2-Methyl-3-phenylpyrido[4,3-d]*pyrimidin-4*(3H)*-one* (VI; R^1 = Me, R^2 = Ph).—The 2-methylpyrido-oxazine (0·16 g.) and aniline (0·25 ml.) were heated together in an open tube at 190° for 45 min. The cooled melt was then triturated with benzene and the extract concentrated to yield the *pyridopyrimidine* (0·08 g., 29%), m. p. 200—202° (from acetic acid) (after sublimation at 170°/2·5 mm.) (Found: C, 70·9; H, 4·7; N, 18·0. $C_{14}H_{11}N_3O$ requires C, 70·9; H, 4·7; N, 17·7%), $\nu_{max.}$ ($CHCl_3$) 1695 $cm.^{-1}$ (C=O). The residue insoluble in benzene was 4-aminonicotinic acid (0·1 g.).

3-Hydroxy-2-methylpyrido[4,3-d]*pyrimidin-4*(3H)*-one* (VI; R^1 = Me, R^2 = OH).—Hydroxylamine hydrochloride (0·28 g.) was added to a solution of sodium (0·07 g.) in ethanol (10 ml.). The precipitated sodium chloride was removed and the 2-methylpyrido-oxazine (0·32 g.) added to the filtrate. The mixture was stirred for 28 hr. and the precipitated pyridopyrimidine (0·2 g., 57%) collected. The product was identical with a sample prepared by the action of hydroxylamine on ethyl 4-acetamidonicotinate (cf. Table 4 for analysis and $\nu_{max.}$).

General Procedure for the Preparation of Pyrido[4,3-d]*-pyrimidin-4*(3H)*-ones. Reaction of the 4-Amidonicotinates with* (a) *Ammonia.*—A suspension of the 4-amidonicotinate (0·5 g.) in ethanol (20 ml.) was saturated with ammonia at 0° and the solution set aside in a stoppered flask at room temperature for the stated time. Evaporation of the solution or suspension yielded either the *4-amidonicotinamide* (IV; R^2 = H) (Table 3) or the *pyrido*[4,3-d]*pyrimidin-4*(3H)*-one* (VI; R^2 = H) (Table 4). The di-amides were cyclised to the *pyridopyrimidines* by heat at the m. p. for the stated time.

(b) *Hydroxylamine.*—The 4-amidonicotinate was set aside at room temperature for the stated time with a solution prepared [11] from hydroxylamine hydrochloride and sodium hydroxide in aqueous ethanol. The pyridopyrimidine (VI; R^2 = OH) (Table 4) was isolated by acidification of the resulting pasty suspension. The cyclic hydroxamic acid was purified by sublimation under reduced pressure below the m. p., followed by crystallisation. No pyridopyrimidine was obtained when ethyl 4-(2-nitrobenzamido)nicotinate and hydroxylamine were set aside at room temperature for 1 week.

(c) *Hydrazine.*—A mixture of the 4-amidonicotinate (1·5 g.), hydrazine hydrate (3·0 ml.) and ethanol (5·0 ml.) was stirred at room temperature for the stated time to yield the *4-amidonicotinic acid hydrazide* (IV; R^2 = NH_2) (Table 3). The hydrazides were cyclised to the *pyridopyrimidines* (VI; R^2 = NH_2) (Table 4) by heat at the m. p. for the stated time and the products purified by crystallisation. 4-Acetamido- (IV; R^1 = Me, R^2 = NH_2) and 4-nicotinamido-nicotinic acid hydrazide (IV; R^1 = 3-pyridyl R^2 = NH_2) could not be cyclised by heating at their m. p.s. for 1 hr., heating under reflux in the presence of an excess of hydrazine, heating with phosphoryl chloride, or heating with polyphosphoric acid.

(d) *Ethanolamine.*—A solution of the 4-amidonicotinate (1·0 mole) and ethanolamine (5·0 mole) in ethanol was heated under reflux for the stated time. The *4-amido-nicotinamide* (IV; R^2 = $[CH_2]_2OH$) (Table 3) or *pyrido-pyrimidine* (VI; R^2 = $[CH_2]_2OH$) (Table 4) was isolated by evaporation of the solution. *3-(2-Hydroxyethyl)-2-phenyl-pyrido*[4,3-d]*pyrimidin-4*(3H)*-one* was prepared by heating the corresponding di-amide (IV; R^1 = Ph, R^2 = $[CH_2]_2OH$) at 225° for 20 min.

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