Synthesis and Properties of Pyrido[1,2-a]pyrimidinium Salts of Potential Biological Activity.

A thesis presented by

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In a moment up they turned
Wide the celestial soil, and saw beneath
The originals of Nature in their crude
Conception; sulphurous and nitrous foam
They found, they mingled, and, with subtle art
Concocted and adjusted, they reduced
To blackest grain, and into store conveyed.

Milton

Paradise Lost

To my parents

SYNTHESIS AND PROPERTIES OF PYRIDO[1,2-a]PYRIMIDINIUM SALTS OF POTENTIAL BIOLOGICAL IMPORTANCE

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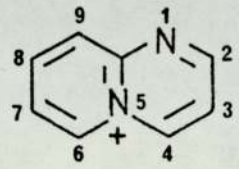
INTRODUCTION

1. MEDICINAL CHEMISTRY

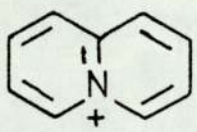
1.1 General

No compounds containing the fully aromatic pyrido[1,2-a]pyrimidinium nucleus (1) have previously been evaluated for biological activity.



(1)

However, several compounds containing the closely related quinolizinium nucleus (2) and derivatives of 4H-pyrido[1,2-a]-pyrimidin-4-ones (3) have been found to have physiological and anti-parasitic properties.



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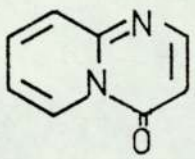

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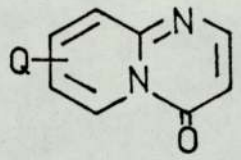
1.2 Physiological Activity

Compounds of the type (4), where Q represents from one to three lower alkyl, hydroxy, lower alkanoylamino, lower alkylamino, benzyl, lower alkoxy, lower alkylmercapto, lower alkylsulphinyl, lower alkylsulphonyl or trihalomethyl substituents at positions 6,7,8 or 9, have been reported by Sterling Drug Incorporated[1] to have anti-inflammatory

properties. These compounds exhibited greater than 30% inhibition in carrageenin-induced local foot oedema in fasted rats when administered



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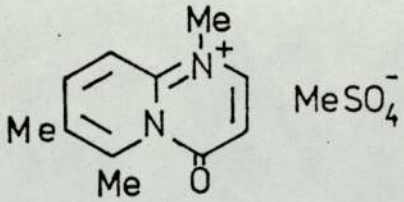
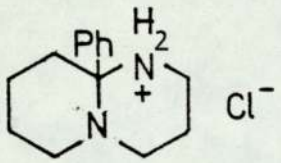


(5)

orally at dose levels in the range 25–200 mg/kg. The quaternary salt (5) showed similar activity at a dose level of 200 mg/kg. This same dose level of the unsubstituted compound (3) produced insignificant inhibition. The saturated salt (6) has also been reported to have anti-inflammatory activity[2], and has been formulated in tablet form.



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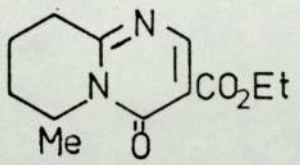
A group working at the Semmelweis University Medical School, Budapest[3,4,5], have synthesised compounds (7), (8) and (9) and many similar compounds based on both the fully unsaturated and partially saturated forms of the 6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one nucleus. Compounds (7), (8) and (9) were found to have analgesic activity[6]. 1,6-Dimethyl-3-carbethoxy-4-oxo-6,7,8,9-tetrahydropyrido-[1,2-a]pyrimidinium methylsulphate (9) (code number: MZ-144) was found to be the most effective, but was thought to exist as the free base (10) *in vivo*, from studies involving varying the pH *in vitro*.



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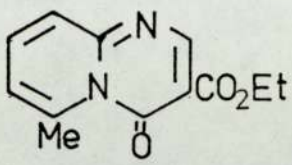

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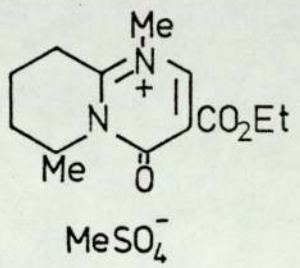

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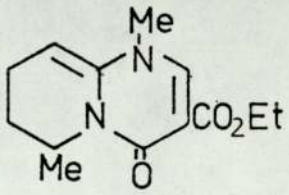

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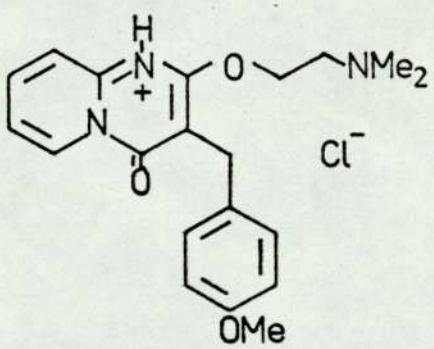
Preliminary clinical trials on 1000 patients have shown that MZ-144 (9) is a therapeutically useful, non-narcotic, analgesic, effective when administered orally as capsules containing 0.15 - 0.3 g.[7]

When administered at relatively large doses and mainly by the parenteral route, MZ-144 (9) exerts a slight hypnotic action, small doses of the compound are mildly sedative.[8]

A strong and long-lasting potentiation of Venobarbital (Inactin) anaesthesia, following administration of the compound was noted in rodents, carnivores and monkeys. Regarding this effect, a potentiation of extraordinary degree between MZ-144 (9) and narcotic analgesics could be established. Anaesthesia potentiated by MZ-144 (9) is claimed to permit the performance of serious surgical

interventions both on rodents and monkeys and is readily antagonised by Redimyl. In contrast to the major analgesics, MZ-144 (9) is claimed not to influence respiration, in fact, when combined with morphine, it antagonises the respiratory depressant action of morphine to a significant extent. Its anti-inflammatory action is similar to that of minor analgesics. The group has also investigated the metabolic breakdown of MZ-144 (9) by ^{14}C labelling[9].

Pruss and Hidalgo[10] have synthesised 2-(2-dimethylaminoethoxy)-3-(4-methoxybenzyl)-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (11) and claim it to be a potent histamine releaser. Oral and intravenous administration to non-anaesthetised dogs induced salivation, vomiting, violent propulsive defecation and seizures. Intravenous doses of 1 mg/kg in anaesthetised dogs produced a pronounced fall in arterial pressure and increased respiration. The hypotension in both



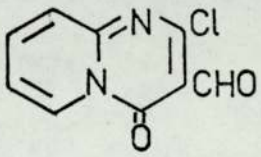
(11)

anaesthetised and non-anaesthetised dogs was associated with a fall in peripheral resistance. Histamine release by (11) was confirmed by cross tachyphylaxis of the vasodepresser responses to the compound and by increased plasma levels of histamine.

Gupta, Bhaduri, Khanna and Mukherjee[11] have found hypoglycemic activity in 4H-pyrido[1,2-a]pyrimidin-4-ones (3) substituted at the 3 position.

They claim that the activity is associated with the cyclic amidine moiety simulated in their molecular structure.

Antihypertensive and monoamine oxidase inhibitory activity has been found in compounds (13 - 21) derived from 2-chloro-3-formyl-4H-pyrido-[1,2-a]pyrimidin-4-one (12)[12].



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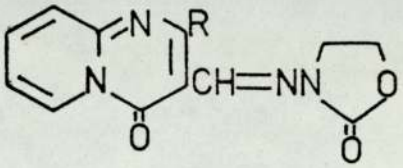
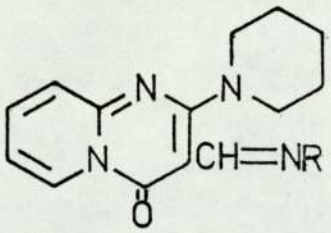


(13) R = -N

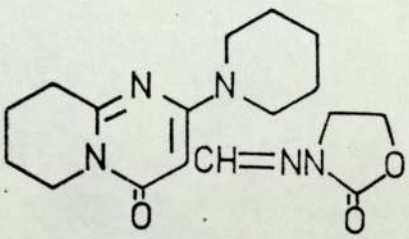
(14) R = -N

(15) R = $-NEt_2$



(16) R = -N

(17) R = -N



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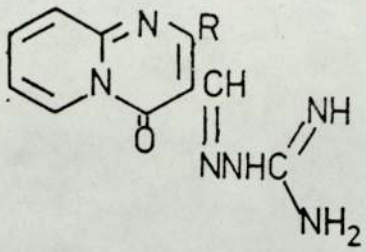
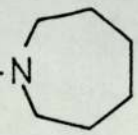
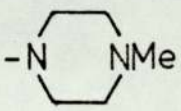
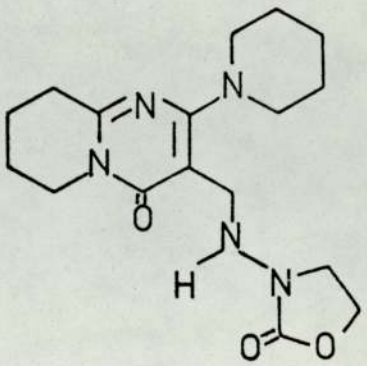


(19) R = 

(20) R = 



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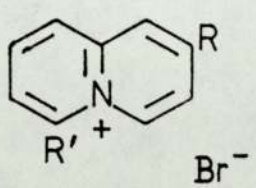
1.3 Antiparasitic Activity

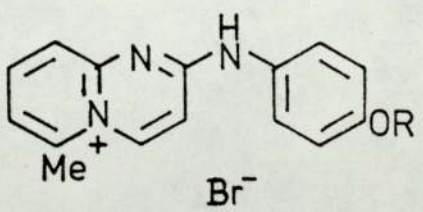
A new class of anthelmintic agents has been found in the derivatives of quinolizinium (2) bromide[13,14]. A series of compounds of type (22) has been screened for prevention of lung invasion by the larvae of Ascaris Suum in mice. The compounds were of varying effectiveness, the best results being shown by (23) and (24). At a dose level of 300 mg/kg, twice daily for five days, they gave a 99% reduction in the number of larvae.



R′ = H or Me

R = substituted anilino

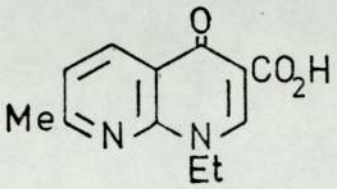
(22)



(23) R = Me

(24) R = Et

In a project to find active heterocyclic compounds related to the potent urinary antiseptic nalidixic acid (25), Richardson and McCarty[15] found that the compound (26) inhibited growth of Trichophyton mentagrophytes, in vitro, at a concentration of 100 $\mu g/cm^3$. It was inactive against Staphylococcus aureus, Salmonella schottmuelleri, and Candida albicans and showed no antitumour or antiviral activity.



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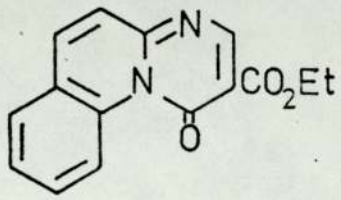

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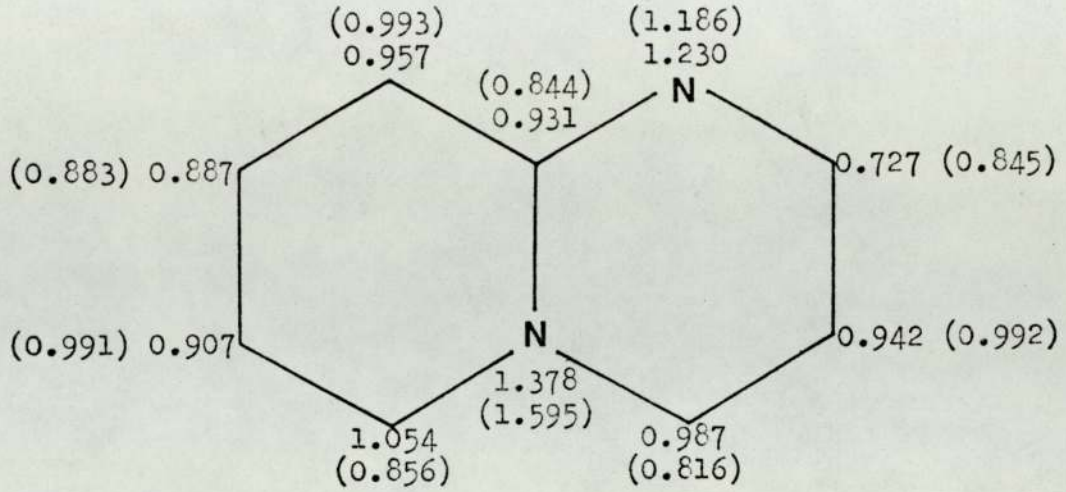
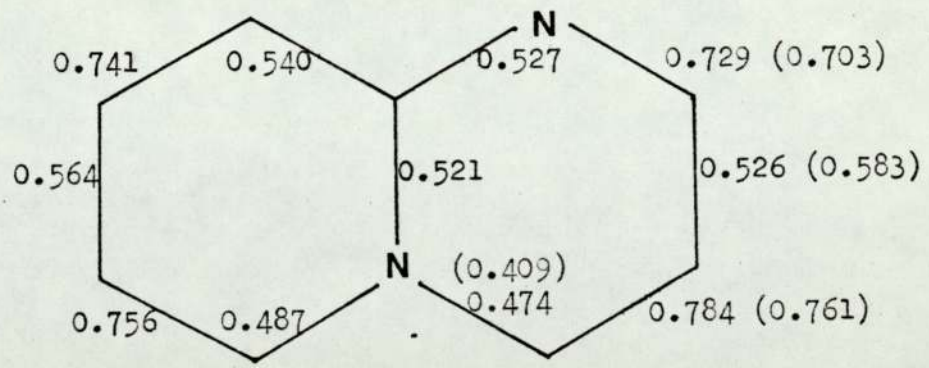
2. THEORETICAL CALCULATIONS

Galasso[16] has applied the Pariser-Parr-Pople[17,18] semi-empirical version of the SCF-MO method and a CI treatment extended to all the singlet mono-excited configurations to calculate the electronic structure and transition energies of the pyrido[1,2-a]pyrimidinium cation (1) as well as those of the quinolizinium cation (2) and its other monoaza-derivatives. A regular bicyclic structure with equal bond lengths of 1.396Å has been assumed. The results for the pyrido[1,2-a]pyrimidinium cation are summarised below. The figures in parentheses are the results obtained by Pollak, Stanovnik and Tišler[19] by an undisclosed method.

The first six excitation energies have been calculated[16] to be 4.105, 4.150, 5.515, 5.820, 6.101 and 6.418 eV. Galasso predicts protonation at the non-bridgehead nitrogen atom and anionoid substitution at the 2-position.



Electron Densities

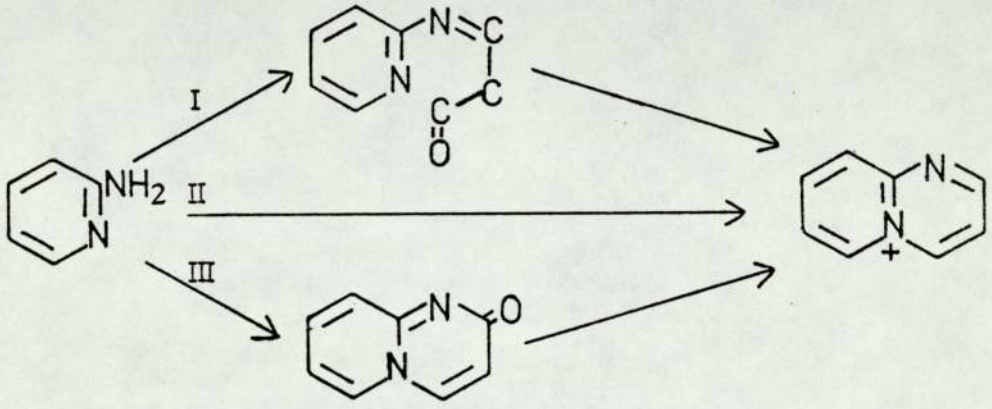


Bond Orders

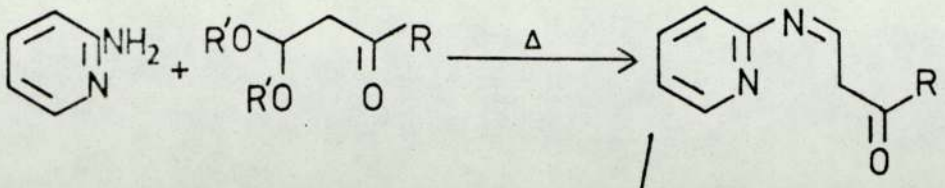
3. SYNTHETIC METHODS

3.1 Pyrido[1,2-a]pyrimidinium Salts

Prior to the commencement of this work only three papers[20-22] concerning pyrido[1,2-a]pyrimidinium salts not bearing an oxo- or an imino-substituent had appeared in the literature. During the course of this work two more papers[19,23] have been published. Three routes (I - III) to the pyrido[1,2-a]pyrimidinium nucleus have been utilised.



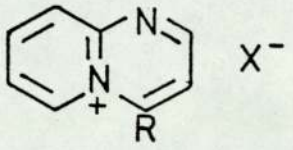
The first pyrido[1,2-a]pyrimidinium salts were prepared by Nesmeianov, Rybinskaia and Belsky[20] using a two step route (I). The β-keto-acetals (27 - 31) and 2-aminopyridine were condensed in a sealed ampoule by heating at 140° to yield compounds claimed by these authors to be β-keto-imines (32 - 35). These intermediates were then treated with perchloric or hydrobromic acid to yield the cyclised products (36 - 40). The phenyl substituted intermediate (35) did not cyclise when treated with aqueous acid, but instead produced a mixture of acetophenone and a 2-aminopyridinium salt.



	R	R′
(27)	Me	Me
(28)	Me	Et
(29)	Et	Me
(30)	Pr	Me
(31)	Ph	Me

	R
(32)	Me
(33)	Et
(34)	Pr
(35)	Ph

HX



	R	X^-
(36)	Me	Br^-
(37)	Me	ClO_4^-
(38)	Et	Br^-
(39)	Et	ClO_4^-
(40)	Pr	ClO_4^-

Route (II) has been utilised by several workers[19,21,23]. Nesmeianov and Rybinskaia[21] have formed the salts (37, 40 and 44) directly, by the reaction of 2-aminopyridine with the β-chlorovinyl ketones (41 - 43) or the β-keto-acetals (27, 30 and 31) in perchloric acid.

SUMMARY OF THESIS

An outline of the biological activity of compounds containing the quinolizinium nucleus and derivatives of 4H-pyrido[1,2-a]pyrimidin-4-ones, which are closely related to pyrido[1,2-a]pyrimidinium salts, is presented. Methods available for the synthesis of pyrido[1,2-a]-pyrimidinium salts, pyrido[1,2-a]pyrimidinones and quinolizinium salts, and the possibility of 1,8-naphthyridine formation are discussed.

The scope and steric restrictions of a route for the preparation of pyrido[1,2-a]pyrimidinium salts from 2-aminopyridines and pentan-2,4-dione, 1,1,3,3-tetramethoxypropane, 4,4-dimethoxybutan-2-one or 1-phenylbutan-1,3-dione in the presence of perchloric or hydrobromic acid, have been investigated. In the case of 6-substituted-2-amino-pyridines and 4,4-dimethoxybutan-2-one, 2-methylpyrido[1,2-a]-pyrimidinium salts are formed, whereas in the absence of the 6-substituent, 4-methylpyrido[1,2-a]pyrimidinium salts are formed. 4,6,8-Trimethylpyrido[1,2-a]pyrimidinium perchlorate has been prepared by utilising acetic anhydride as a dehydrating agent. The salts obtained from 1-phenylbutan-1,3-dione are found to be the 2-methyl-4-phenyl isomers. An attempt has been made to rationalise the orientation of the substituents arising from the 1,3-dicarbonyl compounds in mechanistic terms.

Treatment of the pyrido[1,2-a]pyrimidinium salts with base, cleaved the pyrimidine rings to yield 2-(2-acylvinylamino)-pyridines. The structures of these ring-opened products, determined spectroscopically, have been used to deduce the structures of the pyrido[1,2-a]-

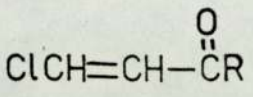
pyrimidinium perchlorate from which they have been derived.

Treatment of 2-amino-4-methylpyridine and pentan-2,4-dione with ortho phosphoric acid followed by sodium hydroxide has been shown to yield 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine and not 2,4,5-trimethyl-1,8-naphthyridine, as reported in the literature.

Unsuccessful attempts to convert pyrido[1,2-a]pyrimidinones to pyrido[1,2-a]pyrimidinium salts are reported.

Diazotisation of 9-aminopyrido[1,2-a]pyrimidinium perchlorates produces 3-(3-v-triazolo[1,5-a]pyrimidinyl)acraldehydes. This is a new route to the v-triazolo[1,5-a]pyrimidine ring system. A mixture of monomethyl substituted-3-(3-v-triazolo[1,5-a]pyrimidinyl)-acraldehydes was isomerised thermally to 3(5)-formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole.

The author would like to thank Professor D.G. Wibberley, for his invaluable help and encouragement throughout the course of this work; and my wife, Pat, for typing the manuscript.

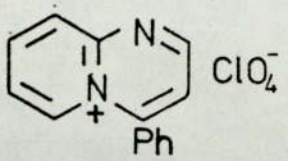


R

(41) Me

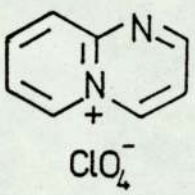
(42) Pr

(43) Ph

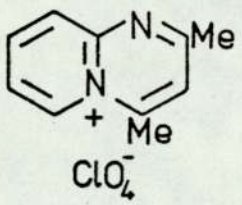


(44)

Pollak, Stanovnik and Tišler[19] have synthesised the two pyrido[1,2-a]-pyrimidinium perchlorates (46 and 47) by refluxing a mixture of 2-aminopyridine, methanol and hydrobromic acid with 1,1,3,3-tetraethoxypropane (to give 46) or pentan-2,4-dione (to give 47), followed by addition of perchloric acid to the cooled solution.

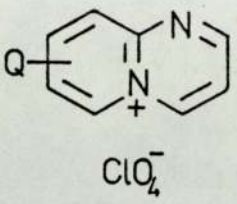


(46)



(47)

Khmaruk, Volovenko and Chuiguk[23] produced a series of pyrido[1,2-a]-pyrimidinium perchlorates (46 - 63) by heating a 2-aminopyridinium perchlorate with the appropriate symmetrical β-diketone. Heating 2-amino-5-pyridinylsulphonic acid and pentan-2,4-dione in water yielded the zwitterion (64).



Q

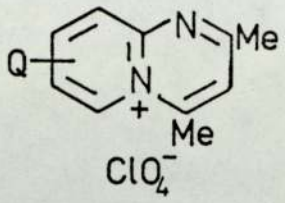
(48) 6-Me

(49) 8-Me

(50) 9-Me

(51) 7-Br

(52) 7,9-Br_2



Q

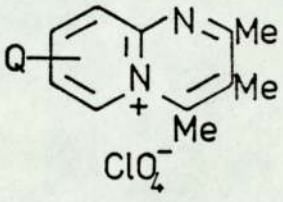
(53) 8-Me

(54) 9-Me

(55) 7-Br

(56) 7,9-Br_2

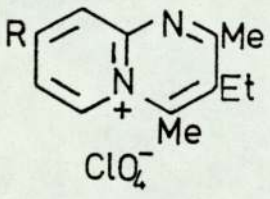
(57) 7-Br, 9-NH_2



Q

(58) 8-Me

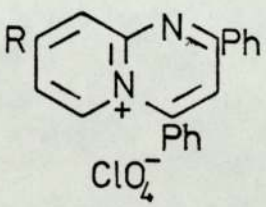
(59) 7,9-Br_2



R

(60) H

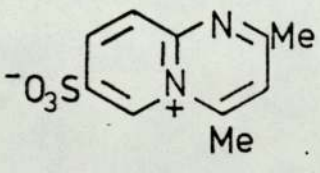
(61) Me



R

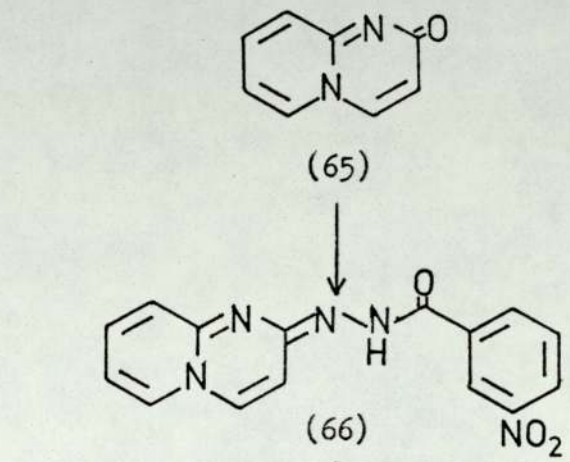
(62) H

(63) Me



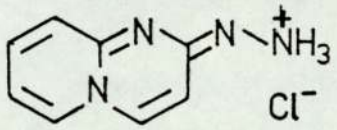
(64)

Only one synthesis from a pyrido[1,2-a]pyrimidone (Route III) has been reported[22]. 2H-Pyrido[1,2-a]pyrimidin-2-one (65) was converted to 2-(4-4′-acetamidoanilinophenylazo)-2-pyrido[1,2-a]pyrimidinium perchlorate (68) via several steps, the last of which was an oxidative coupling utilising $(NH_4)_2S_2O_8$.

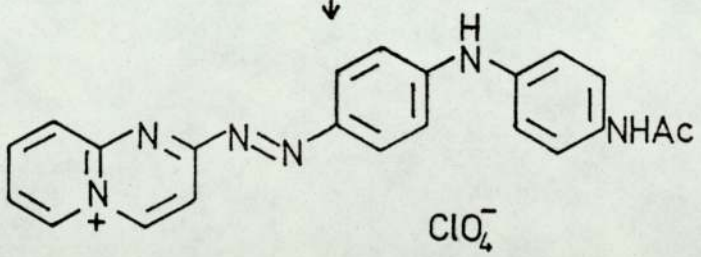


(65)

(66)



(67)

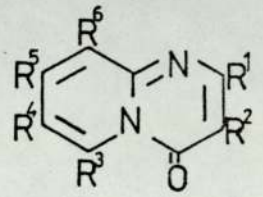


(68)

3.2 Pyrido[1,2-a]pyrimidinones

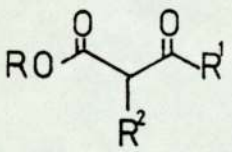
The work on the pyrido[1,2-a]pyrimidine nucleus prior to 1958 has been reviewed by Mosby[24].

3.2.1 4H-Pyrido[1,2-a]pyrimidin-4-ones (69)

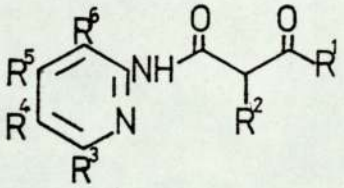


(69)

The most favoured route to pyrido[1,2-a]pyrimidin-4-ones (69) has been the reaction of 2-aminopyridines with 2-acylacetic esters (70) to yield compounds of type (69) with R_1 = alkyl or phenyl. In earlier work,



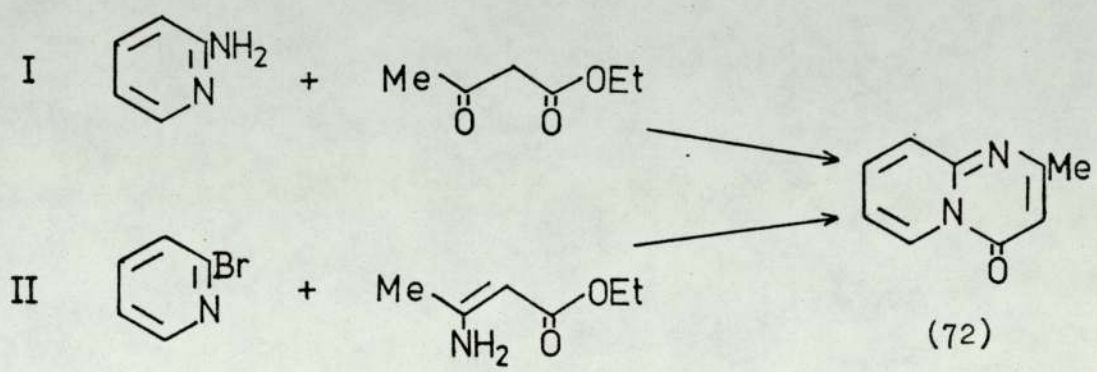
(70)



(71)

the structures of the products from such reactions were in doubt because several authors[25-28] had isolated intermediates of type (71) which they had subsequently cyclised to compounds which they had logically assumed to have structures (106). Antaki and Petrow[28] obtained the same product from both reactions I and II, from which they assumed it must have structure (72). Adams and Pachter[29] confirmed structure (72) by a series of experiments involving ultra violet spectroscopy. Since then several other authors[30-35] have used this route to prepare

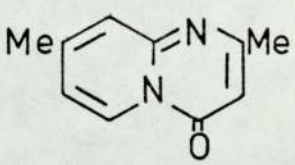
compounds of type (69). Conclusive proof of the structure (69) for the product from this reaction has been provided by Yale, Toeplitz, Gougoutas and Puar[34] who have carried out x-ray crystallographic studies on the hydrobromide of (73) and studied the effects of europium shift reagents on the ^{1}H n.m.r. spectrum of (73).



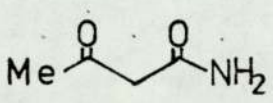
(72)

Khalifa[30] and Shur and Israelstam[31] have attempted to rationalise the rearrangement that must occur in the reaction (71) → (69) in mechanistic terms.

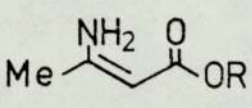
Similarly 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-ones (69, R^1 = Me, R^2 = H) have been prepared from 2-aminopyridines and the derivatives (74)[34], (75)[34,35], (76)[36], and (77)[34,37,38] of aceto acetic acid.



(73)

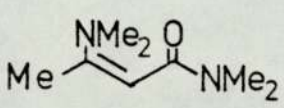


(74)

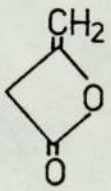


R = Me, Et

(75)

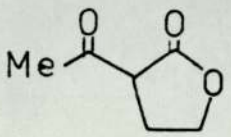


(76)

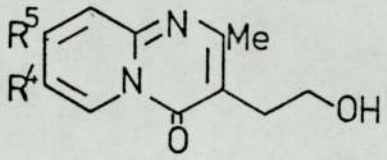


(77)

The cyclic derivative (78) of ethyl acetoacetate forms the pyrido[1,2-a]-pyrimidinones (79 - 81) with the appropriate 2-aminopyridine[39].

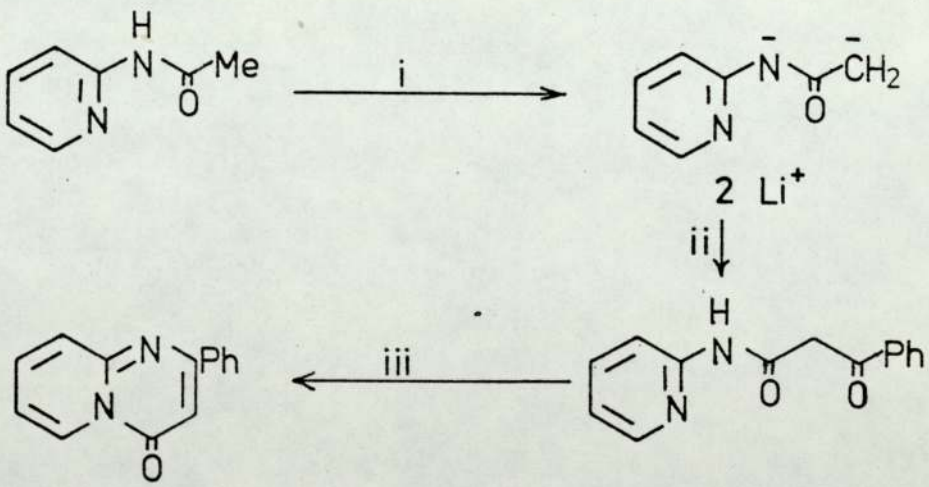


(78)



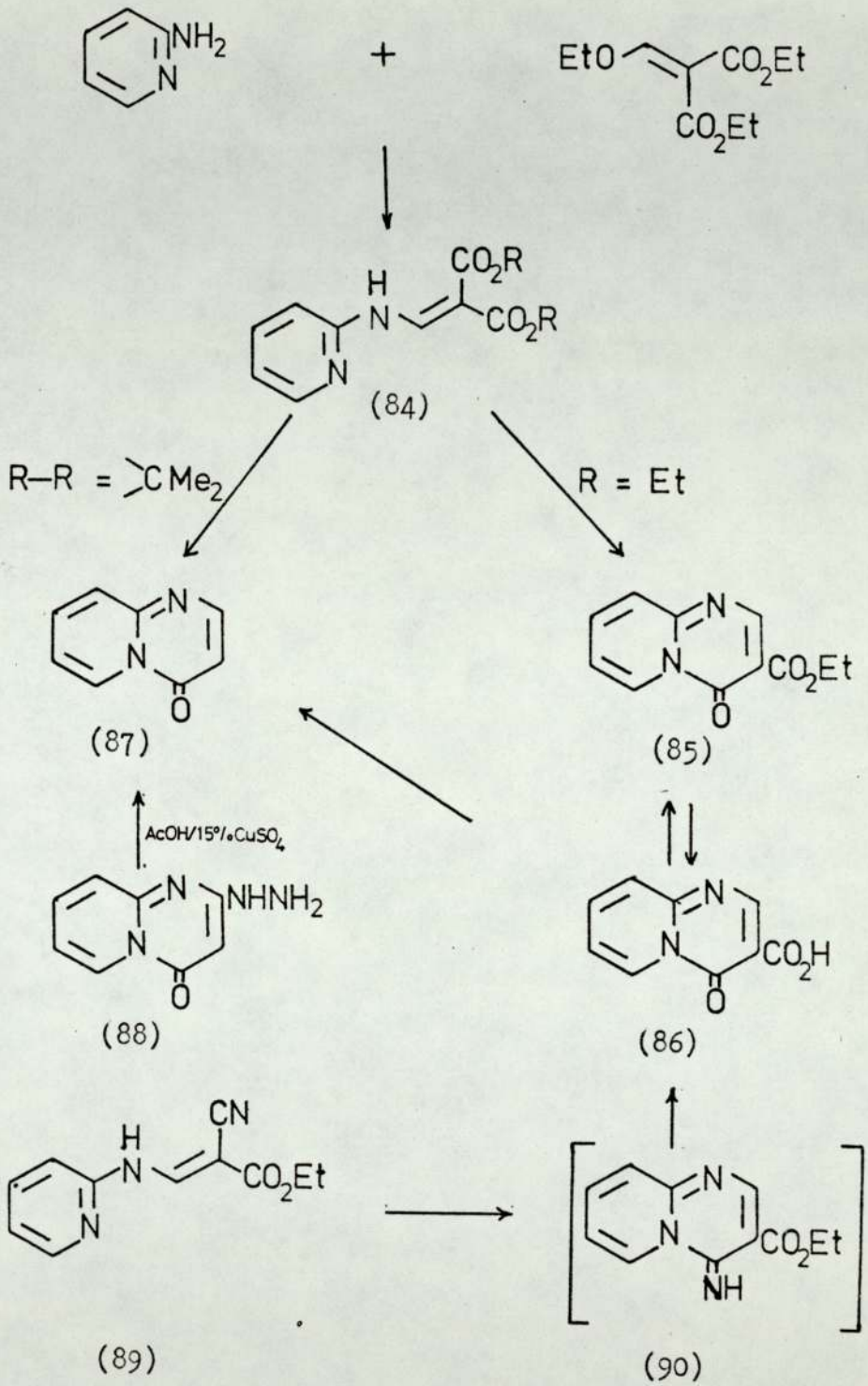
	R	R
(79)	H	H
(80)	H	Me
(81)	Cl	H

Basmich and Hauser[40] have devised a new route to the intermediate (82) which was cyclised, with rearrangement, to (83).



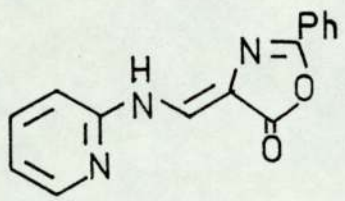
(83) (82)

i excess n-BtLi, ii $PhCO_2Me$, iii H_2SO_4.

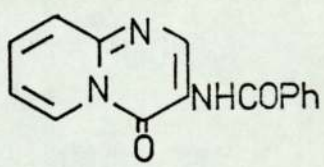

NH2
N
+
EtO
CO2Et
CO2Et
CO2R
H
N
CO2R
N
(84)
R—R = CMe2
R = Et
N
N
O
(87)
N
N
CO2Et
O
(85)
AcOH/15%CuSO4
N
NHNH2
N
O
(88)
N
N
CO2H
O
(86)
CN
H
N
CO2Et
N
(89)
N
N
CO2Et
NH
(90)

4H-Pyrido[1,2-a]pyrimidin-4-ones (85 - 87) unsubstituted at C-2 have been prepared by several routes. The ester (85) has been synthesised by several authors[29,31,41] from 2-aminopyridine and diethyl ethoxymethylenemalonate. Others[42-44] have used this route to prepare compounds of type (85) substituted in the pyridine ring. Adams and Pachter[29] have hydrolysed the ester (85) to the acid (86) and decarboxylated it to yield 4H-pyrido[1,2-a]pyrimidin-4-one (87). The direct synthesis of (87) has been achieved by reduction of the hydrazine (88)[45] and by the thermal treatment of the isopropylidene 2-pyridylaminoethylenemalonate (84, R-R = isopropylidene)[1]. A group of Japanese workers[46] have cyclised ethyl 2-pyridylaminomethylenecyanoacetate (89) in hydrochloric acid to the acid (86). They claim the reaction proceeds via the intermediate (90). The acid (86) has been esterified to the ester (85)[46].

The oxazolone (91) has been cyclised to the amide (92)[47].

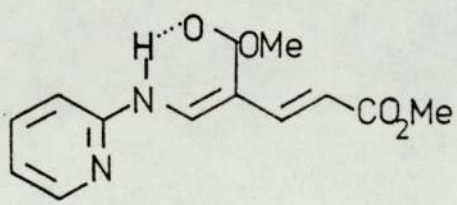


(91)

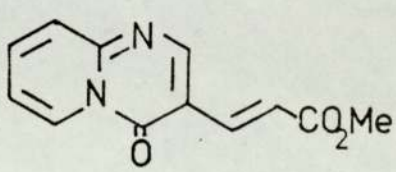


(92)

The reaction of 2-aminopyridine with methyl propiolate produced a by-product (93) which has been cyclised thermally to the methyl acrylate (94)[48].

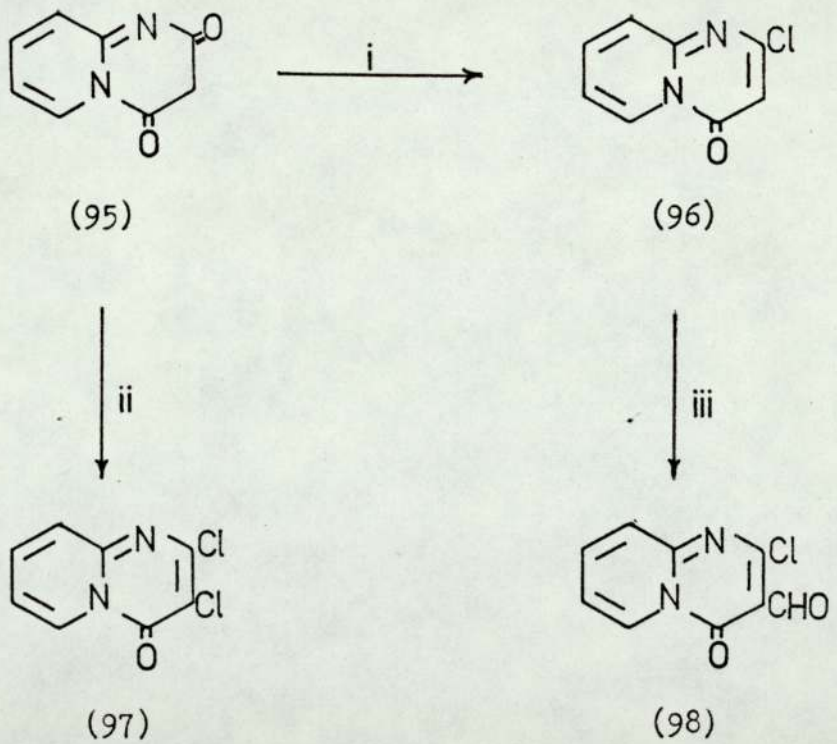


(93)



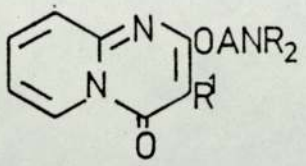
(94)

The chlorinated 4H-pyrido[1,2-a]pyrimidin-4-ones (96) and (97) have been prepared by Oakes and Rydon[45] and Snyder and Robinson[49] from pyrido[1,2-a]-pyrimidin-2,4(3H)-dione (95) (see sec. 3.2.3). The chloro compound (96) has been formylated by several authors[12,50,51] to yield (98). The chloro group at C-2 in (96),(97) and (98) has been substituted by various cyclic and acyclic amines[12,45,51]. The 2-(aminoalkoxy) derivatives (99) have been prepared by direct O-alkylation of diones (95), substituted at C-3[52]. Treatment of (97) with phenol has yielded the 2-phenoxy compound (100)[45].



(95) (96) (97) (98)

i $POCl_3$; ii $POCl_3/PCl_5$; iii Vilsmeier-Haack.

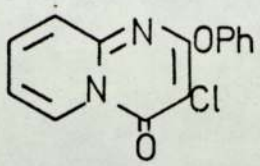


A = alkylene

NR_2 = cyclic or acyclic amines

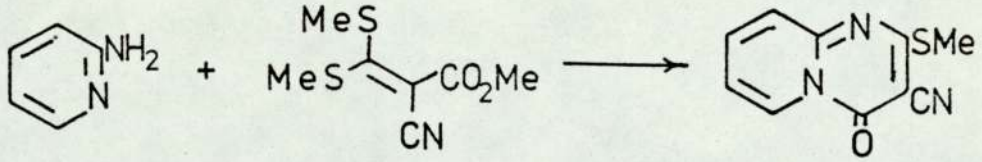
R^1 = alkyl or aryl

(99)

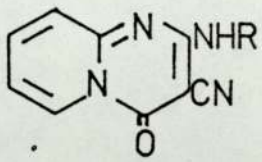


(100)

2-(Methylthio)-3-cyano-4H-pyrido[1,2-a]pyrimidin-4-one (102) has been derived from 2-aminopyridine by reaction with methyl 1-cyano-2,2-bis-(methylthio)acrylate (101) by several authors[53-55]. Replacement of the methylthio group with amines has given the derivatives (103), (104) and (105)[53].



(101) (102)

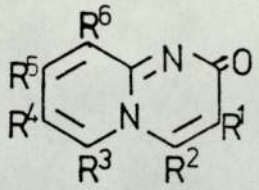


(103) R = CH_2CH_2OH

(104) R = $CH_2CH_2NEt_2$

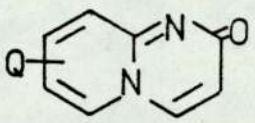
(105) R = CH_2Ph

3.2.2 2H-Pyrido[1,2-a]pyrimidin-2-ones



(106)

2H-Pyrido[1,2-a]pyrimidin-2-ones (106) have been prepared in less abundance than the 4H-pyrido[1,2-a]pyrimidin-4-ones. Methyl propiolate[48,56] and propiolic acid[57] have been the reagents most favoured in deriving the 2H-pyrido[1,2-a]pyrimidin-2-ones (107 - 111) from 2-amino pyridines.



(107) Q = H

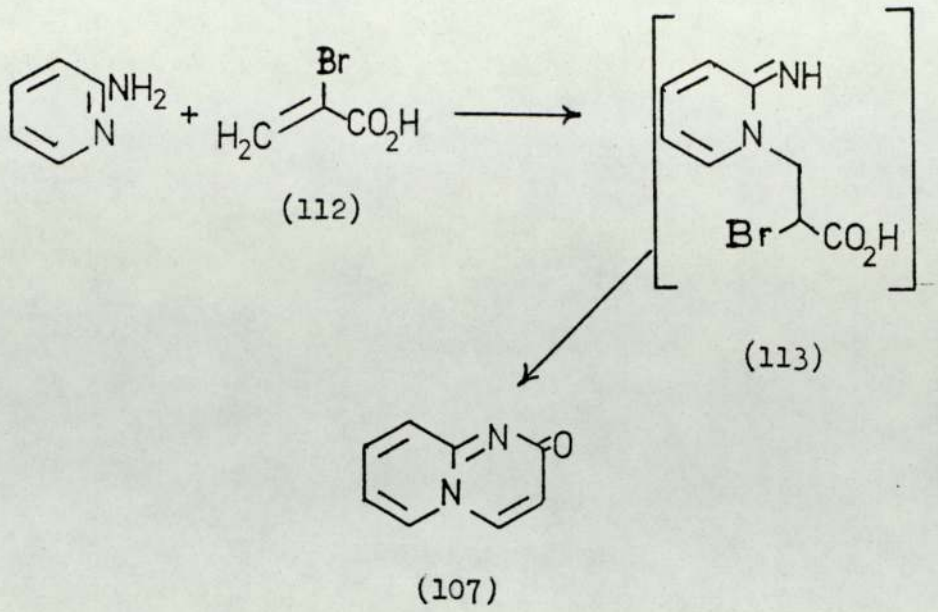
(108) Q = 6-Me

(109) Q = 7-Me

(110) Q = 8-Me

(111) Q = 9-Me

α-Bromoacrylic acid (112) has yielded[29] 2H-pyrido[1,2-a]pyrimidin-2-one (107) by reaction with 2-aminopyridine via the proposed intermediate (113).

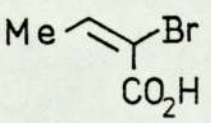


(112)

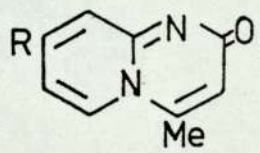
(113)

(107)

A similar reaction with α-bromo crotonic acid (114) has provided[38] the 2H-pyrido[1,2-a]pyrimidin-2-ones (115) and (116).



(114)

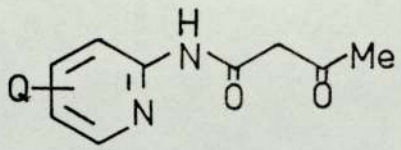


(115) R = H

(116) R = Me

Seidel[44] has prepared intermediates of type (119) from 2-acetoacetylaminopyridines (117) and dimethylformamide dimethyl acetal (118), and induced them to cyclise in acetic anhydride to the 3-acetyl-2H-pyrido-[1,2-a]pyrimidin-2-ones (120).

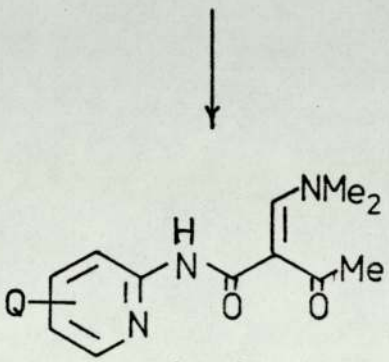
Glushkov and Magidson[58] have claimed the synthesis of 3-nitroso-4-amino-2H-pyrido[1,2-a]pyrimidin-2-one (121).



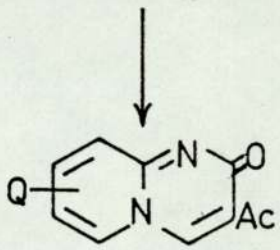
(117)

+ $Me_2NCH(OMe)_2$

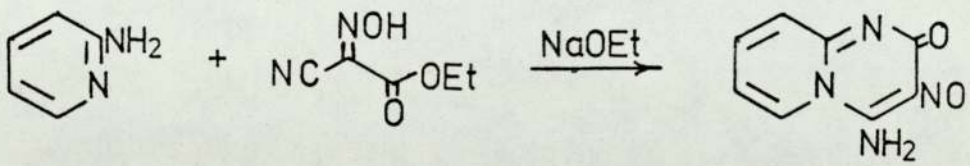
(118)



(119)

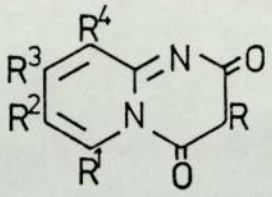


(120)



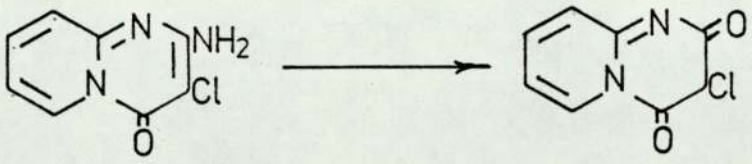
(121)

3.2.3 Pyrido[1,2-a]pyrimidin-2,4(3H)-diones



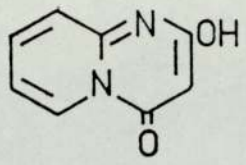
(122)

Syntheses of pyrido[1,2-a]pyrimidin-2,4(3H)-diones (122) are unvaried, nearly all preparations of the pyrido[1,2-a]pyrimidin-2,4(3H)-dione ring system have come from the treatment of 2-aminopyridines with esters and acid chlorides of both substituted and unsubstituted malonic acid[30,31,49,52,59-77]. Dashkevich and Kuvaeva[167] have obtained several pyrido[1,2-a]pyrimidin-2,4(3H)-diones (122, R = H) from 2-aminopyridines and C_3O_2. Oakes and Ryden[45] and Snyder and Robinson[49] have converted the 2-amino compound (123) to the dione (124) by diazotisation in sulphuric acid.

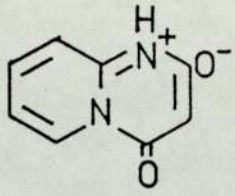


(123) (124)

Many authors have regarded the dione to have the 2-hydroxy structure (125), Katritzky and Waring[168] prefer structure (126).



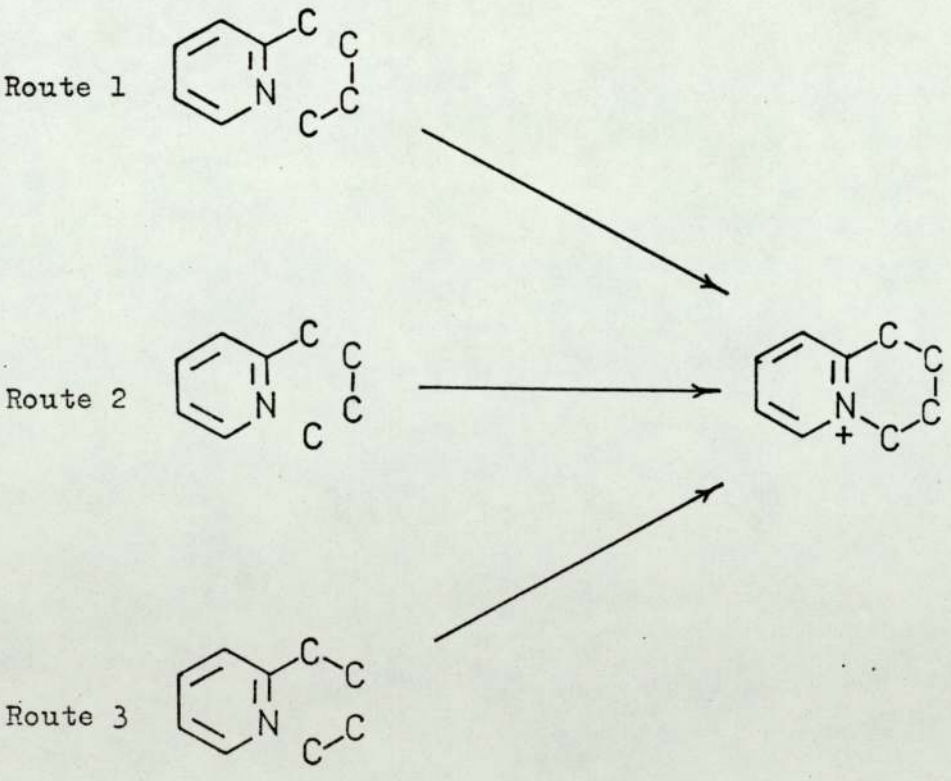
(125)



(126)

3.3 Quinolizinium Salts

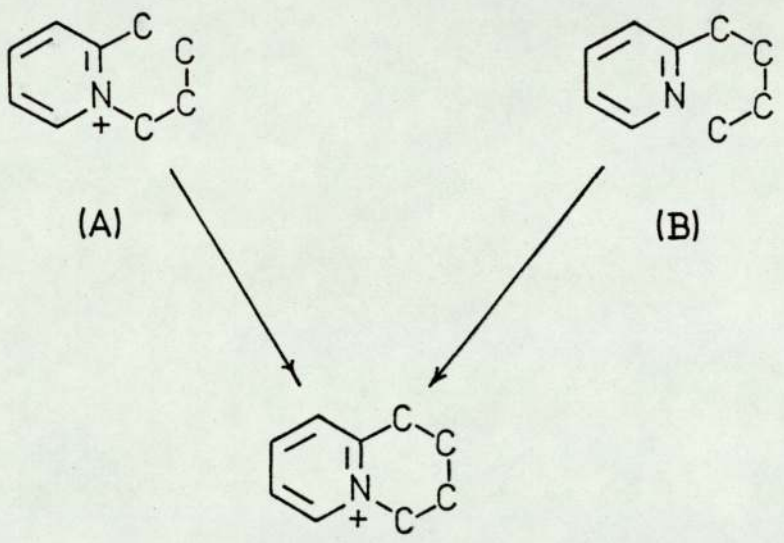
Several fundamentally different routes have been employed to synthesise



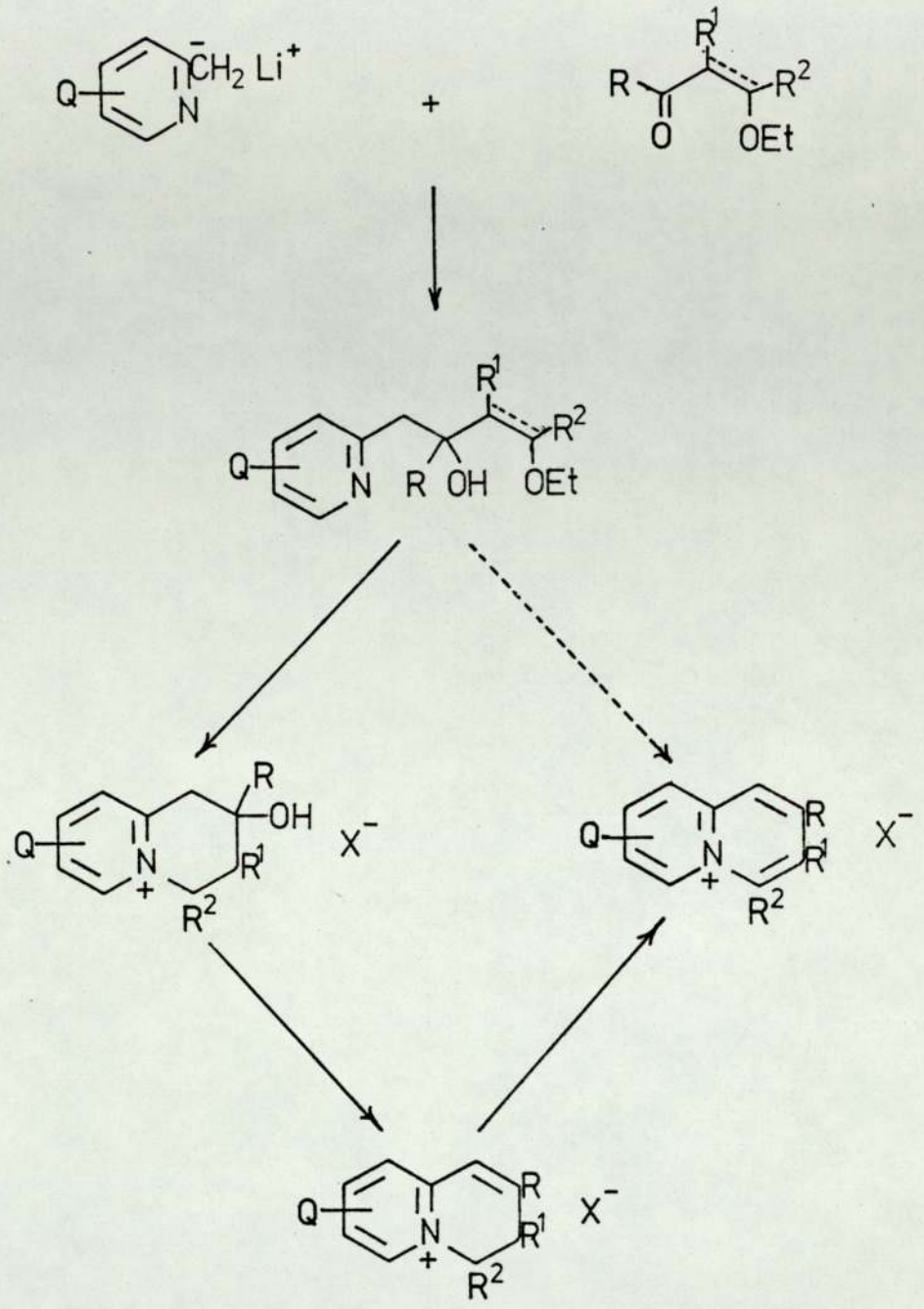
the quinolizinium nucleus (2). Route 1 is the closest analogue of the routes employed in the synthesis of pyrido[1,2-a]pyrimidines.

Route 1

Syntheses are of two types. The first involves attachment of the three carbon chain to the C-2 carbon to give intermediates of type (B), followed by cyclisation. The second involves quaternisation of the ring nitrogen to yield (A), followed by cyclisation.

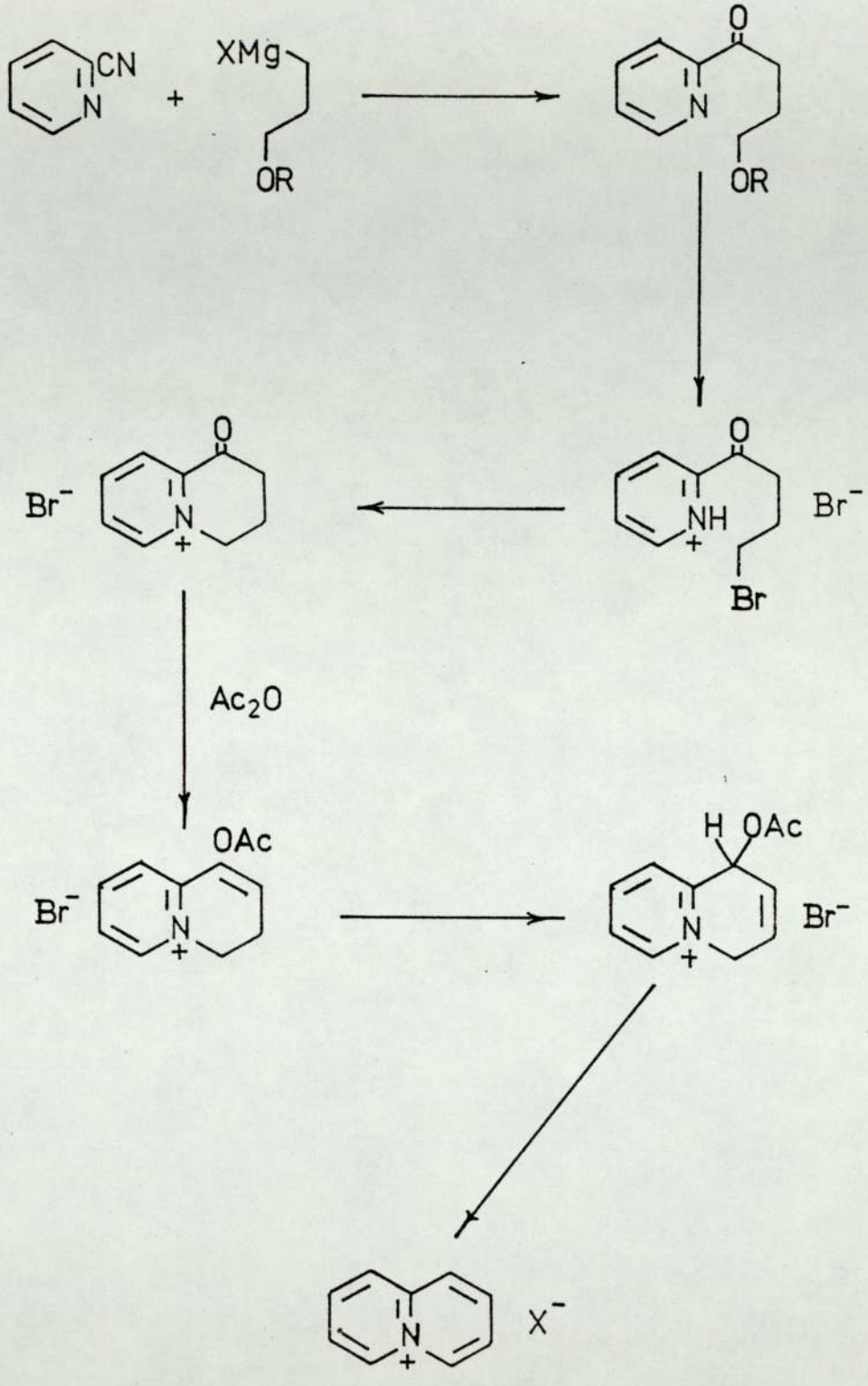


Unsubstituted and many substituted quinolizinium salts have been prepared by several authors[78-80, 169] utilising lithium salts of 2-methylpyridines as outlined in Scheme 1.

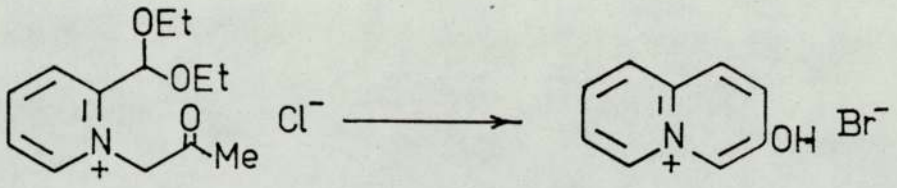


Scheme 1

Glover and Jones[81,82] and Nesmeianov and Rybinskaia[83] have developed a synthetic pathway from 2-cyanopyridine and grignard reagents. The tetrahydroquinolizinium bromide intermediate was aromatised by acetic anhydride.

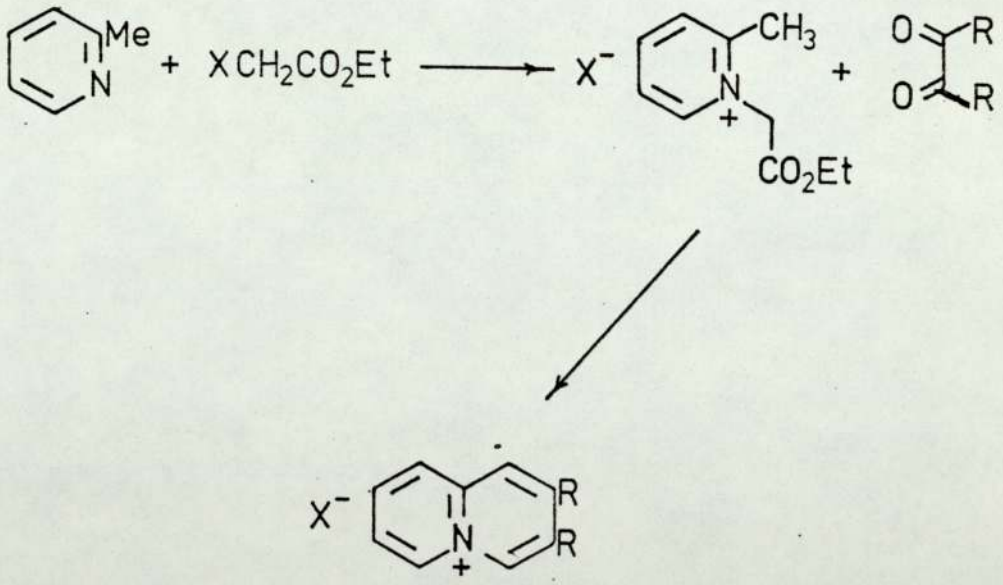

CN
N
+
XMg
OR
O
N
OR
O
NH
+
Br⁻
Br
Br⁻
O
N
+
Br⁻
Ac₂O
OAc
N
+
Br⁻
H OAc
N
+
Br⁻
N
+
X⁻

Schrauffstatter[84] has cyclised intermediates of type (B) in the reaction illustrated below.

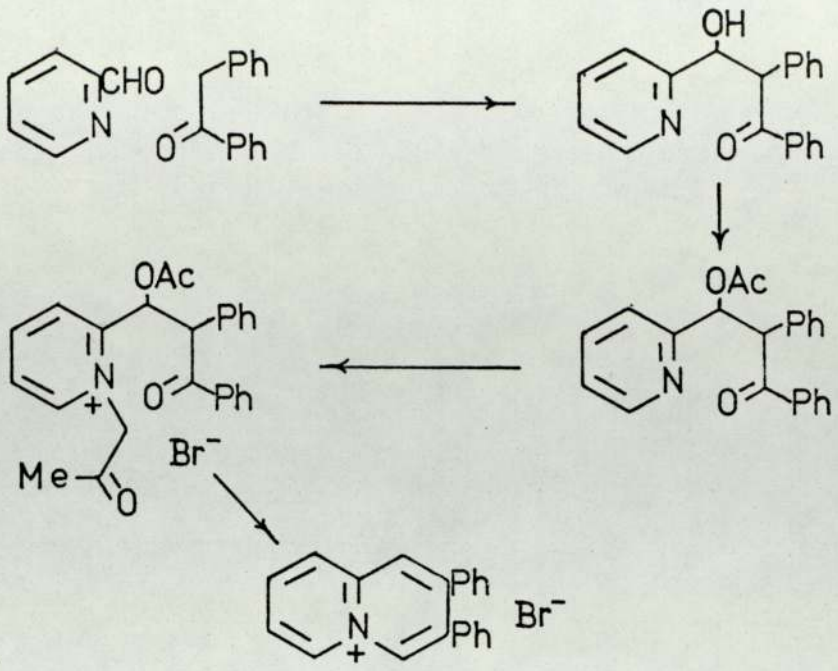


Route 2

Again there are two types of synthesis. The one carbon unit may be introduced firstly, as in the method of Westphal, Jann and Heffe[85] and Wander[86] (Scheme 2) or secondly, as in the method of Westphal and Feix[87] (Scheme 3).



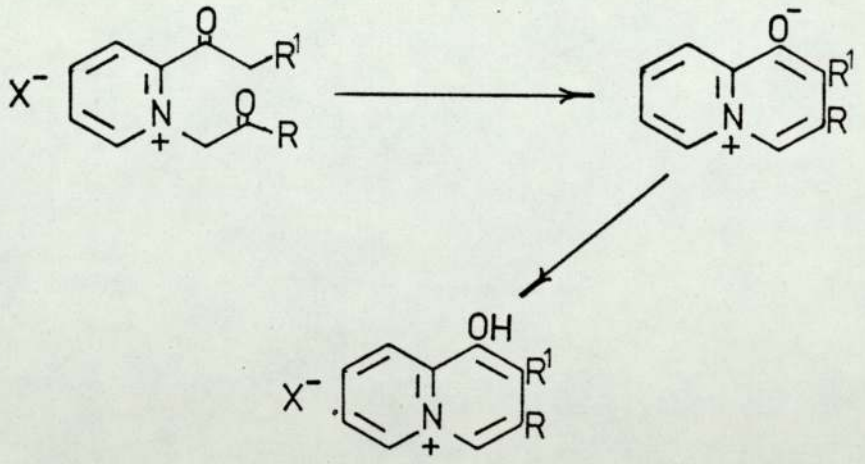
Scheme 2



Scheme 3

Route 3

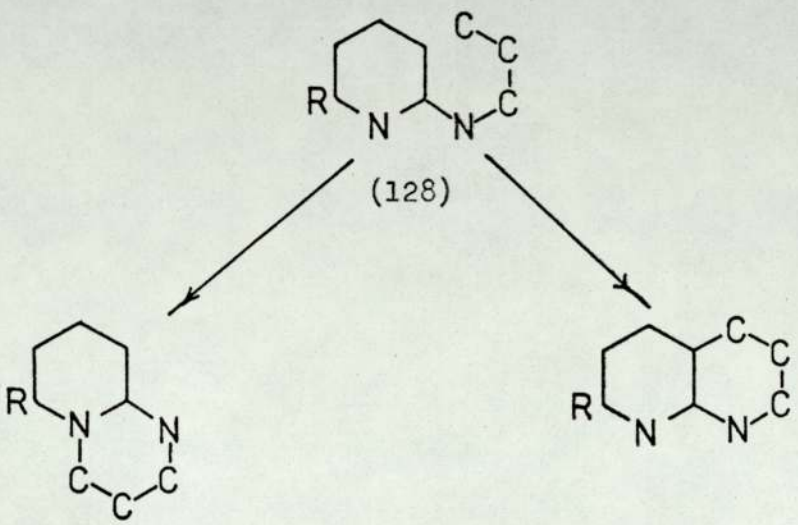
There has only been one example of this route reported in the literature[88] and is outlined in Scheme 4.



Scheme 4

4. COMPETITIVE REACTIONS OF 6-SUBSTITUTED-2-AMINOPYRIDINES

Appropriate derivatives of 6-substituted-2-aminopyridines (128) can theoretically be cyclised to yield pyrido[1,2-a]pyrimidines (129) (cf. Section 3) or 1,8-naphthyridines (130).



(128)

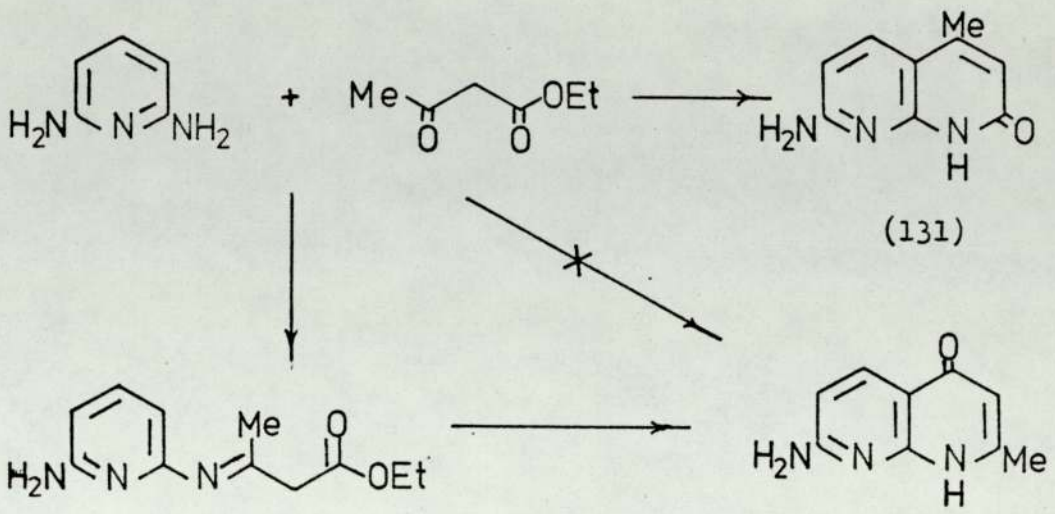
(129) (130)

4.1 Naphthyridine Formation

Naphthyridines have only been produced from (128) when R = NH_2, NHAc, OEt and Me. This has been attributed by several authors[63,64,89] to steric hindrance reducing the possibility of cyclisation at N-1, and inductive and mesomeric effects increasing electron density at both N-1 and C-3, but to a greater extent in the latter. Yields were low when R = Me (128) as the para activation is less than that of the other substituents.

Ethyl acetoacetate yielded 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-ones when reacted with 2-aminopyridines unsubstituted at C-6 (page 14). With 2,6-diaminopyridine a 1,8-naphthyridine is formed. Hauser and Weiss[90] claimed the product as the 4-one (132). Later workers[91,92]

have shown it to be the 2-one (131).



(131)

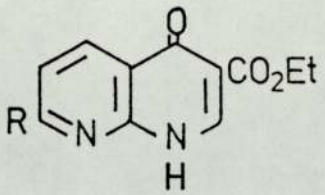
(133)

(132)

The anil (133) has been isolated[93] and subsequently cyclised to the naphthyridine (132). Other 7-amino-2-hydroxy-1,8-naphthyridines have been formed with other β-keto esters[94,95].

The naphthyridines (134 - 136) have been formed from 6-substituted-2-aminopyridines and diethyl ethoxymethylenemalonate[42,96]. A similar reaction has produced the naphthyridine (137)[97].

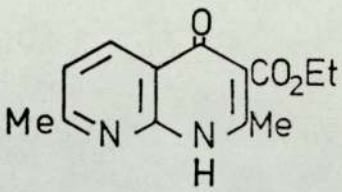
Malonate esters, which form pyrido[1,2-a]pyrimidin-2,4(3H)-diones with 2-aminopyridines unsubstituted at C-6 (page 24) yield naphthyridine-2,4-diones (138) with 6-substituted-2-aminopyridines[63,64].



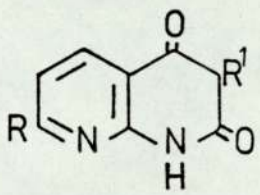
(134) R = Me

(135) R = OEt

(136) R = NH_2



(137)



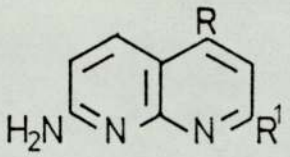
R = NH_2NHAc, OEt, Me.

R = n-C_5H_{11}, n-C_6H_{13}, Ph, $PhCH_2$.

(138)

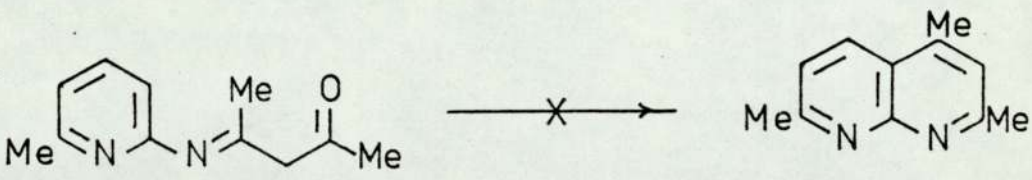
2,6-Diaminopyridines react with β-diketones and α-formylketones in phosphoric acid to yield 1,8-naphthyridines. Pentan-2,4-dione yields 7-amino-2,4-dimethyl-1,8-naphthyridine (139)[98,99]; 1-phenylpropan-1,3-dione yields 7-amino-2-phenyl-1,8-naphthyridine (140)[100]; 4,4-dimethoxybutan-2-one yields 7-amino-2-methyl-1,8-naphthyridine (141)[91]; 1-phenylbutan-1,3-dione yields 7-amino-2-methyl-4-phenyl-1,8-naphthyridine (142)

according to Mangini and Colonna[101] but Harper[100] claims the product to be 7-amino-4-methyl-2-phenyl-1,8-naphthyridine (143).



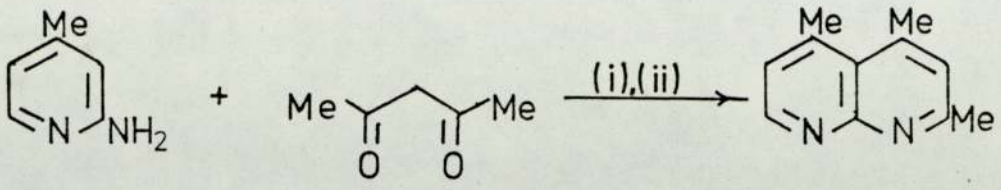
	R	R^1
(139)	Me	Me
(140)	H	Ph
(141)	H	Me
(142)	Ph	Me
(143)	Me	Ph

Attempts to cyclise the imine (144) to 2,4,7-trimethyl-1,8-naphthyridine (145) have failed[90,99].



(144) (145)

Singh, Taneja and Narang[102] have claimed 2,4,5-trimethyl-1,8-naphthyridine (146) as the product of treatment of 2-amino-4-methyl-pyridine with pentan-2,4-dione.



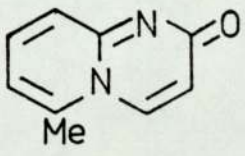
(146)

i heat/H_3PO_4

ii NaOH

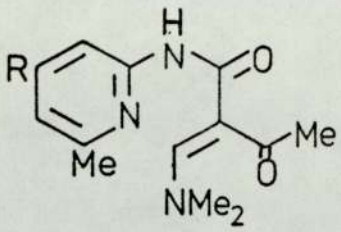
4.2 Pyrido[1,2-a]pyrimidinone Formation

Initial attempts to form pyrido[1,2-a]pyrimidinones from 6-substituted-2-aminopyridines proved unsuccessful[28,42,90]. The first 6-substituted-pyrido[1,2-a]pyrimidinone was obtained[103] in 1961. 6-Methyl-2H-pyrido-[1,2-a]pyrimidin-2-one (147) was formed from 2-amino-6-methylpyridine and methyl propiolate. In a later investigation[48] of this reaction



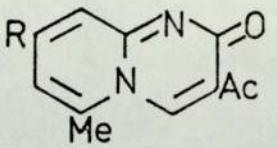
(147)

the same product (147) was obtained, together with uncyclised mono- and di-adducts. 6-Methyl-2H-pyrido[1,2-a]pyrimidin-2-ones (150 and 151) have been prepared from the N-(2-pyridyl)-2-acetyl-3-dimethylamino-acrylamides (148 and 149)[44].



(148) R = H

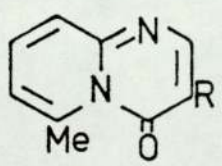
(149) R = Me



(150) R = H

(151) R = Me

The synthesis of 6-substituted-4H-pyrido[1,2-a]pyrimidin-4-ones (152 and 153) was first claimed[104] in 1956, though later attempts[5] to reproduce this work proved unsuccessful.

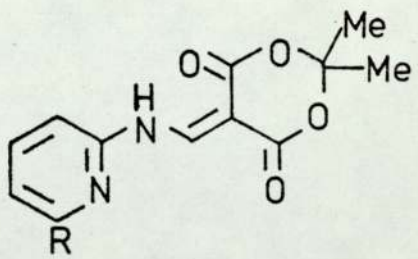


(152) R = CN

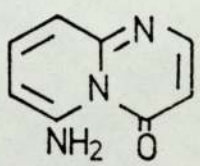
(153) R = Ac

(154) R = H

(155) R = CO_2Et



(156)



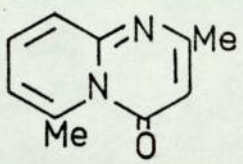
(157)

The formation of 3-carbethoxy-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

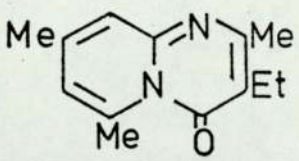
(155) from 2-amino-6-methylpyridine and diethyl ethoxymethylenemalonate has been claimed[31], but this has been refuted by later workers[5] who also claim the synthesis of the pyridopyrimidinone (155), their product having different physical properties to those of the compound obtained previously[31].

6-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (154) has been prepared[1], as well as other 6-substituted-4H-pyrido[1,2-a]pyrimidin-4-ones, by cyclising enamines of type (156). The enamine derivative of 2,6-diaminopyridine (156, R =NH_2) has been cyclised[1] to 6-amino-4H-pyrido[1,2-a]-pyrimidin-4-one (157) and not the expected 1,8-naphthyridine (section 4.1).

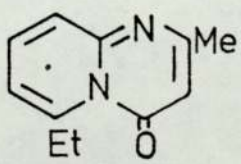
Two groups of workers[5,31] have succeeded in preparing 2,6-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (158) from 2-amino-6-methylpyridine and ethyl acetoacetate using polyphosphoric acid[31] or a mixture of phosphoryl chloride and polyphosphoric acid[5]. The pyrido[1,2-a]pyrimidin-4-ones



(158)



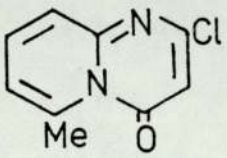
(159)



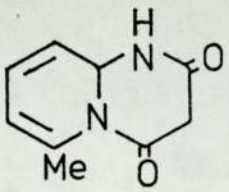
(160)

(159)[31] and (160)[5] were prepared in a similar manner.

The reaction of 2-amino-6-methylpyridine and diethyl malonate in phosphoryl chloride/polyphosphoric acid has been claimed[5] to yield the pyrido[1,2-a]pyrimidin-4-one (161), possibly via chlorination of the 2,4-dione (162), analogous to the reaction of Snyder and Robinson[49] (section 3.2.1) Dashkevich and Kuvaeva[167] have claimed that the 2,4-dione (162) is formed from 2-amino-6-methylpyridine and C_3O_2.

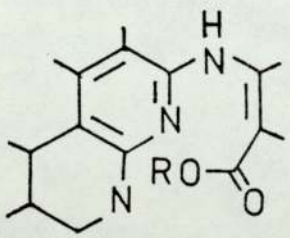


(161)

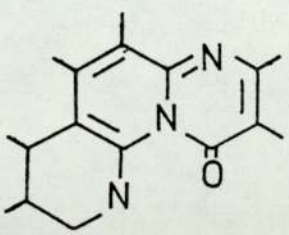


(162)

Other 6-substituted-4H-pyrido[1,2-a]pyrimidin-4-ones are to be found in the tricyclic pyrimido[1,2-a][1,8]naphthyridine system (164), which has been derived from 2-vinylamino-1,8-naphthyridines (163) by thermal

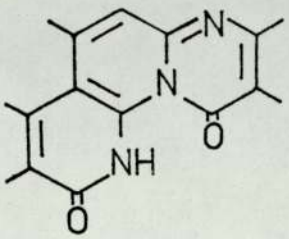


(163)



(164)

cyclisation. Carboni and his co-workers[95,105-107] have synthesised pyrimido [1,2-a] [1,8] naphthyridines of the type (165 and 166) by this method.



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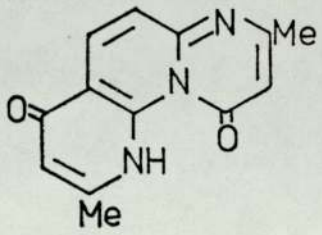
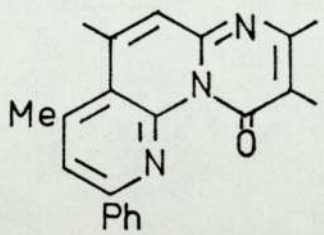


(166)

Harper[100] has extended this synthetic route to cyclise 4-methyl-2-phenyl-7-vinylamino-1,8-naphthyridines to the pyrimido [1,2-a] [1,8] naphthyridines of type (167).

Richardson and McCarty[15] have claimed the synthesis of the angular tricyclic compound (26).



(167)

DISCUSSION

Few papers[20-22] concerning pyrido[1,2-a]pyrimidinium salts have appeared in the literature, and none reports any findings of biological activity. Several of the closely related pyrido[1,2-a]pyrimidinones and quinolizinium salts have been found to have medicinal properties. In view of this, an investigation of pyrido[1,2-a]pyrimidinium salts was undertaken. During the course of this work, two more papers[19,23], concerning pyrido[1,2-a]pyrimidinium salts were published.

5. SYNTHESIS AND STRUCTURE OF PYRIDO[1,2-a]PYRIMIDINIUM SALTS

5.1 Introduction

2-Aminopyridines react with β-dicarbonyl compounds, or their acetals, in perchloric acid to form pyrido[1,2-a]pyrimidinium salts. Discussion of these reactions has been classified according to the β-dicarbonyl used. The reactions of 2,3-diaminopyridine are discussed separately.

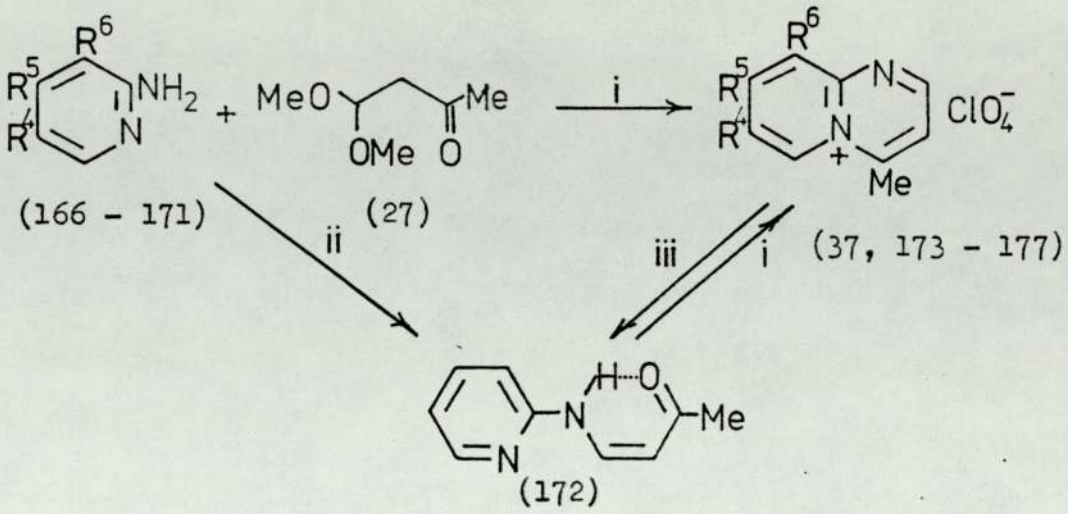
Pyrido[1,2-a]pyrimidinium salts e.g. (37), are attacked at C-4 by hydroxide ions, with cleavage of the C-4, N-5 bond, to yield 2-(2-acylvinylamino)pyridines, e.g. (171). Within this section, use has been made of the structures of these cleaved products in establishing those of the salts. Detailed discussion of the spectroscopic methods used to elucidate the structures of the 2-(2-acylvinylamino)pyridines is to be found in section 7.

5.2 Salts from 4,4-Dimethoxybutan-2-one

5.2.1 4-Methylpyrido[1,2-a]pyrimidinium Salts

4-Methylpyrido[1,2-a]pyrimidinium perchlorate (37) was among the first of the pyrido[1,2-a]pyrimidinium salts to be synthesised[20,21]. The first method employed[20] was to form the intermediate acylvinylamine (172) by heating 2-aminopyridine (166) and 4,4-dimethoxybutan-2-one (27) in a sealed ampoule at 140°, followed by cyclisation using perchloric acid. This method was the first tested as a route to the pyrido[1,2-a]-pyrimidinium nucleus. The use of a sealed ampoule for the thermal reaction appeared unnecessary and hazardous, so this step was modified in that a solution of the reagents in xylene (b.p. 144°) was heated under reflux. N.m.r. and i.r. spectroscopic evidence indicated that the intermediate condensation product existed as 2(2-acetylvinylamino)-pyridine (172), rather than the imine (32), both in solution in

chloroform and in the solid state. A slightly better yield of the intermediate (64.5%) was obtained by this method than was obtained previously (61.3%)[20].

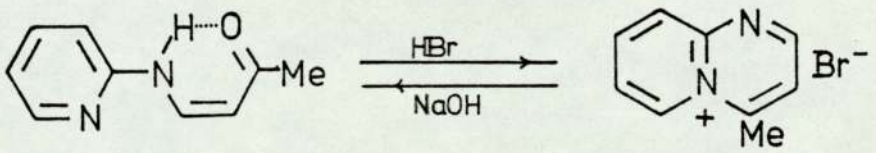


	R_4	R_5	R_6
(37, 166)	H	H	H
(167, 173)	Me	H	H
(168, 174)	H	Me	H
(169, 175)	H	H	Me
(170, 176)	Me	H	Me
(171, 177)	H	H	OH

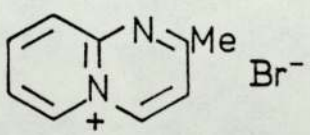
i $HClO_4$, ii heat, iii NaOH

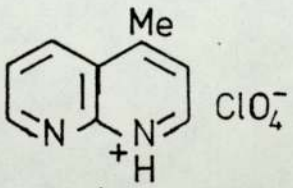
Cyclisation to 4-methylpyrido[1,2-a]pyrimidinium perchlorate (37) was achieved by adding 60% perchloric acid to an ether/methanol solution of the enaminone (172), which precipitated the salt. This resulted in a much better yield (92.8%) than was obtained (77.3%)[20] by heating a mixture of the enaminone (37) and perchloric acid and precipitating the salt with ethanol.

Nesmeianov, Rybinskaia and Belsky[20] described the preparation of several salts by this method. The salts contained five double bonds (by hydrogenation), were of aromatic character (did not decolourise a dilute solution of potassium permanganate), their u.v. spectra were very similar to those of quinoline and isoquinoline, and the molecular formula in each case corresponded to salt formation with loss of water. The product obtained from 2-(2-acetyvinylamino)pyridine and hydrobromic acid regenerated 2-(2-acetylvinylamino)pyridine when treated with sodium hydroxide, thus showing that rearrangement had not occured in the acid solution and that the salt formed was the 4-methyl isomer (178) and not the 2-methyl isomer (179). The i.r. and n.m.r. spectra of the perchlorate salt (37) confirmed that it has the 4-methylpyrido[1,2-a]-pyrimidinium perchlorate structure rather than that of the naphthyridine (180). Thus the i.r. spectrum showed no absorption due to an N-H bond



(172) (178)





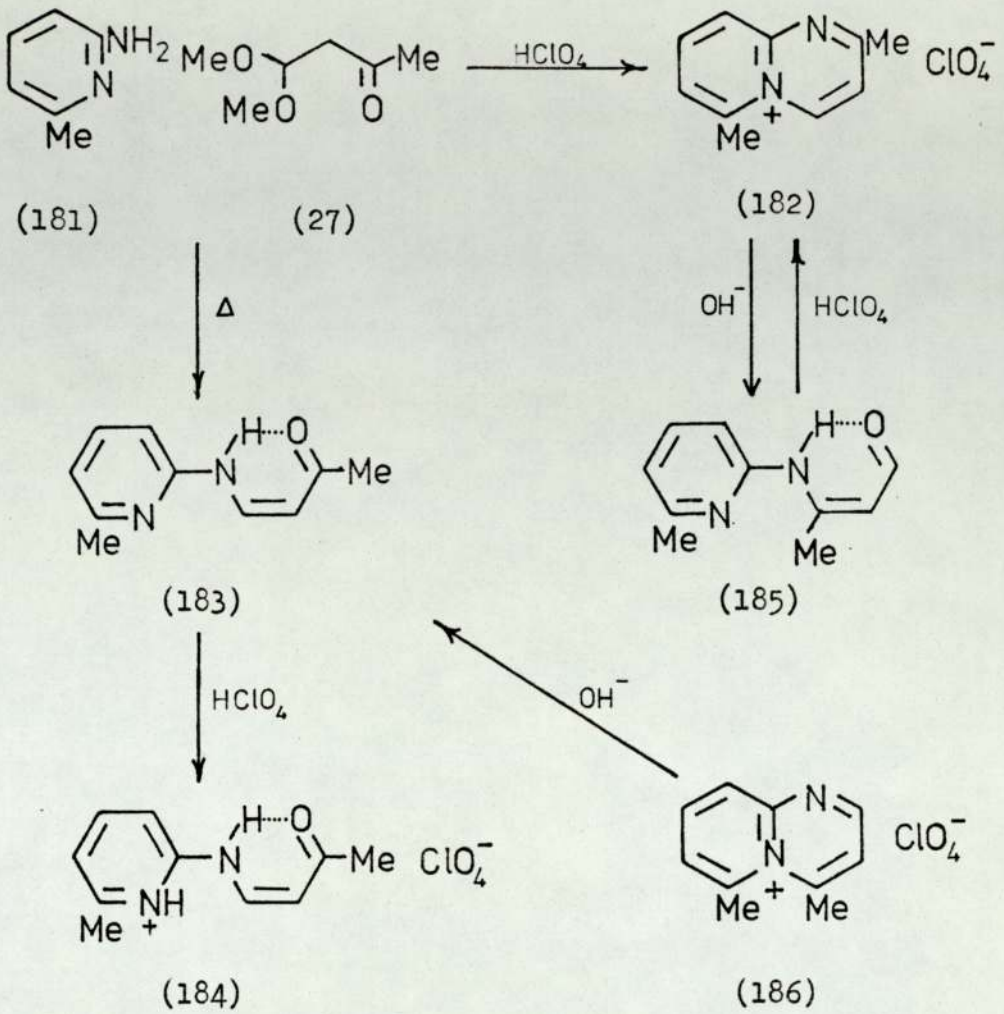
(179) (180)

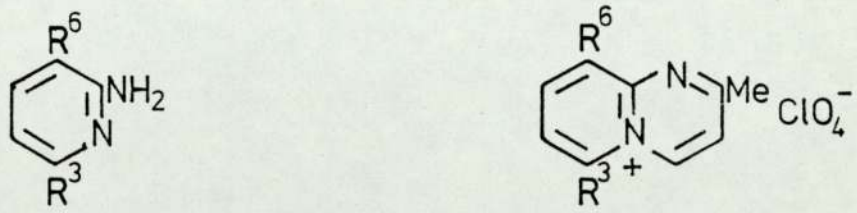
and integration of the peaks in the n.m.r. spectrum recorded in trifluoroacetic acid showed that the ring system bore six ring protons. Nesmeianov and Rybinskaia[21] subsequently improved their method for the formation of pyrido[1,2-a]pyrimidinium salts from 2-aminopyridine and 4,4-dimethoxybutan-2-one by cutting out the initial thermal step with a direct condensation and cyclisation in perchloric acid.

This work was repeated with good results, and because of its simplicity was adopted as a route to other pyrido[1,2-a]pyrimidinium salts. Thus the 2-aminopyridines (167 - 171) were all similarly treated with 4,4-dimethoxybutan-2-one to yield the 4-methylpyrido[1,2-a]pyrimidinium perchlorates (173 - 177). The 2-aminopyridines (169 - 171) are all substituted in the 3-position, thus preventing naphthyridine formation, but allowing pyrido[1,2-a]pyrimidinium salt formation. The ^{1}H n.m.r. spectrum of the salt (174) shows a one proton singlet at τ 1.49, assignable to 9-H. A two proton singlet at τ 1.41 in the ^{1}H n.m.r. spectrum of the salt (173) is assignable to 8- and 9-H, all other protons being accounted for.

5.2.2 2-Methylpyrido[1,2-a]pyrimidinium Salts

6-Substituted-2-aminopyridines normally yield 1,8-naphthyridines when reacted with β-dicarbonyl compounds, however, in some cases pyrido-[1,2-a]pyrimidines have been formed (see Sec. 4). The products of reactions between 6-substituted-2-aminopyridines and 4,4-dimethoxybutan-2-one in perchloric acid may therefore be expected to yield 1,8-naphthyridines, but if pyrido[1,2-a]pyrimidinium salts are formed, the orientation of the methyl group in previous reactions would indicate that they would be 4,6-disubstituted salts, for example, 4,6-dimethylpyrido[1,2-a]pyrimidinium perchlorate (186). ^{1}H n.m.r. spectra of the products obtained from the aminopyridines (181, 187 - 189)





	R^3	R^6		R^3	R^6
(187)	Et	H	(190)	Et	H
(188)	Pr	H	(191)	Pr	H
(189)	Me	Et	(192)	Me	Et

indicated the presence of the 9-H in each case, with the exception of the product from the aminopyridine (189) which is substituted in the 9-position.

An empirical relationship between J_{ortho} and π bond order has been established by several authors[19, 108-110]. For example, the 2,3 bond order in the 4H-pyrido[1,2-a]pyrimidin-4-one (87) has been calculated[19] to be 0.663 and the 3,4 bond order in 2H-pyrido[1,2-a]pyrimidin-2-one (107) to be 0.814. The corresponding J_{ortho} were found to be 6.2 and 7.5 Hz respectively. The π bond orders for pyrido[1,2-a]pyrimidinium salts have been calculated[16,19] (see Sec. 2), the 3,4 bond having greater π character than the 2,3 bond. Thus $J_{3,4}$ is expected to be greater than $J_{2,3}$.

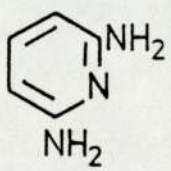
The 4-methylpyrido[1,2-a]pyrimidinium perchlorates (37, 173 - 177) exhibit coupling constants, $J_{2,3}$, in the range 4.0 - 5.0 Hz, in their ^{1}H n.m.r. spectra. The products from the 6-substituted-2-aminopyridines show couplings to the 3-proton of 7.3 - 7.5 Hz. This leads one to suspect that these values are for $J_{3,4}$ and that the products are 2-methylpyrido[1,2-a]pyrimidinium salts (182, 190 - 192).

The larger value of the coupling constant may possibly have been an artefact due to electron redistribution within the π system caused by the 6-substituent. To confirm these structures, the 2,6-dimethylpyrido[1,2-a]pyrimidinium perchlorate (182) was treated with base to yield 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185). This was easily distinguishable, spectroscopically, from 2-(2-acetylvinylamino)-6-methylpyridine (183), which would have been the product if the salt had been 4,6-dimethylpyrido[1,2-a]pyrimidinium perchlorate (186). The enaminone (183) was prepared thermally by the method used previously for 2-(2-acetylvinylamino)pyridine (172). Treatment of

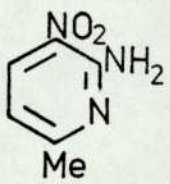
the enaminone (185) with perchloric acid in ether/methanol regenerated the perchlorate salt (182) in excellent yield, but similar treatment of the enaminone (183) yielded only 2-(2-acetylvinylamino)pyridinium perchlorate (184).

Both the 2- and 4-protons are strongly deshielded in trifluoroacetic acid, their chemical shifts being about equal; these values are therefore of little use in determining the orientation of the methyl group in salts formed from 4,4-dimethoxybutan-2-one. However, coupling to the 3-proton is useful in distinguishing a 2-proton from a 4-proton since $J_{3,4} \approx 4 - 5$ Hz and $J_{2,3} \approx 7.5$ Hz.

Attempts to form 2-methylpyrido[1,2-a]pyrimidinium perchlorates from the aminopyridines (193, 194) failed. 2,6-Diaminopyridine (193) yielded



(193)



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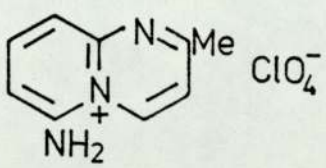
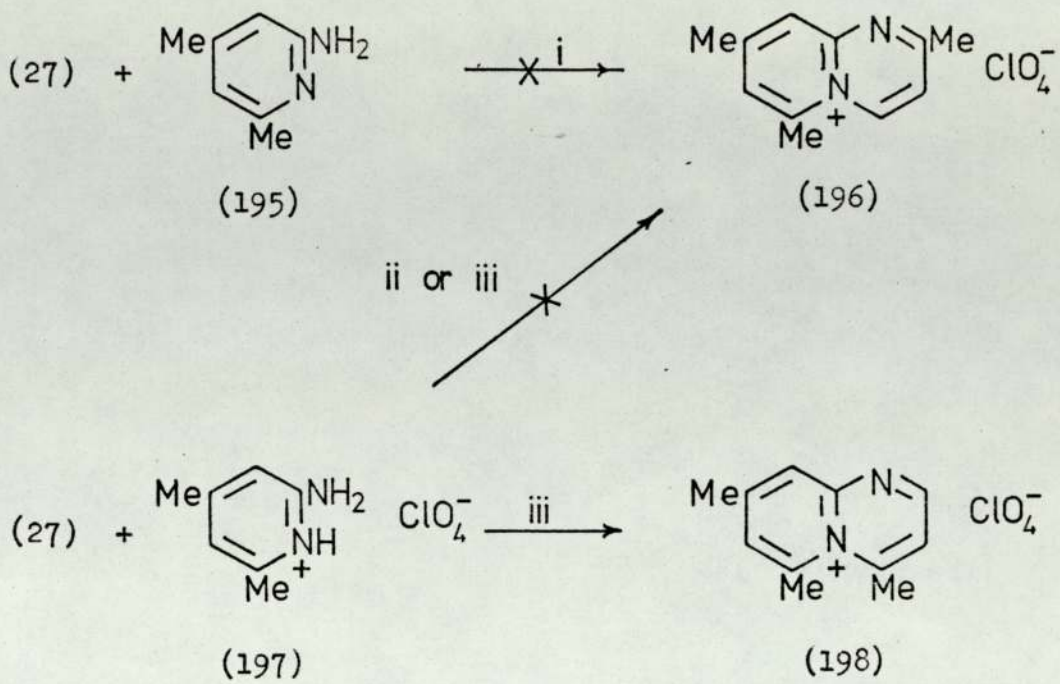


(193a)

an intractible black tar and 2-amino-6-methyl-3-nitropyridine (194) yielded its perchlorate salt.

5.2.3 4,6-Disubstitutedpyrido[1,2-a]pyrimidinium Salts



i $HClO_4$, ii heat, EtOH, iii heat, Ac_2O.

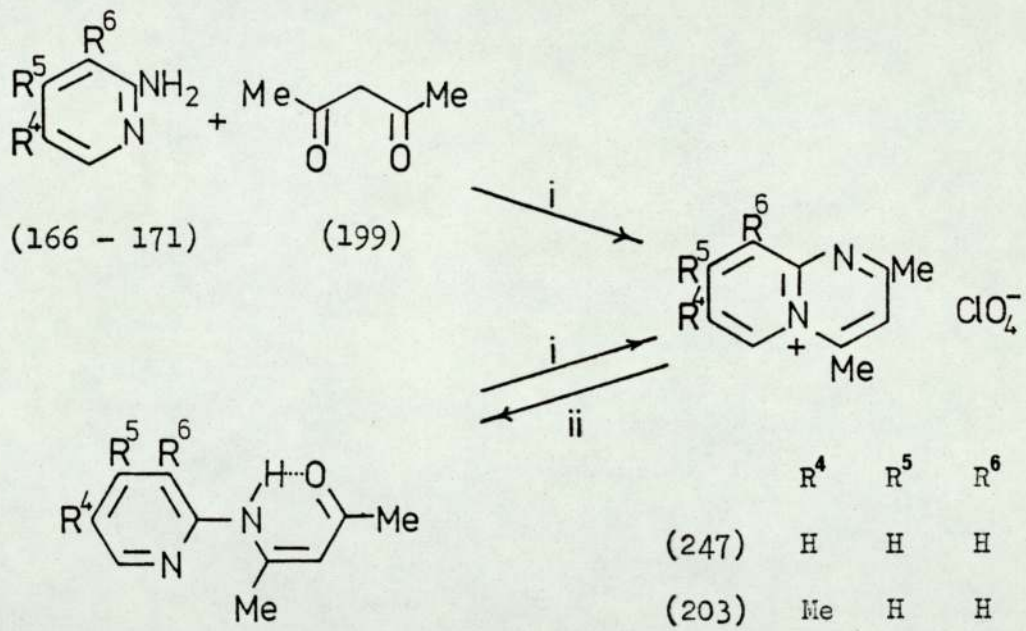
The one-step condensation and cyclisation reaction used successfully to prepare 2-methyl-6-substitutedpyrido[1,2-a]pyrimidinium perchlorates failed to yield the expected 2,6,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (196) from 2-amino-4,6-dimethylpyridine (195). Khmaruk, Volovenko and Chuiguk[23] have used a method involving heating 2-aminopyridinium perchlorates with symmetrical β-diketones to yield pyrido[1,2-a]pyrimidinium salts. Similar treatment of 2-amino-4,6-dimethylpyridinium perchlorate (197) and 4,4-dimethoxybutan-2-one (27) yielded unchanged 2-amino-4,6-dimethylpyridinium perchlorate (197).

More forcing conditions were obviously necessary to facilitate this reaction, so the reactants (197 and 27) were heated in acetic

anhydride. Precipitation with ether yielded a product which was similar to other pyrido[1,2-a]pyrimidinium perchlorates and the ^{1}H n.m.r. spectrum of which showed four ring protons, which confirmed the presence of the pyrido[1,2-a]pyrimidinium nucleus in the product. The coupling between the two doublets was 4.8 Hz, and not the expected 7.5 Hz, showing that the proton which produces the low field doublet is in the 2-position and that the product is therefore 4,6,8-trimethyl-pyrido[1,2-a]pyrimidinium perchlorate (198).

This reaction is similar to the cyclisation step in the synthesis of 4,6-dimethylquinolizinium salts utilised by Hansen and Amstutz[80].

5.3 Salts from Pentan-2,4-dione



(166 - 171) (199)

i

i

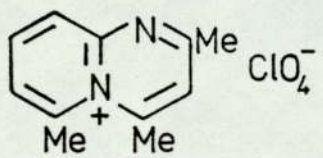
ii

	R^4	R^5	R^6
(200)	H	H	H
(201)	H	Me	H
(202)	Me	H	Me

	R^4	R^5	R^6
(247)	H	H	H
(203)	Me	H	H
(53)	H	Me	H
(54)	H	H	Me
(204)	Me	H	Me
(205)	H	H	OH

i $HClO_4$, ii NaOH.

The 2-aminopyridines (166 - 171) reacted with pentan-2,4-dione (199) in perchloric acid to yield the 2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorates (47, 203, 53, 54, 204 and 205), and ^{1}H n.m.r. spectra showed the presence of a 9-proton or a 9-substituent. The three salts (47, 53, and 54) have also been prepared[23], in better yield, by heating the corresponding 2-aminopyridinium salt with pentan-2,4-dione in ethanol. 2,4-Dimethylpyrido[1,2-a]pyrimidinium perchlorate (47) has also been prepared[19], in lower yield, by heating 2-aminopyridine and pentan-2,4-dione in methanolic hydrobromic acid, then treating the cooled solution with perchloric acid. 2-Amino-6-methylpyridine (181) did not react with pentan-2,4-dione (199) in perchloric acid to yield the salt (206), even when the reagents were in contact for one week.

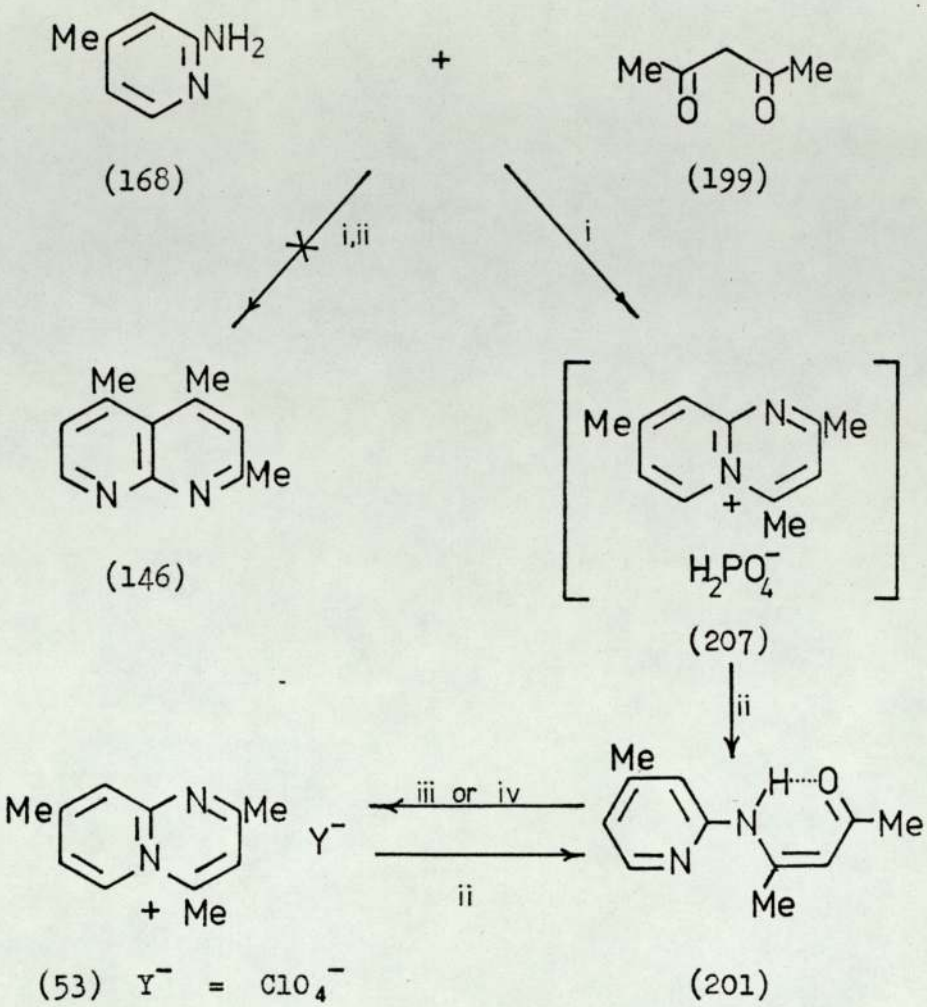


(206)

Three of these salts (47, 53 and 204) were treated with base to yield the enaminones (200 - 202) in order to assist in the determination of the spectroscopic characteristics of this class of compounds.

The enaminone (201) was also important in the elucidation of the reaction path between 2-amino-4-methylpyridine (168) and pentan-2,4-dione (199) in phosphoric acid, at 100°. Singh, Taneja and Narang[102] claimed that these reagents yielded 2,4,5-trimethyl-1,8-naphthyridine (146).

The formation of a naphthyridine under these conditions appeared



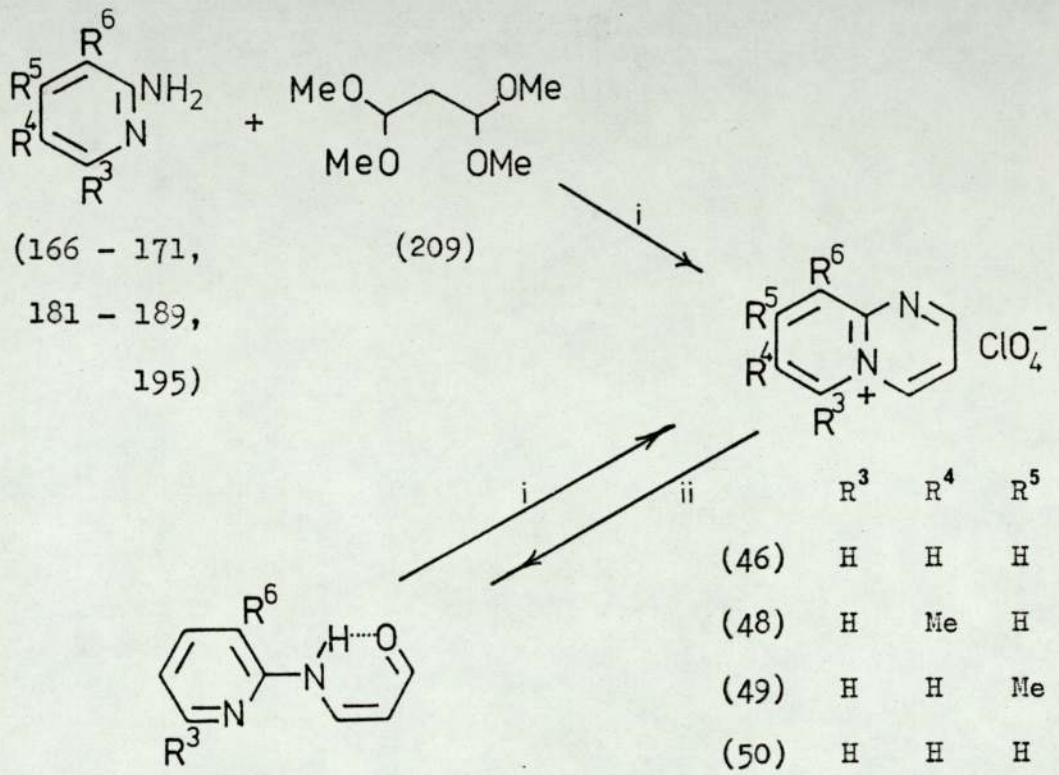
i H_3PO_4, ii NaOH, iii $(NO_2)_3.C_6H_2OH$, iv $HClO_4$.

unlikely for two reasons. Firstly, naphthyridines have only been formed previously from 2-aminopyridines with 6-substituents. Secondly, attempts to form 4,6-disubstituted pyrido[1,2-a]pyrimidinium salts in an acidic medium have been unsuccessful. 4,4-Dimethoxybutan-2-one yields only 2-methylpyrido[1,2-a]pyrimidinium salts with 6-substituted-2-aminopyridines in preference to their 4-methyl isomers, and 2-amino-6-methylpyridine fails to form 2,4,6-trimethylpyrido[1,2-a]pyrimidinium perchlorate (206) with pentan-2,4-dione.

The reaction was repeated under the stated conditions and the sole product isolated, in 80.5% yield, was a pale yellow oil, identified as 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine (201), by comparison of its i.r. and ^{1}H n.m.r. spectra with those of the enaminone derived from 2,4,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (53). The enaminones from both reactions were cyclised with perchloric acid to 2,4,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (53). The proposed naphthyridine was identified, by Singh, Taneja and Narang[102], on the basis of elemental analysis of its picrate. Treatment of the enaminone (201) with picric acid in ethanol yielded a yellow crystalline product. As the picrate may have been the uncyclised derivative of the enaminone (201), the ^{1}H n.m.r. spectrum was recorded in deuterated dimethylsulphoxide, since trifluoroacetic acid may have caused cyclisation and indicated a false structure for this derivative. The ^{1}H n.m.r. spectrum was similar to that of 2,4,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (53), with an additional two proton singlet, assignable to the picryl protons, showing that the picrate was 2,4,8-trimethylpyrido-[1,2-a]pyrimidinium picrate (208). The picrate (208) is isomeric with the picrate of the naphthyridine (146), and therefore has identical required elemental analysis figures.

The formation of the enaminone (201) in this reaction can be explained by initial cyclisation in the phosphoric acid to a pyrido [1,2-a]-pyrimidinium phosphate (207), which is then cleaved by base, as was the pyrido [1,2-a] pyrimidinium perchlorate (53).

5.4 Salts from 1,1,3,3,-Tetramethoxypropane



(166 - 171, 181 - 189, 195)

(209)

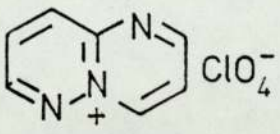
	R^3	R^6
(210)	H	Me
(211)	Me	Et

	R^3	R^4	R^5	R^6
(46)	H	H	H	H
(48)	H	Me	H	H
(49)	H	H	Me	H
(50)	H	H	H	Me
(212)	H	Me	H	Me
(213)	H	H	H	OH
(214)	Me	H	H	H
(215)	Et	H	H	H
(216)	Pr	H	H	H
(217)	Me	H	H	Et
(218)	Me	H	Me	H

i $HClO_4$, ii NaOH.

All the 2-aminopyridines (166 - 171, 181 - 189 and 195) underwent reaction with 1,1,3,3,tetramethoxypropane (209) in perchloric acid to yield the pyrido[1,2-a]pyrimidinium perchlorates (46, 48 - 50, and 212 - 218). N.m.r. and i.r. spectra showed the products to be pyrido-[1,2-a]pyrimidinium perchlorates, as in earlier cases. Four of the salts (46, and 48 - 50) have also been prepared by Khmaruk Volovenko and Chuiguk[23], but in lower yield. The method of Pollak, Stanovnik and Tišler[19] also gave a lower yield of pyrido[1,2-a]pyrimidinium perchlorate (46).

The protons in the 2-, 3- and 4-positions produce an ABX system in the ^{1}H n.m.r. spectra of these compounds, the 2- and 4-protons giving rise to the more deshielded AB portion. Calculations on the ABX system, where this is possible, show that $J_{AX} \sim 6.9 - 7.6$ Hz and $J_{BX} \sim 4.0 - 4.5$ Hz. The ^{1}H n.m.r. spectra of the salts derived from 4,4-dimethoxybutan-2-one show that $J_{3,4} \sim 7.3 - 7.5$ Hz and $J_{2,3} \sim 4.0 - 5.0$ Hz. Thus the 4-H (A) is deshielded more strongly than the 2-H (B). This has also been found in the ^{1}H n.m.r. spectra of pyrimido[1,2-b]-pyridazinium perchlorate (219), (τ 0.00, 4-H; τ 0.21, 2-H)[19], and



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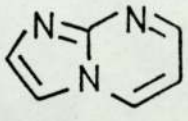


(220)

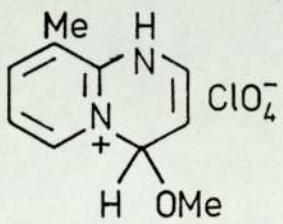
imidazo[1,2-a]pyrimidine (220), (τ 1.28, 4-H; τ 1.40, 2-H)[111] .

2-Amino-3-methylpyridine (169) reacts with 1,1,3,3-tetramethoxypropane in the presence of perchloric acid at room temperature to give an unidentified product (P) which can be converted thermally into the expected product, 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50). The same reaction repeated at 50° gave 9-methylpyrido[1,2-a]pyrimidinium perchlorate directly.

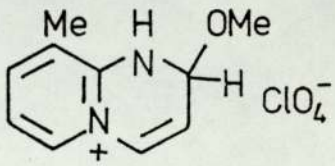
The first indication that the product (P) was not the expected pyrido-pyrimidinium salt was provided by the i.r. spectrum, which showed a strong, sharp absorption band at 3370 cm^{-1}, attributable to a non-protonated N-H grouping ($\overset{+}{N}H$ and $\overset{+}{N}H_2$ groups absorb in the region 2800 - 2000 cm^{-1} [112-114]). The presence of the perchlorate anion is shown by the strong, broad absorption at ca 1100 cm^{-1}, which is common to all the perchlorate salts.

An attempt to record the ^1H n.m.r. spectrum of the product (P) in trifluoracetic acid revealed only an ill-defined replica of the spectrum of 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50) with two additional singlet peaks at τ 5.93 and τ 6.32. After ten minutes at the operating temperature of the instrument (ca 40°) the peak at τ 6.32 had disappeared and the peak at τ 5.93 had increased and now integrated for three protons. The solution now appeared to contain 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50) plus one mole of methanol or methyl trifluoroacetate, indicating that the product (P) was the mono-methanol adduct of 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50). Elemental analysis results did not match those expected for either 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50) or its methanol adduct.

The preparation was repeated at 0°, the product recrystallised by chilling a methanol/ether solution and dried *in vacuo* at room temperature. The elemental analysis results were closer to those expected for the methanol adduct than those obtained earlier. This evidence indicates that the product (P) is an unstable methanol adduct of 9-methylpyrido-[1,2-a]pyrimidinium perchlorate (50), but it is not conclusive. Possible structures for the intermediate (P), which fit the limited data are (221) and (222) below.

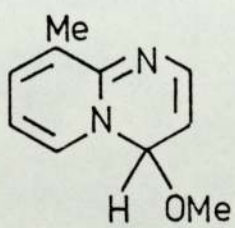


(221)

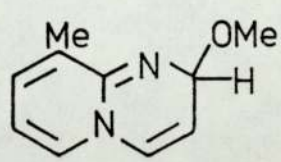


(222)

In an attempt to elucidate which of these structures, if either, is correct, the adduct (P) was treated with one molar equivalent of sodium hydroxide to obtain, it was hoped, the free base (223) or (224). The product obtained, however, was 2-(2-formylvinylamino)-3-methylpyridine (210).

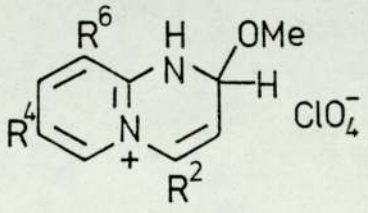


(223)

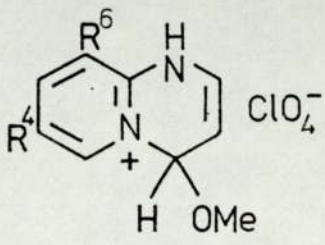


(224)

The reason why the adduct (P) should be stable is not at all clear. If (P) were the 1:1 adduct (222) one might expect the compounds (225 and 226) to be formed under the same conditions, but the electronic effects due to the 4-methyl substituent in (225) may destabilise this adduct. Similarly, if structure (221) were favoured, the adduct (228) might be expected to exist. A 7-methyl substituent has an inductive effect similar to a 9-methyl substituent, both in magnitude and in sites of increased electron density. However, a 7-methyl substituted

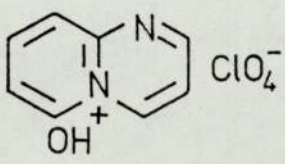


	R^2	R^4	R^6
(225)	Me	H	Me
(226)	H	Me	Me
(227)	H	Me	H

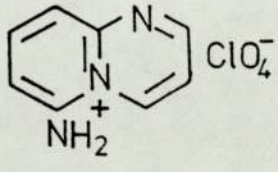


	R^4	R^6
(228)	Me	Me
(229)	Me	H

adduct (227) or (229) has not been detected. It is also surprising that an adduct (226) or (228), where the effect of the 9-methyl substituent is reinforced by that of the 7-methyl substituent, is less stable than the 9-methyl substituted adduct (P). The nature of the adduct (P) and the reasons for its stability thus remain unestablished.



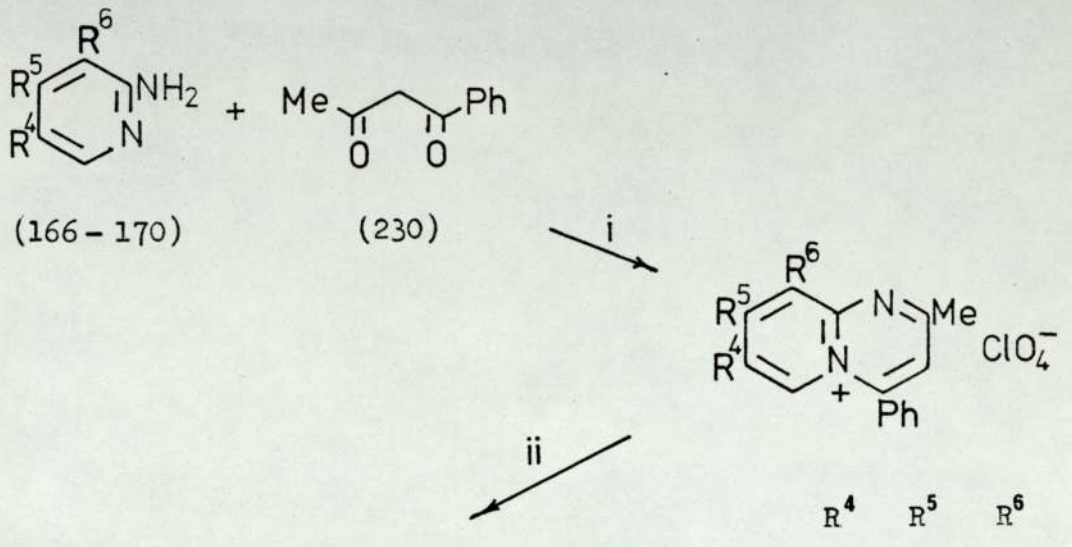
(229a)



(229b)

2-Amino-6-hydroxy- and 2,6-diamino- pyridines both failed to react with 1,1,3,3-tetramethoxypropane to yield the salts (229a and 229b) but gave unidentified coloured products, which were possibly polymeric in nature.

5.5 Salts from 1-Phenylbutan-1,3-dione



(166 - 170) (230)

i ii

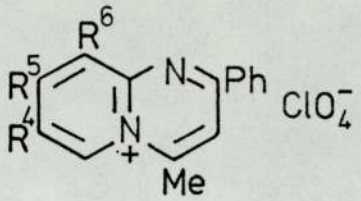
	R^4	R^5	R^6
(231)	H	H	H
(232)	Me	H	H
(233)	H	Me	H
(234)	H	H	Me
(235)	Me	H	Me

	R^4	R^5
(236)	Me	H
(237)	H	Me

i $HClO_4$, ii NaOH.

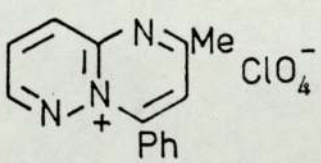
The pyrido[1,2-a]pyrimidinium salts formed from the 2-aminopyridines (166 - 170) and 1-phenylbutan-1,3-dione (230), in perchloric acid, could have the phenyl substituent at the 2-position, as in the salt (238) or in the 4-position, as in the salts (231 - 235), due to the asymmetry of the diketone. Cleavage of two of the salts with hydroxide ions has formed the 2-(2-benzoyl-1-methylvinylamino)pyridines (236 and

237), the structures of which have been elucidated spectroscopically (see section 7). This shows that the salts are in fact the 2-methyl-4-phenyl-pyrido[1,2-a]pyrimidinium perchlorates (231 - 235).

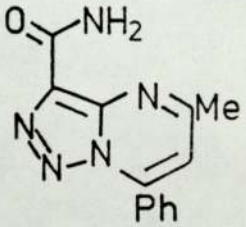


(238)

The behaviour of the 1-phenylbutan-1,3-dione (230) is similar to that of 4,4-dimethoxybutane-2-one (27) in that only one of two possible isomers is formed. This is consistent with preferential condensation between the primary amino group and the more reactive carbonyl group; the acetal group in 4,4-dimethoxybutan-2-one (27) and the acetyl group in 1-phenylbutan-1,3-dione (230). The same orientation of the 1-phenylbutan-1,3-dione fragment has been found by several authors[19,115] in other fused pyrimidine heterocyclic compounds (239 and 240), formed by condensation of α-amino hetercycles with 1-phenylbutan-1,3-dione in acidic media.

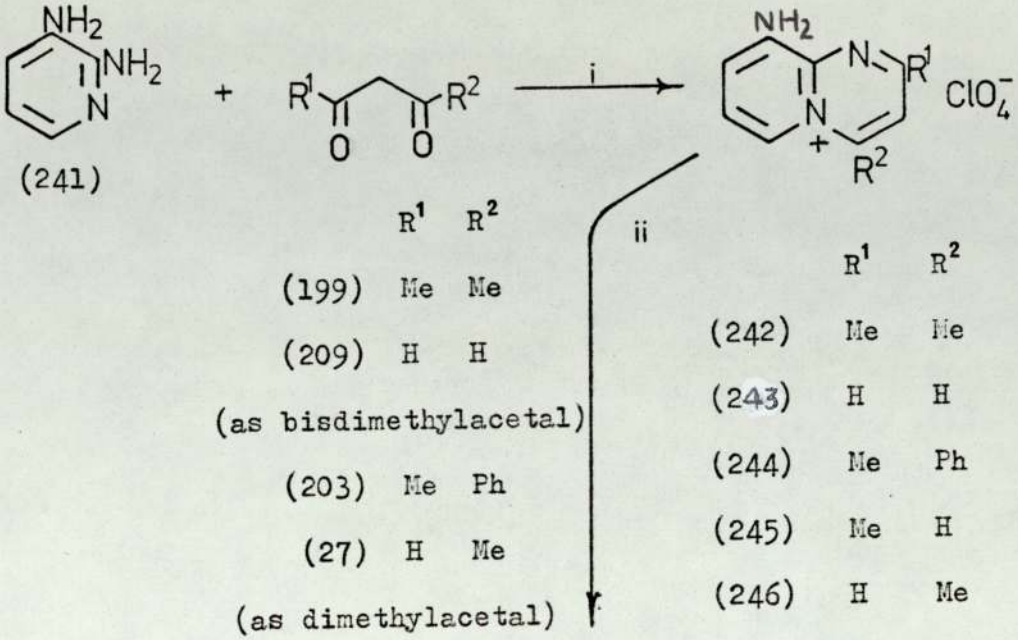


(239)



(240)

5.6 Salts derived from 2,3-Diaminopyridine



	R^1	R^2
(199)	Me	Me
(209)	H	H
(as bisdimethylacetal)		
(203)	Me	Ph
(27)	H	Me
(as dimethylacetal)		

	R^1	R^2
(242)	Me	Me
(243)	H	H
(244)	Me	Ph
(245)	Me	H
(246)	H	Me

	R^1	R^2
(247)	Me	Me
(248)	H	H
(249)	Me	Ph
(250)	Me	H
(251)	H	Me

i $HClO_4$, ii NaOH.

The reactions of 2,3-diaminopyridine (241) have been segregated because of the possible alternative products which may arise by condensation of the 3-amino group with the dicarbonyl compound.

The two symmetrical dicarbonyl compounds, pentan-2,4-dione (199) and 1,1,3,3-tetramethoxypropane (209) form 9-amino-2,4-dimethylpyrido-[1,2-a] pyrimidinium perchlorate (242) and 9-aminopyrido[1,2-a]-pyrimidinium perchlorate (243) respectively, which are easily identifiable from their i.r. and ^{1}H n.m.r. spectra. The unsymmetrical 1-phenylbutan-1,3-dione (230) forms the 2-methyl-4-phenyl salt (244) identified by the i.r., ^{1}H n.m.r. and mass spectra of the derived vinylamine (249). These salts (242 - 244) are those expected by analogy with the salts formed by alkyl and hydroxy substituted 2-aminopyridines.

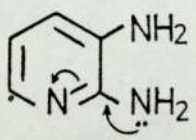
The products from the reaction of 2,3-diaminopyridine (241) and 4,4-dimethoxybutan-2-one (27) are more surprising. In one reaction the product obtained was identified as 9-amino-2-methylpyrido[1,2-a]-pyrimidinium perchlorate (245) by the ^{1}H n.m.r. spectrum which showed a low field doublet, J = 7.6 Hz, indicative of 4-H (see sections 5.2 and 5.4). In a repeat of this reaction the product obtained was a mixture of 9-amino-2-methylpyrido[1,2-a]pyrimidinium perchlorate (245) and 9-amino-4-methylpyrido[1,2-a]pyrimidinium perchlorate (246) in which the former predominates. This was shown by ^{1}H n.m.r. in deutero dimethylsulphoxide where a greater deshielded doublet (τ 0.86) showed a splitting of 7.6 Hz [4-H, salt (245)] and a lesser deshielded doublet (τ 1.01) showed a splitting of 4.7 Hz [2-H, salt (246)].

Attempts to ring-open the first salt formed, to the acylvinylamino-pyridine (250) to confirm the structure of the salt, provided only a red product which could not be identified or purified further. Treatment of the salt mixture with sodium hydroxide provided a similar red product, but column chromatography provided a small trace of 2-(2-acetylvinylamino)-3-aminopyridine (251), identified by the mass spectrum, which was derived from the salt (246).

The red product may be a polymer, produced by condensation between the aldehyde and 3-amino functions of 3-amino-2-(2-formyl-1-methylvinylamino)pyridine (250). A similar product is not found when the vinylaminopyridines (247) and (249) are formed, presumably because acetyl and benzoyl carbonyls are less reactive than an aldehyde carbonyl. As 3-amino-2-(2-formylvinylamino)pyridine (248) is formed without occurrence of a similar red product, it appears that the aldehyde function must be activated further for such a product to be formed. In 3-amino-2-(2-formyl-1-methylvinylamino)pyridine (250) this activation may be provided by the methyl group as it is the only group not present in the vinylamine (248).

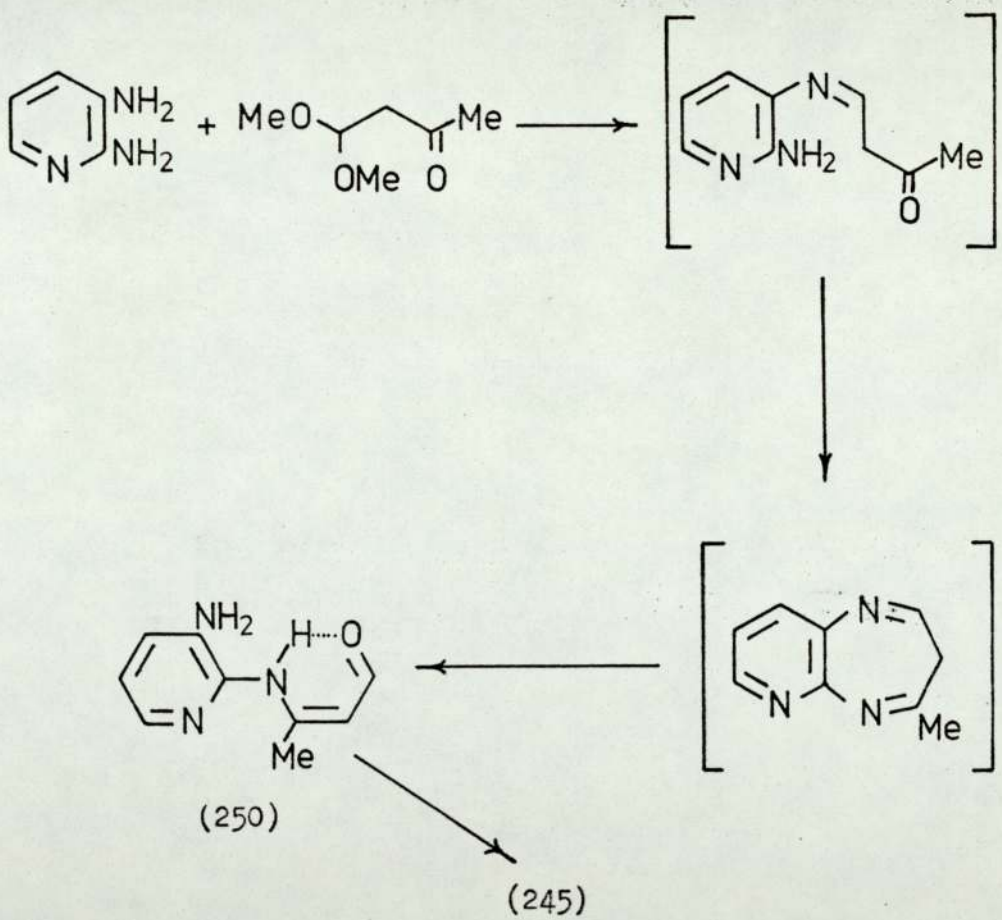
The formation of 3-amino-2-methylpyrido[1,2-a]pyrimidinium perchlorate (245) is unexpected, since 4,4-dimethoxybutan-2-one was induced to react with 2-aminopyridines to yield a 4-methyl substituted pyrido[1,2-a]-pyrimidinium salt as the sole product, except in those examples where the aminopyridine bore a 6-substituent. As 2,3-diaminopyridine (241) bears no substituent at the 6-position, the orientation of the methyl group must be governed by the 3-amino group.

Delocalisation of the lone pair electrons of the 2-amino group (252) make it less basic than the 3-amino group, which cannot couple with the annular nitrogen atom.



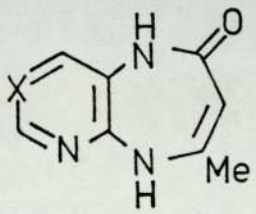
(252)

It is therefore possible that the more reactive acetal function condenses with the more basic 3-amino group in the first instance leaving the acetyl carbonyl free to condense with the 2-amino function (Scheme 5). As the imines (or enamines) so formed are not stabilised by aromatic delocalisation in the seven-membered diazepin ring, hydrolysis in the acidic medium to the 3-amino-2-(2-formyl-1-methylvinylamino)pyridine (250) is possible. The enamine (250) (or the imine tautomer) may then cyclise to the ring nitrogen to give the stabilised 3-amino-2-methyl-pyrido[1,2-a]pyrimidinium perchlorate (245).



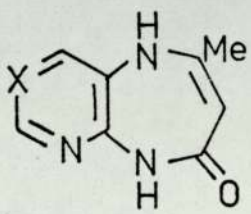
Scheme 5

The diazepinones (253) and (255), which are similar to the bicyclic intermediate in Scheme 5, have been prepared[116] from 2,3-diaminopyridine and ethylacetoacetate. The formation of the two possible isomers has been attributed by the authors to the reaction of either the ester or the acetyl group with the 3-amino group, followed by cyclisation. In a similar reaction with 4,5-diaminopyrimidine, two intermediates (257)



(253) X = CH

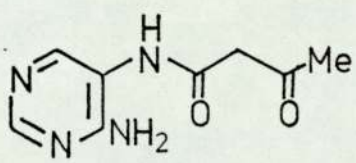
(254) X = N



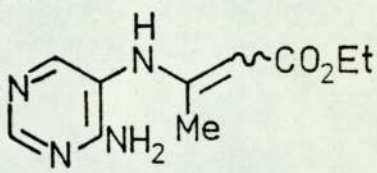
(255) X = CH

(256) X = N

and (258), which are comparable to those postulated for the syntheses of the diazepinones (253) and (255), have been isolated, as well as the diazepinones (254) and (256)[117].



(257)



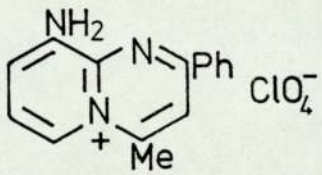
(258)

Since 9-amino-4-methylpyrido[1,2-a]pyrimidinium perchlorate (246) is formed, as well as 9-amino-2-methylpyrido[1,2-a]pyrimidinium perchlorate (245), in the reaction of 2,3-diaminopyridine (241) with 4,4-dimethoxybutan-2-one (27), it is therefore possible that this too is formed by a 'walkabout' mechanism, similar to Scheme 5, with initial

condensation between the acetyl carbonyl and the 3-amino group.

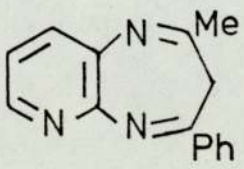
Similar mechanisms are possible in the cases of 1,1,3,3-tetramethoxypropane (209) and pentan-2,4-dione (199) but here the structure of the pyrido pyrimidinium salts will be identical, whether initial condensation is with the 2- or 3-amino group, due to the symmetry of the dicarbonyl compounds.

1-Phenylbutan-1,3-dione may be expected to yield the 'abnormal' salt (259) by the 'walkabout' mechanism, initial condensation being between the more reactive acetyl and 3-amino groups. However, the product obtained by this reaction has been shown to be the 2-methyl-4-phenyl substituted isomer (244). This is not consistant with the 'walkabout' mechanism but could be explained if the diazepin intermediate (260)

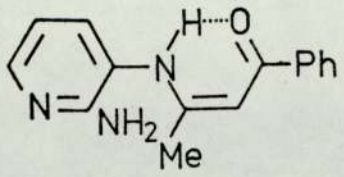


(259)

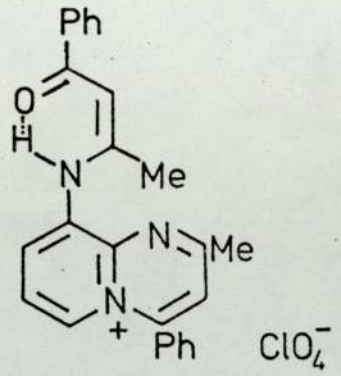
formed in such a mechanism were more susceptible to acid hydrolysis at the benzoyl-imine linkage than at the acetyl-imine linkage to yield the enamine (261). Alternatively, the benzoyl carbonyl in the enamine (261) may react more slowly with the 2-amino group than the acetyl



(260)



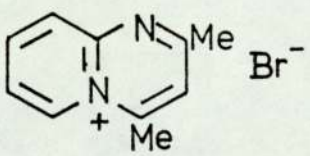
(261)



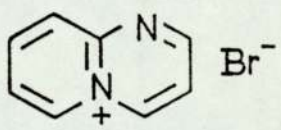
(262)

group of a second molecule of 1-phenylbutan-1,3-dione so that the salt (262) is formed in preference to the diazepin (260). Hydrolysis of the residual enamine function in the salt (262) yields the salt (244).

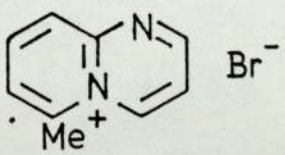
5.7 Pyrido[1,2-a]pyrimidinium Bromides



(263)



(264)



(265)

The three pyrido[1,2-a]pyrimidinium bromides (263 - 265) have been

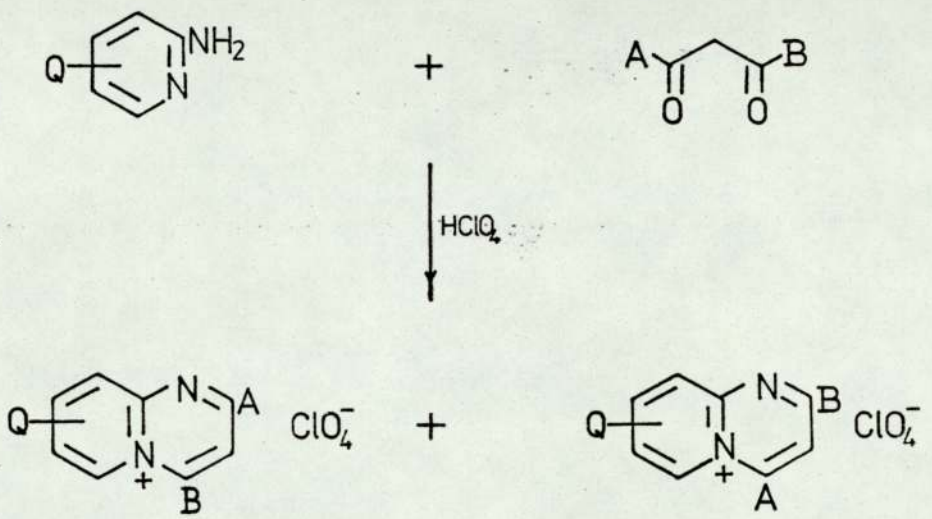
prepared in the same way as their perchlorate salt counterparts (47, 46 and 214) from the 2-aminopyridines and a β-dicarbonyl compound with hydrobromic acid.

Nesmeianov, Rybinskaia and Belsky[20] have stated that the pyrido[1,2-a]-pyrimidinium bromides which they prepared were less stable than the perchlorates. This has also been found to be true in the three cases here, all of which darken upon storage in the crystalline state.

6. MECHANISTIC INTERPRETATION

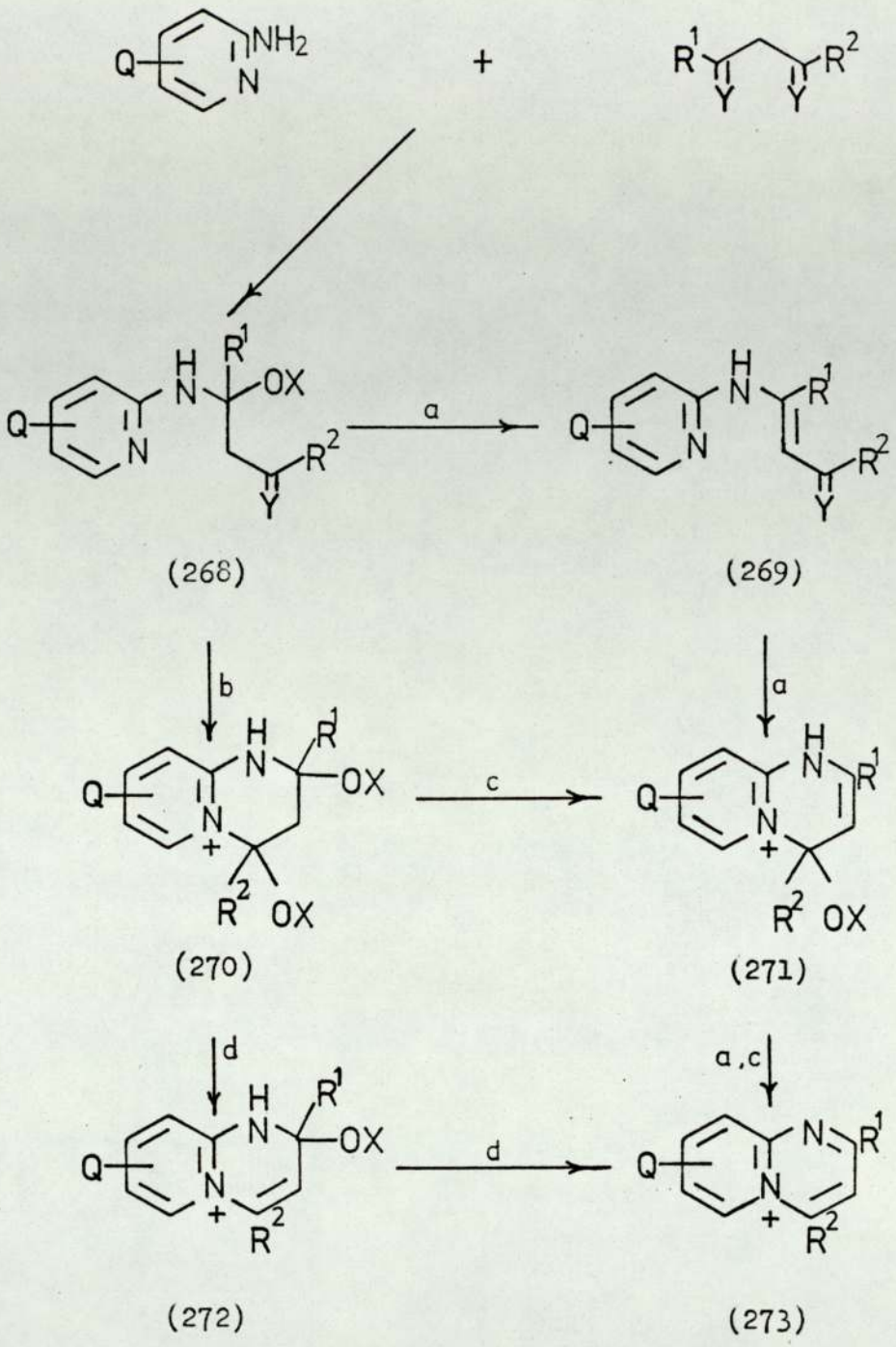
6.1 Formation of Pyrido[1,2-a]pyrimidinium Salts from 2-Aminopyridines and β-Dicarbonyl Compounds

The 2-aminopyridines contain two nucleophilic centres, the ring nitrogen atom and the 2-amino group. The β-dicarbonyl compounds contain two electrophilic centres; the two carbonyl carbon atoms. It is therefore theoretically possible to obtain two isomeric pyrido[1,2-a]-pyrimidinium salts (266) and (267), when the dicarbonyl compound is unsymmetrical. However, in the reaction of 4,4-dimethoxybutan-2-one



(266) (267)

and 1-phenylbutan-1,3-dione with 2-aminopyridines, only one isomer has been isolated in each case, with the exception of the reaction between 2,3-diaminopyridine and 4,4-dimethoxybutan-2-one (see Section 5.6). With the exception of 6-substituted-2-aminopyridines, all the amino-pyridines gave salts which were structurally those which would result from the interaction of the more reactive carbonyl of the β-dicarbonyl (i.e. the acetal of 4,4-dimethoxybutan-2-one and the acetyl carbonyl of



Y = O, $(MeO)_2$; X = H, Me; R^1 = alkyl, H;

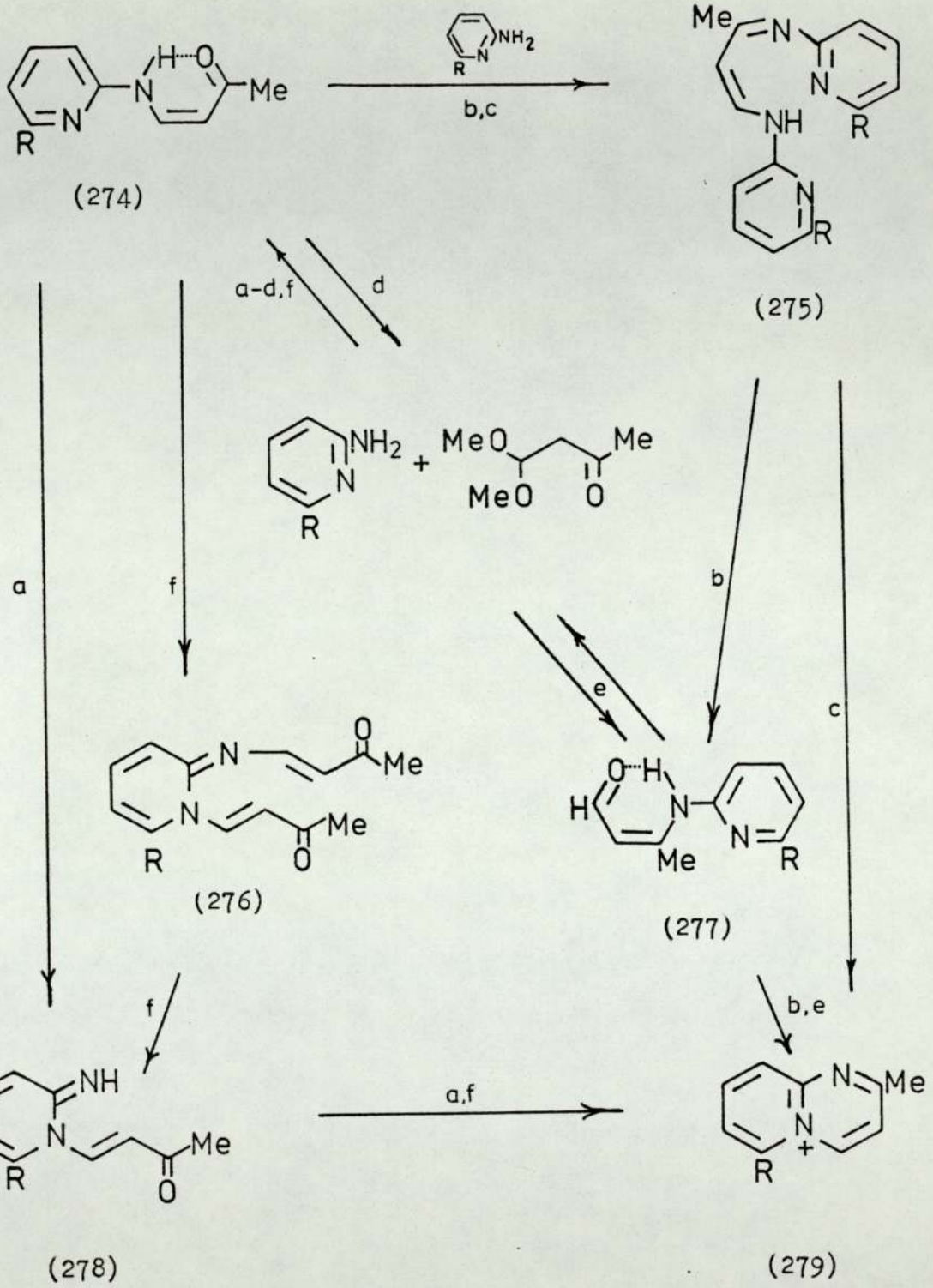
R^2 = alkyl, H, phenyl; Q = alkyl, OH.

Scheme 6

1-phenylbutan-1,3-dione) with the 2-amino group. Condensation of 4,4-dimethoxybutan-2-one with 2-aminopyridines in boiling xylene follows this order of reactivity to yield 2-(2-acetylvinylamino)-pyridines. These vinylamines are rapidly cyclised by perchloric acid to yield 4-methylpyrido[1,2-a]pyrimidinium perchlorates, identical to those formed in the one-step reaction. This would indicate that the immediate precursor (268) of the 2-(2-acylvinylamino)pyridines (269) is an intermediate in the one-step reaction. Elimination of one mole of solvent (HOX, X=H or Me) forms the vinylamine (269), cyclisation of which leads to the pyrido[1,2-a]pyrimidinium salt (273) [Scheme 6, path (a)]. Alternatively, cyclisation of the intermediate (268) without elimination forms (270), loss of solvent (HOX, X=H or Me) from which may proceed *via* either path (c) or path (d) (Scheme 6).

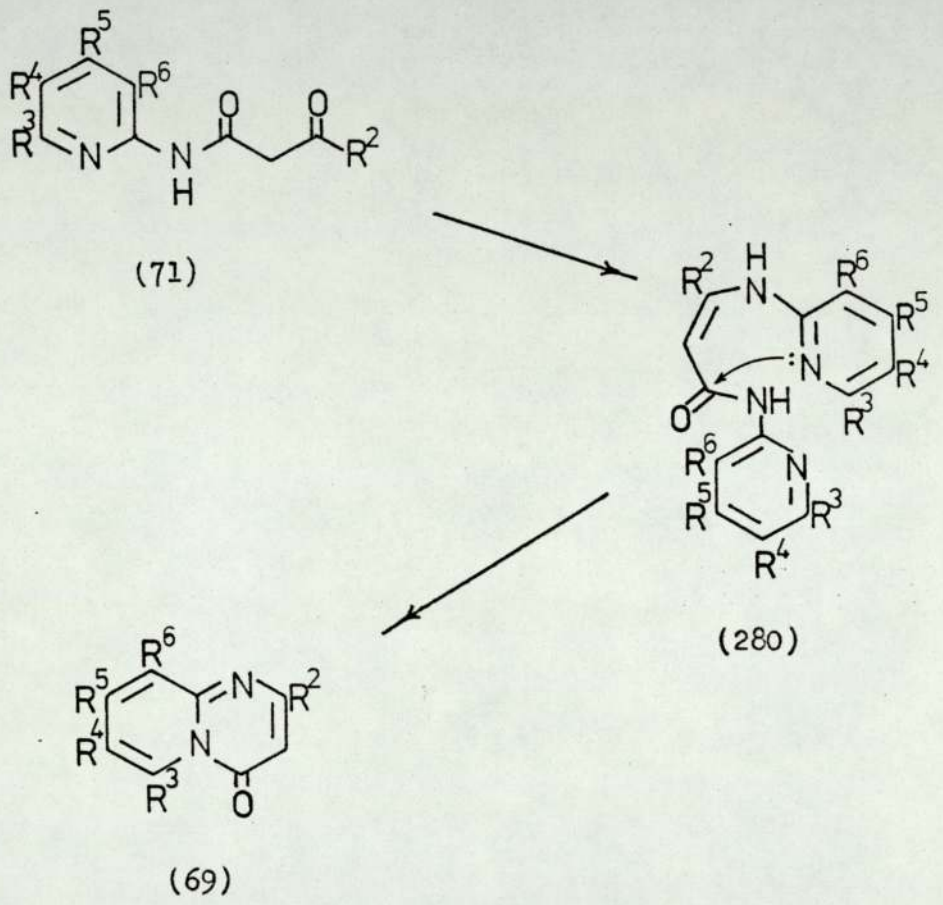
In the reaction between 2-amino-3-methylpyridine and 1,1,3,3-tetramethoxypropane an unidentified product (P) was isolated, which was suggested to be a methanol adduct (221) [(271) $R^1=R^2=H$, X=Me, Q=9-Me] or (222) [(272) $R^1=R^2=H$, X=Me, Q=9-Me]. If either of these is the true structure, then this would indicate that, in the cases where acetal derivatives of β-dicarbonyl compounds have been used, the acetals react directly with the 2-aminopyridine and not as derived aldehydes.

6-Substituted-2-aminopyridines form 2-methyl substituted salts with 4,4-dimethoxybutan-2-one. The switch from the normal 4-methyl derivative to the 2-methyl derivative is attributable to steric crowding by the 6-substituent of the 4-position. This steric inhibition is also responsible for the failure of 2-amino-6-methylpyridine (181) and pentan-2,4-dione (199) to form a stable salt. Several mechanisms for the formation of these products are plausible and are illustrated in Scheme 7.



Scheme 7

All these proposed routes commence with the premise that the more reactive entities, the 2-amino and acetal groups, combine in the first instance to form the 2-(2-acetylvinylamino)pyridines (274). From this initial intermediate there are four possible ways in which it can rearrange.



(71) (280) (69)

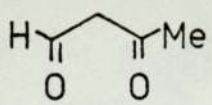
Scheme 8

Path (a) (Scheme 7) is comparable to the mechanism proposed by Khalifa[30] for the cyclisation of 2-(2-acylacetylamino)pyridines (71) to 2-substituted-4H-pyrido[1,2-a]pyrimidin-4-ones (69), where a migration from the 2-amino group to the ring nitrogen occurs prior to ring closure. An alternative mechanism for the cyclisation of (71) to (69) has been postulated by Shur and Israelstam[31], where a second molecule of 2-amino-pyridine combines with the keto carbonyl in (71) to form an enamino

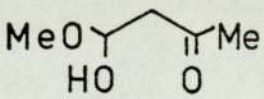
derivative (280) (Scheme 8). Attack by the ring nitrogen of the second pyridine moiety on the amide carbonyl group produces the cyclised product (69) and regenerates the 2-aminopyridine. Path (c) (Scheme 7) illustrates an analogous mechanism for the rearrangement of the 2-(2-acetylvinylamino)pyridine (274). Path (b) is a minor variation of this mechanism, where the aldehyde imine is hydrolysed to yield the 2-(2-formyl-1-methylvinylamino)pyridine (277), which then cyclises to the salt (279).

Similarly a second molecule of the dicarbonyl compound may condense with the ring nitrogen to form a diadduct similar to (276), which then hydrolyses at the 2-amino group to form the monoadduct (278) [path (f)]. This may then cyclise by condensation between the acetyl carbonyl and the 2-imino group as in path (a).

The fourth route is controlled kinetically. Formation of the vinylamine (274) or the immediate precursor (268; R^1=H, R^2=X=Me, Y=O and Q=6-alkyl) may now be followed by cyclisation to the intermediates (270 or 271; R^1=H, R^2=Me, 2-OX=OMe, 4-OX=OH, Q=6-alkyl) which could form, as the configuration at C-4 is staggered relative to the 6-alkyl group, and the steric constraint is not very great. However, loss of the hydroxyl group at C-4 would force the 4-methyl and 6-alkyl groups into coplanarity, where the steric forces would be greater. This energy barrier is too great to be overcome, so hydrolysis back to the immediate precursor (268) of the enamine or to the 2-(2-acetylvinylamino)pyridine (269) itself, allows this product to revert to starting materials, the dicarbonyl derivative probably being formed as either butan-1,3-dione (281) or 4-hydroxy-4-methoxybutan-2-one (282) [Scheme 7 path (d)].



(281)



(282).

Condensation of the acetyl carbonyl with the 2-amino group is much slower than the acetal condensation, as shown by the formation of 4-methylpyrido[1,2-a]pyrimidinium salts with no detectable 2-methyl isomer, when no 6-substituent is present. Any acetyl condensation product that does form may stabilise itself by cyclising to the pyrido[1,2-a]pyrimidinium salt (278) as forcing a proton into coplanarity with the 6-alkyl group has little steric resistance. Cyclisation of 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185) (277; R=Me) is a facile reaction and has been performed by precipitation from an ether/methanol mixture by perchloric acid. This reaction sequence is illustrated in Scheme 7, path (e).

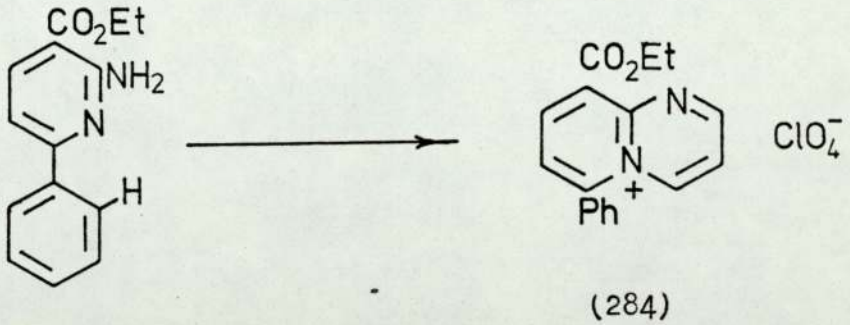
The vinylamine (183) (274; R=Me) is a stable compound formed by the thermal condensation of 2-amino-6-methylpyridine and 4,4-dimethoxybutan-2-one in xylene. The rearrangement in path (a) could not be a spontaneous reaction, but if it does occur in the acid medium it is probably acid catalysed. Treatment of the vinylamine (183) with one molar equivalent of acid for twenty four hours, which was the time in which 2,6-dimethylpyrido[1,2-a]pyrimidinium perchlorate (182) was allowed to form by the one-step route, yielded only the vinylamine perchlorate salt (184). A similar reaction using two molar equivalents of acid yielded 2-amino-6-methylpyridinium perchlorate as the only detectable product. It therefore seems unlikely that path (a) is the route taken in the formation of 2,6-dimethylpyrido-[1,2-a]pyrimidinium perchlorate (182). It is also unlikely that path (f) is correct, for during the hydrolysis of the vinylamine (183) with perchloric acid, a derivative of 4,4-dimethoxybutan-2-one must be formed, which could form a diadduct (276; R=Me) with the remaining vinylamine (183). This route cannot be discounted entirely, for the derivative of 4,4-dimethoxybutan-2-one formed on hydrolysis may not

be sufficiently active to form a diadduct (e.g. a dimer of butan-1,3-dione) whereas 4,4-dimethoxybutan-2-one itself may have the correct reactivity.

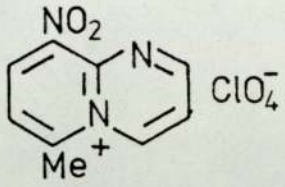
Paths (b) and (c) were tested by treating an equimolar mixture of 2-(2-acetylvinylamino)-6-methylpyridine (183) and 2-amino-6-methylpyridine (181) both with one and two molar equivalents of acid. In both cases only 2-amino-6-methylpyridinium perchlorate was found.

The fourth route, path (e), after path (d) has failed to give a stabilised product, seems to be the most likely mode of reaction.

Both 2-amino-6-methyl-3-nitropyridine (194) and 2-amino-3-carbethoxy-6-phenylpyridine (283) failed to form the pyridopyrimidinium salts (284 and 285). In both cases the 3-substituent is electron withdrawing which lessens the electron density at the ring nitrogen and hence reduces nucleophilic activity. In the case of 2-amino-3-carbethoxy-6-phenyl pyridine, steric hindrance would also inhibit reaction.



(283) (284)



(285)

2-Amino-4,6-dimethylpyridine (195) was combined with 1,1,3,3-tetramethoxypropane (209) to form 6,8-dimethylpyrido[1,2-a]pyrimidinium perchlorate (218) in perchloric acid but with 4,4-dimethoxybutan-2-one (27) the expected 2,6,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (196) was not formed. The other 6-alkylated-2-aminopyridines that have been tested all formed 2-methyl substituted pyrido[1,2-a]-pyrimidinium perchlorates with 4,4-dimethoxybutan-2-one (27) in perchloric acid. 2-Amino-4,6-dimethylpyridine (195) would be expected to be the most reactive of the 2-aminopyridines as methyl substituents increase electron density at the annular nitrogen, those ortho and para to it having greater effect than those in the meta position. The increased electron density at the ring nitrogen is reflected in the pK_a values for the methyl substituted 2-aminopyridines (Table I).

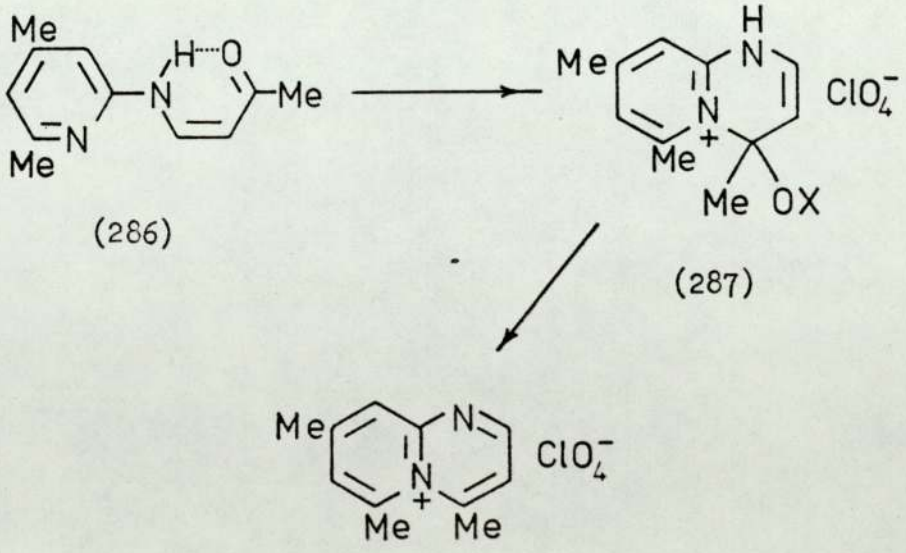
All the possible mechanisms discussed have involved the free base form, as the annular nitrogen in the conjugate acid is not free to react. In the base — salt equilibrium there will always be some free base available for cyclisation, which will be replaced to restore equilibrium. As the value of pK_a for 2-amino-4,6-dimethylpyridine (195) is higher than for the other aminopyridines, it follows that there will be less free base in the equilibrium mixture. This does not effect the formation of 6,8-dimethylpyrido[1,2-a]pyrimidinium perchlorate (218), but the more complex reaction of 4,4-dimethoxybutan-2-one (27) with

TABLE I

pK_a of Methyl Substituted 2-Aminopyridines[118]

2-Aminopyridine	Position of Me(s)	pK_a
(166)	-	6.86
(167)	5	7.22
(169)	3	7.24
(181)	6	7.41
(168)	4	7.48
(195)	4,6	7.84

6-substituted 2-aminopyridines may be effected by this. Formation of 4,6,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (198) in acetic anhydride may arise from the initial thermal condensation of the 2-amino and acetal groups to form the intermediate vinylamine (286), which would then cyclise to the bicyclic intermediate (287; X=H or Ac:



(286)

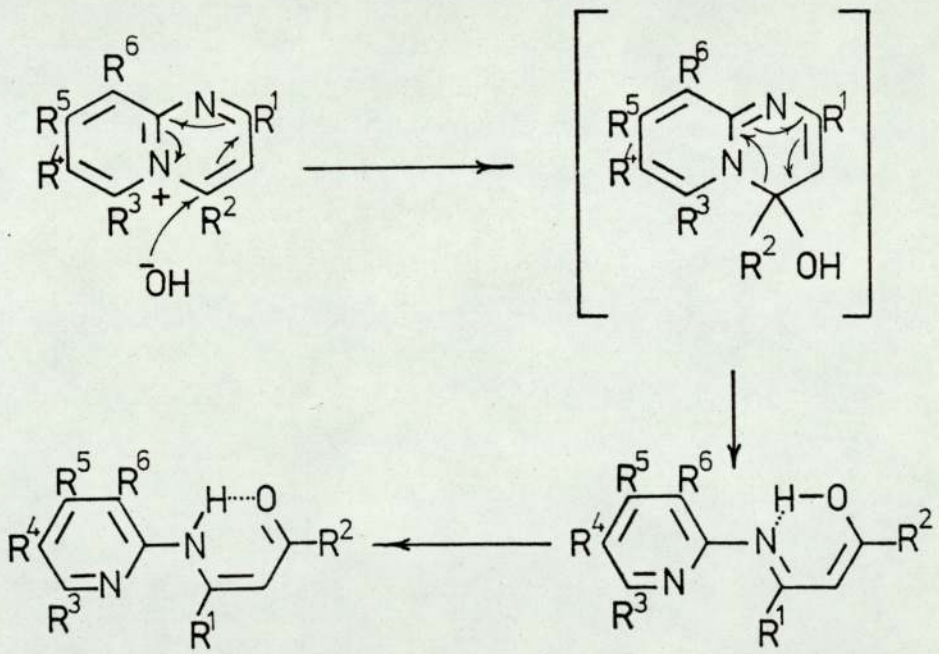
(287)

(198)

cf 267). The reactivity of the acetic anhydride is sufficient to overcome the energy barrier due to steric constraint between the 4- and 6-methyl groups.

6.2 Hydroxylic Ring Cleavage of Pyrido[1,2-a]pyrimidinium Salts

From theoretical calculations[16] on the pyrido[1,2-a]pyrimidinium nucleus (1), the low electron density at the 2-position has lead to the prediction that anionoid substitution will occur at C-2. However, in this work and in previous hydroxylic ring cleavage reactions of 4-methylpyrido[1,2-a]pyrimidinium salts[20], attack of the hydroxide ion has been found to occur at C-4.



Nesmeianov, Rybinskaia and Belsky[20] have stated that the initial step is replacement of the anion by an hydroxide ion. In solution this is simply a question of exchanging anions between ion pairs. As charge separation would result in impossibly high energy states both the

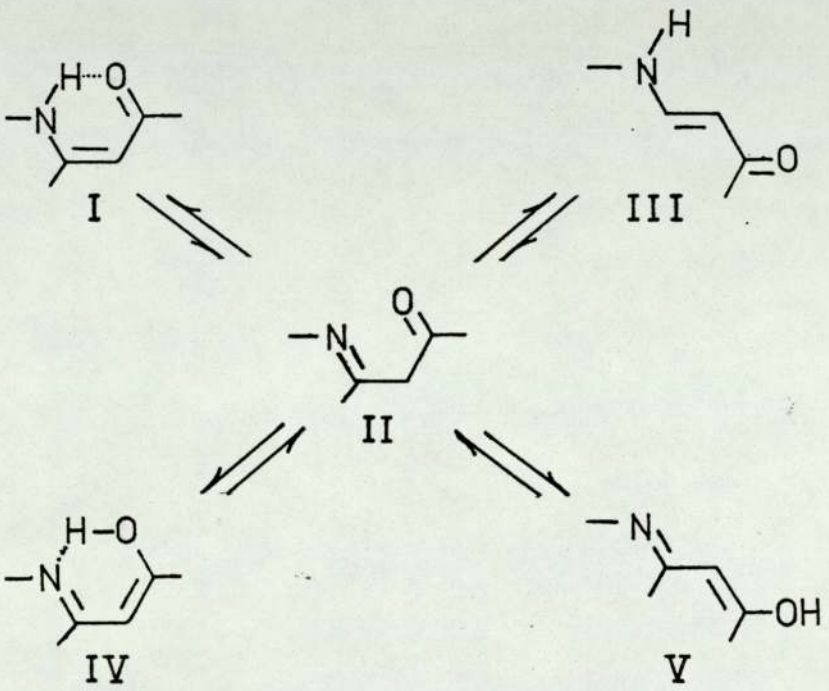
pyrido [1,2-a] pyrimidinium nucleus and the hydroxide ion will remain closely paired, the hydroxide ion residing close by the positively charged bridgehead nitrogen. The low electron density at the nearby C-4 atom encourages attack at this site to yield the intermediate (288) which stabilises itself by ring opening, i.e. aromaticity is restored to the pyridine ring.

The theoretical work[16] was carried out only for the unsubstituted nucleus, the introduction of substituents into the nucleus may have redistributed the electron density slightly, thus favouring anionoid attack at C-4.

7. 2-(2-ACYLVINYLAMINO)PYRIDINES - SPECTROSCOPIC STRUCTURE ELUCIDATION

7.1 Introduction

Replacement of a carbonyl oxygen in a 1,3-dicarbonyl compound with a primary or secondary nitrogen function yields a product which may exist in any or all of the tautomeric forms I - V.

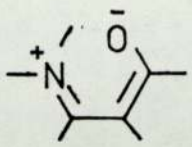


The spectroscopic evidence outlined below shows that the products formed by hydroxylic ring cleavage of pyrido[1,2-a]pyrimidinium perchlorates exist predominantly or exclusively in the cis-enaminone form I.

7.2 Infra-red Spectra

The majority of the ring opened products exhibited NH stretching bands in the range 3320 - 3200 cm^{-1} which corresponds to the absorptions found for a range of chelated enamino-carbonyl compounds[48, 100, 119-121]. In the 3-amino substituted enaminones (247-249) this band is additional to the normal doublet, in the range 3420 - 3320 cm^{-1}, attributable to the primary amino group. It is well documented[120, 121] that, in some cases, chelated NH groups show NH stretching absorptions at wave numbers only slightly different from free NH groups.

Carbonyl absorption frequencies for the enaminones are to be found in the range 1675 - 1620 cm^{-1}. This low value for the carbonyl frequency is not compatible with the strength of the hydrogen bond indicated by the small shift found for the NH stretch frequency. The suggestion[122, 123] has been made that in these cases the valence bond resonance structure (289) may contribute appreciably to the ground state electronic configuration of the enamino carbonyl compounds. This proposal is derived from the low carbonyl frequencies found in the i.r. spectra of enaminones bearing fully substituted amino groups. The π electron delocalisation represented by structure (289) may also account for the other strong bands in the range 1600 - 1500 cm^{-1}, which have been interpreted as being due to coupled C=C and $C=\overset{+}{N}$ intensified by conjugation[122, 123]. Absorptions due to C=C and C=N of the pyridine ring also accour in this region[124] together with a combination bond of N-H deformation and C-N stretch which is comparable to the amide II band[122, 123]. The deformation bands due to the primary amino group in the 3-amino derivatives further complicate



(289)

the spectrum in this region in the cases of the enaminones (247 - 249), as do the frequencies due to benzene ring in the enaminones (236, 237 and 249). The multiplicity of functions present in the enaminones, which give rise to bands in the range 1600 - 1500 cm^{-1}, make detailed assignments impossible without further exhaustive investigation.

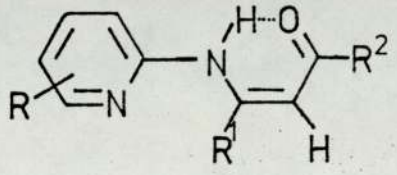
7.3 Proton Magnetic Resonance Spectra

The tautomeric form II is not apparent in the spectra of any of the enaminones (172, 183, 185, 200-202, 210, 211, 236, 237, 247-250). The presence of the hydrogen bonded chelate ring form I is inferred from the large paramagnetic shifts ($\tau \leq 0$) of the signals due to the NH protons both for the cis-enaminones found in the literature [125 - 129] and for the enaminones derived here from pyrido [1,2-a] pyrimidinium salts (Table 2). trans-Enaminones which do not contain intramolecular hydrogen bonds, exhibit NH proton resonance peaks which are deshielded to a lesser extent (τ ca 5)[125, 126] .

The enaminone form I has been shown to be more stable than the enol-imine form IV in the case of the benzylamine condensation product with 2-acetyl-1-naphthol (290) even at the expense of aromatic

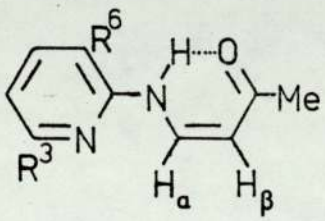
TABLE 2

N.M.R. Spectra of 2-(2-Acylvinylamino)pyridines

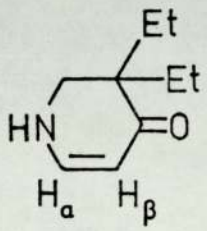


Substituents			τ values					
R	R^1	R^2	H–C(=O)–N	Me–C(=O)–N	HC(=O)–C	O=CMe	O=CH	NH
H	H	Me	2.07	-	4.62	7.86	-	-1.69
$3NH_2$	H	Me	1.97	-	4.54	7.83	-	-1.86
6Me	H	Me	2.09	-	4.74	7.93	-	-1.61
6Me	Me	H	-	7.54	4.85	-	0.91	-2.76
3Me	H	H	1.82	-	4.55	-	0.59	-1.90
3Et, 6Me	H	H	1.83	-	4.67	-	0.72	-1.85
H	Me	Me	-	7.58	4.88	8.00	-	-2.91
$3NH_2$	Me	Me	-	7.71	5.59	7.93	-	-2.60
4Me	Me	Me	-	7.58	4.90	8.00	-	-2.69
$3,5Me_2$	Me	Me	-	7.62	5.03	8.04	-	-2.72
$3NH_2$	Me	Ph	-	7.54	4.03	-	-	-3.15
4Me	Me	Ph	-	7.47	4.20	-	-	-3.48
5Me	Me	Ph	-	7.47	4.12	-	-	-3.47

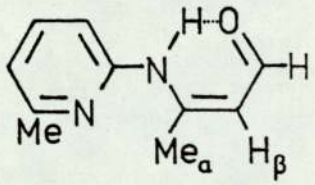
stabilisation energy, by the coupling observed between the benzyl methylene and amino protons[127].



	R^3	R^6
(172)	H	H
(183)	Me	H
(250)	H	NH_2



(291)



(185)

The enaminones (172, 183 and 250) all exhibited a low field proton signal at τ ca 2 attributable to H_α. The α-proton signal in related enamino-carbonyl compounds has been reported[125] to occur at τ 3.1 - 3.4. The greater degree of deshielding is probably due to the close proximity of the annular nitrogen atom to H_α. These α-protons reveal a coupling to the NH protons of 11.9 - 12.2 Hz, indicating a trans arrangement of these protons accross a rigid C-N

bond. These values are in close agreement with the values of 11 - 13 Hz found in the literature[46, 48, 100, 125, 130,] for the trans HC-NH coupling constants in enamino-carbonyl compounds. Coupling across a rigid cis HC-NH bond, in the tetrahydropyridine (291), has been reported[131] to be only 6 Hz. The α-proton also shows cis olefinic coupling which is reflected in the β-proton doublet and is similar in magnitude to the value of 8.0 Hz reported[131] for $J_{\alpha,\beta}$ in the tetrahydropyridine (291).

On the other hand, 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185) shows the presence of a low field aldehydic proton at τ 0.91, which couples to the β-proton with $J_{\beta,CHO}$ 2.6 Hz. Bothner-By and Harris[132] have calculated a theoretical value of 2.6 Hz for cis vicinal coupling across a rigid C-C single bond in the closely related β-keto-enol series. 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185 - fig. 1) is therefore clearly distinguishable from the isomer 2-(2-acetylvinylamino)-6-methylpyridine (183 - fig. 2).

cis-2-Acetyl-1-methylvinylamines found in the literature[125,126,128] exhibit two methyl signals in their ^{1}H n.m.r. spectra with chemical shifts of τ ca 8 and a separation of ca 0.1 p.p.m. 2-(2-Acetyl-1-methylvinylamino)pyridines (292 - Table 2, $R^1=R^2=Me$) show a greater difference between the methyl signals, ca 0.4 p.p.m., the lower signals being at τ ca 7.5. This greater shielding of one of the methyl groups is attributable to the effect of the lone pair electrons on the annular nitrogen on the methyl groups in the α-position, as in the case of H_α. The assignment of the lower signals to the α-methyl protons has been confirmed, in most cases, by a small allylic coupling between the lower methyl signal and the β-proton signal of ca 0.5 Hz.

Fig. 1

2-(2-Formyl-1-methylvinylamino)-6-methylpyridine

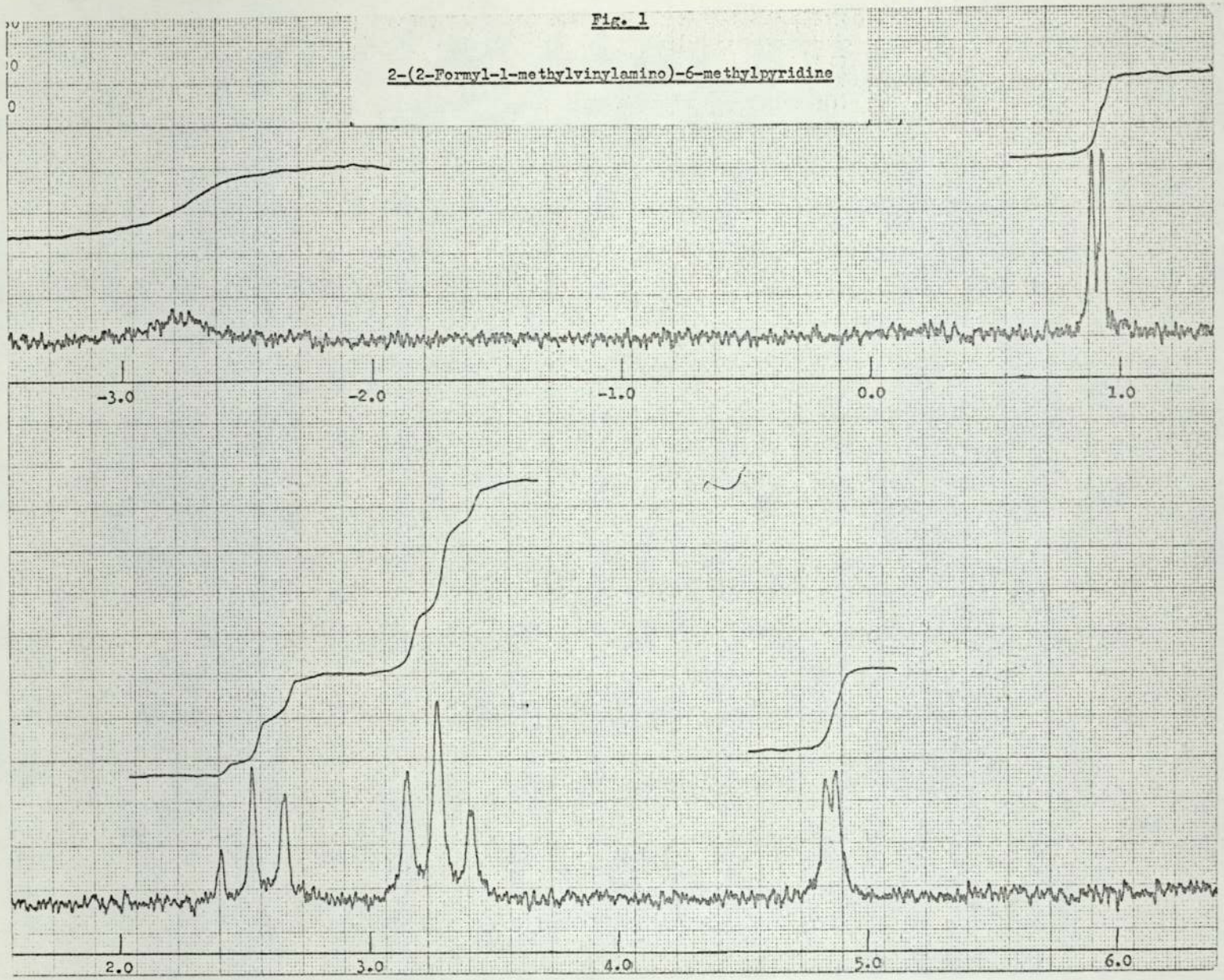
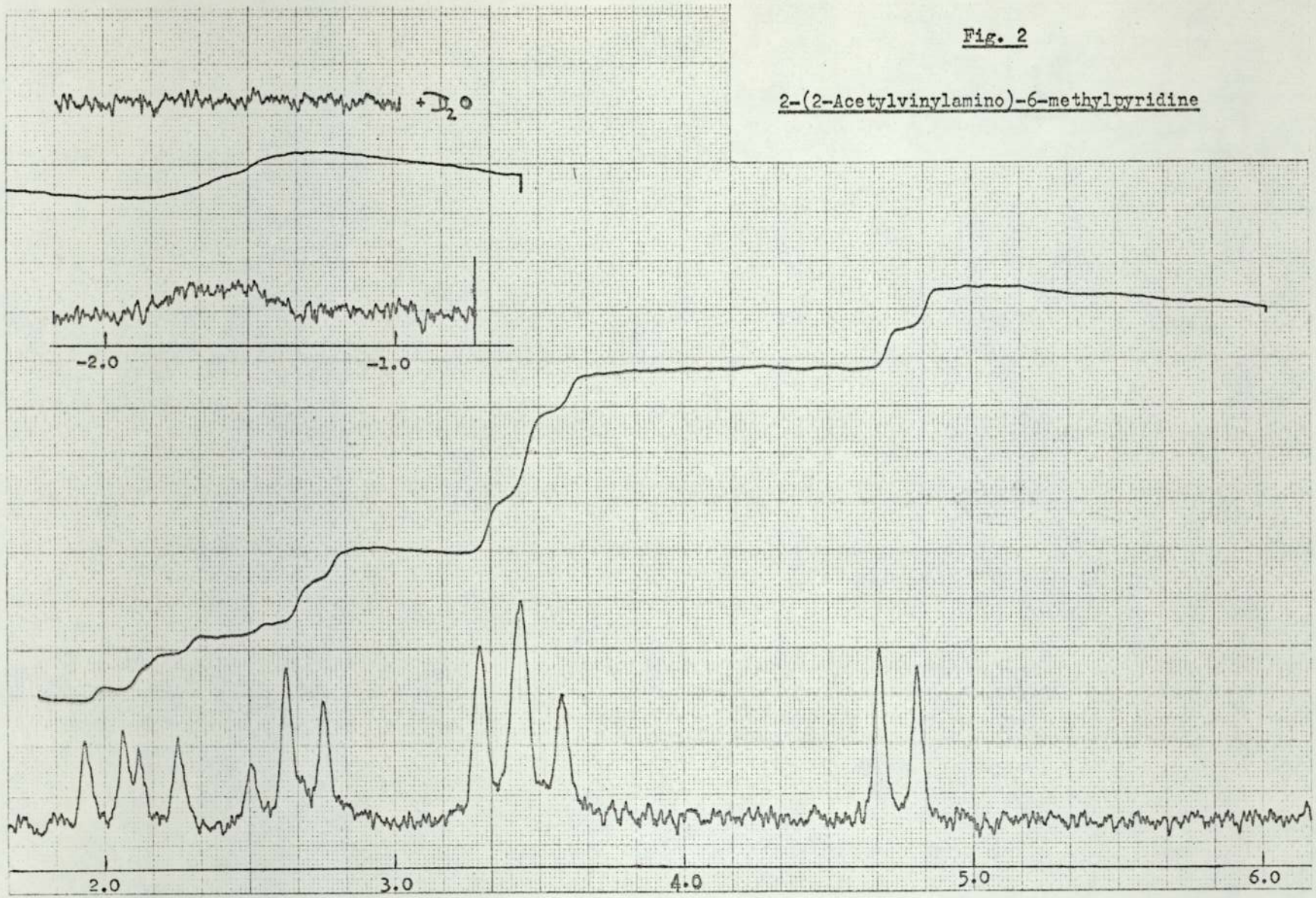
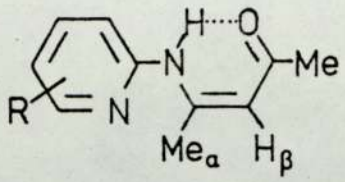


Fig. 2

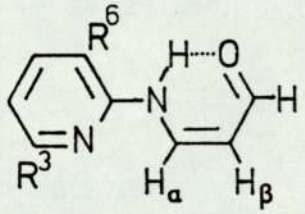
2-(2-Acetylvinylamino)-6-methylpyridine





(292)

This difference in the methyl shifts is also apparent in the spectra of the enaminones (183 and 185). The α-methyl group in the enaminone (185) occurs at τ 7.54, 0.39 p.p.m. lower than the acetyl methyl signal of the enaminone (183), and exhibits a small coupling (0.5 Hz) to the β-proton.



	R^3	R^6
(210)	H	Me
(211)	Me	Et

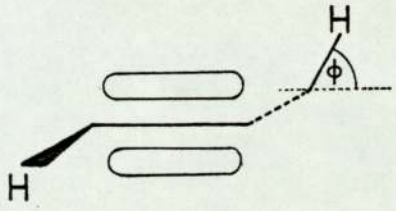
The spectra of the 2-(2-formylvinylamino)pyridines (210 and 211) show α- and β-proton signals at shifts similar to those found for the corresponding protons in the 2-(2-acetylvinylamino)pyridines (172, 183 and 250) with similar $\underline{J}_{\alpha,\beta}$ and $\underline{J}_{\alpha,NH}$. The low field aldehydic protons are also clearly apparent and exhibit a cis C-C single bond coupling of 2.0 Hz to H_β.

Both the formyl and α-proton signals reveal a coupling to each other of 3.4 Hz, which is unexpectedly large for a long range coupling through four bonds. This may be seen more clearly in the spectrum

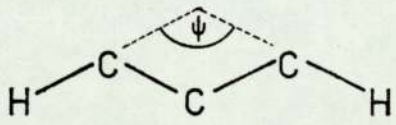
(fig. 3) of 3-ethyl-2-(2-formylvinylamino)-6-methylpyridine (211), as interference from 6-H in the α-proton region, is absent.

Deuterium exchange of the N-H proton with D_2O removes the N-H signal from the spectrum of 3-ethyl-2-(2-formylvinylamino)-6-methylpyridine (211) and reduces the α-H signals to a doublet of doublets, coupling to both β-H and CHO. The signals are sharpened by addition of two drops of concentrated NaOD in D_2O (fig. 4), but no exchange of the β-proton was noted, which would be expected if the imino-aldehyde form (II) were in equilibrium with the enamino-aldehyde form (I).

The large allylic coupling constant is difficult to explain. Allylic coupling due to interaction of σ- and π-bond electrons requires overlap between the orbitals[133]. This overlap is minimal in planar moieties, such as the cis-enaminone system, where the angle φ is 0° (293).



(293)



(294)

Couplings across four σ-bonds in saturated systems are generally very small. Accumulated evidence indicates that the stereochemical requirement of this type of coupling is an approximately planar 'M' arrangement of the four σ-bonds (294)[134-136].

Coupling also appears to be optimal when the small posterior lobes of the C-H bonding orbital are linearly orientated (294, $\psi = 180^\circ$), and is progressively reduced as ψ is decreased[137]. However, the question

Fig. 3 3-Ethyl-2-(2-formylvinylamino)-6-methylpyridine

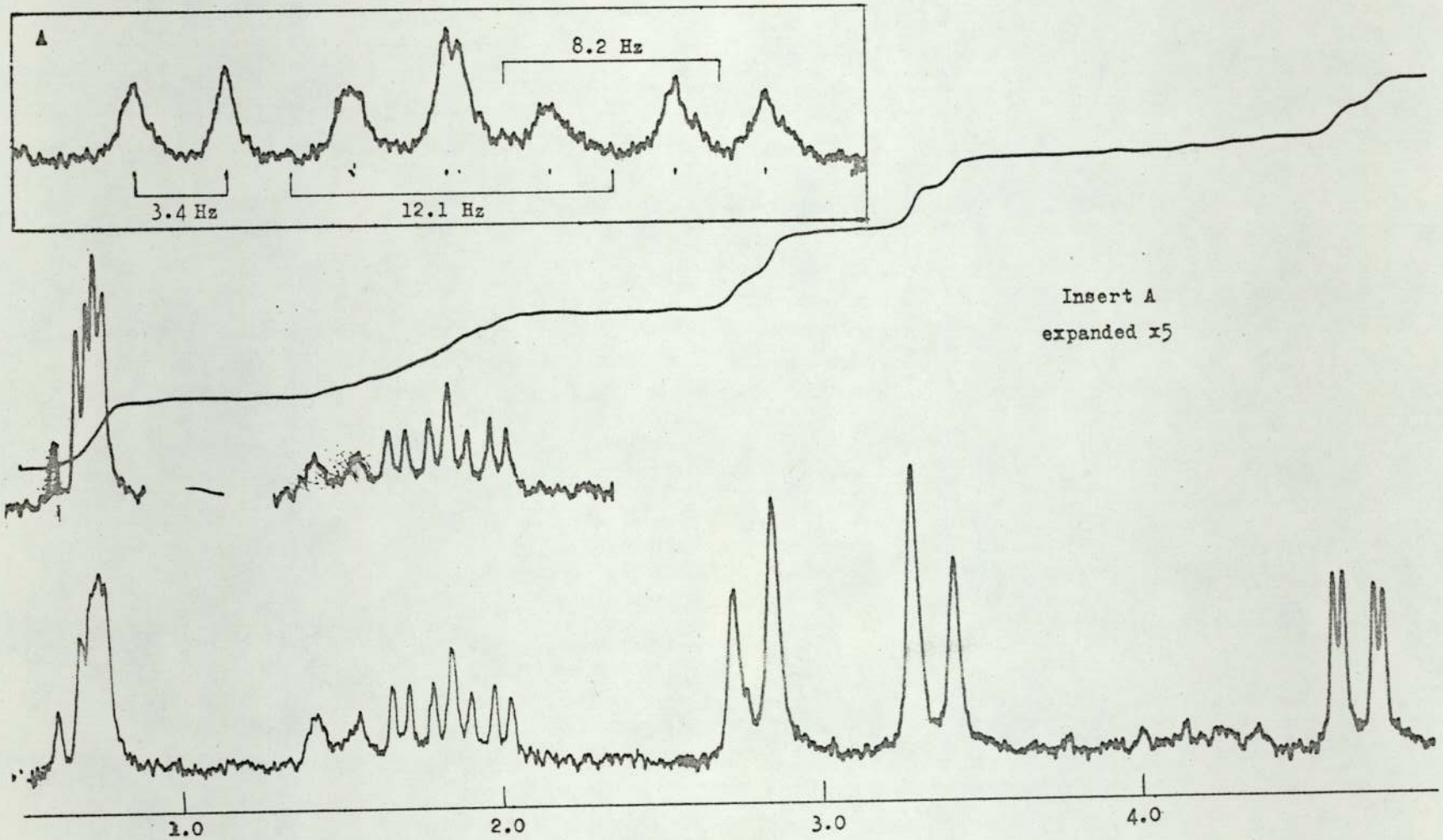
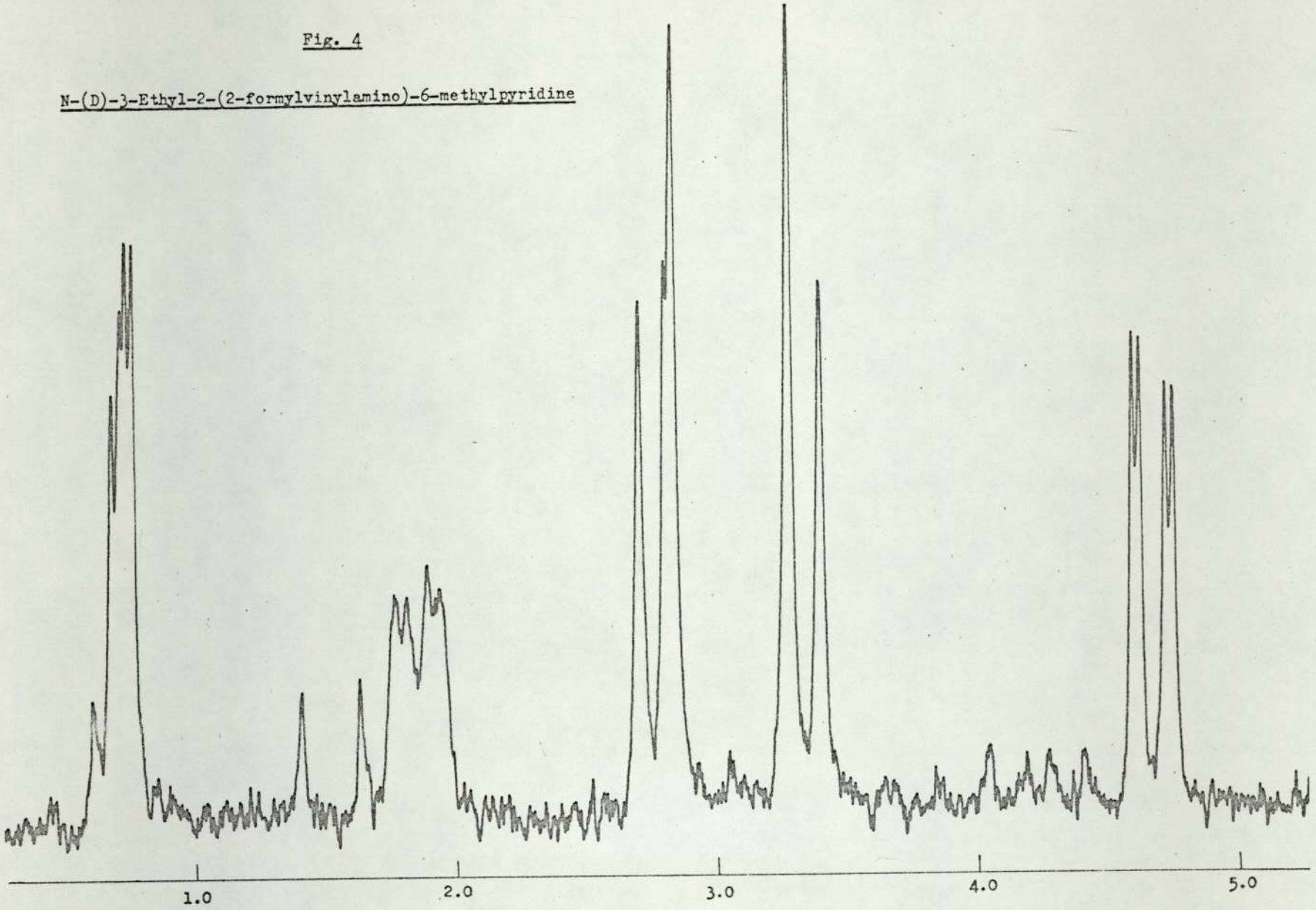
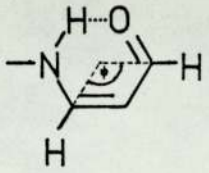


Fig. 4

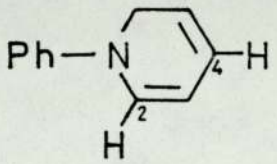
N-(D)-3-Ethyl-2-(2-formylvinylamino)-6-methylpyridine



of whether the mechanism of couplings across four σ-bonds is through-bonds or through-space is unanswered at present. Whatever the mechanism, it is possible that the large value of $\underline{J}_{a.CHO}$ in the enaminones (210 and 211) is due to σ-bond interactions as the four σ-bonds are coplanar, in an 'M' arrangement, and the angle ψ ca 120° (295).



(295)

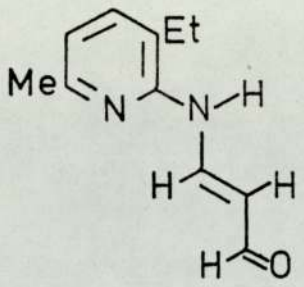


(296)

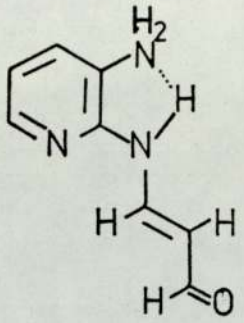
A four σ-bond mechanism has also been considered likely for the large meta-couplings found in substituted benzene compounds[138,139], where the stereochemistry of the atoms concerned is the same as in the enaminones.

The closely related dihydropyridine (296) shows $\underline{J}_{2,4}$ 0.9 Hz[140], which, although large for coupling through four bonds, is much smaller than the values found for $\underline{J}_{a.CHO}$. The large value of $\underline{J}_{a.CHO}$ may be due to factors indigenous to the formyl group, as several very large, unexplained couplings over five-bonds between formyl protons and other aromatic or ethylenic protons have been found[141-145], which Hoffman and Gronowitz[141] conclude are not due to the usual σ - π interaction.

The spectra of 3-ethyl-2-(2-formylvinylamino)-6-methylpyridine (211), recorded in $CDCl_3$, show an additional group of signals of smaller intensity which can be attributed to the trans structure (297) (figs. 3 and 4). 3-Ethyl-2-(2-formylvinylamino)-6-methylpyridine exists



(297)



(298)

entirely in the trans form (297) in hexadeutero dimethylsulphoxide, which is a more polar solvent (fig. 5). 3-Amino-2-(2-formylvinylamino) -pyridine is insufficiently soluble in chloroform to obtain a spectrum by normal techniques so the spectrum was recorded using hexadeutero dimethylsulphoxide as solvent (fig. 6), in which it also exists entirely as the trans form (298).

The trans structures have been deduced from the large values of $J_{\alpha,\beta}$, which are comparable to the value of 13.3 Hz obtained for trans enaminones[125], and $J_{\beta,CHO}$, which are comparable to the values of ca 8 Hz obtained for substituted and unsubstituted acroleins that are largely in the sym-trans conformation[132].

The α- and amino-protons are noticeably coupled in the 3-amino derivative (298) with $J_{\alpha,NH}$ 11.6 Hz, which collapses on deuteration (fig. 6), but there is no measurable coupling for the 3-ethyl-6-methyl derivative (297)(peak width at half height = ca 2 - 3 Hz). Japanese authors[46] have noted that trans-enamino-esters show $J_{\alpha,NH}$ 1 - 2 Hz, whereas the cis-isomers show values of 12 - 13 Hz for this coupling.

Fig. 5

trans-3-Ethyl-2-(2-formylvinylamino)-6-methylpyridine

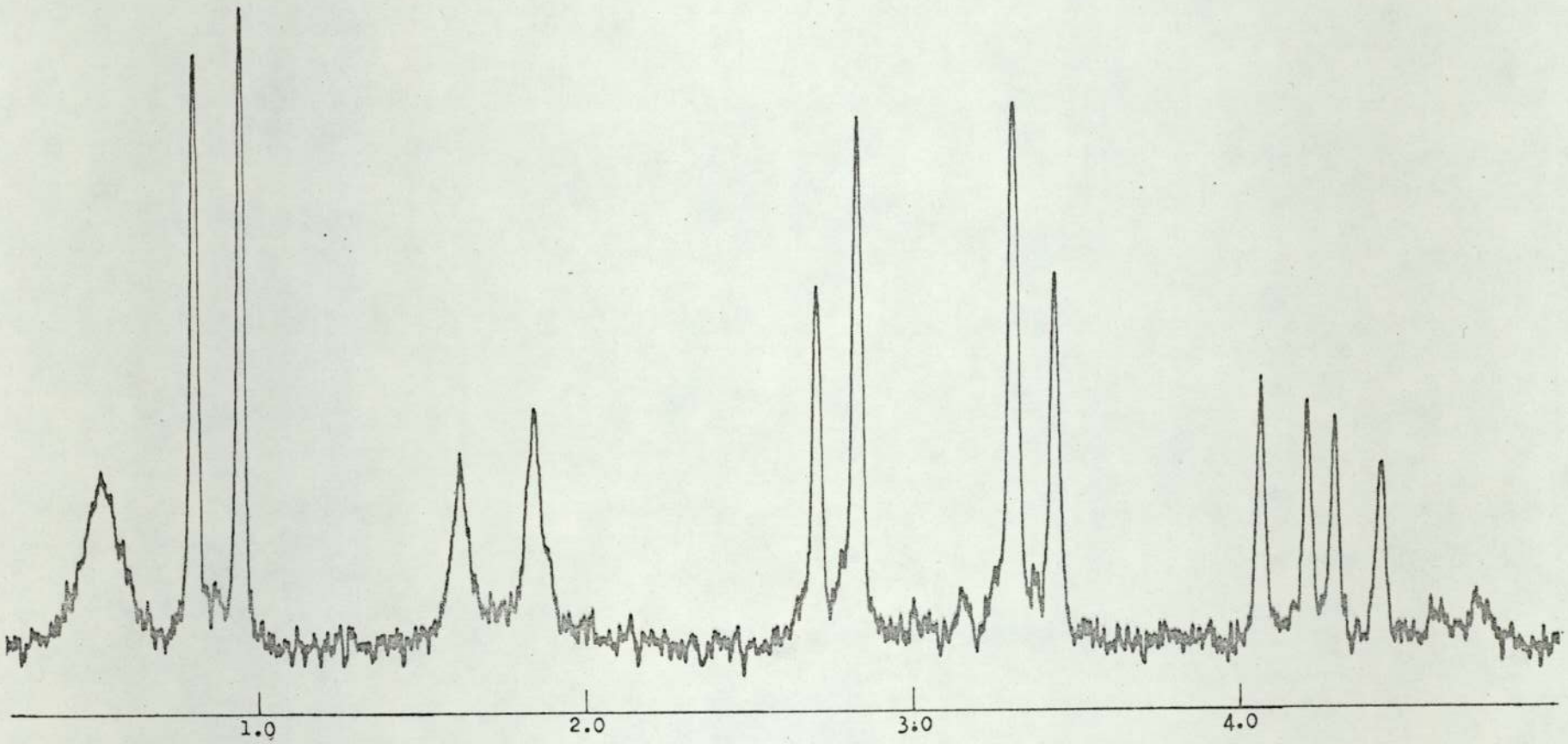
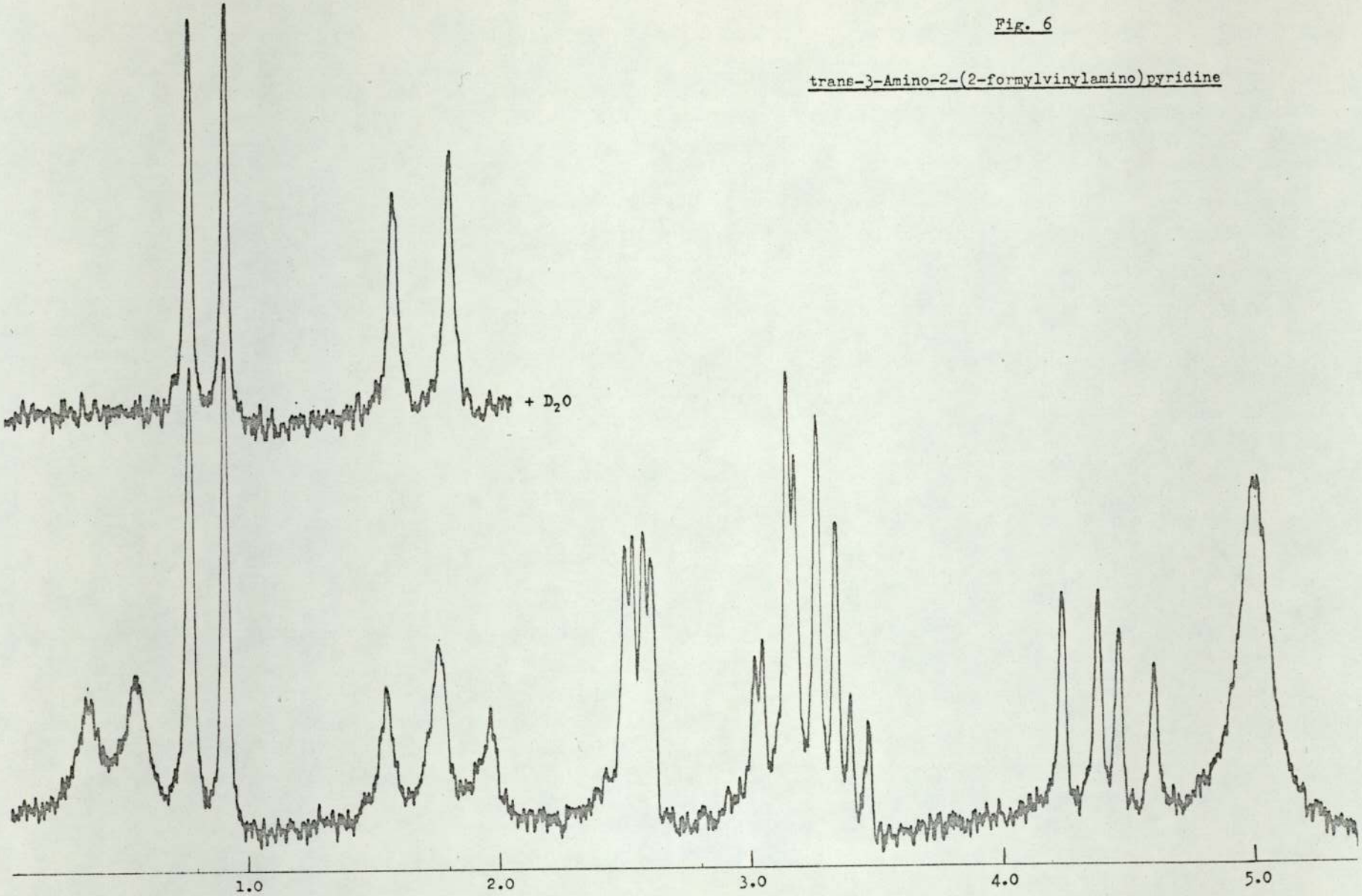


Fig. 6

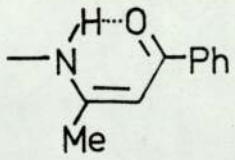
trans-3-Amino-2-(2-formylvinylamino)pyridine



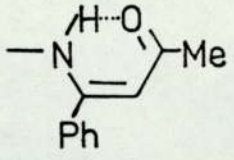
Dudek and Volpp[125] have noted band broadening of the methyl doublet in the trans isomer of an N-methyl enaminone, which they claim may be due to more facile proton exchange on the nitrogen in the open trans structure.

This may be true in the case of the 3-ethyl-6-methyl derivative (297) as facile proton exchange is possible, thus reducing $J_{a.NH}$, but in the 3-amino derivative (298), hydrogen bonding to the 3-amino grouping reduces the facility of proton exchange, thus maintaining coupling between the a- and amino-protons. The large value of $J_{a.NH}$ found for the 3-amino derivative (298) indicates that the a- and amino-protons are trans to each other and thus the preferred conformation of this compound in dimethylsulphoxide is as illustrated in formula (298).

The acylvinylamines derived from 1-phenylbutan-1,3-dione, via cleavage of the pyrido[1,2-a]pyrimidinium salts, may have either the benzoyl (299) or acetyl (300) structure.

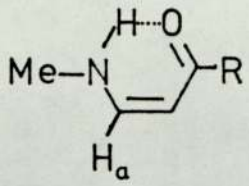


(299)



(300)

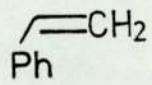
The values found for the shifts of the methyl groups are in better agreement with the values found for the a-methyl groupsthan with those found for the acetyl methyl groups (Table 2). The phenyl group in the benzoyl derivatives (299) is too far distant from the a-methyl group to have any significant effect upon the chemical shift, as shown by the small difference in shift (0.26 p.p.m.) found[125] for the a-protons in the enaminones (301 and 302).



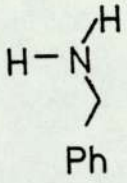
(301) R = Ph

(302) R = Me

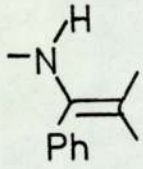
The phenyl protons occur in two groups, at τ ca 2.1 (2-H) and τ ca 2.6 (3-H). This is similar to the separation between the ortho and other phenyl protons found in a benzoyl group[146,147]. Such wide differences are not expected for an α-phenyl group (305) as the amino group in benzylamine (304) has no pronounced effect on the ortho phenyl protons (o-, m- and p-H, τ 2.73)[148] and the olefin group in styrene (303) has a much smaller effect on these protons (o-H, τ 2.7; m-H, τ 2.79; p-H, τ 2.86)[147].



(303)



(304)

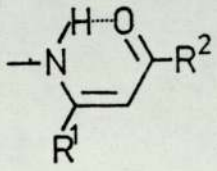


(305)

^{1}H n.m.r. spectra therefore indicate that the enaminones derived from 1-phenyl-butan-1,3-dione are 2-(2-benzoyl-1-methylvinylamino)-pyridines (299). These structures are confirmed by mass spectrometry.

7.4. Mass Spectra

All the acylvinylaminopyridines (172, 183, 185, 200 - 202, 210, 211, 236, 237 and 247 - 250) exhibit the same major breakdown pattern in the mass spectra. The most important feature in the spectra is the base peak which is the key to the orientation of the substituents R^1 and R^2.



The 2-(2-acetyl-1-methylvinylamino)pyridines (200 - 202 and 247) and the 2-(2-acetylvinylamino)pyridines (172, 183 and 250) all exhibit a base peak at M-43, i.e. loss of CH_3CO. All these compounds are known to contain an acetyl group (R^2 = Me). Similarly the 2-(2-formyl-vinylamino)pyridines (210, 211 and 248), which are known to contain a formyl group (R^2 = H), exhibit base peaks at M-29. The structure of 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185) has been deduced from the ^{1}H n.m.r. spectrum. This compound also exhibits a base peak at M-29, confirming the presence of the formyl group.

The structures of the 2-(2-benzoyl-1-methylvinylamino)pyridines (236, 237 and 249) have been deduced by analogy with the mass spectra of the acylvinylaminopyridines of known structure. If the proposed structures type (299), are correct, loss of a benzoyl group should give rise to a base peak at M-105. Similarly, if type (300) were correct, then an acetyl loss should produce a base peak at M-43. The base peak in all three spectra was found to occur at M-105.

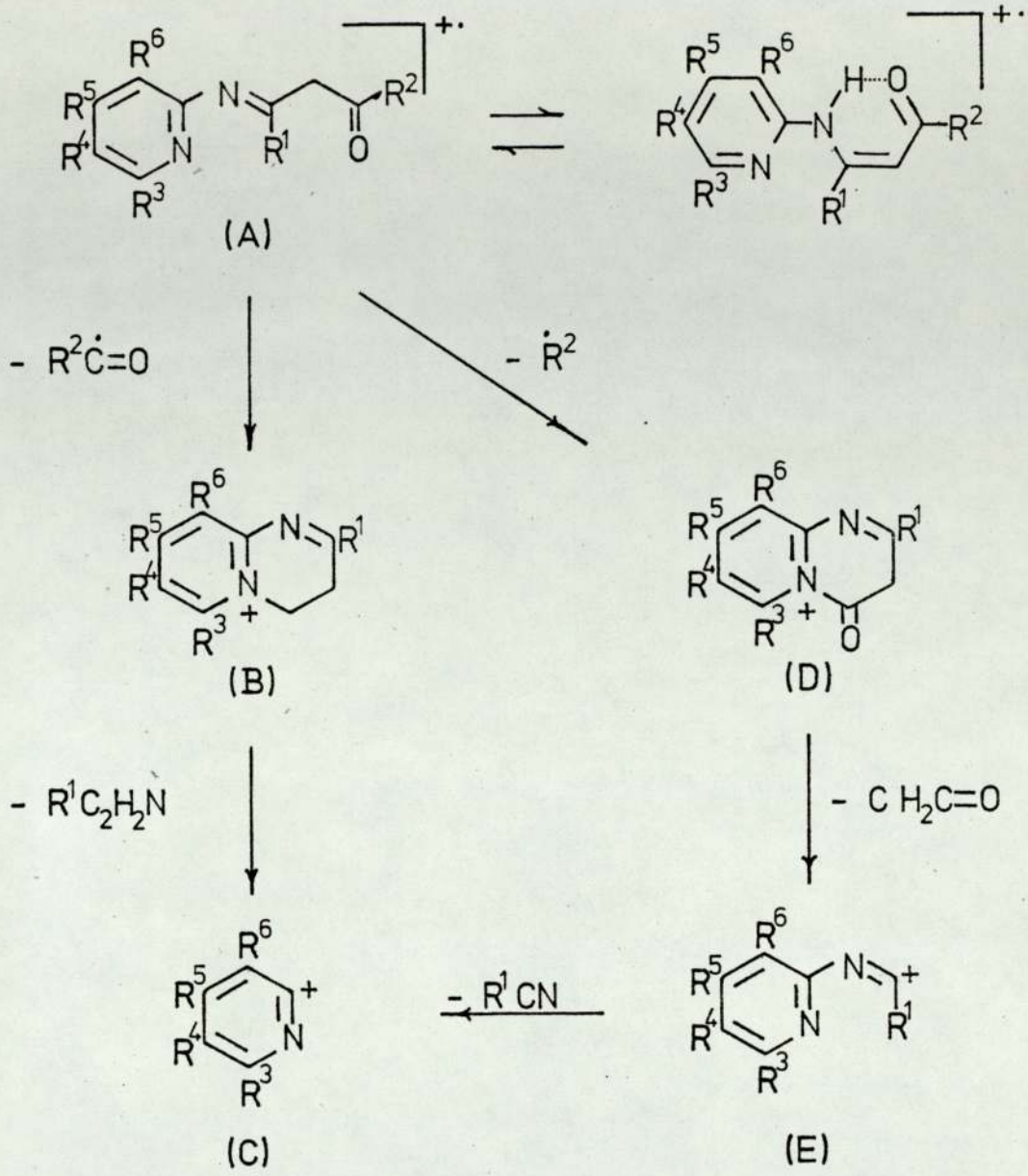
The proposed structures of the main breakdown products are illustrated in Scheme 9 and the masses and relative abundances of these fragments are listed in Table 3. In the majority of cases the fragmentation pathways are confirmed by the presence of meta-stable ions.

The fragmentation of 3-ethyl-2-(2-formylvinylamino)-6-methylpyridine (211) is complicated by the presence of the ehtyl group, as both formyl and ethyl losses may give rise to an M-29 peak. Accurate mass determinations on the M-29 peak show that it has two components, corresponding to both formyl and ethyl losses. The peak due to the formyl loss is sixteen times larger than the peak due to ethyl loss.

TABLE 3

Compound	R_1	R_2	A m/e (%)	B m/e (%)	C m/e (%)	D m/e (%)	E m/e (%)
(172)	H	Me	162(14)	119(100)	78(68)	147(13)	105(16)
(183)	H	Me	176(13)	133(100)	92(47)	161(10)	119 (6)
(250)	H	Me	177(50)	134(100)	93(45)	162(17)	120(26)
(200)	Me	Me	176(11)	133(100)	78(37)	161 (5)	119(16)
(201)	Me	Me	190 (7)	147(100)	92(35)	175 (5)	133(14)
(202)	Me	Me	204 (5)	161(100)	106(21)	189 (4)	147(18)
(247)	Me	Me	191(22)	148(100)	93(30)	176(20)	134(30)
(210)	H	H	162(20)	133(100)	92(21)	161 (3)	119 (8)
(211)	H	H	190(63)	161(100)*	120(89)	189 (5)	147(80)
(248)	H	H	163(68)	134(100)	93(46)	162(19)	120(50)
(185)	Me	H	176 (8)	147(100)	92(23)	175 (3)	133 (3)
(236)	Me	Ph	252 (5)	147(100)	92(12)	175 (2)	133 (2)
(237)	Me	Ph	252 (1)	147(100)	92(27)	175 (2)	133 (4)
(249)	Me	Ph	253(13)	148(100)	93(18)	176 (2)	134(16)

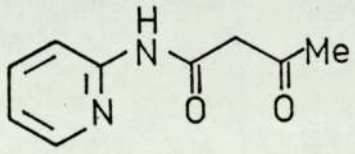
* total abundance of two components



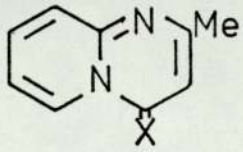
Scheme 9

8. PYRIDO [1,2-a] PYRIMIDINIUM SALTS FROM PYRIDO [1,2-a] PYRIMIDINONES

Of the pyrido [1,2-a] pyrimidinones, 2-methyl-4H-pyrido [1,2-a]-pyrimidin-4-one (72) is the most readily available from simple starting materials. Formation of the intermediate (306), followed by acid induced cyclisation to the pyridopyrimidinone (72) gave a low yield (4.7%). The condensation of 2-aminopyridine and ethyl acetoacetate to form the pyridopyrimidinone (72) directly gave a better yield (11.6%).

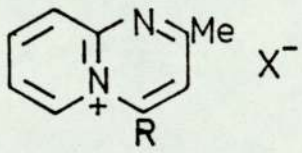


(306)



(72) X = O

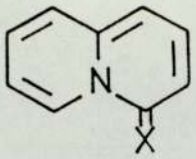
(307) X = S



(308) R = Cl

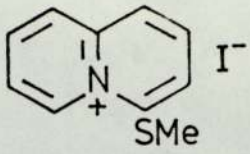
(309) R = SMe, $X^- = I^-$

An attempt to replace the 4-carbonyl group by a=C-Cl group by treatment with phosphoryl chloride produced only the impure hydrochloride of the pyridopyrimidinone (72). Amide carbonyl groups have been successfully treated with phosphoryl chloride, but in these cases [49,149,150] the carbonyl group was able to form the enol tautomer which is not possible here.



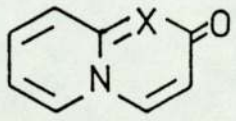
(310) X = O

(311) X = S



(312)

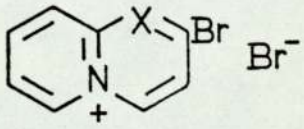
The quinolizinium iodide (312) has been obtained[151] by treating the thione (311) with methyl iodide. The quinolizinone (310) has been converted[152] to the thione (311) with phosphorus pentasulphide. It was anticipated that a similar route could be used to convert the pyridopyrimidinone (72) to the pyridopyrimidinium salt (309), but attempts to form the thione (307) produced only unchanged starting material.



(313) X = CH, R = H

(107) X = N, R = H

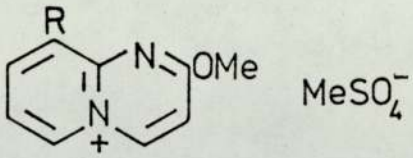
(111) X = N, R = Me



(314) X = CH

(315) X = N

The quinolizinone (313) has been successfully converted to the quinolizinium bromide (314) with phosphorus tribromide[153]. However, the same reaction with 2H-pyrido [1,2-a] pyrimidin-2-one (107) yielded only the hydrobromide of the starting material.



(316) R = H

(317) R = Me

Bredereck[154-156] has found it possible to O-methylate amides with dimethyl sulphate. This reagent, however, fails to yield the required product (316) with pyridopyrimidinone (107).

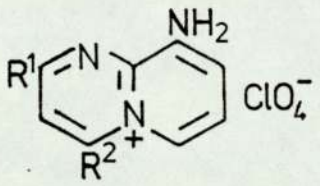
Landquist[157] has alkylated 4H-pyrido [1,2-a] pyrimidin-4-ones at N-1, but his attempts to alkylate a 9-methyl-4H-pyrido [1,2-a] pyrimidin-4-one were unsuccessful. As the 9-methyl group appears to sterically hinder the 1-position, this would aid O-methylation of 9-methyl-2H-pyrido-[1,2-a] pyrimidin-2-one (111). But here again, the reaction failed to produce the required salt (317) and yielded only an unidentified oil.

9. DIAZOTISATION OF 9-AMINOPYRIDO [1,2-a] PYRIMIDINIUM PERCHLORATES

9.1 Reactions and Mechanisms

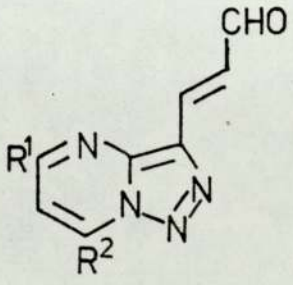
Diazotisation of the 9-aminopyrido [1,2-a] pyrimidinium perchlorates has provided a new route to the v-triazolo [1,5-a] pyrimidine nucleus. The previously reported routes[115, 158, 159] have involved condensation reactions between 1,3-dicarbonyl compounds and amino-v-triazoles.

Treatment of the 9-aminopyrido [1,2-a] pyrimidinium perchlorates (242 and 243) with sodium nitrite in strongly acidic media yielded the trans-3-(3-v-triazolo [1,5-a] pyrimidinyl)acraldehydes (318 and 319). The mixture of monomethylpyrido [1,2-a] pyrimidinium perchlorates (245 + 246) formed a mixture of the trans-acraldehydes (320 + 321) on diazotisation in strong acid.

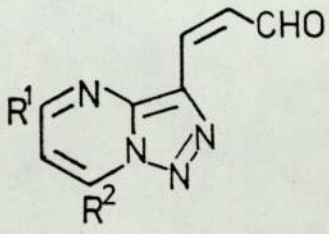


(242, 243, 245, 246)

	R^1	R^2
(243, 318, 322)	H	H
(242, 319, 323)	Me	Me
(245, 320, 324)	Me	H
(246, 321, 325)	H	Me

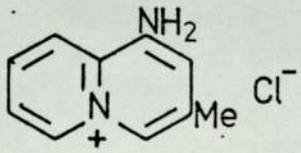


(318 - 321)

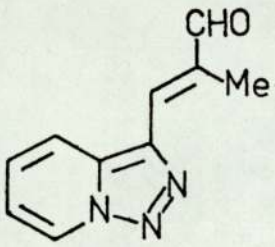


(322 - 325)

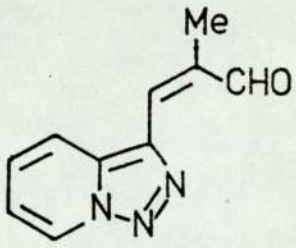
This is similar to the rearrangement[160] of 1-aminoquinolizinium salts, for example (326), to trans-3-(3-v-triazolo [1,5-a] pyridinyl)-acraldehydes, for example (327). In weakly acidic media the quinolizinium salt (326) is reported[160] to form the cis-acraldehyde (328).



(326)



(327)



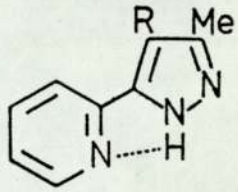
(328)

In weakly acidic media, each of the salts (242 and 243) yielded a mixture of the trans- and cis-acraldehydes (319 + 323, and 318 + 322). Similarly the mixture of monomethyl salts (245 + 246) formed a mixture of the four trans- and cis-isomers (320 + 321 + 324 + 325). This mixture was isomerised to a mixture of trans-isomers (320 + 321) by stirring with acid. The low solubility of the 9-aminopyrido [1,2-a] -pyrimidinium perchlorates in the reaction medium necessitated long reaction times, thus allowing the initially formed cis-isomers to be isomerised, by acid, to the more stable trans-isomers, thus preventing the isolation of pure cis-isomers. In strong acid this isomerisation

is complete.

The mechanism proposed for these rearrangements is shown in Scheme 10. This is similar to that suggested[160] for the ring-opening of 1-amino-quinolizinium salts but the additional nitrogen atom in the intermediate (d) provides a second site for cyclisation. Thus, when R^1 and R^2 are unlike, as in the case of the monomethylpyrido [1,2-a] pyrimidinium perchlorates (245 and 246), two isomers (e and f) may be formed.

The majority of the products formed in the attempted high temperature thermal isomerisation of the cis-acraldehyde (328) to the trans-acraldehyde (327) have been found[161] to be the pyrazoles (329 and 330).

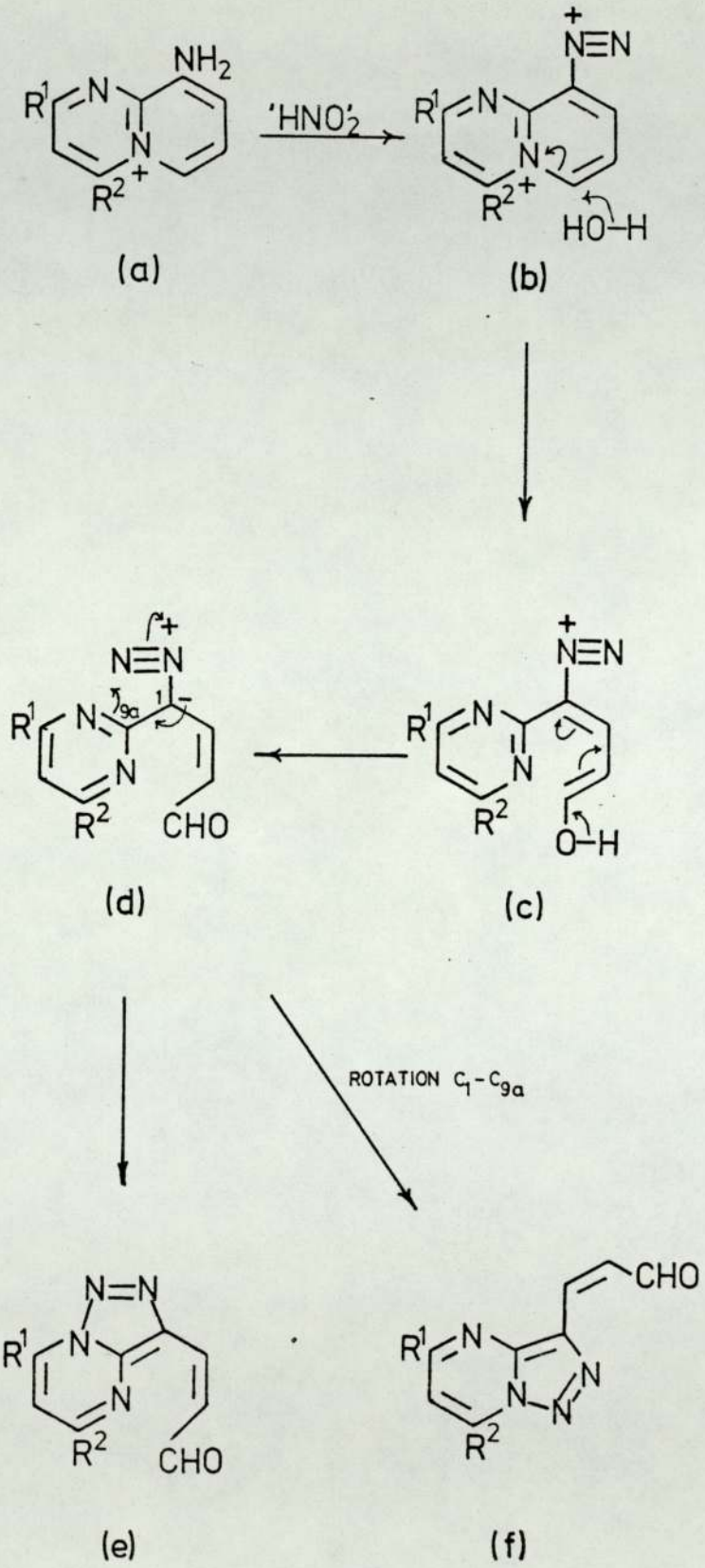


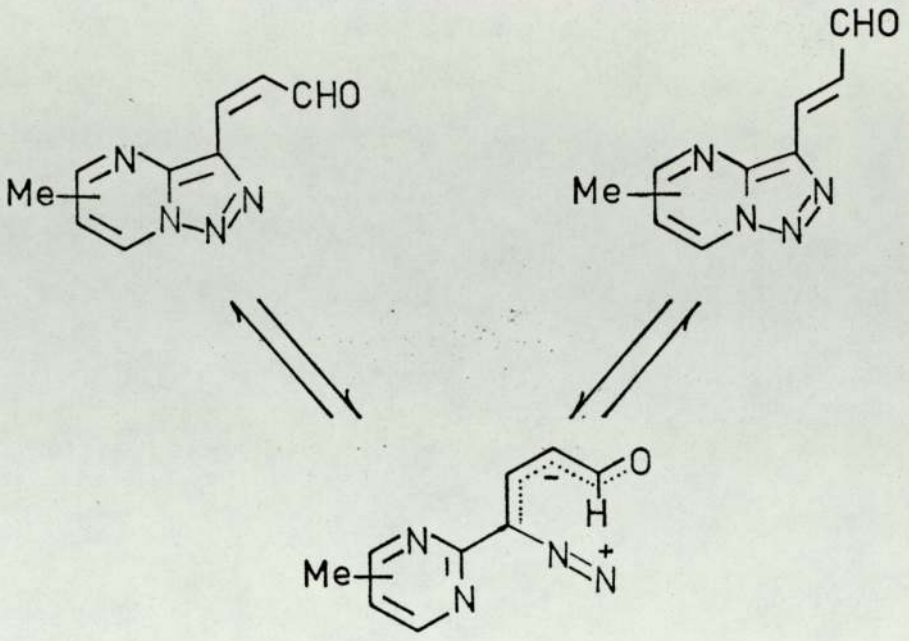
(329) R = CHO

(330) R = H

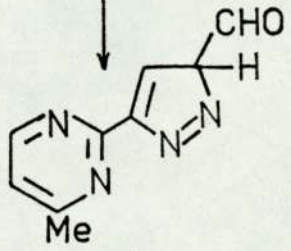
Thermal isomerisation of the cis- and trans-v-triazolo [1,5-a] pyrimidinyl acraldehydes (320, 321, 324 and 325) in hexadeutero dimethyl sulphoxide in an n.m.r. tube proceeds initially to a mixture of the trans-isomers (320 and 321) plus a trace of a third compound. Further heating for a total of fifty-six hours converts the whole mixture to the third compound, which was identified as the pyrazole (333). The preparation was repeated on a larger scale to isolate the pyrazole (333). The similarity of the pyrazole products (329) and (333) suggests that the mechanism for the formation of 3(5)-formyl-5(3)-(4-methyl-2-pyrimidinyl)-pyrazole (333) is similar, as far as intermediate (332), to that proposed[161] for the formation of 4-formyl-3-methyl-5-(2-pyridyl)-

Scheme 10

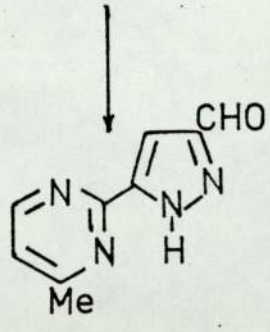

NH2
R1
N
N
R2
+
'HNO2'
+
N≡N
HO–H
(a)
(b)
(c)
(d)
CHO
O–H
9a
1
ROTATION C1 – C9a
N=N
CHO
(e)
(f)



(331)



(332)

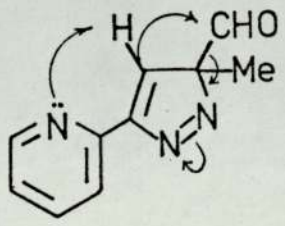


(333)

Scheme 11

pyrazole (329) (Scheme 11).

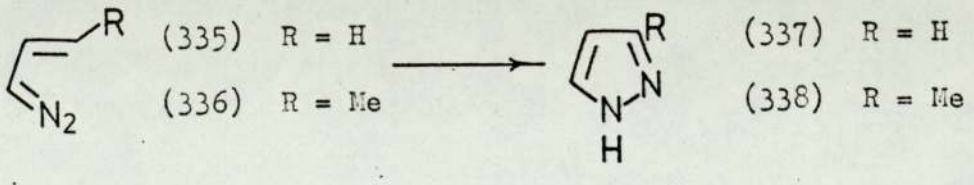
The difference in the position of the formyl group between the pyrazoles (329 and 333) may be accounted for by considering the intermediate (332) and the methyl substituted counterpart (334).



(334)

Stabilisation by formation of the aromatic pyrazole ring is achieved simply, in the case of intermediate (332), by a tautomeric shift of the proton at C-3 to N-1, forming the pyrazole (333), whereas, in the case of the intermediate (334), one of the substituents at C-3 must migrate. It is believed[161] that the formyl group transfers in preference to the methyl group because of the susceptibility of carbonyl groups to nucleophilic attack, which in this case, is initiated by the basic nature of the pyridine ring.

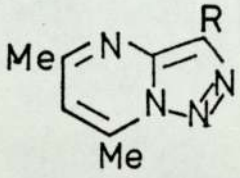
Diazomethane type intermediates have been proposed[159] in the thermal interconversion of v-triazolo[1,5-a]pyrimidinones. The cyclisation of the substituted diazomethane (331) to produce the pyrazole (333) is analogous to the formation of the pyrazoles (337 and 338) from vinyldiazomethane (335)[162] and propenyl diazomethane (336)[163] which occur at room temperature.



9.2 Structures of the Triazolopyrimidines

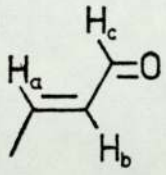
The products obtained by diazotisation of the 9-aminopyrido[1,2-a]-pyrimidinium perchlorates were suspected to be 3-(3-v-triazolo[1,5-a]-pyrimidinyl)acraldehydes by analogy with the products formed from amino uinolizinium salts[160]. Elemental analyses confirmed that the composition of the products was correct for these structures. The i.r. spectra show bands assignable to conjugated aldehyde stretching frequencies and the strong absorbance due to the perchlorate anion, found in the i.r. spectra of the perchlorate salts, was absent.

trans-5,7-Dimethyl-3-(3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (318) is readily identified from the ^{1}H n.m.r. spectrum. The chemical shifts of the 5- and 7-methyl groups and the 6-proton are similar to those found for the corresponding protons in the v-triazolo[1,5-a]-pyrimidines (339 and 340)[115]. The trans-acraldehyde configuration (341) is clearly recognisable, the three protons H_a, H_b and H_c all show shifts similar to those found for 3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde[160]. The coupling, $J_{a,b}$ = 16 Hz, is indicative of the trans HC=CH group[160] and the coupling, $J_{b,c}$ = 8 Hz, is that expected for the trans HC–CHO group[132,160].



(339) R = Ph

(340) R = $CONH_2$



(341)

These same shifts and couplings are found for the trans-acraldehyde group in trans-3-(3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (319).

The remaining three groups of single proton signals reveal a $H_aC-CH_b=CH_c$ grouping as part of a pyrimidine ring by virtue of the shift of H_b, which is in the range found for 6-H[115], and the couplings $J_{a,b}$, $J_{b,c}$ and $J_{a,c}$. The couplings are similar in magnitude to those found for the pyrimidine ring protons in the spectra of the pyrido - [1,2-a] pyrimidinium perchlorates, where bond localisation is suspected (see p. 47). Bond fixation in v-triazolo [1,5-a] pyrimidines (339 and 340) has been reported previously[115].

The value of $J_{b,c}$ = 8 Hz and the position of the localised C=C lead to the assignment of H_c as 7-H, and hence H_a as 5-H. These two groups of signals are well separated, the lower group being that assigned to 7-H, which is in accord with its position adjacent to the bridgehead nitrogen atom, where enhanced deshielding is expected.

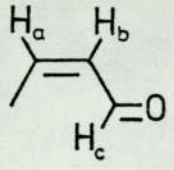
The mixture of trans-monomethyl isomers (320 and 321) show two sets of signals in the ^{1}H n.m.r spectrum, the set attributable to the 5-methyl isomer (320) being the smaller, and having the least deshielded methyl group. The sets are clearly distinct and each proton is found at the chemical shift expected by comparison with the trans-acraldehydes (318 and 319). The only signals which coincide are those of the aldehyde doublets, which are sufficiently far removed from the ring system to avoid influence from the position of the methyl group.

The mixtures of cis- and trans-acraldehydes (319 + 323, and 318 + 322) show, in addition to the expected signals for the trans-compounds, signals assignable to the cis-acraldehyde function (342) as well as slightly shifted signals due to ring and methyl protons.

A greater degree of deshielding is found for the H_c cis and H_b trans

signals than for the corresponding H_c *trans* and H_b *cis* signals. This is in good agreement with the results found for *cis*- and *trans*-3-(3-*v*-triazolo[1,5-*a*]pyridyl)acraldehydes[160], and has been explained by the enhanced deshielding of the grouping (H_b or CHO) lying *cis* to the ring system due to the lone pair electrons on N-2. The values of $J_{a,b}$ (12 Hz) also support *cis* HC=CH coupling[160].

The ^1H n.m.r. spectrum of the mixture of four monomethyl isomers (320, 321, 324 and 325) is more complex, but by careful comparison of the



(342)

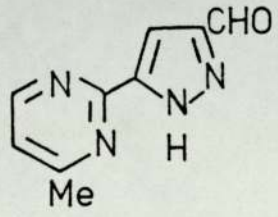
signals, assignments may be made. The H_a proton signals are the most distinctive, being a group of four doublets, two showing *cis* olefinic coupling (12 Hz) and two *trans* olefinic coupling (16 Hz).

The i.r. spectra of the *trans* acraldehydes (318 - 321) show bands assignable to the CH out-of-plane deformation mode of a *trans* HC=CH group. The mixtures of *cis*- and *trans*-compounds also show this band and another band assignable to the *cis* HC=CH group frequency.

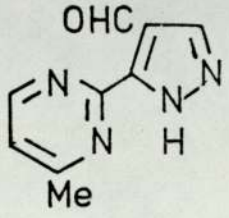
9.3 Structure of 3(5)-Formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole

The close similarity in structure between the 3-(3-*v*-triazolo[1,5-*a*]-pyrimidinyl)acraldehydes and the 3-(3-*v*-triazolo[1,5-*a*]pyridyl)-acraldehydes leads to the assumption that the thermal rearrangement products would have similar structures.

The ^{1}H n.m.r. spectrum recorded in hexadeuterodimethylsulphoxide, shows a low field aldehydic proton signal, a singlet methyl signal, a single proton singlet and two single proton doublets, which would be expected for either of the pyrazole structures (333 or 343).



(333)



(343)

The single proton singlet, assignable to the pyrazole proton, is found at τ 2.90. The 3-proton in pyrazole-4-carbaldehydes occurs at τ 2.2 - 2.6[164] and the 4-proton in pyrazole-3-carbaldehydes occurs at τ 3.4 - 3.6[164]. The signal at τ 2.90 may be assigned to the 4-proton (structure 333) as deshielding of this proton by the pyrimidine nitrogen lone pair electrons will decrease the expected τ value.

Similarly, deshielding of the 4-formyl proton in structure (343) by these lone pair electrons would produce a signal of lower value than that of τ - 0.5 found for the 4-formyl proton in the pyrazole (329)[161]. The formyl signal is found at τ 0.26, a value similar to those found for other pyrazole 3-CHO groups[164]. The ^{1}H n.m.r. spectrum shows quite clearly that the product of thermal isomerisation is the 3-formyl pyrazole (333).

Some confirmatory evidence is found in the i.r. spectrum where the formyl carbonyl absorption band is found at 1690 cm^{-1}. This

absorption is found at 1671 - 1679 cm^{-1} for 4-formyl pyrazoles[160,164] and at 1687 - 1692 cm^{-1} for 3-formyl pyrazoles[164].

9.4 Mass Spectra

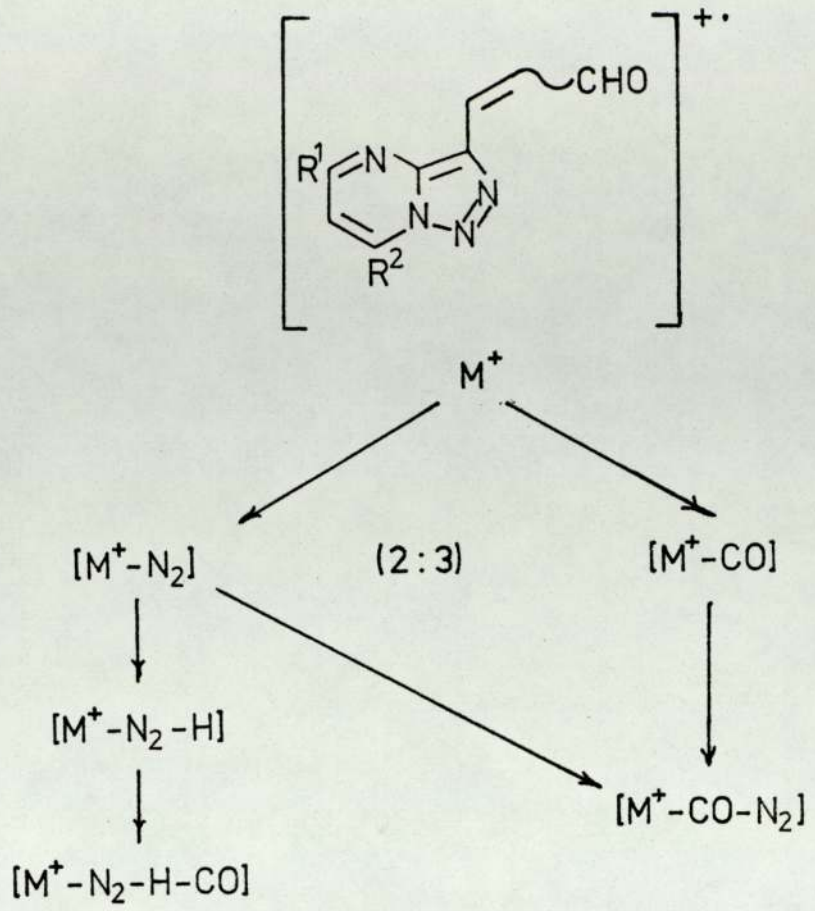
9.4.1

The mass spectra of the 3-(3-v-triazolo[1,5-a]pyridyl)acrolaldehydes (327 and 328) have been described in the literature[160,161]. There appears to be a contradiction in the reports, but the evidence presented indicates that the parent ion loses CO and N_2, with equal probability, with subsequent loss of N_2H and CHO.

The 3-(3-v-triazolo[1,5-a]pyrimidinyl)acraldehydes show a somewhat different pattern. The parent ion loses CO or N_2, CO loss being favoured to N_2 loss, followed by loss of N_2 or CO. The $(M-N_2)^+$ ion shows an alternative breakdown by loss of a hydrogen atom followed by carbonyl loss. There is no evidence to support any single loss of a fragment of 29 mass units (CHO or N_2H). The breakdown pathways are summarised in Scheme 12.

The pathways were determined by accurate mass measurements, the appearance of metastable peaks and metastable scans at low accelerating voltages.

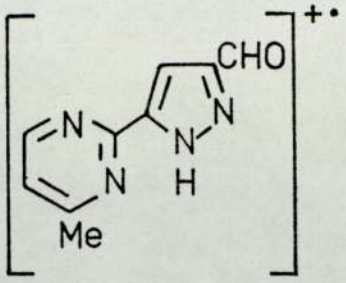
The appearance of a strong parent ion and an abundant (M^+-N_2) peak in the mass spectrum has been claimed[159] as supporting evidence for the presence of a fused v-triazole nucleus.



Scheme 12

9.4.2

The mass spectrum of the pyrazole (329) is reported to be identical with those of the cis- and trans-acraldehyde precursors (327 and 328). In the case of 3(5)-formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole (333), the similarity between the mass spectrum and those of its precursors is restricted. No N_2 loss from the parent ion is detected, the $(M-28)^+$ peak ($C_8H_8N_4^+$) arising from CO loss only, with subsequent loss of H, then N_2 (Scheme 13).



M^+

↓

$[M^+ - CO]$

↓

$[M^+ - CO - H]$

↓

$[M^+ - CO - H - N_2]$

Scheme 13

10. BIOLOGICAL TEST RESULTS

A selection of the pyrido[1,2-a]pyrimidinium salts, prepared during the course of this work, was submitted for inclusion in parasitological and antiviral screening programmes.

The compounds submitted were pyrido[1,2-a]pyrimidinium perchlorate (46) and bromide (264), 2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorate (47) and 2-methyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (231).

10.1 Parasitological Screen

The *in vivo* test procedure was as follows:-

Albino female Charles River mice *ca* 20 g, naturally infected with *S. obvelata*, were artificially infected with *N. dubius* L_3 larvae and *H. nana* eggs.

At the end of a ten day post-infection period, each mouse was treated orally with an experimental compound at 100 mg/kg for five days.

The mice were killed three days after the last treatment, and the helminths were recovered and counted.

Results for 2-methyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (231)

	N. dubius	*H. nana*	*S. obvelata*
mean control count	10.8	13.5	36.8
Yomesan % reduction	0	61	64
Levamizole % reduction	100	12	93
(231) % reduction	0	1	0

Results for 2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorate (47)

	N. dubius	H. nana	S. obvelata
mean control count	13.9	29.2	25.8
Yomesan % reduction	9	67	0
Levamizole % reduction	100	8	81
(47) % reduction	6	0	0

10.2 Antiviral Screen

The pyrido[1,2-a]pyrimidinium salts (47 and 264) were tested, *in vivo*, against influenza, Herpes Simplex, Coxsackie B. and PVM, but were found to be inactive. Pyrido[1,2-a]pyrimidinium perchlorate (46) was also tested against PVM and was found to be inactive.

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

EXPERIMENTAL

INFRA-RED SPECTRA were determined for liquid paraffin mulls on a Unicam SP 200 spectrophotometer (o.o.p. def. = out-of-plane deformation).

ULTRA-VIOLET SPECTRA were recorded on a Unicam SP 800 spectrophotometer.

NUCLEAR MAGNETIC RESONANCE SPECTRA were determined on a Varian A60-A (60 MHz) and HA 100 (100 MHz) spectrometers. Tetramethylsilane was used as internal standard, or as external standard where stated.

Abbreviations used in the interpretation of n.m.r. spectra: s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublets of doublets; t = triplet; q = quartet; m = multiplet; br = broad; deg. = degenerate.

Calculations of the chemical shifts and coupling constants for ABX systems were performed according to the method of Banwell[165].

MASS SPECTRA were determined with an A.E.I. MS 9 spectrometer, operating at 50 μa and 70 eV. Mass spectral data is presented as m/e readings with the figures in parentheses representing the percentage abundance of each peak.

MELTING POINTS were determined on an Electrothermal apparatus and are uncorrected.

MICROANALYSES were performed by Dr. F.B. Strauss, Oxford, England.

11 SYNTHESIS OF PYRIDO[1,2-a]PYRIMIDINIUM SALTS

11.1 Pyrido[1,2-a]pyrimidinium Perchlorates from 2-Aminopyridines

General Method (a).

The 2-aminopyridine (1 g) and an equimolar quantity of the appropriate β-dicarbonyl compound, or its acetal, were dissolved in methanol (5 cm^3) 60% perchloric acid (2 cm^3) was added, and the mixture was stirred at room temperature for 15 - 18 h. In most cases a precipitate separated. Sufficient diethyl ether was added to complete precipitation of the perchlorate, which was filtered, washed with ether, recrystallised from methanol containing a few drops of perchloric acid, and dried at 50° in vacuo. By this general procedure the following perchlorates were prepared, with some modifications as outlined.

2,4 Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (47)

2-Aminopyridine and pentane-2,4-dione yielded 2.35 g (85.3%), colourless plates, m.p. 228 - 230°(decomp.) (lit.[23], yield 96%, m.p. 221 - 222°, Cl analysis only; lit.[19], yield 78%, m.p.229 - 230°).

Found: C, 46.3; H, 4.3; N, 10.6. Calc. for $C_{10}H_{11}ClN_2O_4$: C, 46.4; H, 4.3; N, 10.8%.

λ_{max} (MeOH) 210 (log ε 4.34), 228 (4.51), 305 (3.80), 312 (3.73) and 317 (3.83) nm.

ν_{max} 1645, 1440, 1400, 1100 br (ClO_4^-), 1040, and 785 cm^{-1}.

τ(CF_3CO_2H; 60MHz) 0.87 br.(1H, d, 6-H), 1.25 - 1.55 (2H, m, 8- and 9-H), 1.83 (1H, m, 7-H), 2.02 (1H, s, 3-H), 6.87 (3H, s, 4-Me), and 7.02 (3H, s, 2-Me) (5-H, 6-H, 7-H, and 8-H ≡ ABMX system; from first-order analysis $J_{6,7}$ 7 Hz).

2,4,9-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (54)

2-Amino-3-methylpyridine and pentane—2,4-dione yielded 1.3 g (51.5%), colourless needles, m.p. 167 - 169° (lit.[23], yield 84%, m.p. 162 - 163°, Cl analysis only).

Found: C, 48.7; H, 4.9; N, 10.35. Calc. for $C_{11}H_{13}ClN_2O_4$: C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1650, 1635, 1460, 1420, 1390, 1100 br (ClO_4^-), 1040, and 785 cm^{-1}.

τ (CF_3CO_2H; 100 MHz) 1.48 (1H, dd, J 7 and 1 Hz, 6-H), 1.97 (1H, dd, J 7 and 1 Hz, 8-H), 2.40 (1H, t deg. dd, J 7 and 7 Hz, 7-H), 2.51 (1H, s, 3-H), 7.28 (3H, s, 4-Me) and 7.42 (6H, s, 2- and 9-Me).

2,4,8-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (53)

2-Amino-4-methylpyridine and pentane-2,4-dione yielded 2.1 g (83.2%), colourless needles, m.p. 190 - 191° (lit.[23], yield 95%, m.p. 181 - 183°, Cl analysis only).

Found: C, 48.3; H, 4.7; N, 10.4; Cl, 12.8. Calc. for $C_{11}H_{13}ClN_2O_4$: C, 48.4; H, 4.8; N, 10.3; Cl, 13.0%.

ν_{max} 1640, 1460 sh, 1430 sh, 1370, 1100 br (ClO_4^-), and 1035 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.93 (1H, d, J 7.5 Hz, 6-H), 1.55 (1H, s, 9-H), 1.91 (1H, d, J 7.5 Hz, 7-H), 2.08 (1H, s, 3-H), 6.87 (3H, s, 4-Me), 7.00 (3H, s, 2-Me) and 7.15 (3H, s, 8-Me).

2,4,7-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (203)

2-Amino-5-methylpyridine and pentane-2,4-dione yielded 1.72 g (68.2%), colourless needles, m.p. 226 -227° (decomp.)

Found: C, 48.7; H, 4.9; N, 10.3. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1650, 1575, 1455, 1420, 1100 br (ClO_4^-), and 1040 cm^{-1}.

$\tau(CF_3CO_2H$; 100MHz) 1.48 (1H, d, $\underline{J}$ 1 Hz, 6-H), 1.84 (2H, d, 8- and 9-H), 2.45 (1H, s, 3-H), 7.23 (3H, s, 4-Me), 7.37 (3H, s, 2-Me) and 7.61 (3H, s, 7-Me).

2,4,7,9-Tetramethylpyrido[1,2-a]pyrimidinium Perchlorate (204)

2-Amino-3,5-dimethylpyridine (1 g) and pentane-2,4-dione in 60% perchloric acid (5 cm^3) were stirred for 17 h. Methanol (10 cm^3) was added to the white paste which had formed, then ether, to give a white precipitate. Yield 2.2 g (86.0%), colourless needles, m.p. 141 - 142°.

Found: C, 50.5; H, 5.5; N, 9.6. $C_{12}H_{15}ClN_2O_4$ requires C, 50.3; H, 5.2; N, 9.8%.

ν_{max} 1645, 1470, 1365, 1090 br (ClO_4^-), and 1030 cm^{-1}.

$\tau(CF_3CO_2H$; 60MHz) 1.26 (1H, s, 6-H), 1.65 (1H, s, 8-H), 2.12 (1H, s, 3-H), 6.90 (3H, s, 4-Me), 7.03 (3H, s, 2-Me), 7.07 (3H, s, 9-Me) and 7.30 (3H, s, 7-Me).

9-Hydroxy-2,4-dimethylpyrido[1,2-a]pyrimidinium Perchlorate (205)

2-Amino-3-hydroxypyridine and pentane-2,4-dione yielded 1.85 g (74.3%), colourless needles, m.p. 196 -197°.

Found: C, 43.8; H, 4.1; N, 10.0. $C_{10}H_{11}ClN_2O_5$ requires C, 43.7; H, 4.0; N, 10.2%.

ν_{max} 3320 (OH), 1645, 1580, 1500, 1440, 1310, 1260, 1180, 1100 br (ClO_4^-), 1040, and 750 cm^{-1}.

$\tau(CF_3CO_2H$; 60 MHz) 1.37 (1H, t, X of AA'X, 6-H), 1.97 (2H, d, AA' of AA'X, 7 and 8-H), 2.08 (1H, s, 3-H), 6.90 (3H, s, 4-Me) and 7.02 (3H, s, 2-Me) (Calc. for AA'X system - $\left|\underline{J}_{6,7} + \underline{J}_{6,8}\right|$ = 7.8).

9-Amino-2,4-dimethylpyrido[1,2-a]pyrimidinium Perchlorate (242)

2,3-Diaminopyridine and pentane-2,4-dione yielded 2.50 g, (99.6%), yellow needles (from water), m.p. 263 - 265° (decomp.).

Found: C, 43.7; H, 4.4; N, 15.3. $C_{10}H_{12}ClN_3O_4$ requires C,43.9; H, 4.4; N, 15.4%.

ν_{max} 3450 and 3340 (NH_2), 1640, 1620, 1605, 1430, 1395, 1350, 1100 br (ClO_4^-), and 735 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 1.13 (1H, dd, J 7.5 and 1 Hz, 6-H), 1.45 (1H, dd, J 8.5 and 1Hz, 8-H), 1.94 (1H, dd, J 8.5 and 7.5 Hz, 7-H), 2.08 (1H, s, 3-H), 6.89 (3H, s, 4-Me) and 7.03 (3H, s, 2-Me).

Pyrido[1,2-a]pyrimidinium Perchlorate (46)

2-Aminopyridine and 1,1,3,3-tetramethoxypropane yielded 2.2 g (90.0%), colourless needles, m.p. 216° (decomp.) (lit.[23], yield 75%, m.p. 217 - 218°, Cl analysis only; lit.[19], yield 60%, m.p. 222 - 223°).

Found: C, 42.0; H, 3.2; N, 12.0; Cl, 15.7. Calc. for $C_8H_7ClN_2O_4$: C, 41.65; H, 3.0; N, 12.15; Cl, 15.4%.

λ_{max} (MeOH) 210 (log ε 4.05), 227 (4.10), 267 (3.90), 303 (3.72), 309 (3.71) and 317 (3.83)nm.

ν_{max} 1635, 1385, 1140, 1100 br (ClO_4^-), 1080, 1025, 955, 840, and 800 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.37 - 0.59 (2H, m, 2- and 4-H), 0.83 br (1H, d, J 7 Hz, 6-H), 1.21 - 1.44 (2H, m, 8- and 9-H) and 1.64 - 1.96 (2H, m, 3- and 7-H).

8-Methylpyrido[1,2-a]pyrimidinium Perchlorate (49)

2-Amino-4-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 2.06 g, (91.1%), colourless needles, m.p. 191 - 193° (decomp.) (lit.[23], yield 70%,

m.p. 185 - 186°, Cl analysis only).

Found: C, 44.0; H, 3.7; N, 11.4; Cl, 14.4. Calc. for $C_9H_9ClN_2O_4$: C, 44.3; H, 3.7; N, 11.5; Cl, 14.5%.

ν_{max} 1650, 1640, 1405, 1385, 1185, 1100 br (ClO_4^-), 1045, and 850 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 0.58 - 0.77 (2H, m, AB of ABX, 2- and 4-H), 1.11 (1H, d, $\underline{J}$ 6.8 Hz, 6-H), 1.67 (1H, s, 9-H), 2.05 (1H, dd, X of ABX, 3-H), 205 (1H, d, $\underline{J}$ 6.8 Hz, 7-H) and 7.22 (3H, s, 8-Me). (Calc. for ABX system - τ0.61 4-H, τ0.74 2-H, $\underline{J}_{2,3}$ 4.0, $\underline{J}_{2,4}$ 1.5, $\underline{J}_{3,4}$ 7.0 Hz).

7-Methylpyrido[1,2-a]pyrimidinium Perchlorate (48)

2-Amino-5-methylpyridine and 1,1,3,3-tetramethoxypropane yielded an orange product, which was refluxed in ethanol with activated charcoal. After filtering, colourless needles crystallised from the hot solution. Yield 1.1 g (48.6%), m.p. 183 - 185° (from ethanol).

Found: C, 44.0; H, 3.7; N, 11.2. $C_9H_9ClN_2O_4$ requires C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 1630, 1520, 1390, 1135, 1100 br (ClO_4^-), 1040, and 855 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 0.58 - 0.77 (2H, m, AB of ABX, 2- and 4-H), 1.14 (1H, d, $\underline{J}$ 1 Hz, 6-H), 1.54 (2H, d, 8- and 9-H), 1.96 (1H, dd, X of ABX, 3-H) and 7.32 (3H, s, 7-Me) (Calc. for ABX system - τ0.61 4-H, τ0.73 2-H, $\underline{J}_{2,3}$ 4.5, $\underline{J}_{2,4}$ 1.5, $\underline{J}_{3,4}$ 7.0 Hz).

7,9-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (212)

2-Amino-3,5-dimethylpyridine and 1,1,3,3-tetramethoxypropane yielded 1.9 g (89.6%), colourless needles, m.p. 164 - 165°.

Found: C, 46.3; H, 4.3; N, 10.6. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3 N, 10.8%.

ν_{max} 1640, 1515, 1460, 1415, 1155, 1120, 1090 br (ClO_4^-), and 790 cm^{-1}

τ (CF_3CO_2H; 100 MHz) 0.60 - 0.87 (2H, m, AB of ABX, 2- and 4-H), 1.36 (1H, s, 6-H), 1.74 (1H, s, 8-H), 2.04 (1H, dd, X of ABX, 3-H) and 7.17 and 7.40 (6H, 2 x s, 7- and 9-Me) (Calc. for ABX, system - τ 0.63 4-H, τ 0.83 2-H, $J_{2,3}$ 4.1, $J_{2,4}$ 1.5, $J_{3,4}$ 7.0 Hz).

6,8-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (218)

2-Amino-4,6-dimethylpyridine and 1,1,3,3-tetramethoxypropane (half scale) yielded 0.92 g (85.4%), colourless plates, m.p. 214 - 216° (decomp.).

Found: C, 46.1; H, 4.5; N, 10.6. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%.

ν_{max} 1650, 1635, 1580, 1410, 1360, 1100 br (ClO_4^-), 1045, 885, and 780 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.24 - 0.48 (2H, m, AB of ABX, 2- and 4-H), 1.66 (1H, s, 9-H), 1.91 (1H, dd, X of ABX, 3-H), 2.03 (1H, s, 7-H), 6.90 (3H, s, 6-Me) and 7.16 (3H, s, 8-Me) (Calc. for ABX system - τ 0.31 2-H, τ 0.40 4-H, $J_{2,3}$ 4.9, $J_{2,4}$ 1.7, $J_{3,4}$ 7.9 Hz).

9-Ethyl-6-methylpyrido[1,2-a]pyrimidinium Perchlorate (217)

2-Amino-3-ethyl-6-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 1.78 g (88.6%), colourless needles, m.p. 192 - 195°.

Found: C, 48.75; H, 5.0; N, 10.2. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1640, 1620, 1565, 1520, 1410, 1385, 1350, 1330, 1090 br (ClO_4^-), 1035, and 800 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.41 - 0.64 (2H, m, AB of ABX, 2- and 4-H), 1.49 (1H, d, J 8.3 Hz, 8-H), 1.84 (1H, dd, X of ABX, 3-H), 1.97 (1H, d, J 8.3 Hz, 7-H), 6.56 (2H, q, J 7.5 Hz, $-CH_2\underline{C}H_3$), 6.91 (3H, s, 6-Me) and 8.55 (3H, t, J 7.5 Hz $-CH_2\underline{C}H_3$). (Calc for ABX system - τ 0.46 4-H, τ 0.56 2-H, $J_{2,3}$ 4.4, $J_{2,4}$ 1.8, $J_{3,4}$ 7.6 Hz).

6-Methylpyrido[1,2-a]pyrimidinium Perchlorate (214)

2-Amino-6-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 1.8 g (79.5%), colourless needles, m.p. 224 - 225° (decomp.) (lit.[23], yield 70%, m.p. 217 - 218°, Cl analysis only).

Found: C, 44.4; H, 3.8; N, 11.5. Calc. for $C_9H_9ClN_2O_4$: C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 1635, 1410, 1350, 1100 br (ClO_4^-), 1080, 1045, and 830 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.33 - 0.50 (2H, m, 2- and 4-H), 1.25 - 1.45 (2H, m, 8- and 9-H), 1.61 - 1.86 (2H, m, 3- and 7-H) and 6.82 (3H, s, 6-Me).

6-Ethylpyrido[1,2-a]pyrimidinium Perchlorate (215)

2-Amino-6-ethylpyridine and 1,1,3,3-tetramethoxypropane yielded 0.9 g (42.5%), colourless needles, m.p. 187 - 190°.

Found: C, 46.3; H, 4.45; N, 10.6. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%.

ν_{max} 1630, 1425, 1355, 1140, 1090 br (ClO_4^-), 1060, 840, and 815 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.33 - 0.50 (2H, m, 2- and 4-H), 1.12 - 1.49 (2H, m, 8- and 9-H), 1.66 - 1.91 (2H, m, 3- and 7-H), 6.50 (2H, q, J 7.5 Hz, $-C\underline{H}_2CH_3$) and 8.37 (3H, t, J 7.5 Hz, $-CH_2C\underline{H}_3$).

6-n-Propylpyrido[1,2-a]pyrimidinium Perchlorate (216)

2-Amino-6-n-propylpyridine and 1,1,3,3-tetramethoxypropane yielded 1.6 g (79.9%), colourless needles, m.p. 143 - 144°.

Found: C, 48.3; H, 4.9; N, 10.1. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1630, 1380, 1360, 1350, 1090 br (ClO_4^-), 830, and 820 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.37 - 0.48 (2H, m, 2- and 4-H), 1.15 - 1.50 (2H,

m, 8- and 9-H), 1.66 - 1.92 (2H, m, 3- and 7-H), 6.53 (2H, t, J 7.5 Hz, $-C\underline{H}_2CH_2CH_3$), 7.99 (2H, m, $-CH_2C\underline{H}_2CH_3$) and 8.80 (3H, t, J 7 Hz, $-CH_2CH_2C\underline{H}_3$).

9-Hydroxypyrido[1,2-a]pyrimidinium Perchlorate (213)

2-Amino-3-hydroxypyridine and 1,1,3,3-tetramethoxypropane yielded 0.73 g (32.6%), colourless needles, m.p. 211 - 213° (decomp.).

Found: C, 38.75; H, 3.0; N, 11.2. $C_8H_7ClN_2O_5$ requires C, 38.95; H, 2.8; N, 11.4%.

ν_{max} 3400 (OH), 1635, 1585, 1520, 1410, 1380, 1300, 1180, 1100 br (ClO_4^-), 835, 780, and 730 cm^{-1}.

$\tau(CF_3CO_2H$; 100 MHz) 0.70 (2H, dd, 2- and 4-H), 1.37 (1H, dd, 6-H) and 1.88 - 2.08 (3H, m, 3-, 7- and 8-H).

9-Aminopyrido[1,2-a]pyrimidinium Perchlorate (243)

2,3-Diaminopyridine and 1,1,3,3-tetramethoxypropane yielded 1.50 g (66.6%), yellow needles (from water), m.p. 279 - 280° (decomp.).

Found: C, 39.0; H, 3.3; N, 17.05. $C_8H_8ClN_3O_4$ requires C, 39.1; H, 3.3; N, 17.1%.

ν_{max} 3450 and 3350 (NH_2), 1620 br, 1605, 1525, 1375, 1325, 1090 br (ClO_4^-), and 830 cm^{-1}.

$\tau(CF_3CO_2H$; 100 MHz) 0.72 - 1.02 (2H, m, 2- and 4-H), 1.73 (1H, t, 6-H) and 2.06 - 2.28 (3H, m, 7- and 8-H).

4-Methylpyrido[1,2-a]pyrimidinium Perchlorate (37)

2-Aminopyridine and 4,4-dimethoxybutan-2-one yielded 1.7 g (66.7%), colourless needles, m.p. 232 - 233° (decomp.) (lit.[21], yield 72%, m.p. 224 - 226° (decomp.).

Found: C, 44.2; H, 3.8; N, 11.3. Calc. for $C_9H_9ClN_2O_4$: C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 1640, 1410, 1325, 1100 br (ClO_4^-), 1040, 875, 865, 790, and 780 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.55 (1H, d, J 5 Hz, 2-H), 0.75 br (1H, d, J 7.4 Hz, 6-H), 1.18 - 1.38 (2H, m, 8- and 9-H), 1.69 (1H, m, 7-H), 1.87 (1H, d, J 5 Hz, 3-H) and 6.78 (3H, s, 4-Me).

4,9-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (175)

2-Amino-3-methylpyridine and 4,4-dimethoxybutan-2-one yielded 1.1 g (46.0%), colourless needles, m.p. 185 - 186°.

Found: C, 46.3; H, 4.2; N, 10.7. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%.

ν_{max} 1635, 1625, 1520, 1450, 1415, 1090 br (ClO_4^-), 1035, and 780 cm^{-1}.

τ (CF_3CO_2H; 60 MHz) 0.60 (1H, d, J 4.5 Hz, 2-H), 0.99 br (1H, d, J 7.3 Hz, 6-H), 1.49 br (1H, d, J 8.0 Hz, 8-H), 1.92 (1H, dd, J 7.3 and 8.0 Hz, 7-H), 2.03 (1H, d, J 4.5 Hz, 3-H), 6.82 (3H, s, 4-Me) and 6.99 (3H, s, 9-Me).

4,8-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (174)

2-Amino-4-methylpyridine and 4,4-dimethoxybutan-2-one yielded 1.03 g (43.3%), colourless plates, m.p. 188 - 190°.

Found: C, 46.2; H, 4.2; N, 10.5; Cl, 13.9. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8; Cl 13.7%.

ν_{max} 1650, 1640, 1450, 1330, 1100 br (ClO_4^-), 1080, and 1040 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.58 (1H, d, J 5 Hz, 2-H), 0.88 (1H, d, J 7 Hz, 6-H), 1.49 (1H, s, 9-H), 1.85 (1H, d, J 7 Hz, 7-H), 1.96 (1H, d, J 5 Hz, 3-H), 6.81 (3H, s, 4-Me) and 7.11 (3H, s, 8-Me).

4,7-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (173)

2-Amino-5-methylpyridine and 4,4-dimethoxybutan-2-one yielded 1.9 g (79.4%), colourless needles, m.p. 196 - 199°.

Found: C, 46.6; H, 4.3; N, 10.8. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%.

ν_{max} 1630, 1575, 1520, 1320, 1090 br (ClO_4^-), 1040, and 865 cm^{-1}.

$\tau(CF_3CO_2H$; 100 MHz) 0.63 (1H, d, J 4.5 Hz, 2-H), 1.02 (1H, d, J 1 Hz, 6-H), 1.42 (2H, d, 8- and 9-H), 1.94 (1H, d, J 4.5 Hz, 3-H), 6.78 (3H, s, 4-Me) and 7.17 (3H, s, 7-Me).

4,7,9-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (176)

2-Amino-3,5-dimethylpyridine and 4,4-dimethoxybutan-2-one yielded 1.85 g (82.8%), colourless needles, m.p. 162 - 163°.

Found: C, 48.2; H, 4.8; N, 10.1. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1635, 1525, 1440, 1325, 1100 br (ClO_4^-), 1035, 870, and 790 cm^{-1}.

$\tau(CF_3CO_2H$; 60 MHz) 0.58 (1H, d, J 4.8 Hz, 2-H), 1.13 (1H, d, J 1 Hz, 6-H), 1.56 (1H, d, J 1 Hz, 8-H), 1.95 (1H, d, J 4.8 Hz, 3-H), 6.82 (3H, s, 4-Me) and 7.02 and 7.23 (6H, 2 x s, 7- and 9-Me).

9-Hydroxy-4-methylpyrido[1,2-a]pyrimidinium Perchlorate (177)

2-Amino-3-hydroxypyridine and 4,4-dimethoxybutan-2-one yielded 1.72 g (73.0%), colourless needles, m.p. 233 - 234° (decomp.).

Found: C, 41.2; H, 3.5; N, 10.5. $C_9H_9ClN_2O_5$ requires C, 41.5; H, 3.45; N, 10.75%.

ν_{max} 3350 (OH), 1635, 1525, 1420, 1385, 1310, 1280, 1245, 1100 br (ClO_4^-), and 770 cm^{-1}.

$\tau(CF_3CO_2H$; 60 MHz) 0.77 (1H, d, J 4.6 Hz, 2-H), 1.36 (1H, t, X of AA'X,

6-H), 1.94 (2H, d, AA′ of AA′X, 7- and 8-H), 2.04 (1H, d, $\underline{J}$ 4.6 Hz, 3-H) and 6.87 (3H, s, 4-Me) (Calc. for AA′X system - $|\underline{J}_{6,7} + \underline{J}_{6,8}|$ = 8.0 Hz).

9-Amino-2-methylpyrido[1,2-a]pyrimidinium Perchlorate (245)

2,3-Diaminopyridine and 4,4-dimethoxybutan-2-one yielded 0.80 g (33.6%), yellow needles, (from methanol [x 2]), m.p. 185 - 186° (decomp.).

Found: C, 41.6; H, 3.9: N, 16.2. $C_9H_{10}ClN_3O_4$ requires C, 41.6; H, 3.85; N 16.2%.

ν_{max} 3450 and 3350 (NH_2), 1620, 1605, 1520, 1350, 1325, 1090 br (ClO_4^-), 820, and 735 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.85 (1H, d, $\underline{J}$ 7.6 Hz, 4-H), 1.30 (1H, dd, $\underline{J}$ 7.0 and 1 Hz, 6-H), 1.58 (1H, dd, $\underline{J}$ 8.6 and 1 Hz, 8-H), 2.03 (1H, dd, $\underline{J}$ 8.6 and 7.0 Hz, 7-H), 2.04 (1H, d, $\underline{J}$ 7.6 Hz, 3-H) and 6.75 (3H, s, 2-Me).

The product obtained by repeating the reaction above (but recrystallising only once) appeared to be a mixture of 9-amino-2-methylpyrido[1,2-a]-pyrimidinium perchlorate (245) and 9-amino-4-methylpyrido[1,2-a]-pyrimidinium perchlorate (246) from its ^{1}H n.m.r. spectrum in $(CD_3)_2SO$.

τ[$(CD_3)_2SO$; 60 MHz external Me_4Si standard] 0.86 (d, $\underline{J}$ 7.6 Hz, 4-H, [245]), 1.01 (d, $\underline{J}$ 4.7 Hz, 2-H[246]), 1.73 (dd, X of ABX, 6-H [246]), 1.78 (dd, X of ABX, 6-H [245]), 2.14 (d, $\underline{J}$ 4.7 Hz, 3-H [246]), 2.20 (d, $\underline{J}$ 7.6 Hz, 3-H [245]), 2.35 - 2.75 (m, 2 x AB of ABX, 7- and 8-H [245 and 246]), 4.12 br (s, 9-NH_2 [245 and 246]), 7.15 (s, 4-Me [246]), and 7.30 (s, 2-Me [245]).

2,6-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate (182)

2-Amino-6-methylpyridine and 4,4-dimethoxybutan-2-one yielded 1.6 g

(66.8%), pale yellow plates, m.p. 224 - 226° (decomp.).

Found: C, 46.1; H, 4.4; N, 10.85; Cl, 14.2. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8; Cl, 13.7%.

ν_{max} 1640, 1420, 1365, 1100 br (ClO_4^-), 1035, and 825 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 0.68 (1H, d, $\underline{J}$ 7.4 Hz, 4-H), 1.38 - 1.62 (2H, m, AB of ABX, 8- and 9-H), 1.95 (1H, d, $\underline{J}$ 7.4 Hz, 3-H), 2.03 (1H, dd, X of ABX, 7-H), 6.87 (3H, s, 6-Me) and 6.91 (3H, s, 2-Me). Calc. for ABX system - τ1.48 8-H, τ1.53 9-H, $\underline{J}_{7,8}$ 7.4, $\underline{J}_{7,9}$ 1.6, $\underline{J}_{8,9}$ 8.8 Hz).

6-Ethyl-2-methylpyrido[1,2-a]pyrimidinium Perchlorate (190)

2-Amino-6-ethylpyridine and 4,4-dimethoxybutan-2-one yielded 0.75 g (33.6%), yellow needles, m.p. 194 - 195° (decomp.).

Found: C, 48.1; H, 5.0; N, 10.0. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1635, 1425, 1380, 1090 br (ClO_4^-), 835, and 830 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 1.19 (1H, d, $\underline{J}$ 7.5 Hz, 4-H), 1.87 - 2.15 (2H, m, AB of ABX, 8- and 9-H), 2.42 (1H, d, $\underline{J}$ 7.5 Hz, 3-H), 2.45 (1H, dd, X of ABX, 7-H), 7.03 (2H, q, $\underline{J}$ 7.5 Hz, - $C\underline{H}_2CH_3$), 7.43 (3H, s, 2-Me) and 8.88 (3H, t, $\underline{J}$ 7.5 Hz, $-CH_2C\underline{H}_3$)(Calc. for ABX system - τ1.88 8-H, τ2.00 9-H, $\underline{J}_{7,8}$ 7.6, $\underline{J}_{7,9}$ 1.3, $\underline{J}_{8,9}$ 8.8 Hz).

2-Methyl-6-n-propylpyrido[1,2-a]pyrimidinium Perchlorate (191)

2-Amino-6-n-propylpyridine (2 g) and 4,4-dimethoxybutan-2-one (1.95 g) were dissolved in 60% perchloric acid (4 cm^3) and the mixture stirred at room temperature for 18 h to yield a dark brown solution. Upon addition of methanol (20 cm^3) and ether (1000 cm^3) the solution became cloudy, and after refrigeration for 2 days yellow needles crystallised from solution. The crystals were filtered and washed with ether. Yield 1.0 g (23.7%),

orange plates (from methanol/60% perchloric acid [few drops]/ether), m.p. 103 - 105°.

Found: C, 50.2; H, 5.4; N, 9.6. $C_{12}H_{15}ClN_2O_4$ requires C, 50.3; H, 5.2; N, 9.8%.

ν_{max} 1635, 1425, 1420, 1380, 1340, 1090 br (ClO_4^-), 825, and 820 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 0.74 (1H, d, J 7.3 Hz, 4-H) 1.39 - 1.67 (2H, m, AB of ABX, 8- and 9-H), 1.91 (1H, d, J 7.3 Hz, 3-H), 2.05 (1H, dd, X of ABX, 7-H), 6.64 (2H, t, J 7.5 Hz, $-CH_2CH_2CH_3$), 7.02 (3H, s, 2-Me), 8.07 (2H, m, $-CH_2CH_2CH_3$) and 8.86 (3H, t, J 7.5 Hz, $-CH_2CH_2CH_3$) (Calc. for ABX system - τ 1.49 8-H, τ 1.60 9-H, $J_{7,8}$ 7.6, $J_{7,9}$ 1.3, $J_{8,9}$ 8.8 Hz).

9-Ethyl-2,6-dimethylpyrido[1,2-a]pyrimidinium Perchlorate (192)

2-Amino-3-ethyl-6-methylpyridine and 4,4-dimethoxybutan-2-one yielded 0.65 g (30.9%), yellow needles, m.p. 121 - 123°.

Found: C, 50.2; H, 5.4; N, 9.5. $C_{12}H_{15}ClN_2O_4$ requires C, 50.3; H, 5.2; N, 9.8%.

ν_{max} 1645, 1625, 1420, 1380, 1345, 1320, 1100 br (ClO_4^-), 1030, 1020, 870, and 800 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.78 (1H, d, J 7.5 Hz, 4-H), 1.65 (1H, d, J 7.5 Hz, 8-H), 2.02 (1H, d, J 7.5 Hz, 3-H), 2.14 (1H, d, J 7.5 Hz, 7-H), 6.59 (2H, q, J 7.5 Hz, $-CH_2CH_3$), 6.99 (6H, s, 2- and 6-Me) and 8.55 (3H, t, J 7.5 Hz, $-CH_2CH_3$).

2-Methyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (231)

2-Aminopyridine and benzoyl acetone yielded 1.85 g (54.4%), colourless needles (from methanol), m.p. 209 - 212° (decomp.).

Found: C, 56.3; H, 4.1; N, 8.5; Cl, 11.4. $C_{15}H_{13}ClN_2O_4$ requires C, 56.2; H, 4.1; N, 8.7; Cl, 11.1%.

ν_{max} 1640, 1575, 1425, 1100 br (ClO_4^-), 770, and 700 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 1.08 (1H, d, $\underline{J}$ 6.8 Hz, 6-H) 1.45 (2H, d, AA′ of AA′X 8- and 9-H), 2.08 (1H, dt, $\underline{J}_{6,7}$ 6.8 Hz, X of AA′X, 7-H), 2.17 (1H, s, 3-H), 2.32 br (5H, s, 4-Ph) and 6.99 (3H, s, 2-Me) (Calc. for AA′X system - $\left|\underline{J}_{7,8} + \underline{J}_{7,9}\right|$ = 8.2 Hz).

2,9-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (234)

2-Amino-3-methylpyridine (1 g) and benzoylacetone (1.5 g) were dissolved in methanol (5 cm^3) and 60% perchloric acid (2 cm^3) and stirred for 140 h. More methanol (10 cm^3) and ether (500 cm^3) were then added, whereupon the solution become cloudy. Colourless needles formed overnight. Yield 0.1 g (3.2%), colourless needles (from ethanol), m.p. 194 - 195°.

Found: C, 57.5; H, 4.5; N, 8.4. $C_{16}H_{15}ClN_2O_4$ requires C, 57.4; H, 4.5; N, 8.4%.

ν_{max} 1640, 1630, 1425, 1370, 1090 br (ClO_4^-), 770, and 700 cm^{-1}.

τ(CF_3CO_2H; 100MHz) 1.33 (1H, dd, $\underline{J}$ 6.9 and 1.5 Hz, 6-H), 1.72 (1H, dd, $\underline{J}$ 6.0 and 1.5 Hz, 8-H), 2.24 - 2.50 (7H, m, 4-Ph, 3- and 7-H), 7.07 (3H, s, 2-Me) and 7.12 (3H, s, 9-Me).

2,8-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (233)

2-Amino-4-methylpyridine and benzoyl acetone yielded 2.0 g (64.5%), after 116 h. Colourless needles, m.p. 224.5 - 226.5° (decomp.).

Found: C, 57.6; H, 4.7; N, 8.4. $C_{16}H_{15}ClN_2O_4$ requires C, 57.4; H, 4.5; N, 8.4%.

ν_{max} 1630, 1565, 1445, 1415, 1370, 1280, 1100 br (ClO_4^-), 770 and 700 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 1.10 (1H, d, $\underline{J}$ 7 Hz, 6-H), 1.55(1H, s, 9-H), 2.16 (1H, s, 3-H), 2.18 (1H, d, $\underline{J}$ 7 Hz, 7-H), 2.25 br (5H, s, 4-Ph), 6.91 (3H, s, 2-Me) and 7.14 (3H, s, 8-Me).

2,7-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (232)

2-Amino-5-methylpyridine and benzoyl acetone yielded 1.54 g (49.7%), after 92 h. Colourless needles, m.p. 192 - 195°.

Found: C, 57.3; H, 4.4; N, 8.2. $C_{16}H_{15}ClN_2O_4$ requires C, 57.4; H, 4.5; N, 8.4%.

ν_{max} 1635, 1570, 1435, 1405, 1090 br (ClO_4^-), 1045, 845, 790, and 700 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 1.80 (1H, s, 6-H), 2.07 (2H, s, 8- and 9-H), 2.71 (1H, s, 3-H), 2.84 br (5H, s, 4-Ph), 7.52 (3H, s, 2-Me) and 7.99 (3H, s, 7-Me).

2,7,9-Trimethyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (235)

2-Amino-3,5-dimethylpyridine and benzoyl acetone yielded 0.51 g (2.1%), after 116 h. Colourless plates, m.p. 199 - 200°.

Found: C, 58.7; H, 5.0; N, 7.9. $C_{17}H_{17}ClN_2O_4$ requires C, 58.5; H, 4.9; N, 8.0%.

ν_{max} 1640, 1630, 1580, 1410, 1340, 1250, 1090 br (ClO_4^-), 775, and 705 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 1.96 (1H, d, J 1 Hz, 6-H), 2.27 (1H, d, J 1 Hz, 8-H), 2.76 (1H, s, 3-H), 2.81 br (5H, s, 4-Ph), 7.52 (3H, s, 2-Me), 7.57 (3H, s, 9-Me) and 8.01 (3H, s, 7-Me).

9-Amino-2-methyl-4-phenylpyrido[1,2-a]pyrimidinium Perchlorate (244)

2,3-Diaminopyridine and benzoylacetone yielded 1.15 g (37.4%), yellow needles (from water), m.p. 245 - 247° (decomp.).

Found: C, 53.9; H, 4.3; N, 12.3. $C_{15}H_{14}ClN_3O_4$ requires C, 53.65; H, 4.2; N, 12.5%.

ν_{max} 3450 and 3350 (NH_2), 1640, 1625, 1616, 1530, 1470, 1430, 1400,

1265, 1100 br (ClO_4^-), 780, and 750 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 1.19 (1H, dd, J 7.4 and 1.2 Hz, 6-H), 1.42 (1H, d, J 8.5 Hz, 8-H), 1.97 - 2.39 (7H, m, 4-Ph, 3- and 7-H) and 6.50 (3H, s, 2-Me).

Attempted Synthesis of 2,4,6-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (206)

A. By the general method (a) 2-amino-6-methylpyridine and pentan-2,4-dione, after reaction times of 16 h, 40 h and 7 days, yielded, in all three cases, 2-amino-6-methylpyridinium perchlorate as a colourless precipitate, which was characterised by comparison of its i.r. spectrum with that of an authentic sample.

ν_{max} 3400, 3340 and 3200 (N-H), 1660, 1630, 1180, 1140, 1080 br (ClO_4^-), 1010, 990 and 810 cm^{-1}.

B. 2-Amino-6-methylpyridine (0.5 g) and pentane-2,4-dione (0.5 g) were dissolved in 60% perchloric acid (1 cm^3) and the mixture heated on a water bath for 60 h. Addition of methanol (5 cm^3) and ether (200 cm^3) precipitated a colourless solid, which was filtered, washed with ether and dried by suction at the pump. I.r. spectra showed it to be 2-amino-6-methylpyridinium perchlorate, as above.

Attempted Synthesis of 9-Carbethoxy-6-phenylpyrido[1,2-a]pyrimidinium Perchlorate (284)

A. By the general method (a) with the aminopyridine (0.5 g scale) and ethanol (10 cm^3) instead of methanol, 2-amino-3-carbethoxy-6-phenylpyridine and 1,1,3,3-tetramethoxypropane yielded 0.65 g (91.9%) of 2-amino-3-carbethoxy-6-phenylpyridinium perchlorate as a colourless precipitate, which was characterised by comparison of its i.r. spectrum

with that of an authentic sample.

ν_{max} 3420, 3380 and 3290 (N-H), 1710 (C=O), 1685, 1340, 1100 br (ClO_4^-), cm^{-1}.

B. Method of Khmaruk, Volovenko and Chuiguk[23].

2-Amino-3-carbethoxy-6-phenylpyridinium perchlorate (0.5 g) and 1,1,3,3-tetramethoxypropane (0.3 g) were dissolved in ethanol (10 cm^3) and refluxed for 3 h. Addition of ether (500 cm^3) precipitated a colourless solid, which was filtered, washed with ether and dried by suction at the pump. I.r. spectra showed it to be 2-amino-3-carbethoxy-6-phenylpyridinium perchlorate, as above.

Attempted Synthesis of 6-Hydroxypyrido[1,2-a]pyrimidinium Perchlorate (229a)

2-Amino-6-hydroxypyridine and 1,1,3,3-tetramethoxypropane yielded 1.72 g of a purple powder which could not be further purified or identified.

Attempted Synthesis of 6-Aminopyrido[1,2-a]pyrimidinium Perchlorate (229b)

2,6-Diaminopyridine and 1,1,3,3-tetramethoxypropane yielded 2.10 g of a brick red powder which could not be further purified or identified.

Attempted Synthesis of 6-Amino-2-methylpyrido[1,2-a]pyrimidinium Perchlorate (193a)

2,6-Diaminopyridine and 4,4-dimethoxybutan-2-one yielded a black intractable tar.

Attempted Synthesis of 2,6-Dimethyl-9-nitropyrido[1,2-a]pyrimidinium Perchlorate (285)

2-Amino-6-methyl-3-nitropyridine and 4,4-dimethoxybutan-2-one yielded 1.55 g (93.6%) of 2-amino-6-methyl-3-nitropyridinium perchlorate as a yellow precipitate, which was characterised by comparison of its i.r. spectrum with that of an authentic sample.

ν_{max} 3420, 3300 and 3170 (NH), 1665 br, 1630, 1520 (NO_2 assym. str.), 1330 (NO_2 sym. str.), 1285, 1225, 1160, 1100 br (ClO_4^-), 1005, 855, and 770 cm^{-1}.

9-Methylpyrido[1,2-a]pyrimidinium Perchlorate (50)

A. By the general method (a), on a 2 g scale and 1000 cm^3 ether, 2-amino-3-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 2.3 g of an unidentified product (P) as colourless needles.

Found: C, 41.05; H, 5.0; N, 9.5. $C_9H_9ClN_2O_4.CH_3OH$ requires C, 43.4; H, 4.7; N, 10.1%. $C_9H_9ClN_2O_4$ requires C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 3370, 1640, 1580, 1300, 1090 br (ClO_4^-), and 755 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.34 - 0.75 (2H, m), 1.05 (1H, d, J 6.5 Hz), 1.48 (1H, d, J 8 Hz), 1.93 (2H, m), 5.93 (s), 6.32 (s), 7.00 (3H, s). (After 10 min at the operating temperature, the peak at τ 6.32 disappears and the peak at τ 5.93 increases in size and integrates for 3H).

B. 2-Amino-3-methylpyridine (2 g) and 1,1,3,3-tetramethoxypropane (3.2 g) were dissolved in methanol (4 cm^3) and the solution cooled in an ice bath. 60% Perchloric acid (3 cm^3) was added slowly to prevent the temperature rising above 0°. The mixture was stirred for 26 h. Addition of methanol (5 cm^3) and ether (1000 cm^3), precipitated the unidentified

product (P) as colourless needles. The product was dissolved in methanol and ether added until cloudy. The mixture was refrigerated overnight. The colourless needles which had formed were filtered and dried in vacuo at room temperature for 7 days. Yield 3 g, m.p. 115 - 117°.

Found: C, 41.7; H, 4.7; N, 10.1. $C_9H_9ClN_2O_4.CH_3OH$ requires C, 43.4; H, 4.7; N, 10.1%. $C_9H_9ClN_2O_4$ requires C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 3370, 1640, 1580, 1300, 1090 br (ClO_4^-), and 755 cm^{-1}.

The above product (P) (0.5 g) was dissolved in dimethyl sulphoxide (3 cm^3) and heated on a water bath for 10 min. Methanol (3 cm^3) and ether (50 cm^3) were added to precipitate the 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50). Yield 0.33 g, m.p. 156 - 158° (from methanol/ether).

Found: C, 44.4; H, 3.9; N, 11.4. $C_9H_9ClN_2O_4$ requires C, 44.3; H, 3.7; N, 11.5%.

ν_{max} 1640, 1625, 1400, 1100 br (ClO_4^-), 850 and 790 cm^{-1}.

τ(CF_3CO_2H; 100 MHz) 0.58 - 0.83 (2H, m, AB of ABX, 2- and 4-H), 1.21 (1H, d, J 6.5 Hz, 6-H), 1.64 (1H, d, J 7.7 Hz, 8-H), 2.05 (1H, dd, X of ABX, 3-H), 2.09 (1H, dd, J 6.5 and 7.7 Hz, 7-H), 7.11 (3H, s, 9-Me) (Calc. for ABX system - τ 0.61 4-H, τ 0.79 2-H, $J_{2,3}$ 4.2, $J_{3,4}$ 6.9, $J_{2,4}$ 1.7 Hz)

C. By the general method (a), on a 2 g scale with stirring for 5 h at 50°, 2-amino-3-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 4.3 g (95.0%) of 9-methylpyrido[1,2-a]pyrimidinium perchlorate (50).

Attempted Synthesis of 2,6,8-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (53)

A. By the general method (a) 2-amino-4,6-dimethylpyridine and 4,4-dimethoxybutan-2-one, on 0.5 g scale after 7 days, yielded 0.90 g of 2-amino-4,6-dimethylpyridinium perchlorate (197), as colourless needles.

The product was characterised by comparison of its i.r. spectrum with that of an authentic sample.

ν_{max} 3450, 3350 and 3220 (NH), 1655, 1640, and 1100 br (ClO_4^-) cm^{-1}.

B. Method of Khmaruk, Volovenko and Chuiguk[23].

2-Amino-4,6-dimethylpyridinium perchlorate (197) (1 g) and 4,4-dimethoxybutan-4-one (0.7 g) were dissolved in 95% ethanol (25 cm^3) and the solution refluxed for 3.5 h. The volume was reduced to 5 cm^3 by evaporation in vacuo. Addition of ether precipitated 2-amino-4,6-dimethylpyridinium perchlorate, characterised by its i.r., as above.

C. 2-Amino-4,6-dimethylpyridinium perchlorate (1 g) and 4,4-dimethoxybutan-2-one (0.7 g) were dissolved in acetic anhydride (10 cm^3) and the solution heated on a water bath for 1 h. The mixture was cooled and poured into ether (200 cm^3). A brown solid precipitated which was filtered and washed with ether. Treatment with activated charcoal in methanol afforded 4,6,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate (198) as a yellow powder. Yield 0.96 g (78.4%), separating from methanol as pale yellow needles, m.p. 201 - 203° (decomp.).

Found: C, 48.7; H, 4.9; N, 10.15. $C_{11}H_{13}ClN_2O_4$ requires C, 48.4; H, 4.8; N, 10.3%.

ν_{max} 1655, 1635, 1595, 1475, 1340, 1275, 1100 br (ClO_4^-), 1035, and 880 cm^{-1}.

τ(CF_3CO_2H; 60 MHz) 0.80 (1H, d, J 4.8 Hz, 2-H), 1.75 (1H, s, 9-H), 2.12 (1H, s, 7-H), 2.15 (1H, d, J 4.8 Hz, 3-H), 6.70 and 6.77 (6H, 2 x s, 4- and 6-Me) and 7.23 (3H, s, 8-Me).

11.2 Pyrido[1,2-a]pyrimidinium Perchlorates from 2-Acylvinylaminopyridines

General Method (b)

The appropriate 2-(2-acylvinylamino)pyridine (0.1 g) was dissolved in ether (100 cm^3) and methanol (2 cm^3) and stirred during the addition of 60% perchloric acid (0.2 cm^3). The solution immediately went milky and then cleared as the pyrido[1,2-a]pyrimidinium perchlorate coagulated. The precipitate was filtered, washed with ether and dried at 50° *in vacuo*. By this procedure, the following salts were prepared:

4-Methylpyrido[1,2-a]pyrimidinium perchlorate, 0.14 g (92.8%), from 2-(2-acetylvinylamino)pyridine (172).

2,4-Dimethylpyrido[1,2-a]pyrimidinium perchlorate, 0.13 g (88.5%), from 2-(2-acetyl-1-methylvinylamino)pyridine (200).

2,4,8-Trimethylpyrido[1,2-a]pyrimidinium perchlorate, 0.13 g (90.6%), from 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine (201).

2,6-Dimethylpyrido[1,2-a]pyrimidinium perchlorate, 0.14 g (95.3%), from 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185).

2,4,7,9-Tetramethylpyrido[1,2-a]pyrimidinium perchlorate, 0.14 g (99.7%), from 2-(2-acetyl-1-methylvinylamino)-3,5-dimethylpyridine (202).

The m.p's. and i.r. spectra of the above products were identical to those of the corresponding compound prepared by method (a).

2-(2-Acetylvinylamino)-6-methylpyridinium Perchlorate (184)

Treatment of 2-(2-acetylvinylamino)-6-methylpyridine (183) by method (b) above, yielded 2-(2-acetylvinylamino)-6-methylpyridinium perchlorate

0.15 g (95.5%), as colourless needles, m.p. 139 - 141° (decomp.).

Found: C, 43.4; H, 4.9; Cl, 12.6; N, 9.9. $C_{10}H_{13}ClN_2O_5$ requires C, 43.4; H, 4.7; Cl, 12.8; N, 10.1%.

ν_{max} 3300 and 3180 (2 x NH), 1640 (C=O), 1595, 1545 and 1520 cm^{-1}.

11.3 2,6-Dimethylpyrido[1,2-a]pyrimidinium Perchlorate - A Mechanistic Investigation

11.3.1

A. 2-(2-Acetylvinylamino)-6-methylpyridine (183) (0.5 g) and 2-amino-6-methylpyridine (0.31 g) were dissolved in methanol (5 cm^3) and 60% perchloric acid (0.4 cm^3) and the solution stirred, at room temperature, for 24 h. Addition of ether precipitated 0.60 g of 2-amino-6-methylpyridinium perchlorate as a colourless solid, which was characterised by comparison of its i.r. spectrum with that of an authentic sample.

B. 2-(2-Acetylvinylamino)-6-methylpyridine (183) (0.5 g) was dissolved in methanol (5 cm^3) and 60% perchloric acid (0.4 cm^3) and the solution stirred, at room temperature, for 24 h. Addition of ether precipitated 0.63 g of 2-(2-acetylvinylamino)-6-methylpyridinium perchlorate (184), as a colourless solid, which was characterised by comparison of its i.r. spectrum with that of an authentic sample.

11.3.2

A. Repeating 11.3.1 A. above, but using 60% perchloric acid (0.7 cm^3), 0.82 g of 2-amino-6-methylpyridinium perchlorate was obtained. It was characterised by comparative i.r.

B. Repeating 11.3.1 B. above, but using 60% perchloric acid (0.7 cm^3), 0.19 g of 2-amino-6-methylpyridinium perchlorate was obtained. It was characterised by comparative i.r.

11.3.3

Repeating 11.3.1 B. above, but with stirring for 93 h, yielded 0.05 g (6.8%) of 2,6-dimethylpyrido[1,2-a]pyrimidinium perchlorate (182), identical to that prepared by the general method (a).

11.4 Pyrido[1,2-a]pyrimidinium Bromides from 2-Aminopyridines

General Method

The 2-aminopyridine (2 g) and an equimolar quantity of the appropriate β-dicarbonyl compound, or its acetal, were dissolved in 60% hydrobromic acid (5 cm^3) and stirred at room temperature for 15 - 18 h. Methanol (20 cm^3) and ether (200 cm^3) were added to precipitate the bromide, which was filtered, washed with ether, recrystallised from methanol containing a few drops of hydrobromic acid, and dried at 50° in vacuo. The following bromides were prepared by this general method.

2,4-Dimethylpyrido[1,2-a]pyrimidinium Bromide (263)

2-Aminopyridine and pentane-2,4-dione yielded 3.4 g (66.7%) of the bromide (263) as cream needles. M.p. 265 - 266° (decomp.).

Found: C, 50.3; H, 4.7; N, 11.7; Br, 33.4. $C_{10}H_{11}BrN_2$ requires C, 50.2; H, 4.6; N, 11.7; Br, 33.5%.

ν_{max} 1640, 1570, 1430. 1215, 1200, 1030, 790, and 780 cm^{-1}.

Pyrido[1,2-a]pyrimidinium Bromide (264)

2-Aminopyridine and 1,1,3,3-tetramethoxypropane yielded 3.75 g (83.3%) of the bromide (264) as cream needles. M.p. 268° (decomp.).

Found: C, 45.7; H, 3.6; N, 13.3; Br, 36.7. $C_8H_7BrN_2$ requires C, 45.5; H, 3.3; N, 13.3; Br, 37.9%.

ν_{max} 1640, 1510, 1380, 1130, 840, and 790 cm^{-1}.

6-Methylpyrido[1,2-a]pyrimidinium Bromide (265)

2-Amino-6-methylpyridine and 1,1,3,3-tetramethoxypropane yielded 3.5 g (83.3%) of the bromide (265) as cream needles. M.p. ca 292° (melts only when placed in a preheated melting point apparatus).

Found: C, 47.7; H, 4.05; N, 12.2; Br, 36.0. $C_9H_9BrN_2$ requires C, 48.0; H, 4.0; N, 12.4; Br, 35.6%.

ν_{max} 1635, 1580, 1415, 1345, 840, and 820 cm^{-1}.

11.5 Synthesis of Pyrido[1,2-a]pyrimidones and Attempted Conversion to Pyrido[1,2-a]pyrimidinium Salts

2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (72)

A. Method of Antaki and Petrow[28].

2-Aminopyridine (9.4 g) and ethyl acetoacetate (26 g) were heated at 100° for 4 h. Excess of the reactants was removed by distillation under reduced pressure and the solid residue crystallised from benzene/light petrol (b.p. 100 - 120°) to yield 2-acetoacetamidopyridine (306) as off-white plates, m.p. 112 - 113° (lit.[28], m.p. 112 - 113°).

ν_{max} 3250 (NH), 1715 (ketone C=O), 1670 br (amide C=O + pyridine C=N), 1580, 1555, 1445, 1330, 1310, 1180, 1160, 1140, and 780 cm^{-1}.

The intermediate so obtained was carefully added to concentrated sulphuric acid (20 cm^3) at room temperature, an exothermic reaction occuring. After stirring for 24 h, the solution was poured onto ice, basified with aqueous ammonia and extracted with chloroform. Evaporation of the chloroform yielded 0.75 g (4.7%) of 2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one (72) as colourless needles, m.p. 120° (from benzene/light petrol, b.p. 100 - 120°) (lit.[28], yield <10%, m.p. 123°).

ν_{max} 1700 (C=O), 1630 (C=N), 1540, 1410, and 775 cm^{-1}.

τ ($CDCl_3$; 60 MHz) 0.96 br (1H, d, J 7 Hz, 6-H), 2.33 - 3.00 (3H, m, 7-, 8- and 9-H), 3.65 (1H, s, 3-H) and 7.56 (3H, s, 2-Me).

B. Method of Khalifa[30] (modified).

2-Aminopyridine (22.8 g) and ethyl acetoacetate (100 cm^3) were refluxed for 30 h. Excess ethyl acetoacetate was removed by distillation under reduced pressure. The solid residue was crystallised from benzene/light petrol (b.p. 100 - 120°) to give yellow needles. Elution through a charcoal column with benzene yielded 4.5 g (11.6%) of 2-methyl-4H-

pyrido[1,2-a]pyrimidin-4-one (72) as colourless needles (from benzene/light petrol [b.p. 100 - 120°]), m.p. 122° (lit.[30], m.p. 128°).

2H-Pyrido[1,2-a]pyrimidin-2-one (107)

Method of Lappin[42] (modified).

To a cold solution of 2-aminopyridine (4.7 g) in dry ether (50 cm^3), a solution of ethyl propiolate (4.9 g) in dry ether (25 cm^3) was added. The mixture was stirred for 48 h, a precipitate was observed after 30 min. The product was collected by filtration, and extracted with dry ether in a Soxhlet extractor until the effluent from the extraction was colourless. There remained undissolved 0.8 g (11.0%) of off-white solid, m.p. 251 - 254° (lit.[42], yield 24%, m.p. 248 - 250°).

ν_{max} 1650 (C=O), 1610, 1585, 1390, 1115, and 780 cm^{-1}.

9-Methyl-2H-pyrido[1,2-a]pyrimidin-2-one (111)

2-Amino-3-methylpyridine (5.6 g) and ethyl propiolate (5.0 g), by the modified method of Lappin[42] (as above), with cooling to 5 - 10°, yielded 0.92 g (10.6%) of off-white solid m.p. 226 - 227° (lit.[42], yield 37%, m.p. 226 - 228°).

Attempted Synthesis of a 4-Chloro-2-methylpyrido[1,2-a]pyrimidinium Salt (308)

2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (72) (0.2 g) and phosphoryl chloride (5 cm^3) were mixed and refluxed for 1 h. Excess phosphyl chloride was distilled off at reduced pressure, to yield a red tarry solid, which was identified as impure 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride by comparison of the i.r. spectrum with that of an authentic sample.

ν_{max} 2520 ($\overset{+}{N}H$), 1715 (C=O), 1645, 1515, and 760 cm^{-1}.

Attempted Synthesis of 2-Bromopyrido[1,2-a]pyrimidinium Bromide (315)

2H-Pyrido[1,2-a]pyrimidin-2-one (107) (0.2 g) and phosphorus tribromide (3 cm^3) were heated for 2 h on a water bath. Addition of methanol and ether precipitated a tacky brown solid, which was redissolved in methanol and reprecipitated with ether. Its i.r. spectrum showed it to be 2-oxo-pyrido[1,2-a]pyrimidinium bromide by comparison with that of an authentic sample.

ν_{max} 3450 (NH), 1705 (C=O), 1650, 1420, 1290, and 860 cm^{-1}.

Attempted Synthesis of 2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-thione (307)

A. 2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (72) (0.3 g) and phosphorus pentasulphide (0.1 g) were mixed with benzene, and the mixture refluxed for 65 h, filtered and evaporated to dryness. The solid residue was unchanged 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

B. 2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (72) (0.3 g) and phosphorus pentasulphide (0.12 g) were heated together at 110° for 30 min in a vacuum sublimation apparatus, then sublimed under reduced pressure to give unchanged 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

C. 2-Methyl-4H-pyrido[1,2-a]pyrimidin-4-one (72) (0.3 g) and phosphorus pentasulphide (0.1 g) in pyridine (5 cm^3) were refluxed for 6.5 h. Evaporation of the pyridine under reduced pressure yielded unchanged 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Attempted Synthesis of 2-Methoxypyrido[1,2-a]pyrimidinium Methyl Sulphate (316) and 2-Methoxy-9-methylpyrido[1,2-a]pyrimidinium Methyl Sulphate (317)

Dimethyl sulphate (5 m Moles) in ethanol (10 cm^3) was added to the appropriate 2H-pyrido[1,2-a]pyrimidin-2-one (5 m Moles) in ethanol (10 cm^3) and stirred for 4 h with the temperature maintained at 50 - 60°. After cooling, ether (400 cm^3) was added and the solution became cloudy. After refrigeration for 16 h an oily deposit separated. The ether layer was decanted off to leave a pale yellow oil. Attempts to isolate a solid by trituration proved fruitless in both cases.

12. REACTIONS AND PROPERTIES OF PYRIDO[1,2-a]PYRIMIDINIUM SALTS

12.1 Hydrolytic Fission of Pyrido[1,2-a]pyrimidinium Perchlorates to Yield 2-(2-Acylvinylamino)pyridines

2-(2-Acetyl-1-methylvinylamino)pyridine (200)

A. 2,4-Dimethylpyrido[1,2-a]pyrimidinium perchlorate (47) (1 g) was suspended in water (20 cm^3) and stirred vigorously, whilst excess 40% sodium hydroxide solution was added dropwise. The solution became red and the product was extracted with ether (6 x 25 cm^3). The extracts were combined, dried ($MgSO_4$) and evaporated at reduced pressure to yield a brown oil. Chromatography on basic alumina with CCl_4–$CHCl_3$ (4:1) yielded 0.45 g (66.1%) of 2-(2-acetyl-1-methylvinylamino)pyridine (200) as a pale yellow oil, (lit.[166], m.p. 36°, structure given as imino-ketone).

Found: C, 67.8; H, 6.8; N, 15.9%; M^+, 176.0947. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.8; N, 15.9%; M, 176.0950.

ν_{max} 3200 (NH), 1625 (C=O), 1595, 1570, and 1505 cm^{-1}.

τ (CCl_4; 60 MHz) −2.91 br (1H, s, exchanges D_2O, NH), 1.82 (1H, m, 6-H), 2.51 (1H, ddd, 4-H), 3.10 – 3.32 (2H, m, 3- and 5-H), 4.88 (1H, q, J 0.6 Hz, -NH-CMe=CH-), 7.58 (3H, d, J 0.6 Hz, -NH-CMe=CH-) and 8.0 (3H, s, COMe) (first-order analysis for 3-H, 5-H, 4-H and 6-H, ABMX system).

m/e 177 (2), 176 (11), 175 (3), 161 (4), 159 (2), 134 (11), 133 (100), 132 (4), 131 (2), 120 (2), 119 (16), 118 (2), 95 (2), 94 (3), 79 (5), 78 (37), 67 (7) 66 (4), 65 (2), 60 (2), 53 (2), 52 (6), 51 (10), 50 (2), 43 (14), 42 (3), 41 (3), 40 (3), 39 (10), 38 (3), 28 (3), 27 (4).

m* 100.6 (176 ⟶ 133), 88.0 (161 ⟶ 119), 51.1 (119 ⟶ 78), 45.7 (133 ⟶ 78).

B. Several attempts to prepare 2-(2-acetyl-1-methylvinylamino)pyridine (200) from 2-aminopyridine and pentane-2,4-dione by the two methods of Kudryavtsev and Savich[166] produced only unchanged starting materials (lit.[166], yields 45% and 60%, m.p. 36°, assigned imino-ketone structure).

2-(2-Acetyl-1-methylvinylamino)-4-methylpyridine (201)

2,4,8-Trimethylpyrido[1,2-a]pyrimidinium perchlorate (53) (1 g) was suspended in water (10 cm^3), to which ether (10 cm^3) had been added, and stirred vigorously whilst excess 40% sodium hydroxide solution was added dropwise. The mixture became brown. The ether layer was separated and the remaining product extracted from the aqueous layer with more ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated at reduced pressure to yield a brown oil. Chromatography on basic alumina with CCl_4 yielded 0.5 g (71.7%) of 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine (201) as a pale yellow oil.

Found: C, 69.5; H, 7.4; N, 14.8%; M^+, 190.1094. $C_{11}H_{14}N_2O$ requires C, 69.5; H, 7.4; N, 14.7%; M, 190.1106.

ν_{max} 1625 (C=O), 1605, 1560, and 1505 cm^{-1}.

τ (CCl_4; 60 MHz) -2.69 br (1H, s, exchanges D_2O, NH), 1.97 (1H, dd, J 5.1 and 0.8 Hz, 6-H), 3.36 br (2H, d, 3- and 5-H), 4.90 (1H, q, J 0.6 Hz, -NH-CMe=CH-), 7.58(3H, d, J 0.6 Hz, -NH-CMe=CH-), 7.75 (3H, s, 4-Me) and 8.0 (3H, s, COMe) (first-order analysis for 3-H, 5-H, and 6-H, ABX system).

m/e 191 (1), 190 (7), 189 (3), 175 (5), 148 (12), 147 (100), 146 (4), 145 (2), 134 (2), 133 (14), 132 (2), 108 (3), 93 (4), 92 (35), 81 (2), 80 (4), 78 (3), 67 (4), 66 (4), 65 (13), 53 (3), 52 (3) 51 (3), 43 (14), 42 (2), 41 (4), 40 (2), 39 (11), 28 (3), 27 (4).

m* 113.7 (190 → 147), 101.1 (175 → 133), 63.6 (133 → 92), 57.6 (147 → 92).

2-(2-Acetyl-1-methylvinylamino)-3,5-dimethylpyridine (202)

2,4,7,9-Tetramethylpyrido[1,2-a]pyrimidinium perchlorate (204) (3 g) was suspended in water (20 cm^3), to which CCl_4 (50 cm^3) had been added, and stirred vigorously whilst excess 40% sodium hydroxide solution was added dropwise. The mixture became red-brown. Stirring was continued for 30 min. The CCl_4 layer was separated and the remaining product extracted from the aqueous layer with CCl_4 (2 x 25 cm^3). The CCl_4 extracts were combined, dried ($MgSO_4$) and reduced in bulk under reduced pressure. The concentrated CCl_4 solution was eluted through a neutral alumina column with more CCl_4. Evaporation of the CCl_4 under suction yielded 1.65 g (72.4%) of 2-(2-acetyl-1-methylvinylamino)-3,5-dimethylpyridine (202) as a pale yellow solid, m.p. 89 - 91° [colourless needles, from light petrol (b.p. 40 - 60°)].

Found: C, 70.4; H, 7.7; N, 13.6. $C_{12}H_{16}N_2O$ requires C, 70.6; H, 7.8; N, 13.7%.

ν_{max} 1630 (C=O), 1605, 1570, and 1500 cm^{-1}.

τ (CCl_4; 60 MHz) -2.72 br (1H, s, exchanges D_2O, NH), 2.36 br (1H, s, 6-H), 3.05 br (1H, s, 4-H), 5.03 (1H, q, J 0.5 Hz, -NH-CMe=CH-), 7.62 (3H, d, J 0.5 Hz, -NH-CMe=CH-), 7.77 and 7.87 (6H, 2 x s, 3- and 5-Me) and 8.04 (3H, s, COMe).

m/e 205 (1), 204 (5), 203 (2), 189 (4), 187 (2), 162 (15), 161 (100), 160 (3), 159 (2), 148 (3), 147 (18), 146 (3), 145 (3), 133 (2), 122 (2), 121 (2), 107 (3), 106 (21) 94 (2), 93 (2), 92 (5), 80 (4), 79 (8), 78 (3), 77 (11), 74 (2), 73 (2), 67 (3), 66 (3), 65 (5), 63 (2), 54 (2), 53 (6), 52 (3), 51 (4), 44 (2), 43 (19), 42 (4), 41 (8), 40 (3), 39 (13), 29 (2), 28 (5), 27 (8), 26 (2).

m* 127.0 (204 → 161), 114.3 (189 → 147), 76.5 (147 → 106), 70.0 (161 → 106).

2-(2-Acetyl-1-methylvinylamino)-3-aminopyridine (247)

9-Amino-2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorate (242) (0.5 g) was suspended in water (100 cm^3) and stirred vigorously whilst N/10 sodium hydroxide solution (18.28 cm^3) was added dropwise from a burette. $CHCl_3$ (50 cm^3) was added and the mixture stirred for 10 min. The $CHCl_3$ layer was separated and the remaining product extracted from the aqueous layer with more $CHCl_3$ (4 x 50 cm^3). The $CHCl_3$ extracts were combined, dried ($MgSO_4$) and evaporated at room temperature under reduced pressure to yield 0.32 g (91.6%) of 2(-2-acetyl-1-methylvinylamino)-3-aminopyridine (247), m.p. 90 - 91°, [yellow needles, from benzene/light petrol (b.p. 60 - 80°)].

Found: C, 62.8; H, 6.7; N, 21.9%; M^+, 191.1059. $C_{10}H_{13}N_3O$ requires C, 62.8; H, 6.8; N, 22.0%; M, 191.1059.

ν_{max} 3420 and 3370 (NH_2), 3250 (NH), 1655 (C=O), 1615, 1590, 1570, and 1515 cm^{-1}.

τ ($CDCl_3$; 60 MHz) -2.60 br (1H, s, exchanges D_2O, NH), 2.25 (1H, dd, X of ABX, 6-H), 2.91 - 3.33 (2H, m, AB of ABX, 4- and 5-H), 5.59 (1H, s, -NH-CMe=CH-), 6.00 br (2H, s, exchanges D_2O, NH_2), 7.71 (3H, s, -NH-CMe=CH-) and 7.93 (3H, s, COMe) (Calc. for ABX system - τ 3.13 5-H, τ 3.31 4-H, $J_{4,5}$ 8.3, $J_{4,6}$ 1.8, $J_{5,6}$ 5.0 Hz).

m/e 192 (3), 191 (22), 190 (3), 177 (3), 176 (20), 174 (6), 173 (4), 158 (2), 149 (16), 148 (100), 147 (5), 146 (2), 135 (4), 134 (30), 133 (10), 132 (3), 131 (3), 120 (2), 110 (2), 109 (5), 108 (3), 94 (3), 93 (30), 92 (2), 82 (4), 81 (4), 80 (2), 79 (2), 67 (43), 66 (12), 65 (3), 64 (2), 56 (2), 55 (3), 54 (5), 53 (5), 52 (4), 43 (17), 42 (4), 41 (5), 40 (3), 39 (18), 38 (3), 28 (6), 27 (5).

m* 162.5 (191 → 176), 114.8 (191 → 148), 102 (176 → 134), 58.5 (148 → 93).

2-(2-Formylvinylamino)-3-methylpyridine (210)

The unidentified product (P) (0.2 g), obtained in the attempted synthesis of 9-methylpyrido[1,2-a]pyrimidinium perchlorate (method B.), was dissolved in water (20 cm^3) and stirred vigorously whilst N/10 sodium hydroxide solution (7.23 cm^3) was added dropwise from a burette. A white solid suspension was visible, which dissolved upon addition of more water (25 cm^3). The mixture was stirred for 2 h, then the product extracted with $CHCl_3$ (4 x 25 cm^3). The extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield a red solid, m.p. 107 - 109°, identified as 2-(2-formylvinylamino)-3-methylpyridine (210).

Found: C, 67.0; H, 6.4; N, 15.4%; M^+, 162.0792. $C_9H_{10}N_2O$ requires C, 66.7; H, 6.2; N, 17.3%; M, 162.0793.

ν_{max} 3300 (NH), 2700, 1645 (C=O), 1620, 1590, and 1505 cm^{-1}.

τ ($CDCl_3$; 60 MHz) -1.90 br (1H, s, exchanges D_2O, NH), 0.59 (1H, dd, J 2.0 and 3.4 Hz, CHO), 1.82 (1H, ddd, J 3.4, 8.2 and 12.1 Hz, -NH-CH=CH-), 1.88 (1H, dd, J 1.8 and 5.2 Hz, 6-H), 2.58 (1H, dd, J 1.8 and 8.0 Hz, 4-H), 3.14 (1H, dd, J 5.2 and 8.0 Hz, 5-H), 4.55 (1H, dd, J 2.0 and 8.2 Hz, -NH-CH=CH-) and 7.72 (3H, s, 3-Me).

m/e 163 (2), 162 (20), 161 (3), 160 (2), 147 (4), 134 (12), 133 (100), 132 (5), 131 (4), 119 (8), 118 (3), 111 (2), 109 (2), 108 (11), 107 (3), 106 (2), 105 (3), 104 (2), 99 (2), 97 (3), 95 (2), 94 (2), 93 (18), 92 (21), 91 (4), 85 (7), 84 (2), 83 (4), 82 (2), 81 (6), 80 (7), 79 (3), 78 (3), 77 (3), 71 (12), 70 (4), 69 (7), 67 (5), 66 (9), 65 (21), 64 (4), 63 (4), 57 (22), 56 (5), 55 (10), 54 (3), 53 (8), 52 (7), 51 (6), 50 (2), 43 (20), 42 (4), 41 (15), 40 (4), 39 (19), 38 (3), 29 (7), 28 (8), 27 (12).

m* 109.2 (162 → 133), 63.6 (133 → 92).

3-Ethyl-2-(2-formylvinylamino)-6-methylpyridine (211)

9-Ethyl-6-methylpyrido[1,2-a]pyrimidinium perchlorate (217) (0.5 g) was dissolved in water (75 cm^3) and stirred vigorously whilst N/10 sodium hydroxide solution (18.35 cm^3) was added dropwise from a burette. The mixture was stirred for a further 10 min and the product extracted with $CHCl_3$ (4 x 50 cm^3). The extracts were combined, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield 0.31 g (83.0%) of 3-ethyl-2-(2-formylvinylamino)-6-methylpyridine (211) as pale yellow microprisms, m.p. 106 - 107°.

Found: C, 69.55; H, 7.3; N, 14.8%; M^+, 190.1110. $C_{11}H_{14}N_2O$ requires C, 69.5; H, 7.4; N, 14.7%; M, 190.1106.

ν_{max} 3320 (NH), 2730, 1650 (C=O), 1620, 1600, 1580, 1570, and 1515 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz, external Me_4Si standard] 0.52 br (1H, s, NH trans), 0.88 (1H, d, J 8.5 Hz, CHO trans), 1.73 (1H, d, J 13.5 Hz, -NH-CH=CH- trans), 2.77 (1H, d, J 7.5 Hz, 4-H trans), 3.37 (1H, d, J 7.5 Hz, 5-H trans), 4.25 (1H, dd, J 8.5 and 13.5 Hz, -NH-CH=CH- trans), 7.69 (2H, q, J 7.5 Hz, $-CH_2CH_3$ trans), 7.80 (3H, s, 6-Me) and 9.03 (3H, t, J 7.5 Hz, $-CH_2CH_3$).

τ ($CDCl_3$; 60 MHz) -1.85 br (s, exchanges D_2O, NH cis), 0.69 (d, J 8.5 Hz, CHO trans), 0.72 (dd, J 1.9 and 3.4 Hz, CHO cis), 1.36 (d, J 13.5 Hz, -NH-CH=CH- trans), 1.83 (ddd, J 3.4, 8.2 and 12.1 Hz, -NH-CH=CH- cis; with D_2O becomes dd, J 3.4 and 8.2 Hz, broad peaks, sharpen with NaOD, -ND-CH=CH- cis), 2.77 (d, J 7.0 Hz, 4-H cis and trans), 3.35 (d, J 7.0 Hz, 5-H, cis and trans), 4.21 (dd, J 8.5 and 13.5 Hz, -NH-CH=CH trans), 4.67 (dd, J 1.9 and 8.2 Hz, -NH-CH=CH- cis), 7.49 (q, J 8 Hz, $-CH_2CH_3$ cis), 7.52 (q, J 7.5 Hz, $-CH_2CH_3$ trans), 7.69 (s, 6-Me, cis and trans), 8.82 (t, J 8 Hz, $-CH_2CH_3$ cis) and 8.89 (t, J 7.5 Hz, $-CH_2CH_3$

trans).

m/e 191 (10), 190 (63), 189 (5), 175 (5), 174 (4), 173 (9), 163 (5), 162 (71), 161 (100), 160 (7), 159 (15), 148 (9), 147 (80), 146 (67), 145 (47), 144 (6), 136 (7), 135 (18), 134 (5), 133 (21), 132 (13), 131 (10), 122 (5), 121 (29), 120 (89), 119 (11), 118 (13), 117 (10), 116 (6), 108 (7), 107 (7), 106 (16), 105 (8), 104 (14), 94 (11), 93 (42), 92 (20), 91 (30), 90 (5), 89 (5), 80 (10), 79 (16), 78 (23), 77 (50), 76 (5), 73 (16), 72 (5), 70 (8), 67 (10), 66 (19), 65 (43), 64 (11), 63 (15), 55 (11), 54 (9), 53 (35), 52 (27), 51 (34), 50 (10), 43 (9), 42 (27), 41 (35), 40 (12), 39 (58), 38 (9), 29 (14), 28 (31), 27 (63) 26 (12).

m* 136.5 (190 → 161), 132.4 (161 → 146), 89.5 (161 → 120), 83.5 (132 → 105), 75.5 (146 → 105), 71.0 (119 → 92), 70.5 (120 → 92).

meta-stable determinations

4 - 8 kv 190 → 161, 190 → 133, 175 → 133, 162 → 133, 189 → 120, 161 → 120, 147 → 120, 161 → 119, 147 → 119.

2 - 8 kv 161 → 92, 147 → 92, 133 → 92, 119 → 92.

accurate mass determinations

Found: m/e 190.1110 ($C_{11}H_{14}N_2O^+$ requires 190.1106), 161.1079 ($C_{10}H_{13}N_2^+$ requires 161.1079), 161.0714 ($C_9H_9N_2O^+$ requires 161.0715), (ht. $C_{10}H_{13}N_2^+$: ht. $C_9H_9N_2O^+$ = 16:1), 175.0871 ($C_{10}H_{11}N_2O^+$ requires 175.0871), 133.0764 ($C_8H_9N_2^+$ requires 133.0766), and 120.0813 ($C_8H_{10}N^+$ requires 120.0813).

3-Amino-2-(2-formylvinylamino)pyridine (248)

9-Aminopyrido[1,2-a]pyrimidinium perchlorate (243) (0.5 g) was suspended in water (50 cm^3) and chloroform (25 cm^3). The suspension was stirred whilst N/10 sodium hydroxide solution (20.37 cm^3) was added

dropwise from a burette. The mixture was stirred for a further 10 min. The chloroform layer was separated and the remaining product was extracted from the aqueous layer with more chloroform (2 x 50, 4 x 25 cm^3). The chloroform extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure to yield 0.27 g (81.0%) of 3-amino-2-(2-formylvinylamino)pyridine (248) as yellow microprisms, m.p. 130 - 132° (decomp.).

Found: C, 58.85, H, 5.7; N, 25.4%; M^+, 163.0745. $C_8H_9N_3O$ requires C, 58.9; H, 5.6; N, 25.75%; M, 163.0746.

ν_{max} 3400 and 3320 (NH_2), 3250 (NH), 1675 (C=O), 1620, 1600, 1570, and 1510 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz, external Me_4Si standard] 0.46 br (1H, d, J 11.6 Hz, exchanges D_2O, NH trans), 0.85 (1H, d, J 9.2 Hz, CHO trans), 1.76 (1H, dd, J 11.6 and 14.2 Hz, -NH-CH=CH- trans; with D_2O becomes d, J 14.2 Hz, -ND-CH=CH- trans), 2.57 (1H, dd, X of ABX, 6-H trans), 3.01 - 3.48 (2H, m, AB of ABX, 4- and 5-H trans), 4.41 (1H, dd, J 9.2 and 14.2 Hz, -NH-CH=CH- trans), and 5.00 br (2H, s, exchanges D_2O, 3-NH_2) (Calc. for ABX system - τ 3.11 5-H, τ 3.35 4-H, $J_{4,5}$ 8.4, $J_{4,6}$ 1.8, $J_{5,6}$ 5.0 Hz).

The product was insufficiently soluble in chloroform to obtain a spectrum of the cis form.

m/e 164 (7), 163 (68), 162 (19), 148 (3), 147 (27), 146 (33), 145 (6), 135 (13), 134 (100), 133 (10), 132 (3), 121 (4), 120 (50), 119 (8), 118 (5), 117 (3), 109 (14), 108 (3), 107 (4), 106 (3), 105 (2), 95 (3), 94 (23), 93 (46), 92 (6), 91 (3), 85 (5), 83 (8), 82 (9), 81 (9), 80 (4), 79 (5), 78 (5), 77 (3), 76 (2), 72 (2), 70 (5), 69 (2), 68 (3), 67 (30), 66 (25), 65 (7), 64 (5), 63 (2), 57 (2), 56 (3), 55 (9), 54 (13), 53 (13), 52 (15), 51 (5), 50 (3), 47 (2), 44 (2), 43 (5), 42 (7), 41 (12), 40 (9), 39 (41), 38 (10), 37 (3), 32 (16), 29 (7), 28 (86), 27

(19), 26 (8).

m* 110.2 (163 → 134), 72.0 (120 → 93), 64.6 (134 → 93).

2-(2-Formyl-1-methylvinylamino)-6-methylpyridine (185)

A. 2,6-Dimethylpyrido[1,2-a]pyrimidinium perchlorate (182) (0.8 g) was suspended in water (5 cm^3) and ether (15 cm^3) and stirred vigorously whilst excess 40% sodium hydroxide solution was added dropwise. The two layers become orange-red. The ether layer was separated and the remaining product was extracted from the aqueous layer with more ether (4 x 50 cm^3). The ether extracts were combined, dried ($MgSO_4$) and evaporated at room temperature under reduced pressure to leave a brown solid residue. The residue was extracted with light petrol (b.p. 30 - 40°) and the insoluble material filtered off. The petrol was evaporated at room temperature under reduced pressure to yield 0.4 g (73.4%) of 2-(2-formyl-1-methylvinylamino)-6-methylpyridine (185) as pale yellow microprisms, m.p. 82.5 - 84°.

Found: C, 68.1; H, 6.8; N, 15.85%; M^+, 176.0949. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.8; N, 15.9%; M, 176.0950.

ν_{max} 3290 (NH), 1625 (C=O), 1605, 1585, and 1540 cm^{-1}.

τ(CCl_4; 60 MHz) -2.76 br (1H, s, exchanges D_2O, NH), 0.91 (1H, d, J 2.6 Hz, CHO), 2.52 [1H, t (deg. dd), J 8.3 and 8.3 Hz, 4-H], 3.22 br and 3.35 br (2H, 2 x d, J 8.3 and 8.3 Hz, 3- and 5-H), 4.85 (1H, dq, J 2.6 and 0.5 Hz, -NH-CMe=CH-), 7.54 (3H, d, J 0.5 Hz, -NH-CMe-CH-) and 7.57 (3H, s, 6-Me) (first-order analysis for 3-H, 5-H and 4-H, ABX system).

m/e 177 (1), 176 (8), 175 (3), 159 (3), 148 (13), 147 (100), 146 (4), 133 (3), 132 (3), 108 (7), 107 (3), 93 (4), 92 (23), 81 (6), 80 (5), 67 (4), 66 (7), 65 (18), 64 (3), 53 (3), 52 (3), 51 (3), 42 (7), 41 (7), 40 (4), 39 (15), 38 (4), 29 (2), 28

(4), 27, (4).

m* 123.0 (176⟶147), 63.7 (133⟶92), 57.6 (147⟶92).

B. 2-Amino-6-methylpyridine (2 g) and 4,4-dimethoxybutan-2-one (2.45 g) were dissolved in xylene (10 cm^3) and refluxed (140°) for 42 h. Evaporation of the xylene under reduced pressure left a blackish residue. Chromatography on neutral alumina with CCl_4-$CHCl_3$ (3:2) yielded 1.8 g (55.2%) of 2-(2-acetylvinylamino)-6-methylpyridine (183) m.p. 85 - 87° [pale yellow needles from light petrol (b.p. 60 - 80°)]. Found: C, 68.0; H, 6.75; N, 16.05%; M^+, 176.0945. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.8; N, 15.9%; M, 176.0950.

ν_{max} 3230 (NH), 1650 (C=O), 1600, 1570, and 1500 cm^{-1}.

τ (CCl_4; 60 MHz) -1.61 br (1H, s, exchanges D_2O, NH), 2.09 (1H, dd, J 12.2 and 8.6 Hz, -NH-CH=CH-), 2.63 [1H, t (deg. dd), J 8.2 and 8.2 Hz, 4-H], 3.36 and 3.51 (2H, 2 x d, J 8.2 and 8.2 Hz, 3- and 5-H), 4.74 (1H, d, J 8.6 Hz, -NH-CH=CH-), 7.62 (3H, s, 6-Me) and 7.93 (3H, s, COMe) (first-order analysis for 3-H, 5-H, and 4-H, ABX system).

m/e 177 (2), 176 (13), 161 (10), 134 (10), 133 (100), 132 (4), 131 (2), 119 (6), 94 (2), 93 (25), 92 (47), 91 (3), 81 (2), 80 (4), 79 (2), 78 (2), 77 (2), 67 (2), 66 (11), 65 (26), 64 (4), 63 (3), 53 (3), 52 (4), 51 (4), 50 (2), 43 (20), 42 (5), 41 (5), 40 (5), 39 (23), 38 (4).

m* 100.5 (176⟶133), 88.0 (161⟶119), 71.1 (119⟶92), 63.7 (133⟶92).

2-(2-Benzoyl-1-methylvinylamino)-4-methylpyridine (237)

A. 2,8-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (233) (0.5 g) was suspended in water (200 cm^3) to which carbon tetrachloride (200 cm^3) had been added. The mixture was stirred vigorously

whilst N/10 sodium hydroxide solution (14.95 cm^3) was added dropwise from a burette. The mixture was stirred for a further 2.5 h. The carbon tetrachloride was separated and the remaining product extracted from the aqueous layer with more carbon tetrachloride (2 x 50 cm^3). The carbon tetrachloride extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to leave a brown solid residue. The residue was extracted with light petrol (b.p. 60 - 80°), and the insoluble material was collected by filtration. The light petrol was evaporated under reduced pressure to leave a pale yellow solid. Chromatography on basic alumina with carbon tetrachloride yielded 0.24 g (63.7%) of 2-(2-benzoyl-1-methylvinylamino)-4-methylpyridine (237) as pale yellow microprisms, m.p. 63 - 64°.

Found: C, 75.9; H, 6.5; N, 11.0%; M^+, 252. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.35; N, 11.1%; M, 252.

ν_{max} 1620 (C=O), 1600, 1590, 1560, and 1530 cm^{-1}.

τ (CCl_4; 60 MHz) -3.48 br (1H, s, exchanges D_2O, NH), 2.00 (1H, d, J 6.0 Hz, 6-H pyridine), 2.00 - 2.22 (2H, m, 2- and 6-H phenyl), 2.57 - 2.78 (3H, m, 3-, 4- and 5-H phenyl), 3.40 - 3.50 (2H, m, 3- and 5-H pyridine) 4.20 (1H, s, -NH-CMe=CH-), 7.47 (3H, s, -NH-CMe=CH-) and 7.85 (3H, s, 4-Me pyridine).

m/e 252 (1), 251 (2), 175 (2), 148 (12), 147 (100), 146 (4), 145 (3), 133 (4), 132 (3), 131 (2), 122 (3), 121 (8), 120 (2), 119 (25), 117 (27), 115 (3), 109 (3), 108 (18), 107 (2), 106 (3), 105 (28), 104 (3), 103 (2), 102 (2), 98 (9), 97 (3), 93 (6), 92 (27), 91 (6), 84 (4), 83 (6), 82 (5), 81 (18), 80 (53), 79 (7), 78 (10), 77 (51), 76 (5), 75 (4), 74 (3), 73 (9), 72 (4), 70 (6), 69 (6), 68 (5), 67 (6), 66 (10), 65 (28), 64 (5), 63 (7), 62 (3), 61 (6), 60 (2), 59 (4), 58 (7), 57 (12), 56 (4) 55 (13), 54 (30), 53 (15), 52 (11), 51 (39), 50 (16), 49 (2), 45 (3), 44 (11), 42 (14), 41 (30), 40 (9), 39 (48), 38 (7), 37 (3), 36 (9), 35

(2), 32 (5), 31 (2), 30 (6), 29 (4), 28 (36), 27 (19), 26 (5).

m* 63.5 (133 → 92), 57.5 (147 → 92), 56.5 (105 → 77), 33.8 (77 → 51).

B. 2,8-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (233) (0.5 g) was suspended in water (200 cm^3). The mixture was stirred vigorously whilst N/10 sodium hydroxide solution (14.95 cm^3) was added dropwise from a burette. The mixture was stirred vigorously for a further 2.5 h. The product was extracted with carbon tetrachloride (5 x 50 cm^3). The extracts were combined, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield 2-amino-4-methylpyridine, identified by its i.r. spectrum.

C. 2-Amino-4-methylpyridine (1 g) and benzoylacetone (1.5 g) were dissolved in xylene (10 cm^3) and the solution refluxed for 70 h. Evaporation of the xylene under reduced pressure yielded only unchanged starting materials.

2-(2-Benzoyl-1-methylvinylamino)-5-methylpyridine (236)

2,7-Dimethyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (232) (0.5 g) was suspended in water (20 cm^3) to which carbon tetrachloride (30 cm^3) had been added. The mixture was stirred vigorously whilst N/10 sodium hydroxide solution (14.95 cm^3) was added dropwise from a burette. The carbon tetrachloride layer was separated and the remaining product was extracted from the aqueous layer with more carbon tetrachloride (2 x 25 cm^3). The extracts were combined, dried ($MgSO_4$) and evaporated to dryness to leave a yellow solid residue. Chromatography on basic alumina with carbon tetrachloride yielded 0.21 g (55.8%) of 2-(2-benzoyl-1-methylvinylamino)-5-methylpyridine (236) as pale yellow microprisms, m.p. 78 - 80°.

Found: C, 76.0; H, 6.3; N, 10.9%; M^+, 252. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.35; N, 11.1% M, 252.

ν_{max} 1620 (C=O), 1595, 1560, and 1500 cm^{-1}.

τ ($CDCl_3$; 60 MHz) -3.47 br (1H, s, exchanges D_2O, NH), 1.90 br (1H, s, 6-H pyridine), 2.01 - 2.27 (2H, m, 2- and 6-H phenyl), 2.50 - 2.76 (4H, m, 3-, 4- and 5-H phenyl, 4-H pyridine), 3.17 (1H, d, J 8.7 Hz, 3-H pyridine), 4.12 (1H, s, -NH-CMe=CH-), 7.47 (3H, s, -NH-CMe=CH-) and 7.79 (3H, s, 5-Me pyridine).

m/e 253 (1), 252 (4), 251 (3), 235 (1), 175 (2), 148 (11), 147 (100), 146 (2), 145 (2), 133 (2), 112 (2), 108 (2), 107 (2), 105 (8), 93 (2), 92 (12), 80 (2), 77 (14), 66 (2), 65 (9), 53 (2), 52 (2), 51 (5), 41 (2), 39 (6), 36 (5), 32 (2), 28 (8), 27 (2).

m* 101.1 (175 → 133), 85.8 (252 → 147), 63.6 (133 → 92), 57.6 (147 → 92), 56.5 (105 → 77), 33.8 (77 → 51).

3-Amino-2-(2-benzoyl-1-methylvinylamino)pyridine (249)

9-Amino-2-methyl-4-phenylpyrido[1,2-a]pyrimidinium perchlorate (244) (0.5 g) was suspended in water (50 cm^3) to which chloroform (25 cm^3) had been added. The mixture was stirred vigorously whilst N/10 sodium hydroxide solution (14.95 cm^3) was added dropwise from a burette. The mixture was stirred for a further 10 min. The chloroform was separated and the remaining product was extracted from the aqueous layer with more chloroform (8 x 50 cm^3). The extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure to leave a brown solid residue. The residue was extracted with benzene (250 cm^3) and the insoluble material collected. Evaporation of the benzene left a green and yellow solid residue. The residue was dissolved in chloroform and light petrol (b.p. 60 - 80°) was added to precipitate a green solid which was collected to leave a yellow solution. Evaporation of the solvents

yielded 3-amino-2-(2-benzoyl-1-methylvinylamino)pyridine (249) 0.11 g (29.2%) as yellow needles, from light petrol (b.p. 60 - 80°), m.p. 141-143°.

Found: C, 70.8; H, 6.2; N, 16.4%; M^+, 253.1209. $C_{15}H_{15}N_3O$ requires C, 71.15; H, 5.9; N, 16.6%; M, 253.1215.

ν_{max} 3400 and 3350 (NH_2), 3250 sh (NH), 1650 (C=O), 1610, 1570, 1550, and 1530 cm^{-1}.

τ ($CDCl_3$; 60 MHz) -3.15 br (1H, s, exchanges D_2O, NH), 2.00 - 2.25 (3H, m, 2- and 6-H phenyl, 6-H pyridine), 2.48 - 2.68 (3H, m, 3-, 4-, and 5-H phenyl), 2.90 - 3.28 (2H, m, AB of ABX, 4- and 5-H pyridine), 4.03 (1H, s, -NH-CMe=CH-), 6.00 br (2H, s, exchanges D_2O, NH), and 7.54 (3H, s, -NH-CMe=CH-).

m/e 254 (2), 253 (13), 252 (3), 239 (2), 238 (10), 236 (3), 235 (1), 188 (7), 187 (1), 176 (2), 160 (4), 149 (11), 148 (100), 147 (3), 146 (2), 135 (2), 134 (16), 133 (6), 132 (2), 131 (4), 120 (4), 115 (2), 109 (4), 106 (2), 105 (22), 94 (7), 93 (18), 92 (2), 91 (2), 82 (3), 81 (3), 79 (2), 78 (5), 77 (26), 67 (5), 66 (9), 65 (3), 64 (3), 57 (2), 56 (2), 55 (3), 54 (4), 53 (4), 52 (4), 51 (9), 50 (3), 45 (6), 44 (2), 43 (3), 42 (4), 41 (6), 40 (4), 39 (21), 38 (3), 32 (6), 29 (30).

m* 122.5 (253⟶176), 86.6 (253⟶148), 64.5 (134⟶93), 58.5 (148⟶93), 56.5 (105⟶77).

Attempted Synthesis of 3-Amino-2-(2-formyl-1-methylvinylamino)-pyridine (251)

A. 9-Amino-2-methylpyrido[1,2-a]pyridinium perchlorate (245) (0.5 g) was suspended in water (50 cm^3) to which chloroform (50 cm^3) had been added. The suspension was stirred vigorously whilst N/10 sodium hydroxide solution (19.27 cm^3) was added dropwise from a burette. The

chloroform layer was separated and the remaining product was extracted from the aqueous layer with more chloroform (6 x 50 cm^3). The extracts were combined, dried (Na_2SO_4) and evaporated at room temperature under reduced pressure to leave a red tarry solid, which could not be purified further.

B. Repeating the above on the suspected mixture of 2- and 4-methyl substituted 9-aminopyrido[1,2-a]pyrimidinium perchlorates (245 and 246) (0.5 g) yielded, after chromatography on basic alumina with chloroform, 3-amino-2-(2-acetylvinylamino)pyridine (250), 0.07 g (20.6% overall), as orange microprisms.

Found: M^+, 177.0898. $C_9H_{11}N_3O$ requires M, 177.0902.

τ ($CDCl_3$; 60 MHz) -1.86 br (1H, s, exchanges D_2O, NH), 1.97 (1H, dd, J 8.3 and 11.9 Hz, -NH-CH=CH-), 2.20 (1H, dd, X of ABX, 6-H), 2.90 - 3.35 (2H, m, AB of ABX, 4- and 5-H), 4.54 (1H, d, J 8.3 Hz,-NH-CH=CH-), 6.33 br (2H, s, exchanges D_2O, 3-NH_2) and 7.83 (3H, s, COMe). (Calc. for ABX system - τ 3.00 5-H, τ 3.22 4-H, $J_{4,5}$ 8.1, $J_{4,6}$ 1.7, $J_{5,6}$ 5.1 Hz).

m/e 178 (6), 177 (49), 176 (9), 163 (2), 162 (17), 161 (2), 160 (6), 159 (2), 135 (10), 134 (100), 133 (8), 132 (2), 121 (3), 120 (26), 119 (3), 118 (2), 109 (10), 108 (2), 107 (3), 106 (2), 105 (2), 95 (3), 94 (25), 93 (45), 92 (3), 83 (2), 82 (4), 81 (6), 80 (3), 79 (3), 78 (3), 77 (2), 71 (2), 70 (2), 69 (2), 68 (2), 67 (15), 66 (16), 65 (4), 64 (3), 57 (3), 56 (2), 55 (5), 54 (7), 53 (7), 52 (7), 51 (3), 50 (2), 43 (18), 42 (4), 41 (8), 40 (4), 39 (24), 38 (4), 29 (2), 28 (14), 27 (9), 26 (4).

m* 148.3 (177 → 162), 144.6 (177 → 160), 110.8 (162 → 134), 101.5 (177 → 134), 89.0 (162 → 120), 72.1 (120 → 93), 64.5 (134 → 93).

Thermal Preparation of 2-(2-Acetylvinylamino)pyridine (172)

2-Aminopyridine (1 g) and 4,4-dimethoxybutan-2-one (1.3 g) were dissolved in xylene (10 cm^3) and the solution was refluxed for 21.5 h. The xylene was evaporated under reduced pressure to leave a brown solid residue. The residue was washed with ether and crystallised from acetone to yield 1.05 g (64.5%) of 2-(2-acetylvinylamino)pyridine (172), m.p. 114 - 115° (lit.[20], m.p. 121°, yield 61.3%).

Found: C, 66.3; H, 6.25; N, 17.3%; M^+, 162.0793. Calc. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3%; M, 162.0793.

ν_{max} 3250 (NH), 1645 (C=O), 1600, 1565, and 1515 cm^{-1}.

τ ($CDCl_3$; 60 MHz) -1.69 br (1H, s, exchanges D_2O, NH), 1.75 br (1H, d, 6-H), 2.07 (1H, dd, J 12.0 and 8.6 Hz, -NH-CH=CH-), 2.46 (1H, ddd, 4-H), 3.00 - 3.40 (2H, m, 3- and 5-H), 4.62 (1H, d, J 8.6 Hz, -NH-CH=CH-) and 7.86 (3H, s, COMe) (3-H, 5-H, 4-H and 6-H ≡ ABMX system; from first-order analysis $J_{3,4}$ and $J_{4,5}$ 7.6 and 8.4, $J_{4,6}$ 1.8 and $J_{5,6}$ 6.0 Hz).

m/e 163 (2), 162 (14), 147 (13), 120 (9), 119 (100), 118 (3), 105 (16), 94 (2), 92 (2), 80 (2), 79 (24), 78 (68), 73 (2), 67 (5), 66 (4), 65 (5), 64 (2), 56 (7), 53 (4), 52 (14), 51 (18), 50 (4), 43 (21), 42 (3), 41 (5), 40 (5), 39 (14), 38 (5), 37 (2), 29 (2), 28 (10), 27 (10), 26 (4).

m* 87.5 (162 → 119), 75.0 (147 → 105), 57.9 (105 → 78), 51.1 (119 → 78), 33.3 (78 → 51).

12.2 Diazotisation of 9-Aminopyrido[1,2-a]pyrimidinium Perchlorates - Rearrangement to v-Triazolo[1,5-a]pyrimidines and 3(5)-(2-Pyrimidinyl)pyrazoles.

trans-3-(5,7-Dimethyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (319)

9-Amino-2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorate (242) (0.5 g) was suspended in a mixture of water (20 cm^3) and concentrated hydrochloric acid (2 cm^3) and stirred whilst a solution of sodium nitrite in water (0.2 g in 2 cm^3) was added, whereupon the suspension became a clear solution. A colourless precipitate was visible almost immediately. Stirring was continued for 2 h. The solid product was collected by filtration and dried *in vacuo* at room temperature. Crystallisation from 95% ethanol yielded 0.35 g (94.8%) of trans-3-(5,7-dimethyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (319) as off-white needles, m.p. 165 - 166° (decomp.).

Found: C, 59.4; H, 4.9; N, 28.0%; M^+, 202.0854. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 4.95; N, 27.7%; M, 202.0855.

ν_{max} 1660 (C=O), 1635, 1625, 1555, 1165, 1105, 980 (CH o.o.p. def. -CH=CH- trans), and 760 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] 0.45 (1H, d, J 8 Hz, CHO), 2.20 (1H, d, J 16 Hz, -CH=CH-CHO), 2.91 (1H, s, 6-H), 3.10 (1H, dd, J 16 and 8 Hz, -CH=CH-CHO), 7.31 (3H, s, 7-Me) and 7.52 (3H, s, 5-Me).

m/e 203 (2), 202 (14), 175 (6), 174 (55), 173 (9), 159 (3), 149 (2), 148 (2), 147 (9), 146 (28), 145 (55), 134 (3), 133 (2), 131 (5), 130 (2), 122 (2), 119 (3), 118 (7), 117 (3), 116 (3), 108 (3), 107 (4), 106 (4), 105 (6), 104 (6), 101 (2), 97 (2), 95 (2), 94 (13), 93 (18), 92 (4), 91 (4), 88 (2), 87 (3), 84 (2), 83 (3), 82 (3), 81 (5), 80 (5), 79 (4), 78 (7), 77 (8),

76 (3), 75 (3), 73 (6), 71 (3), 70 (2), 69 (4), 68 (3), 67 (21), 66 (36), 65 (29), 64 (32), 63 (7), 62 (2), 60 (4), 59 (4), 58 (7), 57 (6), 56 (4), 55 (8), 54 (8), 53 (16), 52 (15), 51 (17), 50 (9), 49 (2), 48 (4), 45 (12), 44 (7), 43 (9), 42 (78), 41 (30), 40 (26), 39 (100), 38 (30), 37 (11), 36 (4), 32 (13), 31 (11), 30 (3), 29 (38), 28 (73), 27 (31), 26 (11).

m* 149.8 (202 → 174), 122.6 (174 → 146).

meta-stable determinations

4 - 8 kv 202 → 174, 201 → 173, 174 → 146, 202 → 146, 173 → 145, 201 → 145.

accurate mass determinations

Found: m/e 202.0854 ($C_{10}H_{10}N_4O^+$ requires 202.0855), 174.0906 ($C_9H_{10}N_4^+$ requires 174.0905), 174.0793 ($C_{10}H_{10}N_2O^+$ requires 174.0793), 173.0714 ($C_{10}H_9N_2O^+$ requires 173.0715), 146.0840 ($C_9H_{10}N_2^+$ requires 146.0844), and 145.0764 ($C_9H_9N_2^+$ requires 145.0766).

cis- and trans-3-(5,7-Dimethyl-3-v-triazolo[1,5-a]pyrimidinyl)-acraldehyde (323 and 319).

9-Amino-2,4-dimethylpyrido[1,2-a]pyrimidinium perchlorate (242) (0.5 g) and sodium nitrite (0.5 g) were dissolved in water (200 cm^3) and stirred. Two drops of concentrated hydrochloric acid were added and the mixture stirred vigorously. A white precipitate was visible after 5 min. The stirring was continued for 20 min and the resulting precipitate filtered and dried in vacuo at room temperature to yield 0.12 g (32.5%) of a mixture of trans-3-(5,7-dimethyl-3-v-triazolo[1,5-a]pyrimidinyl)-acraldehyde (319) and cis-3-(5,7-dimethyl-3-v-triazolo[1,5-a]pyrimidinyl)-acraldehyde (323) as colourless microprisms, m.p. 137 - 140°.

Found: C, 59.1; H, 5.1; N, 28.0%; M^+, 202.0851. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 4.95; N, 27.7%; M, 202.0855.

ν_{max} 1660 (C=O), 1630 br, 1550, 1385, 1365, 1200, 1165, 1120, 1090, 980 (CH o.o.p. def. CH=CH trans), 760, and 720 (CH o.o.p. def CH=CH cis) cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] -0.71 (d, J 8 Hz, CHO cis), 0.39 (d, J 8 Hz, CHO trans), 2.12 (d, J 16 Hz, CH=CH-CHO trans), 2.46 (d, J 12 Hz, CH=CH-CHO cis), 2.87 br (s, 6-H cis and trans), 3.02 (dd, J 8 and 16 Hz, CH=CH-CHO trans), 4.02 (dd, J 8 and 12 Hz, CH=CH-CHO cis), 7.26 (s, 7-Me cis), 7.28 (s, 7-Me trans), 7.48 (s, 5-Me trans), and 7.50 (s, 5-Me cis) (ratio cis:trans ca 2:3).

m/e 203 (2), 202 (16), 175 (10), 174 (79), 173 (10), 161 (5), 159 (4), 147 (8), 146 (38), 145 (65), 144 (2), 134 (2), 133 (2), 132 (2), 131 (8), 120 (2), 119 (4), 118 (10), 117 (3), 108 (6), 107 (5), 106 (5), 105 (6), 104 (8), 94 (20), 93 (25), 92 (5), 91 (4), 90 (2), 87 (2), 82 (3), 81 (3), 80 (6), 79 (5), 78 (8), 77 (9), 76 (4), 75 (2), 73 (3), 68 (2), 67 (25), 66 (43), 65 (34), 64 (27), 63 (8), 62 (2), 55 (3), 54 (7), 53 (14) 52 (14), 51 (14), 50 (8), 43 (3), 42 (82), 41 (20), 40 (26), 39 (100), 38 (29), 37 (11), 29 (12), 28 (45), 27 (22).

m* 149.8 (202 ⟶ 174), 122.6 (174 ⟶ 146).

trans-3-(3-v-Triazolo[1,5-a] pyrimidinyl)acraldehyde (318)

9-Aminopyrido[1,2-a] pyrimidinium perchlorate (243) (0.75 g) was suspended in a mixture of water (20 cm^3) and concentrated hydrochloric acid (2 cm^3) and stirred whilst a solution of sodium nitrite in water (0.3 g in 2 cm^3) was added, whereupon the suspension became a clear solution. A colourless precipitate was visible almost immediately. Stirring was continued for 3 h. The solid product was collected by filtration and dried in vacuo at room temperature. Crystallisation

from 95% ethanol yielded trans-3-(3-v-triazolo[1,5-a]pyrimidinyl)-acraldehyde (318) (0.27 g, 50.8%) as off-white needles, m.p. 168 - 169° (decomp.).

Found: C, 54.9; H, 3.5; N, 32.4%; M^+, 174.0547. $C_8H_6N_4O$ requires C, 55.2; H, 3.45; N, 32.2%; M, 174.0542.

ν_{max} 1660 (C=O), 1640, 1610, 1530, 1390, 1325, 1125, 1100, and 980 (m, CH o.o.p. def. CH=CH trans) cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] 0.40 (1H, d, J 8 Hz, CHO), 0.55 (1H, dd, J 1.7 and 7 Hz, 7-H), 1.18 (1H, dd, J 1.7 and 4.5 Hz, 5-H), 2.12 (1H, d, J 16 Hz, CH=CH-CHO), 2.69 (1H, dd, J 4.5 and 7 Hz, 6-H), and 3.07 (1H, dd, J 8 and 16 Hz, CH=CH-CHO).

m/e 175 (1), 174 (8), 147 (10), 146 (100), 145 (5), 120 (2), 119 (6), 118 (23), 117 (31), 105 (2), 94 (7), 93 (44), 92 (25), 91 (33), 90 (7), 80 (3), 79 (9), 78 (5), 77 (4), 76 (5), 75 (3), 68 (2), 67 (9), 66 (19), 65 (39), 64 (49), 63 (19), 62 (4), 61 (2), 59 (5), 54 (10), 53 (28), 52 (38), 51 (19), 50 (12), 49 (4), 44 (4), 43 (2), 42 (6), 41 (20), 40 (29), 39 (54), 38 (47), 37 (29), 36 (3), 31 (3), 29 (36), 28 (80), 27 (46), 26 (46), 25 (4).

m* 122.6 (174 → 146), 95.4 (146 → 118).

meta-stable determinations

4 - 8 kv 174 → 146, 146 → 145, 146 → 118, 174 → 118, 145 → 117, 173 → 117.

accurate mass determinations

Found: m/e 146.0480 ($C_8H_6N_2O^+$ requires 146.0480), 146.0591 ($C_7H_6N_4^+$ requires 146.0592), 145.0399 ($C_8H_5N_2O^+$ requires 145.0402), 118.0528 ($C_7H_6N_2^+$ requires 118.0531), and 117.0451 ($C_7H_5N_2^+$ requires 117.0453).

cis- and trans-3-(3-v-Triazolo[1,5-a]pyrimidinyl)acraldehyde (322 and 318)

9-Aminopyrido[1,2-a]pyrimidinium perchlorate (243) (0.5 g) and sodium nitrite (1 g) were dissolved in water (30 cm^3) and stirred. One drop of concentrated hydrochloric acid was added and the mixture stirred vigorously for 15 min. A yellow precipitate formed, which was collected by filtration and dried *in vacuo* at room temperature to yield 0.08 g (22.6%) of a mixture of trans-3-(3-v-triazolo[1,5-a]-pyrimidinyl)acraldehyde (318) and cis-3-(3-v-triazolo[1,5-a]pyrimidinyl-acraldehyde (322) as yellow microprisms, m.p. 133 - 134°.

Found: C, 53.0; H,3.7; N, 31.9%; M^+, 174.0542. $C_8H_6N_4O$ requires C, 55.2; H, 3.45; N, 32.2%; M, 174.0542.

ν_{max} 1660 (C=O), 1640, 1610, 1530, 1390, 1100, 1080, 980 (w. CH o.o.p. def. -CH=CH- trans) and 745 (CH o.o.p. def. -CH=CH- cis) cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] -0.63 (d, J 8 Hz, CHO cis), 0.40 (d, J 8 Hz, CHO trans), 0.55 (dd, J 1.5 and 7 Hz, 7-H trans), 0.57 (dd, J 1.5 and 7 Hz, 7-H cis), 1.18 (dd, J 1.5 and 4 Hz, 5-H trans), 1.30 (dd, J 1.5 and 4 Hz, 5-H cis), 2.12 (d, J 16 Hz, -CH=CH-CHO trans), 2.43 (d, J 11.5 Hz, -CH=CH-CHO cis), 2.65 (dd, J 4 and 7 Hz, 6-H cis), 2.69 (dd, J 4 and 7 Hz, 6-H trans), 3.07 (dd, J 8 and 16 Hz, -CH=CH-CHO trans) and 3.97 (dd, J 8 and 11.5 Hz, -CH=CH-CHO cis) (ratio cis : trans ca 3 : 2).

m/e 175 (2), 174 (17), 147 (8), 146 (77), 145 (12), 120 (4), 119 (11), 118 (46), 117 (51), 106 (2), 105 (3), 103 (2), 94 (7), 93 (44), 92 (38), 91 (45), 90 (14), 89 (2), 80 (8), 79 (13), 78 (7), 77 (6), 76 (6), 75 (4), 73 (2), 68 (2), 67 (9), 66 (19), 65 (58), 64 (64), 63 (26), 62 (6), 61 (2), 59 (5), 54 (12), 53 (29), 52 (43), 51 (20), 50 (14), 49 (4), 47 (2), 46 (3), 45 (3), 44 (2), 43 (2), 42 (5), 41 (20), 40 (24), 39 (74), 38 (63), 37 (34), 36 (5), 32 (2), 30 (18), 29 (36), 28 (100), 27 (41), 26 (43).

m* 122.6 (174 → 146), 95.5 (146 → 118).

trans-3-(7-Methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (321) and trans-3-(5-Methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (320)

A mixture of 9-amino-2-methylpyrido[1,2-a]pyrimidinium perchlorate (245) and 9-amino-4-methylpyrido[1,2-a]pyrimidinium perchlorate (246) (0.5 g) was dissolved in water (15 cm^3) and concentrated hydrochloric acid (2 cm^3) and stirred whilst a solution of sodium nitrite in water (0.2 g in 2 cm^3) was added. The mixture was stirred for 2 h. The cream precipitate which had formed was collected by filtration and dried *in vacuo* at room temperature. Crystallisation from 95% ethanol yielded 0.20 g (55.2%) of a mixture of trans-3-(7-methyl-3-v-triazolo[1,5-a]-pyrimidinyl) acraldehyde (321) and trans-3-(5-methyl-3-v-triazolo-[1,5-a]pyrimidinyl) acraldehyde (320) as cream needles, m.p. 143 - 145° (decomp.).

Found: C, 57.2; H, 4.5; N, 30.05%; M^+, 188.0696. $C_9H_8N_4O$ requires C, 57.4; H, 4.3; N, 29.8%; M, 188.0698.

ν_{max} 1670 br (C=O), 1630, 1615, 1540, 1355, 1305, 1255, 1120, 985 (CH o.o.p. def. -CH=CH- trans), and 800 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] 0.46 (d, J 8.5 Hz, CHO [7 methyl and 5 methyl]), 0.77 (d, J 8 Hz, 7-H [5 methyl]), 1.37 (d, J 4.5 Hz, 5-H [7 methyl]), 2.21 (d, J 16 Hz, -CH=CH-CHO [7 methyl]), 2.26 (d, J 16 Hz, -CH=CH-CHO [5 methyl]) 2.83 (d, J 4.5 Hz, 6-H [7 methyl]), 2.86 (d, J 8 Hz, 6-H, [5 methyl]), 3.12 (dd, J 8.5 and 16 Hz, -CH=CH-CHO [7 methyl]), 3.17 (dd, J 8.5 and 16 Hz, -CH=CH-CHO [5 methyl]), 7.25 (s, 7-Me [7 methyl]), and 7.49 (s, 5-Me [5 methyl]) (ratio [7 methyl : 5 methyl] ca 5:2).

m/e 189 (5), 188 (39), 187 (3), 161 (11), 160 (100), 159 (12), 145

(5), 133 (7), 132 (33), 131 (83), 130 (2), 120 (5), 119 (2), 118 (2), 117 (4), 106 (2), 105 (7), 104 (11), 103 (2), 94 (18), 93 (22), 92 (5), 91 (6), 90 (2), 80 (5), 79 (9), 78 (10), 77 (9), 76 (3), 75 (2), 68 (4), 67 (10), 66 (19), 65 (22), 64 (20), 63 (7), 54 (4), 53 (13), 52 (20), 51 (11), 50 (6), 42 (10), 41 (15), 40 (12), 39 (37), 38 (16), 37 (8), 29 (6), 28 (26), 27 (11), 26 (7).

m* 136.2 (188⟶160), 108.9 (160⟶132).

accurate mass determinations

Found: m/e 160.0747 ($C_8H_8N_4^+$ requires 160.0749), and 160.0637 ($C_9H_8N_2O^+$ requires 160.0637).

cis- and trans-3-(7-Methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (325 and 321) and cis- and trans-3-(5-Methyl-3-v-triazolo[1,5-a]-pyrimidinyl)acraldehyde (324 and 320)

A mixture of 9-amino-2-methylpyrido[1,2-a]pyrimidinium perchlorate (245) and 9-amino-4-methylpyrido[1,2-a]pyrimidinium perchlorate (246) (1.0 g) was dissolved in water (20 cm^3) and concentrated hydrochloric acid (2 cm^3) and cooled in an ice/salt bath. The mixture was stirred whilst a solution of sodium nitrite in water (1 g in 2 cm^3) was added. The mixture was stirred for a further 30 min. The cream precipitate which had formed was collected by filtration and dried in vacuo at room temperature to yield 0.49 g (67,6%) of a mixture of trans-3-(7-methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (321), trans-3-(5-methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (320), cis-3-(7-methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (325) and cis-3-(5-methyl-3-v-triazolo[1,5-a]pyrimidinyl)acraldehyde (324) as cream microprisms, m.p. 130 - 131° (decomp.).

Found: M^+, 188.0696. $C_9H_8N_4O$ requires M, 188.0698.

ν_{max} 1670 br (C=O), 1630, 1615, 1540, 1360, 1305, 1125 br, 1075, 985 (w, CH o.o.p. def. -CH=CH- trans), 860, and 720 (m, CH o.o.p. def. -CH=CH- cis) cm^{-1}.

τ[$(CD_3)_2SO$; 60 MHz external Me_4Si standard] -0.59 (d, J 8.5 Hz, CHO [7 Me cis and 5 Me cis]), 0.46 (d, J 8.5 Hz, CHO [7 Me trans and 5 Me trans]), 0.77 br (d, J 7 Hz, 7-H [5 Me cis and 5 Me trans]), 1.37 (d, J 4.5 Hz, 5-H [7 Me trans]), 1.40 (d, J 4.5 Hz, 5-H [7 Me cis]), 2.21 (d, J 16 Hz, -CH=CH-CHO [7 Me trans]), 2.26 (d, J 16 Hz, -CH=CH-CHO [5 Me trans]), 2.52 (d, J 11.5 Hz, -CH=CH-CHO [7 Me cis]), 2.58 (d, J 11.5 Hz, -CH=CH-CHO [5 Me trans]), 2.75 - 3.42 (m, 6-H [7 Me cis, 7 Me trans, 5 Me cis, and 5 Me trans], -CH=CH-CHO [7 Me trans and 5 Me trans]), 4.06 (dd, J 8.5 and 11.5 Hz, -CH=CH-CHO [7 Me cis]), 4.11 (dd, J 8.5 and 11.5 Hz, -CH=CH-CHO [5 Me cis]), 7.25 (s, 7-Me [7 Me cis and 7 Me trans]), 7.46 (s, 5-Me [5 Me cis]), and 7.49 (s, 5-Me [5 Me trans]) (ratio [7 Me cis + 7 Me trans]:[5 Me cis + 5 Me trans] ca 3:1, [7 Me cis + 5 Me cis]: [7 Me trans + 5 Me trans] ca 3:2).

m/e 189 (3), 188 (23), 161 (12), 160 (100), 159 (8), 149 (2), 145 (6), 134 (2), 133 (7), 132 (2), 131 (63), 130 (2), 120 (2), 119 (3), 118 (2), 117 (3), 114 (2), 106 (2), 105 (5), 104 (7), 101 (2), 97 (2), 95 (2), 94 (9), 93 (18), 92 (4), 91 (5), 86 (9), 84 (9), 83 (2), 81 (2), 80 (5), 79 (28), 78 (20), 77 (6), 76 (2), 73 (2), 71 (2), 70 (2), 69 (4), 68 (3), 67 (7), 66 (18), 65 (12), 64 (10), 63 (15), 62 (2), 61 (3), 60 (3), 59 (7), 58 (3), 57 (4), 56 (2), 55 (4), 54 (3), 53 (8), 52 (26), 51 (13), 50 (8), 48 (3), 46 (5), 45 (5), 44 (9), 43 (8), 42 (7), 41 (12), 40 (8), 39 (33), 38 (10), 37 (4), 36 (12), 32 (16), 31 (2), 30 (5), 29 (9), 28 (92), 27 (12), 26 (7).

m* 136.2 (188 $\longrightarrow$ 160), 108.9 (160 $\longrightarrow$ 132).

accurate mass determinations

Found: m/e 160.0747 ($C_8H_8N_4^+$ requires 160.0749), and 160.0637 ($C_9H_8N_2O^+$ requires 160.0637).

The mixture of four isomers (0.1 g) obtained above, was added to a mixture of water (20 cm^3) and concentrated hydrochloric acid (1 cm^3) and stirred at room temperature for 4 h. The solid product was filtered at the pump and dried *in vacuo* at room temperature to yield 0.6 g (60%) of a mixture of *trans*-3-(7-methyl-3-*v*-triazolo[1,5-*a*]-pyrimidinyl)acraldehyde (321) and *trans*-3-(5-methyl-3-*v*-triazolo-[1,5-*a*]pyrimidinyl)acraldehyde (320) which was identified by the n.m.r. spectrum.

3(5)-Formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole (333)

A. Heating the sample of the 4 isomers of methyl substituted 3-(3-*v*-triazolo[1,5-*a*]pyrimidinyl)acraldehyde (320, 321, 324 and 325) in $(CD_3)_2SO$ in an n.m.r. tube on a water bath for 1.5 h and rerunning the ^1H n.m.r. spectrum showed that only *trans* products (320 and 321) remained together with a trace of what was later identified as 3(5)-formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole (333). With continued heating at 100° the pyrazole (333) became predominant and after heating for 54 h was the sole product detectable. Pouring the contents of the n.m.r. tube into water produced a small quantity of cream precipitate.

B. The mixture of 4 isomers of methyl substituted 3-(3-*v*-triazolo-[1,5-*a*]pyrimidinyl)acraldehyde (320, 321, 324 and 325) (0.5 g) was dissolved in dimethyl sulphoxide (10 cm^3) and the solution heated at 100° for 6 days. The dimethyl sulphoxide solution was poured into water (500 cm^3), but only a small quantity of black material precipitated, which was collected. The filtrate was reduced in bulk

to 100 cm^3 by evaporation *in vacuo*. A pale brown solid precipitated, which was collected by filtration and washed with water (10 cm^3). Crystallisation from water yielded 3(5)-formyl-5(3)-(4-methyl-2-pyrimidinyl)pyrazole (333) (0.25 g, 50.0%) as cream needles, m.p. 193 - 195°.

Found: C, 57.1; H, 4.55; N, 30.0%; M^+, 188.0695. $C_9H_8N_4O$ requires C, 57.45; H, 4.3; N, 29.8%; M, 188.0698.

ν_{max} 3150 (NH), 1685 (C=O), 1590, 1580, 1555, 1475, 1350, 1000, and 770 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz external Me_4Si standard] 0.26 (1H, s, CHO), 1.50 (1H, d, J 5.5 Hz, 6-H pyrimidine), 2.88 (1H, d, J 5.5 Hz, 5-H pyrimidine), 2.90 (1H, s, 4-H pyrazole), and 7.50 (3H, s, 4-Me pyrimidine).

τ (CF_3CO_2H; 60 MHz external Me_4Si standard) 0.50 (1H, s, CHO), 1.47 (1H, d, J 5.5 Hz, 6-H pyrimidine), 2.42 (1H, s, 4-H pyrazole), 2.62 (1H, d, J 5.5 Hz, 5-H pyrimidine), and 7.50 (3-H, s, 4-Me pyrimidine).

m/e 189 (13), 188 (100), 187 (13), 161 (4), 160 (35), 159 (9), 158 (2), 134 (3), 133 (6), 132 (5), 131 (38), 122 (2), 121 (3), 120 (23), 119 (3), 105 (2), 104 (3), 95 (5), 94 (58), 93 (12), 92 (3), 91 (2), 90 (2), 80 (3), 79 (7), 78 (5), 77 (5), 76 (2), 72 (2), 68 (2), 67 (16), 66 (17), 65 (9), 64 (10), 63 (4), 54 (2), 53 (11), 52 (12), 51 (7), 50 (3), 42 (11), 41 (15), 40 (14), 39 (28), 38 (9), 37 (5), 32 (8), 29 (8), 28 (46), 27 (14), 26 (6).

m* 136.2 (188 → 160), 158.0 (160 → 159).

meta stable determinations

4 - 8 kv 187 → 159, 187 → 131, 159 → 131.

accurate mass determinations

Found: m/e 160.0750 ($C_8H_8N_4^+$ requires 160.0749), 159.0673 ($C_8H_7N_4^+$ requires 159.0671), and 131.0607 ($C_8H_7N_2^+$ requires 131.0609).

13 THE REACTION BETWEEN 2-AMINO-4-METHYLPYRIDINE AND PENTANE-2,4-DIONE IN PHOSPHORIC ACID

13.1 Method of Singh, Taneja and Narang[102].

2-Amino-4-methylpyridine (5 g), pentane-2,4-dione (5 cm^3) and 85% phosphoric acid (25 cm^3) were mixed and the reaction mixture heated on a water bath for 1 h. The mixture was cooled, diluted with water (200 cm^3) and basified with 40% sodium hydroxide solution to ca pH 11 (Universal pH paper). A brown oil separated. The oil was extracted from the whole liquid mass with carbon tetrachloride (5 x 100 cm^3). The extracts were combined, dried ($MgSO_4$) and the carbon tetrachloride evaporated under reduced pressure to yield the brown oil. The oil was eluted through basic alumina with carbon tetrachloride to yield 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine (201) 7.08 g (80.5%) as a yellow oil [Singh, Taneja and Narang[102] claim the product to be 2,4,5-trimethyl-1,8-naphthyridine (146), m.p. 160 - 162°]

ν_{max} 1625 (C=O), 1605, 1560, and 1505 cm^{-1}.

τ (CCl_4; 60 MHz) -2.69 br (1H, s, exchanges D_2O, NH), 1.97 (1H, dd, J 5.1 and 0.8 Hz, 6-H), 3.36 br (2H, d, 3- and 5-H), 4.90 (1H, q, J 0.6 Hz, -NH-CMe=CH-), 7.58 (3H, d, J 0.6 Hz, -NH-CMe=CH-), 7.75 (3H, s, 4-Me), and 8.0 (3H, s, COMe) (first-order analysis for 3-H, 5-H, and 6-H, ABX system).

13.2 2,4,8-Trimethylpyrido[1,2-a]pyrimidinium Picrate (208)

The 2-(2-acetyl-1-methylvinylamino)-4-methylpyridine (201) (ca 0.5 g), obtained 13.1 above, was dissolved in ethanol (ca 2 cm^3). Saturated ethanolic picric acid solution (ca 3 cm^3) was added and the mixture heated on a water bath for 1 min. Yellow crystals separated on cooling the solution, which were collected by filtration and recrystallised from

ethanol to yield 2,4,8-trimethylpyrido[1,2-a]pyrimidinium picrate (208) as yellow needles, m.p. 164 - 165°.

Found: C, 50.9; H, 3.8; N, 17.65. $C_{17}H_{15}N_5O_7$ requires C, 50.9; H, 3.7; N, 17.5%.

ν_{max} 1640 sh, 1625, 1610, 1555, 1500, 1460 sh, 1430 sh, 1370, 1340, 1310, 1295, and 1270 cm^{-1}.

τ [$(CD_3)_2SO$; 60 MHz] 0.63 (1H, d, J 7.5 Hz, 6-H), 1.27 (2H, s, picryl protons), 1.56 (1H, d, J 2.0 Hz, 9-H), 1.77 (1H, dd, J 7.5 and 2.0 Hz, 7-H), 1.79 (1H, s, 3-H), 6.80 (3H, s, 4-Me), and 7.02 and 7.07 (6H, 2 x s, 2- and 8-Me).

13.3 2,4,8-Trimethylpyrido[1,2-a]pyrimidinium Perchlorate (53)

Treatment of the 2-(2-acetyl-1-methylvinyl)-4-methylpyridine (201), obtained in 13.1 above, by the General Method (b) for the formation of pyrido[1,2-a]pyrimidinium perchlorates (p.141), yielded 2,4,8-trimethylpyrido[1,2-a]pyrimidinium perchlorate. The melting point and i.r. spectrum were identical to those of 2,4,8-trimethylpyrido[1,2-a]-pyrimidinium perchlorate prepared by General Method (a) (p.122).

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