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Naphthyridines. Structure, physicochemical properties and general methods of synthesis

V P Litvinov, S V Roman, V D Dyachenko

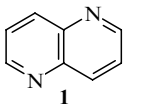
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Abstract. Data on the synthesis, chemical properties and applications of naphthyridines published mainly over the last 15 years are described systematically and analysed. The bibliography includes 238 references.

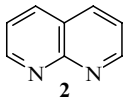
I. Introduction

Naphthyridines (pyridopyridines, diazanaphthalenes) represent a group of six isomeric heterocyclic systems containing two fused pyridine rings with different mutual arrangements of nitrogen atoms. They include two groups of compounds — N(1),N(*i*)-naphthyridines (*i* = 5, 6, 7, 8) **1** – **4** and N(2),N(*j*)-naphthyridines (*j* = 6, 7) **5**, **6**.



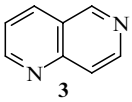
1

1,5-naphthyridine



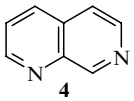
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1,8-naphthyridine



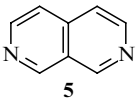
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1,6-naphthyridine



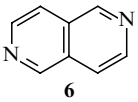
4

1,7-naphthyridine



5

2,7-naphthyridine



6

2,6-naphthyridine

The first derivative of the cyclic naphthyridine system was obtained in 1893 by Reissert,[1] who proposed this name for the new class of heterocyclic compounds. The first representatives of unsubstituted naphthyridines — 1,5-naphthyridine **1**[2] and 1,8-naphthyridine **2**[3] — were described only in 1927. Naphthyridines containing nitrogen atoms at positions 1,6 (**3**),[4] 1,7 (**4**),[5] and 2,7 (**5**)[6] were prepared in 1958, and 2,6-naphthyridine (**6**)[7,8] was synthesised only in 1965. Since then, researchers have shown ever increasing interest in the chemistry of naphthyridines. Indeed, the bibliography of a review[9] published in 1950 included 75 references, while that of a review[10] which appeared in 1970 comprised 242 references. More recent reviews[11,12] (1983) present 223 studies. Several reviews dealing with more specific aspects were also published before 1983.[13–22] In recent years, the number of publications devoted to various aspects of naphthyridine chemistry has sharply increased. More than 1000 publications have appeared during the last 15 years, 40% of them being patents.

This interest in naphthyridine derivatives is due to the exceptionally broad spectrum of their biological activities. They are used for the diagnostics and therapy of diseases of humans including AIDS; for combating exo- and endo-parasites in agriculture and in cattle breeding; as preservatives and ingredients of cutting fluids, as ligands in analytical chemistry, *etc*.

This review mainly surveys the data published over the last 15 years; however, earlier fundamental studies are also invoked in the discussion of structures, physicochemical properties and reactivities of naphthyridines.

II. Physicochemical properties

1. Structure

X-Ray diffraction study was first performed for unsubstituted 1,5- (**1**) and 2,6-naphthyridines (**6**).[10,23,24] It was found that transition from pyridine to naphthyridines is accompanied by shortening and lengthening of C–C bonds approximately equal to that observed on passing from benzene to naphthalene. In addition, the N–C bonds in naphthyridines were found to be shorter than these bonds in pyridine. X-Ray diffraction analysis was also used to determine the structures of several naphthyridine derivatives, **1**, **2**, **4** and **6**.[25–37]

2. Quantum-chemical calculations

Since the 1950s, quantum chemistry methods have been used to elucidate structure – property relationships in the naphthyridine series.[38–57] The intensities of bands in the UV spectra of naphthyridines have been found to be correlated with the energies of lower unoccupied molecular orbitals;[38–40] quantum-chemical calculations have also been used in the ^{1}H and ^{13}C NMR spectroscopy[47–51] and for comparison of the total π-energy and delocalisation energy for naphthyridines and naphthalene.[41,43] Other results include determination of π-electron distribution;[43,44] elucidation of correlations of the total π-electron energy with specific features of electrophilic[43] and nucleophilic[43,44] substitution and with the hyperfine splitting constants in the EPR spectra.[47]

In recent years, quantitative structure – biological activity relationships for 6-[2-(4-arylpiperazino)ethyl]-5,6,7,8-tetrahydro-

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1,6-naphthyridines have been established [53] and complexes of antitumour antibiotics — naphthyridinomycins — with DNA have been studied by molecular modelling methods.[54]

3. Spectroscopy

Spectroscopic techniques (UV, IR, ^{1}H and ^{13}C NMR) are widely used not only to identify naphthyridines but also to elucidate fine points concerning their structures.[10, 12]

Thus it has been found that the UV spectra of 1,5-, 1,6-, 1,7- and 1,8-naphthyridines **1**–**4** are fairly similar to one another and contain three separate groups of bands, analogous to the bands displayed in the spectra of quinoline and isoquinoline. However, the spectra of 2,7- and 2,6-naphthyridines **5** and **6** differ both from each other and from the spectra of any other naphthyridines.[10, 58] The UV spectra of 4-hydroxy-1,5-naphthyridine [59] and of a large number of substituted 1,8-naphthyridines [60] have been analysed in detail. In order to disclose the influence of substituents on the absorption spectra, UV spectra of 1,8-naphthyridines monosubstituted at position 2 (Me, Cl, Br, OMe, OEt, SMe, NH_2, OH, SH), position 3 (Me, Cl, Br, NO_2, NH_2) and position 4 (Me, Cl, Br, OMe, OEt, OH, SH) have been studied.[61]

Transmission and absorption spectra of 1,8-naphthyridine **2** in the range of 50 000–20 000 cm^{-1} have been investigated in solutions and in various mixed crystals at 4.2 and 300 K. [52] The pattern of the band corresponding to the $\pi \rightarrow \pi^*$ transition was found to be similar to that observed in the spectrum of the related naphthalene molecule with allowance for perturbations induced by the replacement of carbon by nitrogen. The position of the long-wavelength $\pi \rightarrow \pi^*$ band at about 27 000 cm^{-1} complies with the theoretical predictions based on extended Hückel calculations. The bands at about 31 600–31 900 cm^{-1} were assigned empirically to the second $n \rightarrow \pi^*$ transition.[52]

All bands in the IR spectra of several substituted 1,5-naphthyridines have been assigned; the spectrum of 1,5-naphthyridine **1** was compared with the spectrum of 5-substituted quinoline.[62] IR spectroscopy was used to study the keto–enol tautomerism of 4-hydroxy-1,5-naphthyridine in solution and in the solid state; it was found that the keto form predominates in polar solvents and the enol form, in nonpolar solvents.[59]

Study of the IR and Raman spectra of 1,6- and 1,8-naphthyridines permitted the assignment of all 42 fundamental vibrations of these two heterocyclic systems.[63]

Data on the ^{1}H NMR spectra (chemical shifts and spin–spin coupling constants) for the naphthyridines **1**–**4** and **6** can be found in the literature.[7, 8, 10, 12, 42, 43, 49–51, 64–77] The chemical shifts observed in the ^{13}C NMR spectra of the naphthyridines **1**–**6** were compared with those for quinoline and isoquinoline.[12, 49–51] The resonance signals in the ^{1}H NMR spectrum of 2-(2′-pyridyl)-1,8-naphthyridine were completely assigned using homonuclear 2D NMR spectroscopy.[75]

The behaviour of derivatives of the isomeric naphthyridines **1**–**4** under electron impact has been studied and the main fragmentation pathways have been identified.[10, 78–80] The structures and destruction pathways of the isomeric ions $[M-HCN]^{-\bullet}$ and $[M-2\,HCN]^{-\bullet}$, resulting from fragmentation of the naphthyridines **1**–**4** and benzazines, were studied using collisional activation.[81] It was found that the $[M-2\,HCN]^{-\bullet}$ ions can exist as two isomers, one of them being characteristic of naphthyridines and the other being characteristic of benzazines.

High-resolution photoelectron spectra of the naphthyridines **1**–**6** have been described.[82] The ionisation potentials for the *n* and π orbitals are listed in Table 1.

Polarised phosphorescence spectra of 1,5-naphthyridine **1** [83–85] and the EPR spectrum of 1,6-naphthyridine **3** were recorded.[86]

A number of publications deal with the capacity for ionisation (including the pK_a values) of the naphthyridines **1**–**4** and their derivatives.[10, 58, 70, 87–91]

Table 1. Ionisation potentials (eV) of naphthyridines **1**–**6**.[82]

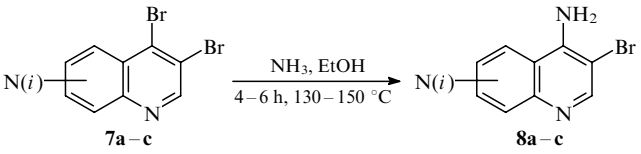
Compound	*n*-Orbital	π-Orbital
1,5-Naphthyridine **1**	9.20	11.05
	10.40	
	1.20	
1,8-Naphthyridine **2**	9.20	11.33
	10.10	
	0.90	
1,6-Naphthyridine **3**	9.50	9.07
	9.90	11.10
	0.40	
1,7-Naphthyridine **4**	9.30	8.99
	10.00	11.14
	0.70	
2,7-Naphthyridine **5**	9.35	8.98
	10.10	
	0.75	
2,6-Naphthyridine **6**	9.40	8.87
	10.00	
	0.75	

III. The reactivity of naphthyridines

Reactions of naphthyridines including electrophilic substitution (bromination, nitration), nucleophilic substitution (amination, metallation), reduction, oxidation, complexation, *etc*., have been considered fairly comprehensively in reviews. [10, 12] In yet another review, attention is focussed on the reactivity of naphthyridines towards N-nucleophiles.[11] Here we survey the data on the reactivity of naphthyridines published over the last 15 years.

Electrochemical reduction of the naphthyridines **1**–**6** has been reported.[92, 93] On exposure to UV radiation in the presence of sodium nitrite, 3-amino-1,6-naphthyridine-4(1*H*)-one eliminates a nitrogen molecule being thus converted into 5-azaindole-3-carboxylic acid.[94, 95]

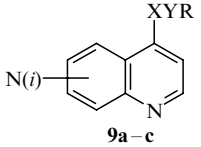
Nucleophilic substitution of bromine at position 4 in 3,4-dibromonaphthyridines **7a**–**c** on treatment with a saturated alcoholic solution of ammonia in an autoclave affords 4-amino-3-bromo-N(1),N(*i*)-naphthyridines **8a**–**c**.[96]



7a–**c** **8a**–**c**

i = 5 (**a**), 6 (**b**), 7 (**c**).

The naphthyridine derivatives **9a**–**c**, possessing fungicidal activity, have been synthesised using nucleophilic substitution of the halogen atoms in isomeric halo naphthyridines. These products can also be employed for combating exo- and endo-parasites in agriculture and cattle breeding, for wood protection, and as preservatives for paints, varnishes and cutting fluids during metal working.[97]

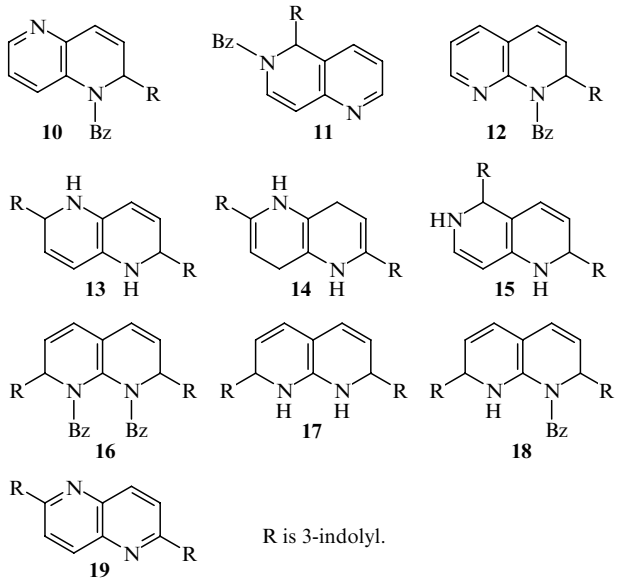


9a–**c**

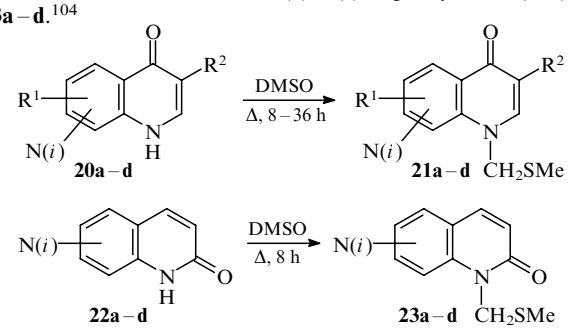
i = 5 (**a**), 6 (**b**), 7 (**c**); X = O, S, SO, SO_2; Y is alkenyl or a single bond; R is cycloalkyl or piperidin-2-yl.

In recent years, nucleophilic addition reactions have been widely used for the synthesis of various derivatives of isomeric naphthyridines. For example, nucleophilic addition of indole to 1,5-, 1,6- and 1,8-naphthyridine derivatives in the presence of

benzoyl chloride in toluene or DMF yields, depending on the temperature and reactant ratio, hydrogenated mono- (**10**–**12**) or bis-(3-indolyl)naphthyridines **13**–**18**.[98–100] Hetarylation includes the *in situ* formation of *N*-acyl heteroaromatic cations and the addition of nucleophiles to them. Aromatisation of the *N*-acylated hydrogenated naphthyridine derivatives **13** and **14** on treatment with tetrachloroquinone affords the same compound, naphthyridine **19**.

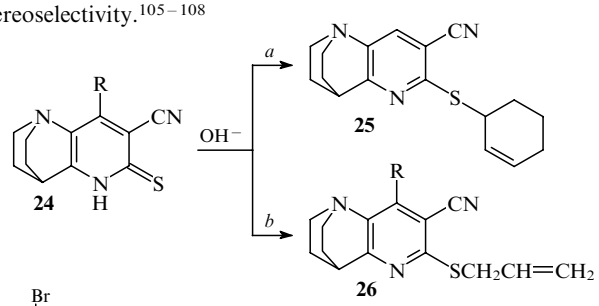


Refluxing of N(1),N(*i*)-naphthyridin-4(1*H*)-ones **20a**–**d** in DMSO gives rise to 1-methylthiomethyl naphthyridine derivatives **21a**–**d**, which depress microbial growth.[100–103] Similar methylthiomethylation of naphthyridin-2(1*H*)-ones **22a**–**d** has resulted in *N*-substituted N(1),N(*i*)-naphthyridin-2(1*H*)-ones **23a**–**d**.[104]

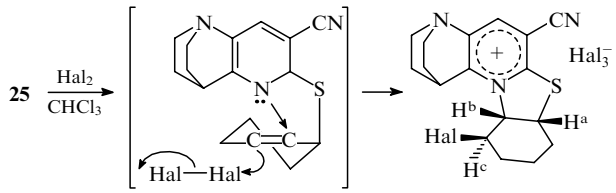


i = 5 (**a**), 6 (**b**), 7 (**c**), 8 (**d**); R^1 = H, Me; R^2 = H, CO_2H, CO_2Et.

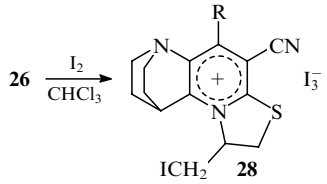
Regioselective alkylation of quinuclidinopyridine-2(1*H*)-thiones **24**, containing a 1,5-naphthyridine fragment, with 3-bromocyclohexene or allyl bromide in the presence of a base affords the corresponding 2-(cyclohex-2-enylthio)- (**25**) and 2-allylthio-derivatives **26**. Halogen-induced quaternisation of these products is a synchronous process yielding salts **27** and **28** with high regio- and stereoselectivity.[105–108]



(*a*) , R = H; (*b*) $CH_2=CHCH_2Br$, R = H, Ph, 4-FC_6H_4.

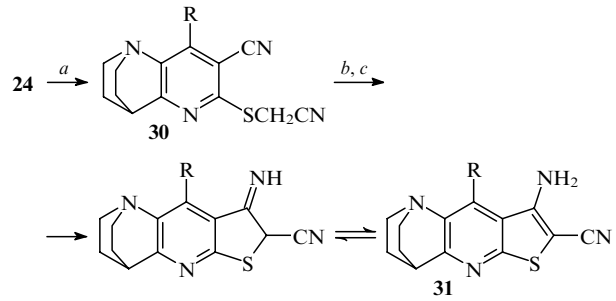


Hal = Br, I.



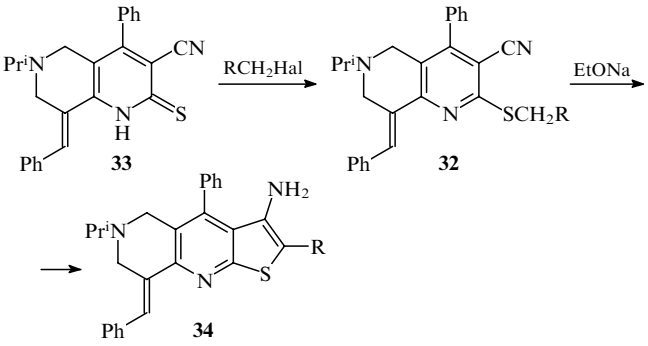
X-Ray diffraction analysis has shown that the pyridine nitrogen atom in the compound **25** has a short non-valence contact with the C=C bond of the cyclohexene fragment. The close arrangement of these reaction sites is favourable for synchronous cyclisation in intermediate **29** involving the H^a, H^b and H^b, H^c systems of protons. The high stereoselectivity of this reaction is apparently due to the synchronism of the action of the donor (*i.e.* the lone electron pair of the naphthyridine nitrogen atom) on the π-electrons of the cyclohexene double bond and electrophilic rupture of the double bond, which are followed by quaternisation. Thus the H^b and H^c protons occupy *trans*-positions. This intramolecular electrophilic quaternisation of the compound **25** can be regarded as synchronous *trans*-quaternisation with *cis*-annelation.[108]

2-Cyanomethylthio derivatives **30**, prepared by alkylation of the compounds **24** with chloroacetonitrile, cyclise under conditions of the Thorpe–Ziegler reaction to give the corresponding thieno[2,3-*b*]pyrido[3,2-*e*]quinuclidines **31**, containing a 1,5-naphthyridine fragment.[107]



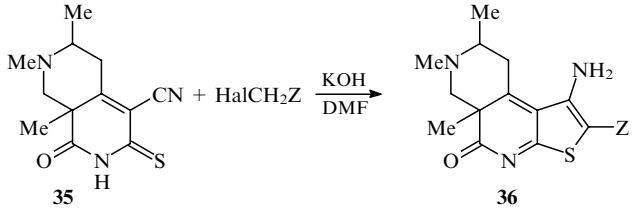
R = H, Ph, 4-FC_6H_4;
(*a*) $ClCH_2CN$, KOH, DMF, 25 °C, 3 h; (*b*) OH^-; (*c*) H^+.

Similar treatment with sodium ethoxide of thioethers **32**, prepared by the reaction of 1,2,5,6,7,8-hexahydro-1,6-naphthyridine-2-thiones **33** with halo ketones, esters, amides or nitriles, resulted in the synthesis of thieno[2,3-*b*]-1,6-naphthyridines **34**.[109]



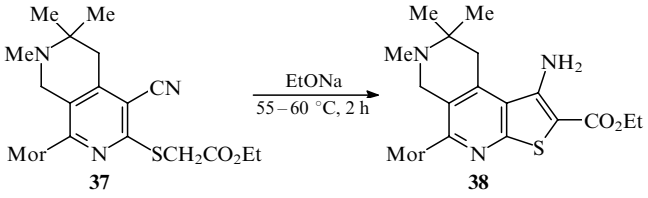
R = MeCO, PhCO, EtO_2C, $CONH_2$, CONHPh, CN, $CONHC_6H_4Me$-4, $CONHC_6H_4OMe$-4, $CONHC_6H_4COMe$-4.

The reaction of 6,7,8*a*-trimethyl-1-oxo-3-thio-1,2,3,5,6,7,8,8*a*-octahydro-2,7-naphthyridine-4-carbonitrile (**35**) with 4-bromophenacyl bromide or *N*-cyanochloroacetamidine in the presence of a base gives thieno[2,3-*c*]-2,7-naphthyridines **36**.[110]



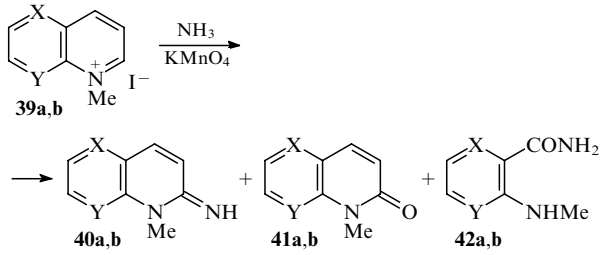
Hal = Br, Z = 4-BrC_6H_4CO; Hal = Cl, Z = C(NH_2)NCN.

Cyclocondensation of 3-ethoxycarbonylmethylthio-2,7-naphthyridine **37** on heating in anhydrous ethanol in the presence of an equimolar amount of sodium ethoxide affords thienonaphthyridine **38**. The dihydrochloride of the compound **38** possesses a mutagenic activity.[111]



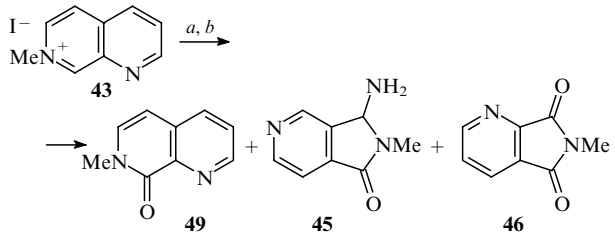
Mor is morpholin-1-yl.

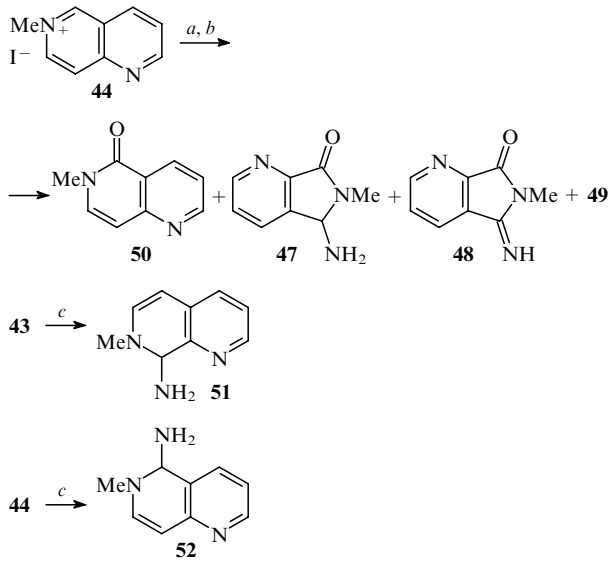
Treatment of 1-methyl-N(1),N(*i*)-naphthyridinium iodides **39a**,**b** with liquid ammonia in the presence of potassium permanganate gives rise to mixtures of imino (**40a**,**b**) and oxo (**41a,b**) derivatives of dihydronaphthyridines and vicinal methylaminopyridinecarboxamides **42a**,**b**.[112]



X = N, Y = CH (**a**); X = CH, Y = N (**b**).

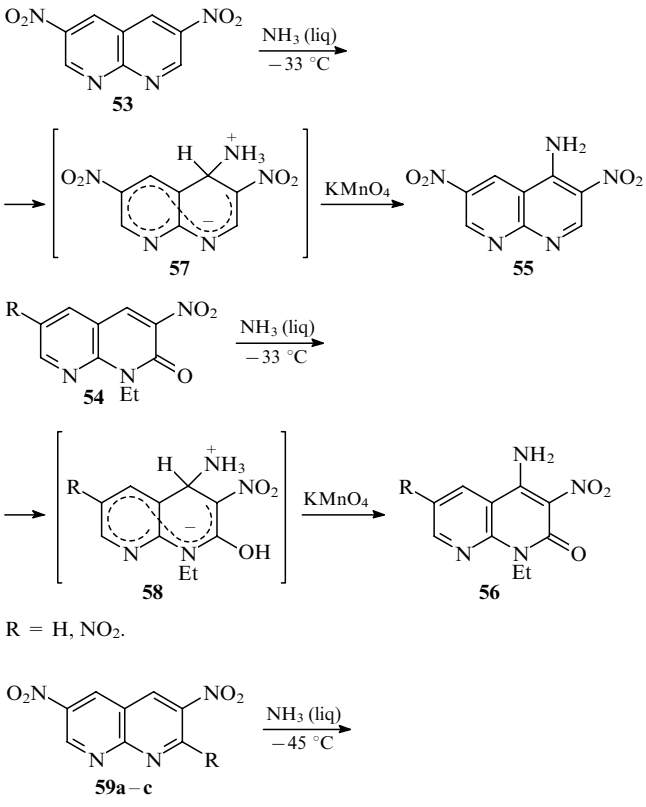
Unlike compounds **39a**,**b**, 7-methyl-1,7-naphthyridinium iodide **43** and 6-methyl-1,6-naphthyridinium iodide **44** react with liquid ammonia and $KMnO_4$ with ring contraction as the predominant reaction pathway yielding 4-azaindole derivatives **45**–**48** together with the oxo derivatives of the corresponding dihydronaphthyridines **49** and **50**. Study of the ^{1}H NMR spectra showed that on treatment with liquid ammonia in the absence of potassium permanganate, the compounds **43** and **44** are converted into amino derivatives **51** and **52**.[113]



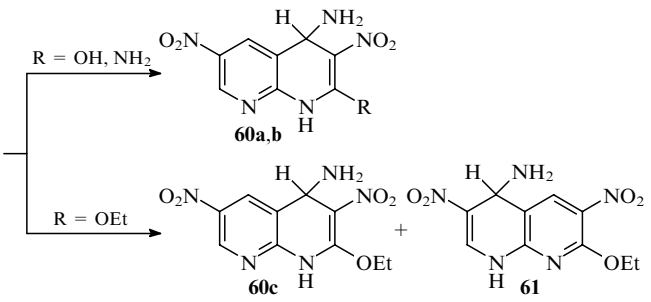


(*a*) NH_3 (liq), $KMnO_4$, −33 °C; (*b*) OH^-; (*c*) NH_3 (liq).

When 3,6-dinitro-1,8-naphthyridine **53** or 6-R-1-ethyl-3-nitro-1,8-naphthyridin-2(1*H*)-ones **54** are made to react with a solution of potassium permanganate in liquid ammonia at −33°C, amination proceeds giving rise to the corresponding 4-amino derivatives **55** and **56**. The intermediate formation of σ-adducts **57** and **58** was detected by ^{1}H NMR spectroscopy.[114, 115] It was also shown that 1-ethyl-3-nitro-1,8-naphthyridin-4-one is not aminated under these conditions.[115] However, treatment of 1,8-naphthyridine derivatives **59a**,**b** with liquid ammonia at −45 °C affords 4-amino-1,4-dihydro-3,6-dinitro-2-R-1,8-naphthyridines **60a**,**b**. The compound **59c** was converted into a mixture of the naphthyridine **60c** and isomeric 5-amino-2-ethoxy-3,6-dinitro-5,8-dihydro-1,8-naphthyridine **61**.[116]

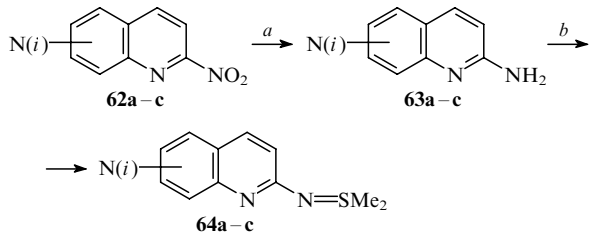


R = H, NO_2.



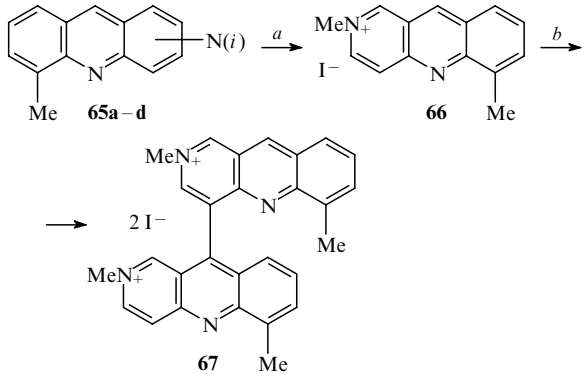
R = OH (**a**), NH_2 (**b**), OEt (**c**).

2-Nitro-N(1),N(*i*)-naphthyridines **62a–c** undergo replacement of the nitro group rather than amination on treatment with a solution of potassium permanganate in liquid ammonia; this gives the corresponding 2-aminonaphthyridines **63a–c**, although their yields are relatively low. These products react with DMSO and trifluoromethanesulfonic anhydride giving rise to *S*,*S*-dimethyl-[N(1),N(*i*)-naphthyridin-2-yl]sulfylimines **64a–c**.[115]



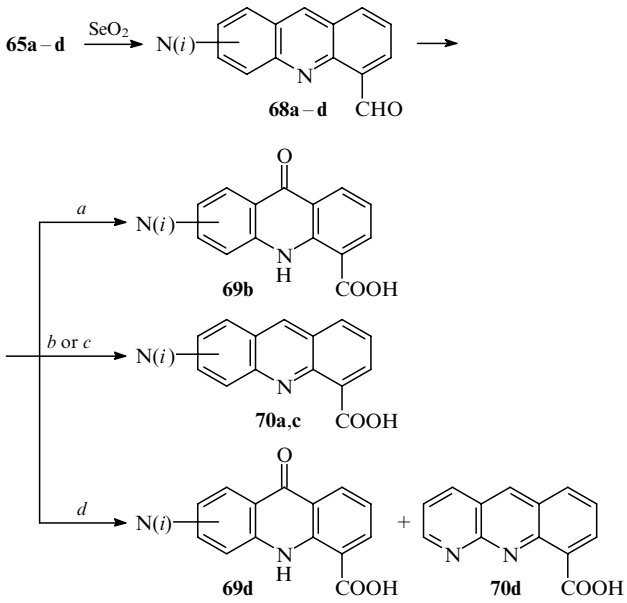
i = 5 (**a**), 6 (**b**), 8 (**c**);
(*a*) NH_3 (liq), $KMnO_4$, −33 °C; (*b*) DMSO, $(CF_3SO_2)_2O$.

The kinetics of N-methylation of benzonaphthyridines **65a–d** with methyl iodide in DMSO have been studied.[117] It was shown that the salt **66**, formed from the naphthyridine **65b**, slowly dimerises in a 10% aqueous solution of DMSO to give compound **67**.



i = 5 (**a**), 6 (**b**), 7 (**c**), 8 (**d**);
(*a*) *i* = 6, MeI, $MeCO_2Et$, Δ, 0.5 h; (*b*) DMSO – H_2O (1 : 9), 10 h.

The methyl group in benzo[2,3]naphthyridines **65a–d** can be easily modified. Thus refluxing of these compounds with SeO_2 in chloro-, 1,2-dichloro- or 1,2,4-trichlorobenzene gives aldehydes **68a–d**, which serve as the starting compounds for the synthesis of diverse functional derivatives of benzonaphthyridines.[118–120] Oxidation of the compounds **65a–d** to the aldehydes **68a–d** and further oxidation to the corresponding acids are the key stages of the synthesis of compounds **71–75**, which are the aza analogues of the potential antitumour preparation, *N*-[2-(dimethylamino)-ethyl]acridine-4-carboxamide.[118–120]



i = 5 (**a**), 6 (**b**), 7 (**c**), 8 (**d**); (*a*) *i* = 6, $NaClO_2$; (*b*) *i* = 7, Ag_2O; (*c*) *i* = 5; (*d*) *i* = 8, $NaClO_2$.

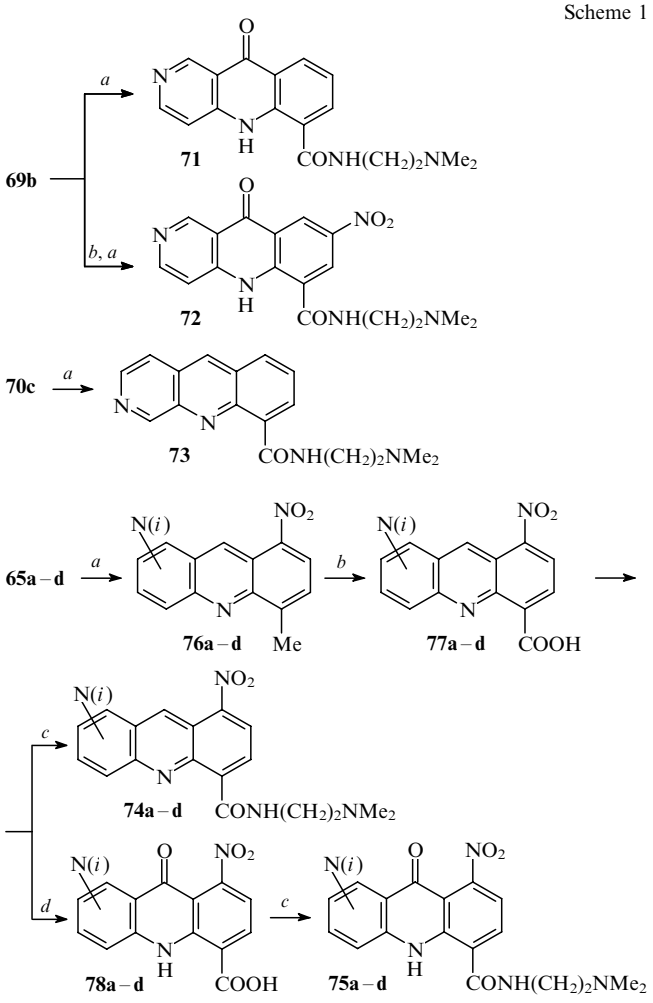
The aldehydes **68a–d** can be oxidised using Ag_2O, $NaClO_2$, $K_2Cr_2O_7$, *etc.*; oxidation can proceed to different extents depending on the structure of the initial compound and the reagent employed. For instance, oxidation of the aldehyde **68b** with $NaClO_2$ involves the central ring and gives oxo acid **69b**. The oxidation of the aldehyde **68c** with Ag_2O affords acid **70c** as the only product. The aldehyde **68a** is oxidised by Ag_2O to **70a** but the reaction does not proceed to completion, up to 10% of the starting compound being recovered unchanged. The reaction of the aldehyde **68d** with $NaClO_2$ yields a mixture of acids **69d** and **70d**. The oxo acids **69a–d** are also produced upon oxidation of **68a–d** with $NaClO_2$ in Bu^tOH.

Further modification of the acids **69** and **70** includes reactions of the carboxy group with 2-(*N*,*N*-dimethylamino)ethylamine and nitration of the benzene ring. Thus compounds **74** and **75** were prepared by oxidation of the methyl group in nitro derivatives **76** followed by modification of the acids **77** and **78** formed (Scheme 1).

Dipolar 1,3-cycloaddition of various dienophiles to benzo[3,4]naphthyridinium ylides **79–81**, generated *in situ* by dehydrobromination of the corresponding quaternary salts, has been studied; this gives rise to benzo[*h*]pyrrolonaphthyridines **82–88** (Scheme 2).[121–126] The compounds **82–84** exhibit bactericidal activities.[124, 125]

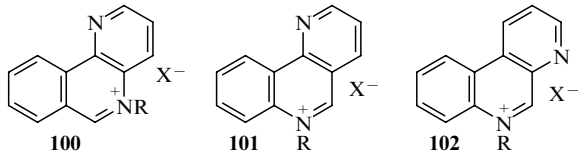
The dipolar 1,3-cycloaddition of *N*-dichloromethylides **89–91**, generated *in situ* from the corresponding benzo[*h*]naphthyridines **92–94** and dichlorocarbene[127] (produced from CCl_3CO_2Na on heating or from $CHCl_3$ in the presence of a base and $Et_3BnN^+Cl^-$), to dimethyl acetylenedicarboxylate is less selective; only the ylide **89** is converted into the corresponding adduct **95** in 52% yield. In the case of **90** and **91**, the reaction gives a mixture of dipolar 1,3-addition products **96** and **97** and bisadducts **98** and **99** (Scheme 3). Quaternisation of naphthyridines **92–94**[128–130] (the compounds **92** and **93** were prepared by the Skraup method[128] and **94** was synthesised by photocyclisation of diazastilbene[131]) induced by alkyl, aryl or benzyl halides gave

Scheme 1



(*a*) KNO_3, H_2SO_4; (*b*) $K_2Cr_2O_7$, H_2SO_4; (*c*) $Me_2N(CH_2)_2NH_2$; (*d*) $NaClO_2$.

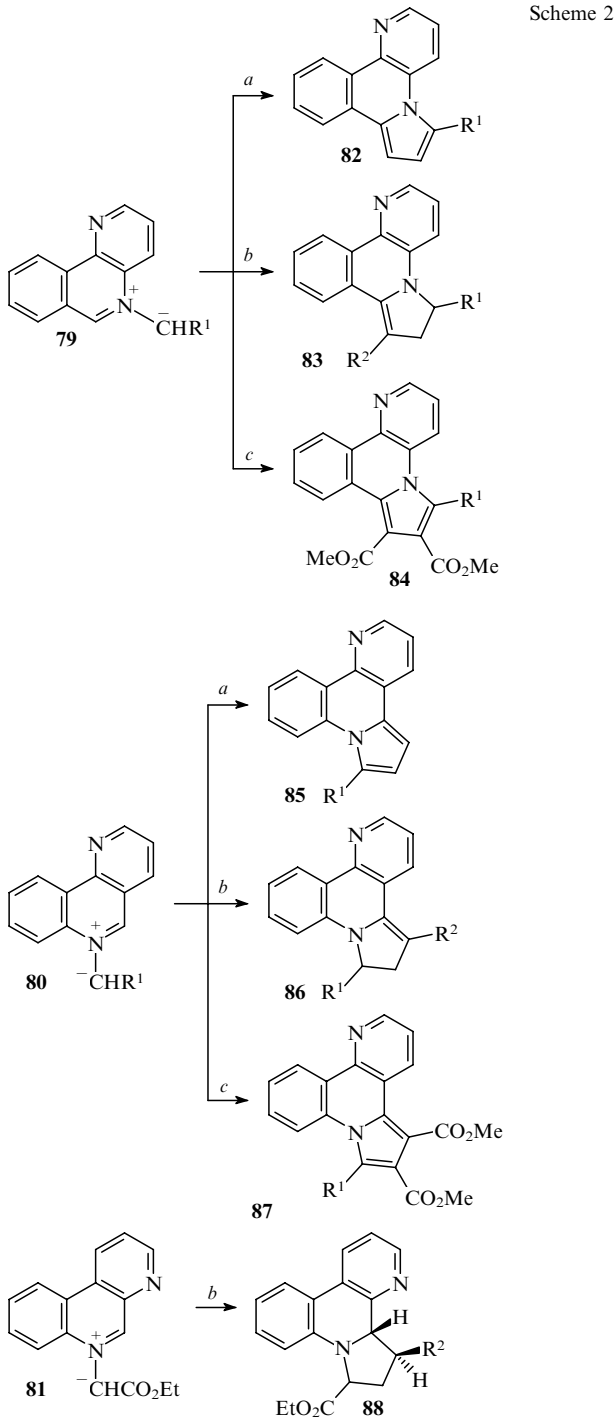
quaternary salts **100**–**102**. The salts **101**, **102** exhibit bactericidal and fungicidal activities.[128]



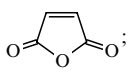
R = 2,4-$(NO_2)_2C_6H_3$, $H_2C{=}CHCH_2$, Bn, $Me(CH_2)_9$; X = Cl, I.

In order to elucidate the influence of the structure of benzo[*h*]-naphthyridines on their reactivity, charge distributions, excitation energies, and the oscillator strengths for the molecules **92**–**94** and their amino derivatives have been calculated. The calculation was carried out by a semiempirical self-consistent field method in the Pariser–Parr–Pople π-electron approximation with allowance for the configurational interaction between singly excited states and by the Hückel method. The results are in satisfactory agreement with the data of the UV spectra.[132] The populations of the atomic π-orbitals, the order of π-bonds and the frequency and oscillator strengths for three electron transitions in the molecules of the naphthyridines **92**–**94** and their salts **100**–**102** were also calculated. By comparing the calculated and experimental spectra, correlation coefficients for the relation $v_{calc} = av_{exp} + b$ were determined.[133]

Scheme 2



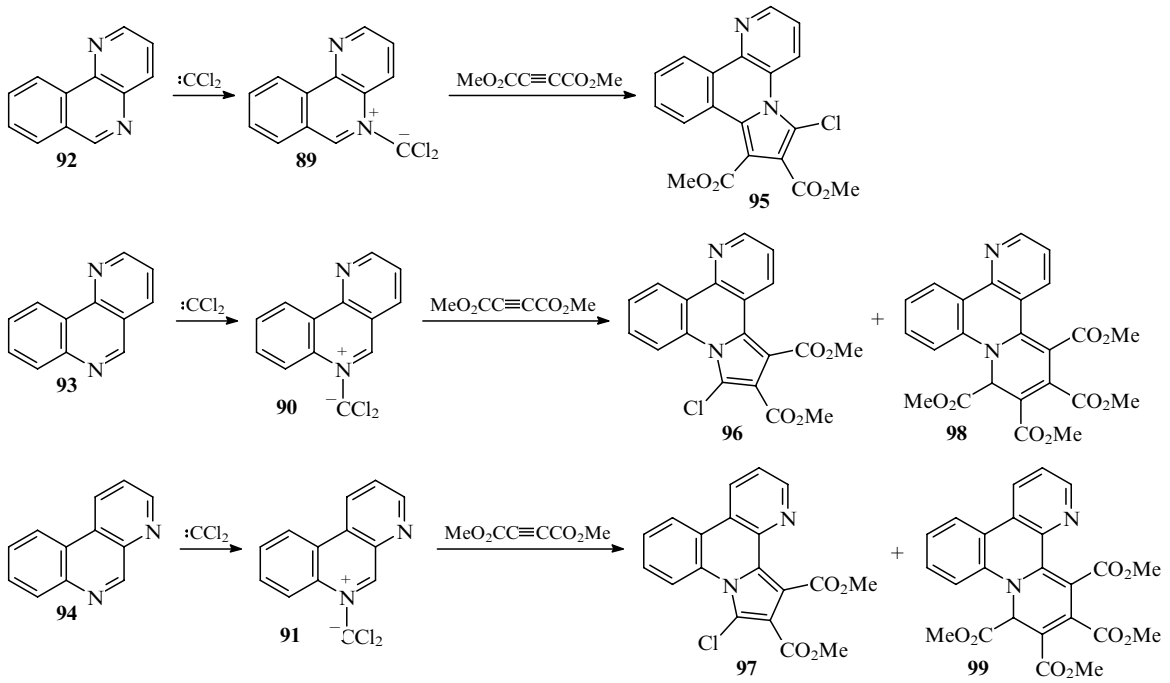
R^1 = COPh, CO_2Et; R^2 = CN, CO_2Et, Ac;

(*a*) ; (*b*) $CH_2{=}CHR^2$; (*c*) $MeO_2CC{\equiv}CCO_2Me$.

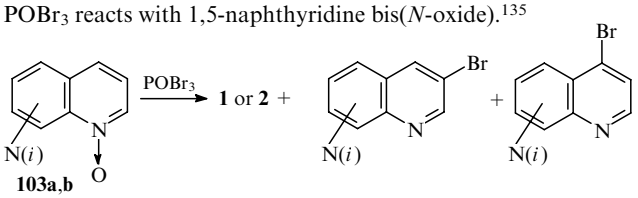
The formation of *N*-ylides of the benzonaphthyridinium series upon dipolar 1,3-addition of benzonaphthyridine *N*-oxides to dimethyl acetylenedicarboxylate at room temperature has been reported.[134]

Treatment of *N*-oxides **103a**,**b** with $POBr_3$ affords a mixture of 1,5- (**1**) or 1,8-naphthyridines (**2**) with their brominated deriva-

Scheme 3

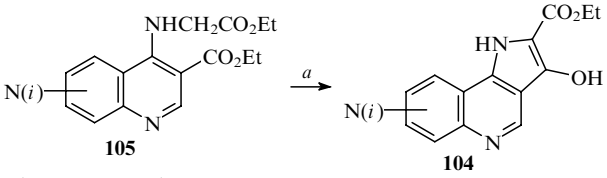


tives. A similar mixture of reaction products is also formed when $POBr_3$ reacts with 1,5-naphthyridine bis(*N*-oxide).[135]



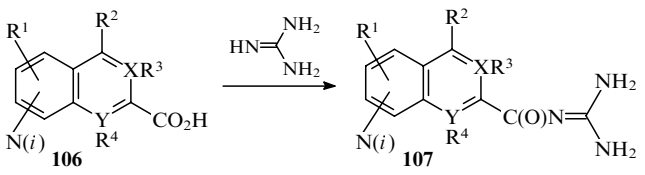
i = 5 (**a**), 8 (**b**).

Carboxylic acid derivatives **104** of the pyrrolonaphthyridine series — potential preparations for treatment of degenerative, ischemic, and autoimmune diseases — have been synthesised using intramolecular cyclisation of ethyl (3-ethoxycarbonylnaphthyridin-4-ylamino)acetates **105** induced by potassium *tert*-butoxide in a toluene – Bu^tOH mixture.[136]



(*a*) Bu^tOK, PhMe, Bu^tOH, 20 h.

The reaction of naphthyridinecarboxylic acids **106** with guanidine in the presence of carbonyldiimidazole in anhydrous THF results in hetaroylguanidines **107**, which can be used for the therapy of heart diseases, for surgical operations and organ transplantation, for the diagnostics and treatment of hypertension and proliferative diseases.[137]



R^1, R^2 = H, Hal, Alk, alkenyl, alkynyl, CN, Alk_F;
R^3, R^4 = H, Hal, Alk, Alk_F, AlkO, Alk_2N, CON=C$(NH_2)_2$ or none;
X = N, Y = C; X = C, Y = N.

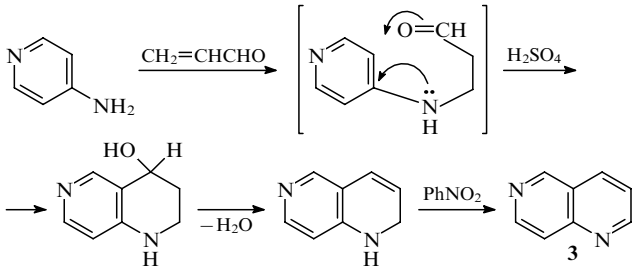
IV. General methods for the synthesis of naphthyridines

General synthetic methods used to prepare various types of naphthyridine include the Skraup, Friedlander and some other name reactions; cyclisation, cyclocondensation, dimerisation reactions, *etc*.

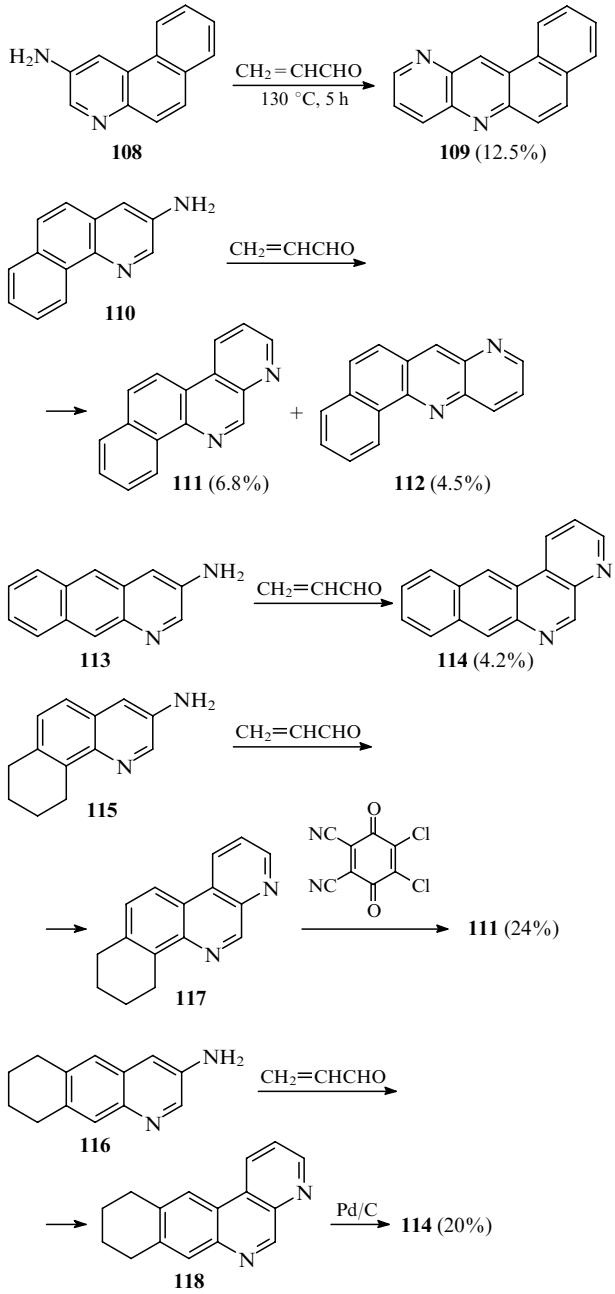
1. The Skraup method and its modifications

The Skraup reaction was first employed to synthesise unsaturated 1,5-naphthyridine **1** from 3-aminopyridine in the late 1920s.[2, 138, 139] Subsequently this reaction and its modifications have been successfully used to prepare other naphthyridines and their derivatives.[9, 10, 12]

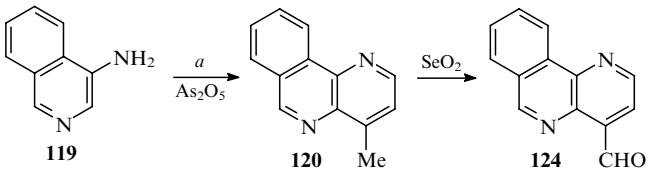
Recently 1,6-naphthyridine **3** has been prepared by the Skraup method, namely, by heating (135 °C, 48 h) of 4-aminopyridine with glycerol, fuming sulfuric acid and nitrobenzene.[140]

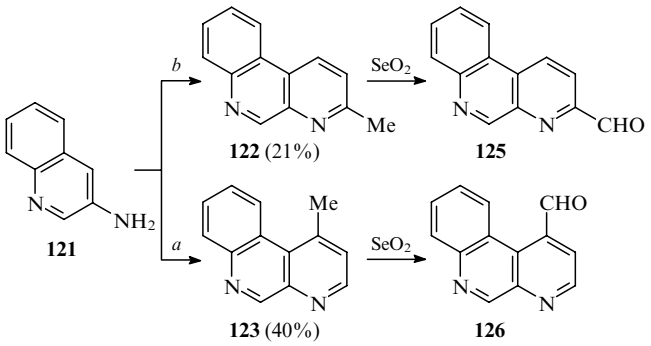


In recent years, a modified Skraup reaction (20% oleum, nitrobenzene, $FeSO_4 \cdot 7H_2O$, H_3BO_3) has been used to synthesise fused naphthyridines. Thus 3-aminobenzo[*f*]quinoline **108** was converted in this way into naphtho[2,1-*b*]-1,5-naphthyridine **109**.[141] Similarly 2-aminobenzo[*h*]quinoline **110** was transformed into a mixture of naphthonaphthyridines **111** and **112** (yields 6.8% and 4.5%, respectively), and 3-aminobenzo[*g*]quinoline **113** gave rise to naphthonaphthyridine **114** (yield 4.2%). The naphthonaphthyridines **111** and **114** were also prepared from hydrogenated benzoquinolines **115** and **116**. Intermediates **117** and **118** were dehydrogenated by treatment with dichlorodicyanoquinone and palladium supported on carbon, respectively. In this case, the overall yields of products were substantially higher.[142]



A modified Skraup method, namely, the reaction of 4-aminoisoquinoline **119** with methyl vinyl ketone in the presence of As_2O_5 and concentrated sulfuric acid, was used to prepare 4-methylbenzo[*c*]-1,5-naphthyridine **120** in 36% yield.[143] A similar reaction of 3-aminoquinoline **121** with crotonaldehyde or methyl vinyl ketone results in 2-methyl- (**122**) or 4-methyl-benzo[*f*]-1,7-naphthyridine **123**. Oxidation of the compounds **120**, **122** and **123** on treatment with SeO_2 in dioxane yields aldehydes **124** – **126**.

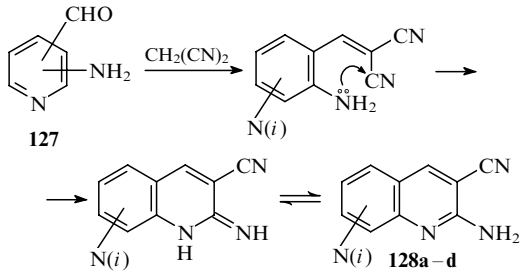




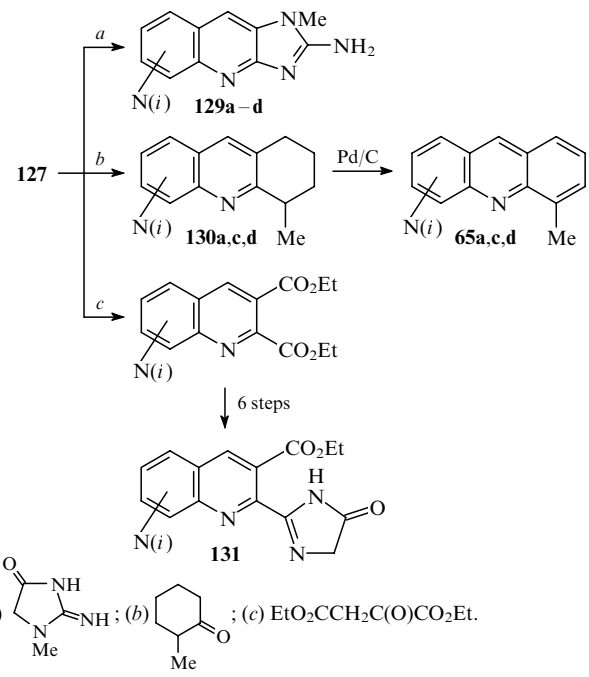
(*a*) $CH_2=CHCOMe$; (*b*) $MeCH=CHCHO$.

2. The Friedlander reaction in the synthesis of naphthyridines

The condensation of vicinal aminopyridinecarbaldehydes **127** with malononitrile in ethanol in the presence of a base (according to the Knoevenagel reaction pattern) furnished 2-amino-3-cyano-N(1),N(*i*)-naphthyridines **128a** – **d**; some of them were found to be effective diuretics.[144, 145] The condensation of the aldehydes **127** with creatinine in ethylene glycol affords imidazo[4,5-*b*]-N(1),N(*i*)-naphthyridines **129a** – **d**.[146] The reaction of the compounds **127** with 2-methylcyclohexanone in Bu^{t}OH in the presence of Bu^{t}OK (1.5 h, refluxing) followed by dehydrogenation of the products **130a**,**c**,**d** thus formed (refluxing with Pd/C in Ph_2O) gives rise to benzo[*b*]-N(1),N(*i*)-naphthyridines **65a**,**c**,**d**. Using the Friedlander reaction, naphthyridines **131** have been synthesised; they are active components of herbicide formulations.[147, 148] Benzo[*b*]-1,6-naphthyridine **65b** has been prepared by condensation of the amino acid salt **132** (obtained from 7-methylisatin **133**)

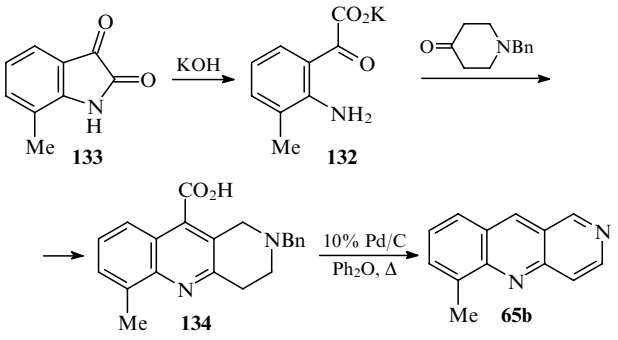


i = 5 (**a**), 6 (**b**), 7 (**c**), 8 (**d**).



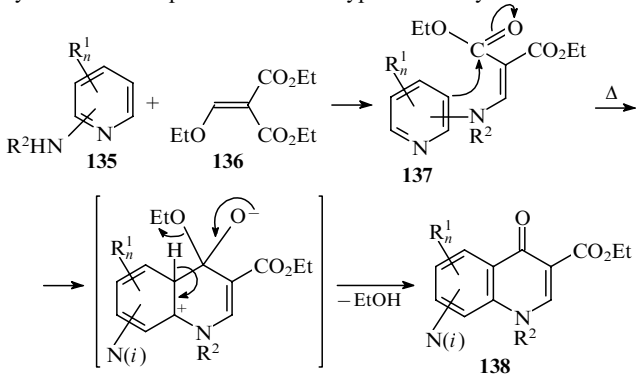
(*a*) ; (*b*) ; (*c*) $EtO_2CCH_2C(O)CO_2Et$.

with *N*-benzylpiperidone (KOH, 0.5 h, < 40 °C; refluxing, 20 h) followed by dehydrogenation of the reaction product **134**.[117–119]



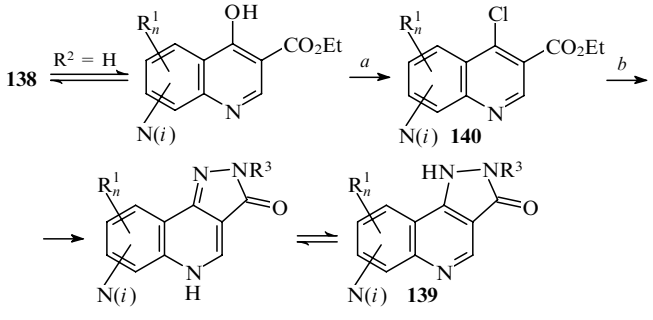
3. Condensation of aminopyridines with diethyl ethoxymethylidenemalonate

As in the previous cases, the use of condensation of aminopyridines with diethyl ethoxymethylidenemalonate for the synthesis of naphthyridines attracts attention because it provides the possibility of synthesising diverse naphthyridines exhibiting a broad range of biological activities. Thus the condensation of substituted aminopyridines **135** with diethyl ethoxymethylidenemalonate **136** and subsequent cyclisation on refluxing of the resulting diesters of *N*-(pyridyl)aminomethylidenemalonic acids **137** gives derivatives of naphthyridinecarboxylic acids **138**, possessing antibacterial activity or serving as intermediates in the synthesis of compounds with this type of activity.[130, 149–161]

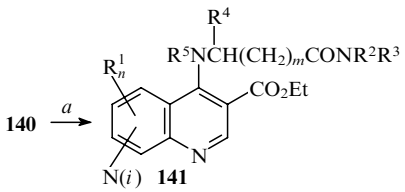


n = 1, 2; R^1 = Me, EtO, EtS, F, 4-pyridyl; R^2 = H, cyclopropyl.

Naphthyridines **138** (R^2 = H) without substituents at nitrogen have served as the starting compounds *en route* to pyrazolo[3,4-*c*]naphthyridines **139**, which act as modulators of benzodiazepine receptors and possess sedative and antispasmodic activities.[162–164] The reactions of chloronaphthyridines **140** with amino acid amides afford compounds **141**, which possess anxiolytic, anticonvulsive, sedative and hypnotic activities, antimicrobial and analgesic properties; they are capable of reducing blood pressure and are used as pharmaceuticals.[165–167]

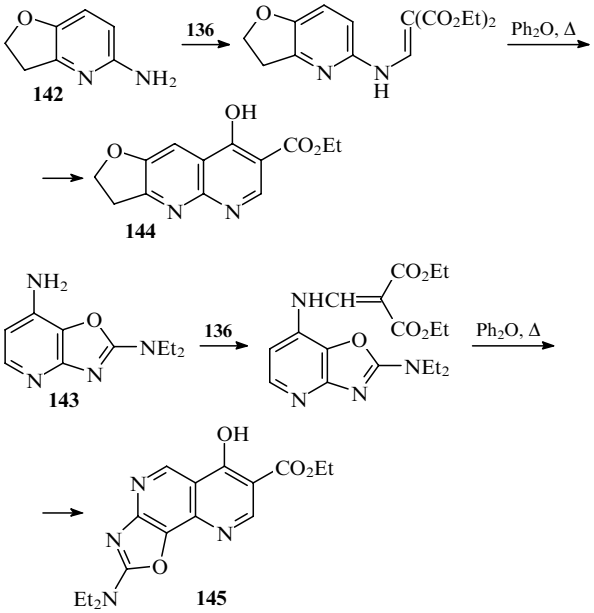


n = 1, 2; R^1 = Me, MeO; R^2 = Ph, pyridyl, quinolyl, isoquinolyl, pyrimidyl, thiazolyl; (*a*) $(COCl)_2$, MeCN, DMF, from −30 to 20 °C; (*b*) R^3NHNH_2, xylene, Δ.



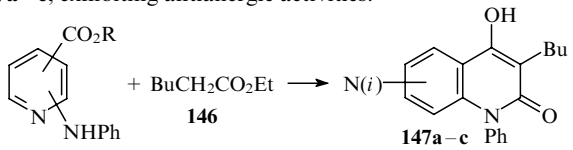
(*a*) $R^2R^3NC(O)(CH_2)_mCH(R^4)NHR^5$; n = 1, 2; m = 0–2; R^1 = Hal, Alk, AlkO, NO_2, CF_3; R^2, R^3 = H, Alk, Ph, Bn; R^2-R^3 = $(CH_2)_x$ (x = 4–8); R^4 = H, Alk, Bn; R^5 = H, Alk.

The condensation of diethyl ethoxymethylidenemalonate **136** with 5-amino-2,3-dihydrofuro[3,2-*b*]pyridine **142**[154] or 7-aminooxazolo[4,5-*b*]pyridine **143**[168] results in annelated naphthyridines **144** and **145**. 2,3-Dihydrofuro[3,2-*b*]-1,8-naphthyridine **144** shows antibacterial activity.[154]



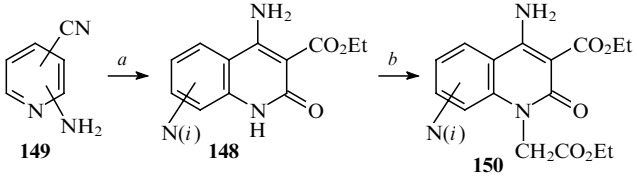
4. Condensation of aminopyridinecarboxylic acids and their derivatives with compounds containing an active methylene group

The condensation of vicinal aminopyridinecarboxylic acids or esters with ethyl hexanoate **146** in the presence of Bu^tOK under a nitrogen atmosphere gave N(1),N(*i*)-naphthyridin-2(1*H*)-ones **147a–c**, exhibiting antiallergic activities.[169]



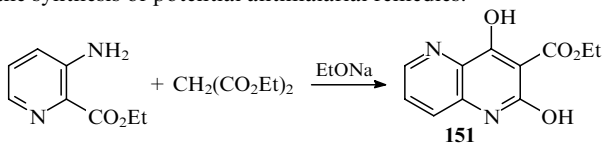
R = H, Me, Et; i = 5 (**a**), 7 (**b**), 8 (**c**).

Naphthyridones **148**, which are of interest as pharmacological preparations, have been synthesised by the reaction of vicinal aminopyridinecarbonitriles **149** with diethyl malonate. Alkylation of these products with ethyl monobromoacetate results in *N*-substituted compounds **150**.[170]



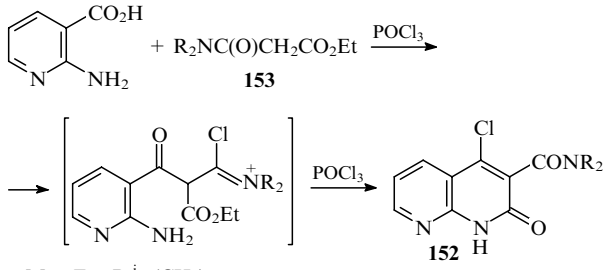
(*a*) $CH_2(CO_2Et)_2$, EtONa; (*b*) $BrCH_2CO_2Et$, BuOH, K_2CO_3; i = 5–8.

When diethyl malonate is made to react with ethyl 3-aminopicolinate, substituted 1,5-naphthyridine **151** is formed; it is used in the synthesis of potential antimalarial remedies.[171]



151

1,8-Naphthyridine-3-carboxamides **152** — starting compounds for the preparation of products with antihypertensive, antiphlogistic and antiaggressive activities — have been synthesised from 2-aminonicotinic acid and amido esters **153**. The synthesis includes the formation of the chloride and a salt of 2-aminonicotinic acid upon the reaction of **153** with $POCl_3$. The subsequent reaction of these intermediates results in the C-acylated product, the condensation of which gives the compound **152**.[172]



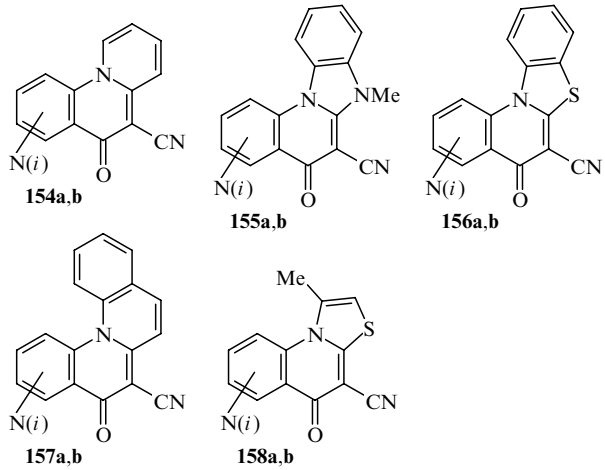
153

152

R_2 = Me_2, Et_2, Pr^i_2, $(CH_2)_5$.

5. Acylation of α-hetarylacetonitriles with halo-substituted nicotinic and isonicotinic acid chlorides

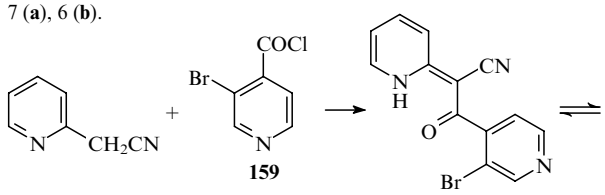
Fused azahetareno-1,7-naphthyridines **154a**–**158a**, containing a nitrogen atom in the bridgehead position, were obtained by the reaction of 3-bromoisonicotinic acid chloride **159** with 2-cyanomethyl derivatives of pyridine, 1-methylbenzoimidazole, benzo-1,3-thiazole, quinoline or 4-methyl-1,3-thiazole followed by cyclisation of the resulting C-acylated derivatives on heating to the melting point or on refluxing in *N*-methyl-2-pyrrolidone (as shown for compound **154a** taken as an example).[173]



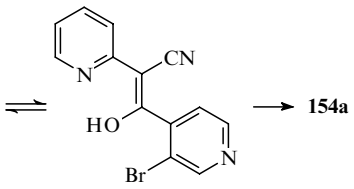
154a,**b** **155a**,**b** **156a**,**b**

157a,**b** **158a**,**b**

i = 7 (**a**), 6 (**b**).



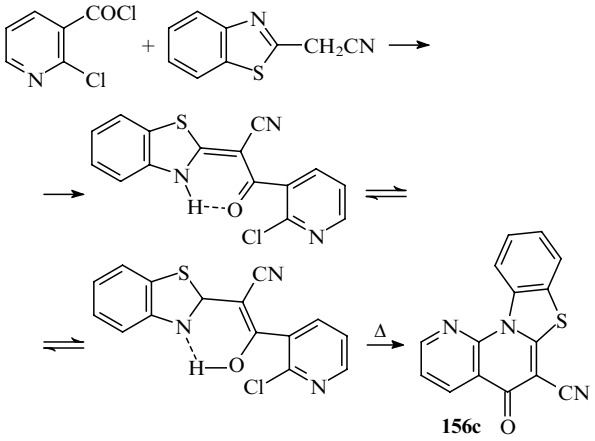
159



154a

A similar reaction of 2-cyanomethyl derivatives of hetarenes with 4-chloronicotinoyl chloride yielded annelated azahetareno-1,6-naphthyridines **154b**–**158b**.[173] In this case, the intermediate C-acylated derivatives were not isolated because they easily cyclised to give **154b**–**158b**. 4,6-Dichloronicotinoyl chloride was used as the initial compound in this synthesis.[174]

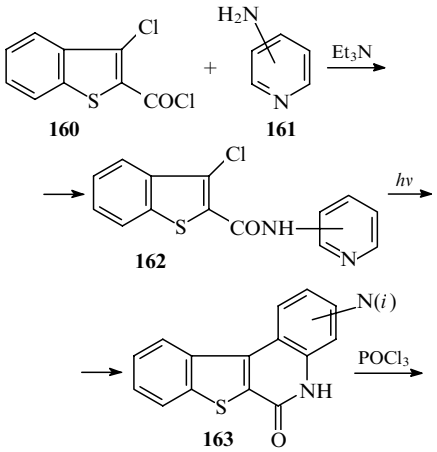
The product of interaction of 2-cyanomethylbenzo-1,3-thiazole with 2-chloronicotinoyl chloride cyclises on refluxing in DMF to give benzothiazolo[3,2-*a*]-1,8-naphthyridin-4-one derivative **156c**.[173]



156c

6. Photocyclisation of aminopyridines with chlorides of *ortho*-chlorinated hetarenecarboxylic acids

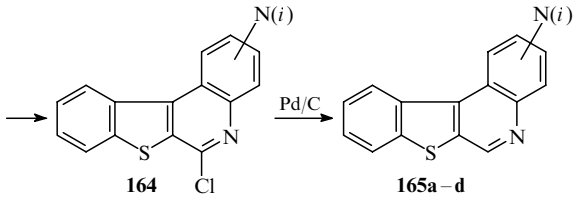
The reaction of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid chloride **160** with 2-, 3- or 4-aminopyridine **161** in benzene in the presence of triethylamine has resulted in the synthesis of amides **162**, which undergo photocyclisation (UV irradiation by a medium-pressure mercury lamp, 450 W), giving rise to naphthyridines **163**.[175] Deoxygenation of these products on treatment with $POCl_3$ followed by dechlorination of compounds **164** results in [1]benzothieno-N(1),N(*i*)-naphthyridines **165a**–**d**.



160 **161**

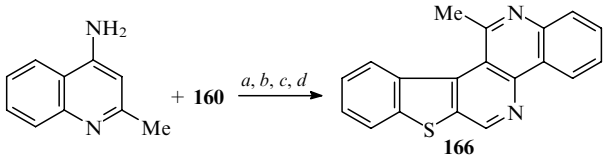
162

163



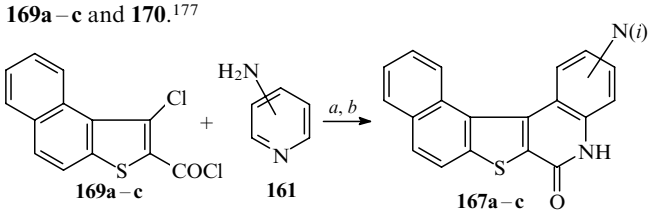
i = 5 (**a**), 6 (**b**), 7 (**c**), 8 (**d**).

Similarly, the reaction of chloride **160** with 4-amino-2-methylquinoline gave 1-methylbenzo[*h*][1]benzothieno[2,3-*c*]-1,6-naphthyridine **166**.[176]

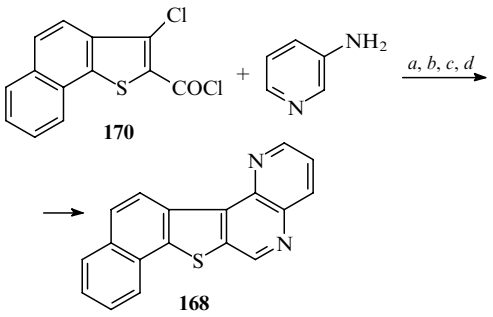


(*a*) Et_3N; (*b*) *hv*; (*c*) $POCl_3$; (*d*) Pd/C.

Photocyclisation is also one of the stages in the synthesis of naphthothieno-N(1),N(*i*)-naphthyridines **167a–c** and **168** from the chlorides of vicinal chloronaphthothiophenecarboxylic acids **169a–c** and **170**.[177]



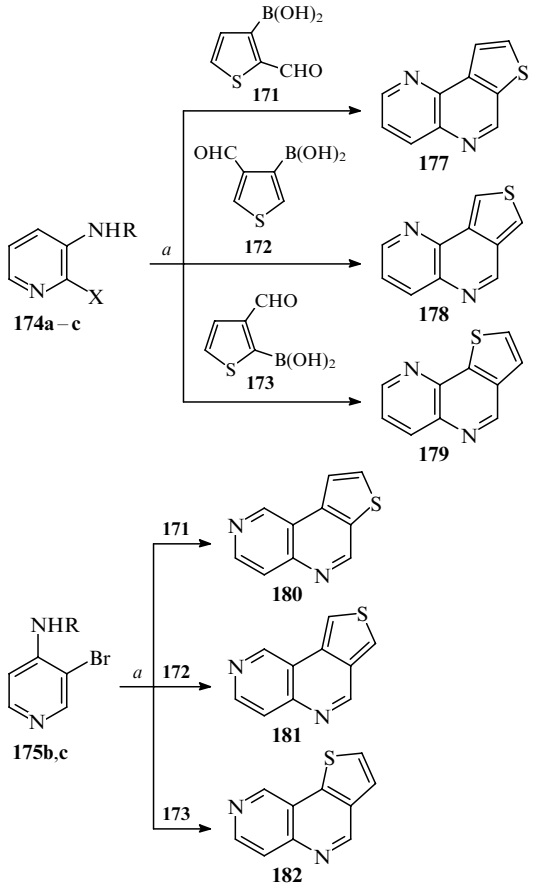
i = 5 (**a**), 6 (**b**), 7 (**c**).



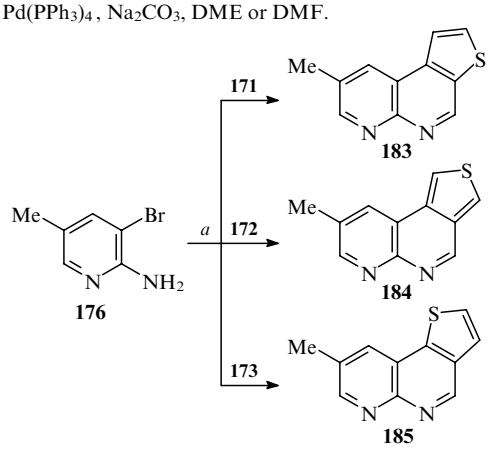
(*a*) PhH, Δ, 4 h; (*b*) *hv* (Hg lamp, 450 W), 1% MeOH in PhH, 3 h;
(*c*) $POCl_3$, Δ, 4 h; (*d*) 10% Pd/C, KOH, MeOH–PhH (1 : 1), 20 °C, 24 h.

7. Synthesis of naphthyridines fused to a thiophene ring

A one-stage procedure has been proposed [178–181] for the preparation of isomeric N(1),N(*i*)-naphthyridines; the procedure includes $Pd(PPh_3)_4$-catalysed cross-coupling of thiopheneboronic acids **171**, **172** or **173** containing an *ortho*-formyl group with *o*-aminohetaryl halides **174–176**. The cross-coupling products cyclise spontaneously during the reaction to give thiophenonaphthyridines **177–185** with all possible types of ring fusion. The effects of the amount of the catalyst, the nature of the base and the reaction time on the yield of the naphthyridines **178** and **181** have been studied.[180]

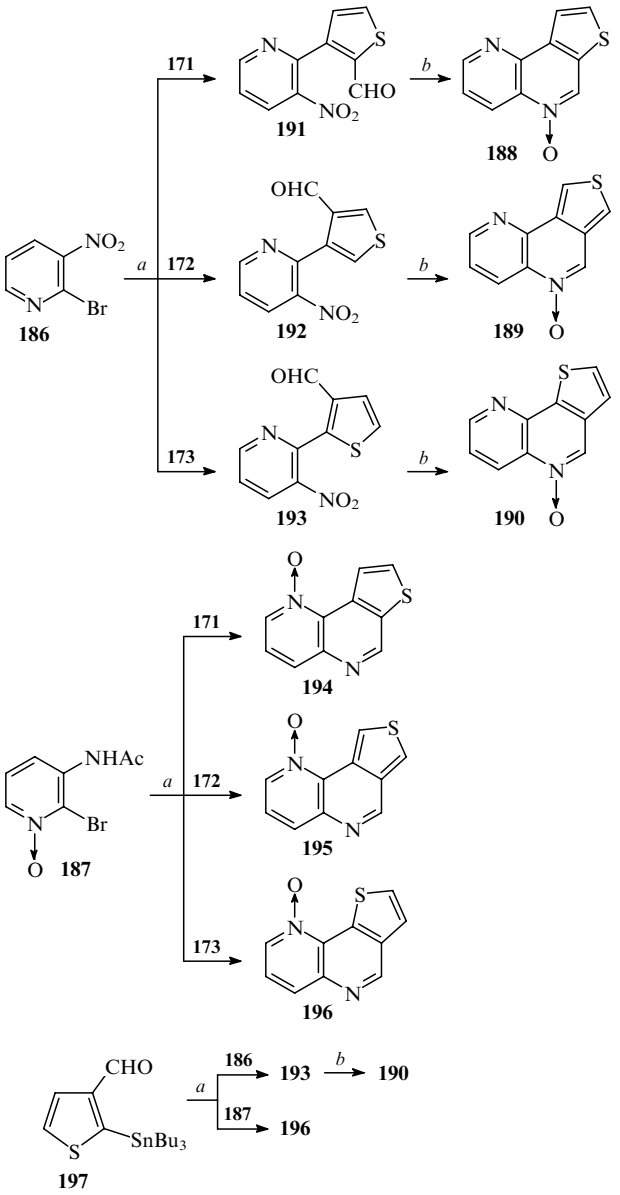


R = H: X = Cl (**a**), Br (**b**); R = Ac, X = Br (**c**);
(*a*) $Pd(PPh_3)_4$, Na_2CO_3, DME or DMF.



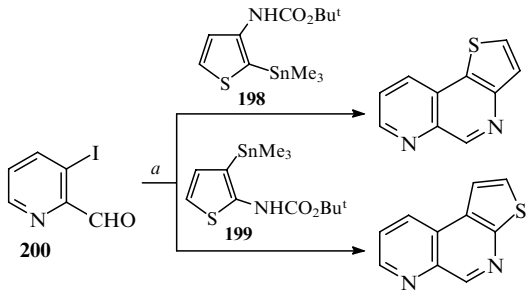
(*a*) $Pd(PPh_3)_4$, Na_2CO_3, DME or DMF.

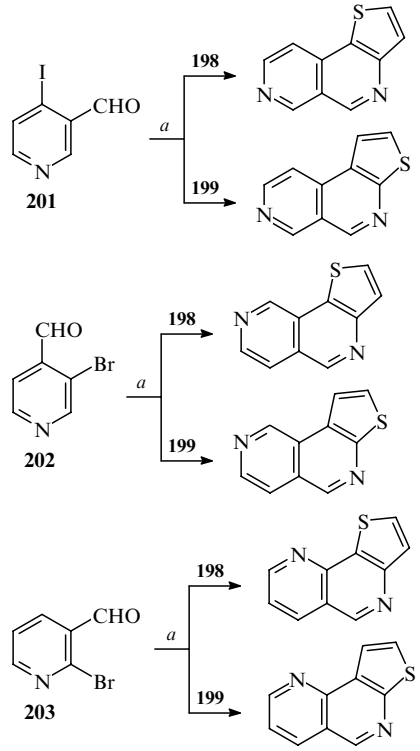
When 2-bromo-3-nitropyridine **186** is employed in the cross-coupling with formylthiopheneboronic acids **171–173**, thieno-1,5-naphthyridine 5-oxides **188–190** are produced. However, in this case, cyclisation of the cross-coupling products **191–193** proceeds on treatment with $FeSO_4$ in NH_4OH. Isomeric thieno-1,5-naphthyridine 9-oxides **194–196** are formed upon cross-coupling of the formylboronic acids **171–173** with 3-acetylamino-2-bromopyridine oxide **187**. 2-Tributylstannyl-3-formylthiophene **197** can be used in the cross-coupling with arenyl halides **186** and **187** instead of arylboronic acids. A mixture of *N*-oxide isomers **190** and **196** is also formed upon oxidation of thienonaphthyridine **179** with *m*-chloroperbenzoic acid.[181]



(*a*) Pd(0), Na_2CO_3, DME or DMF; (*b*) $FeSO_4$, NH_4OH.

The reaction of vicinal trimethylstannyl derivatives of *tert*-butoxycarbonylaminothiophenes **198** and **199** with halo-substituted pyridinecarbaldehydes **200**–**203** in the presence of $PdCl_2$, CuO and bis(diphenylphosphino)butane results in fused thienonaphthyridines of all the possible types.[182]

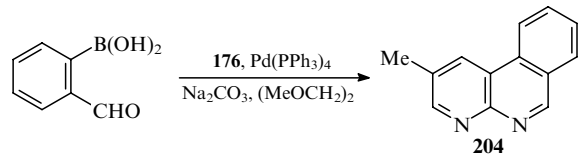




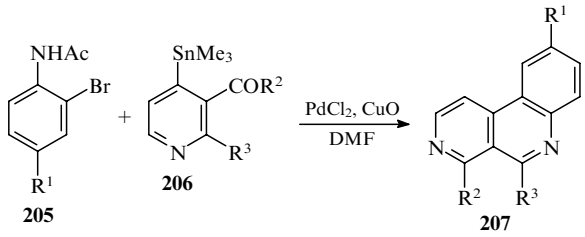
(*a*) $PdCl_2$, CuO, $Ph_2P(CH_2)_4PPh_2$.

The photoelectron spectra of all the thienonaphthyridine isomers have been analysed using semiempirical methods for the calculation of the ionisation energies of molecular orbitals.[183, 184]

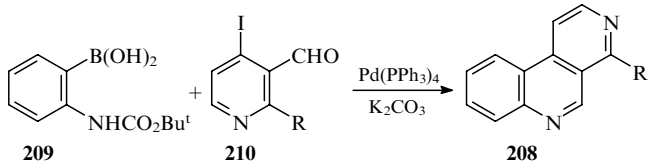
Cross-coupling catalysed by zerovalent palladium complexes has been employed to obtain other annelated naphthyridines. Thus the reaction of bromoaminopyridine **176** with 2-formylphenylboronic acid provided 9-methylbenzo[*c*]-1,8-naphthyridine **204**.[178]



Cross-coupling of *o*-bromoacetanilides **205** with trimethylstannylpyridyl ketones **206** in the presence of $PdCl_2$ and CuO in DMF affords benzo[*c*]-2,7-naphthyridines **207**.[185] Benzo[*c*]-2,7-naphthyridines **208** were prepared by refluxing 2-*tert*-butoxycarbonylaminophenylboronic acid **209** with substituted iodonicotinaldehydes **210** in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in a mixture of ethanol and toluene.[186]



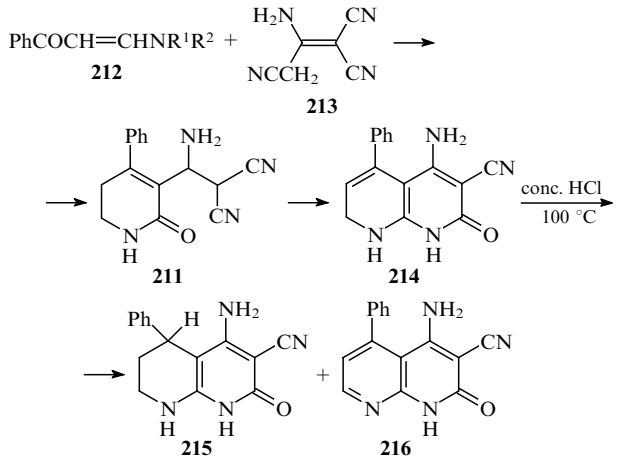
R^1 = H, Me, OMe; R^2 = H, Me; R^3 = H, OMe.



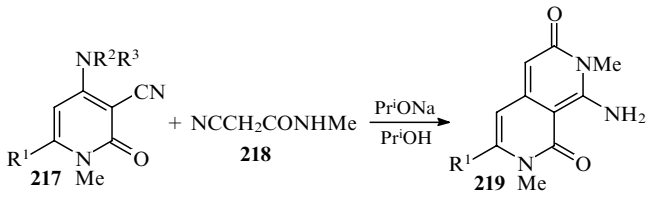
R = F, Cl, $CONPr^i_2$.

8. β-Enaminocarbonyl compounds in the synthesis of naphthyridines

β-Enaminocarbonyl compounds have long been used successfully in the synthesis of isomeric naphthyridines. Thus pyridone **211**, prepared by the reaction of β-enamino ketone **212** with 4,4-dicyano-3-aminobut-2-enenitrile **213**, cyclises to give substituted 1,2,7,8-tetrahydro-1,8-naphthyridin-2-one **214**. On treatment with concentrated hydrochloric acid at 100 °C, compound **214** undergoes disproportionation giving rise to a mixture of hexahydro (**215**) and dihydro derivatives of 1,8-naphthyridin-2-ones **216**.[187, 188]

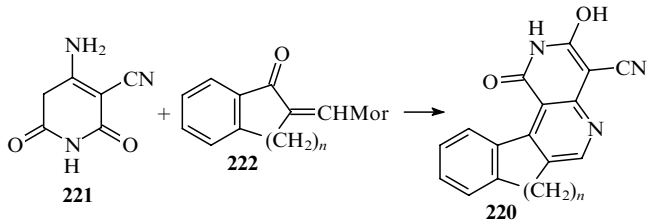


The reaction of 4-dialkylaminopyridones **217**, containing a β-enaminoamide fragment, with *N*-methylcyanoacetamide (**218**) is accompanied by replacement of the endocyclic amino group followed by cyclisation to give 2,7-naphthyridine **219**.[189]

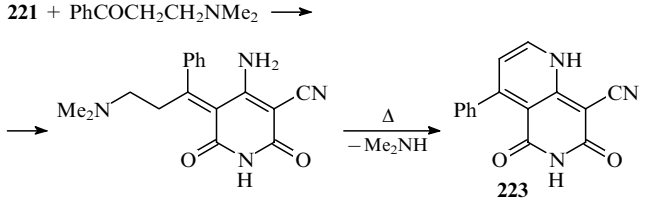


R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^2 = Et, Ph, CH_2Ph, $CH_2CH(OEt)_2$; R^3 = H, $CH_2CH_2OCH_2CH_2$.

One approach to the construction of fused 1,6-naphthyridines **220** includes the reaction of 4-amino-2,6-dioxo-1,2,5,6-tetrahydro-3-pyridinecarbonitrile **221** with cyclic β-enamino ketones **222**. The pyridinedione **221** reacts with 3-dimethylamino-1-phenylpropan-1-one to give 1,5,6,7-tetrahydro-1,6-naphthyridine-5,7-dione **223**.[190–192]

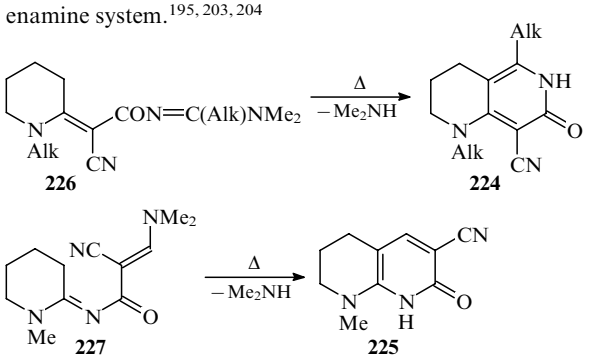


n = 1–3.



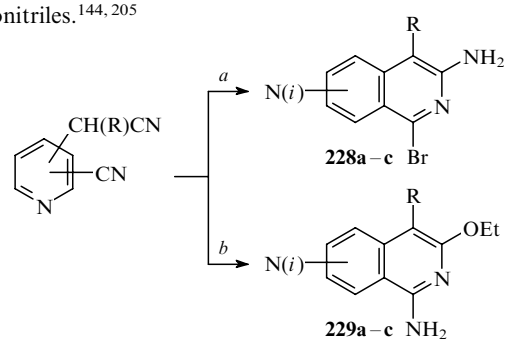
Enamino amides **226** and **227**, containing a β-enaminocarbonyl fragment, are promising starting compounds in the synthesis of hydrogenated naphthyridines **224** and **225**.[193–204]

Study of the kinetics of these reactions demonstrated that the rate of cyclisation of the compounds **226** is much higher than that for the amidine **227**, due to the more pronounced delocalisation of the positive charge in the amidine system compared to the enamine system.[195, 203, 204]

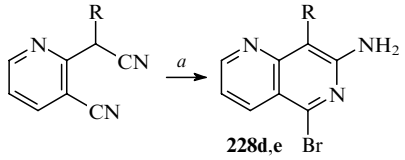


9. Cyclisation of 1,5-dinitriles and 1,5-amino(amido)nitriles of the pyridine series

Acid hydrolysis of 3- or 4-cyanopyridylacetonitriles or their reaction with sodium ethoxide affords isomeric amino derivatives of naphthyridines **228a–c** and **229a–c**. The 1,6-naphthyridines **228d,e** have been prepared by hydrolysis of 2-cyanomethylnicotinonitriles.[144, 205]

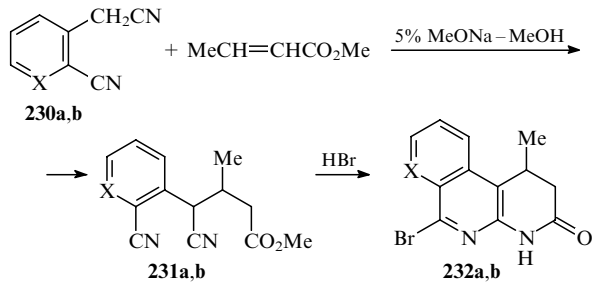


R = H: *i* = 6, 7; R = Me, *i* = 6; (*a*) HBr; (*b*) EtONa.



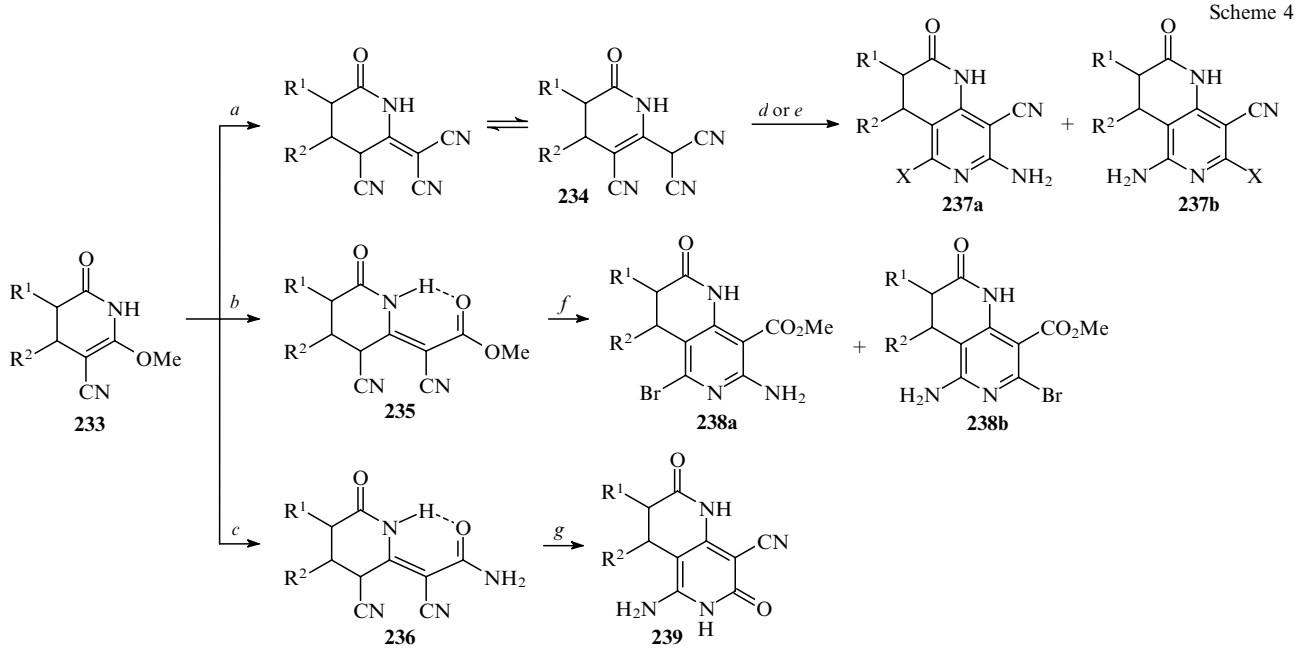
R = H, 4-FC_6H_4; (*a*) 30% HBr–AcOH.

2-Cyanophenyl- (**230a**) or 2-cyano-3-pyridylacetonitriles **230b** react with methyl crotonate to give adducts **231a,b**. Subsequent acid-catalysed cyclisation of compounds **231a,b** gives rise to the corresponding pyrido- and benzo[*c*]-1,8-naphthyridines **232a,b** — potential means for treating heart weakness, stenocardia and hypertension.[206, 207]



X = CH (**a**), N (**b**).

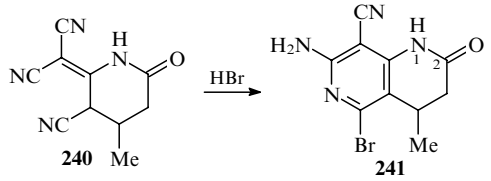
Scheme 4



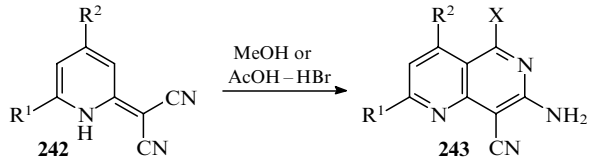
R^1, R^2 = H, Me, Ph; (*a*) $CH_2(CN)_2$; (*b*) $NCCH_2CO_2Me$; (*c*) $NCCH_2CONH_2$; (*d*) HX, X = Cl, Br; (*e*) MeONa, MeOH, X = OMe; (*f*) HBr; (*g*) OH^-, H_2O or RO^-, ROH.

The methoxy group in 5-cyano-6-methoxy-3,4-dihydro-2(1*H*)-pyridones **233** is replaced by malononitrile, methyl cyanoacetate or cyanoacetamide. The intermediates **234**–**236** cyclise in acid or basic media to give 3,4-dihydro-1,6-naphthyridin-2(1*H*)-ones **237**–**239** (Scheme 4).[208, 209]

Cyclisation of piperidone **240** yields 1,6-naphthyridine monohydrate **241**. An X-ray diffraction study showed that the C(2)–N(1) bond (1.362 Å) is longer than these bonds in other cyclic amides due to less efficient conjugation with the carbonyl group.[210]

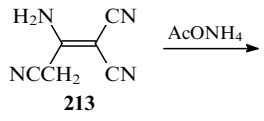


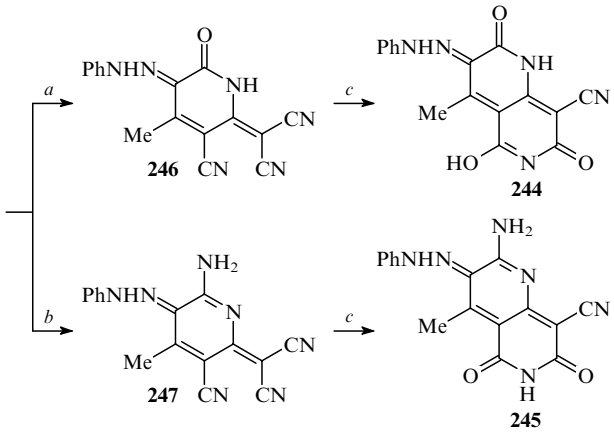
Dinitriles **242** have been used to perform regioselective synthesis of 7-amino-8-cyano-1,6-naphthyridines **243**.[144, 211, 212]



R^1, R^2 = Me, Et; X = Br, OMe.

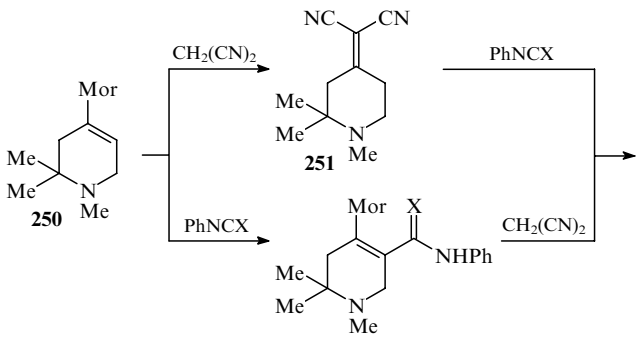
Naphthyridinediones **244** and **245** have been synthesised using reactions of 3-amino-4,4-dicyanobut-2-enenitrile (**213**) with α-diketone monophenylhydrazones. Cyclisation of intermediate dinitriles **246** and **247** was performed on treatment with a mixture of AcOH and HCl.[213]

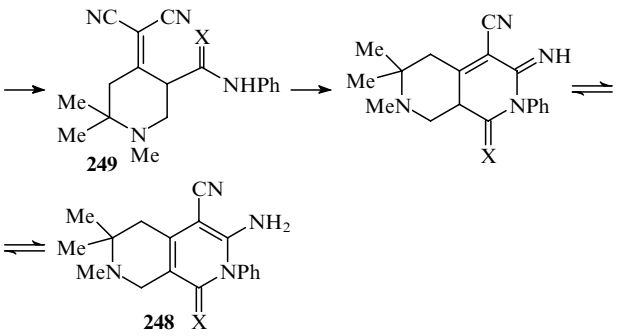




(*a*) PhNHN=C(Ac)CO_2Et; (*b*) PhNHN=C(Ac)CN; (*c*) AcOH, HCl.

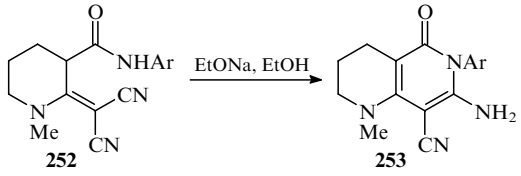
Enamino nitriles of 2,7-naphthyridinone(or -thione) **248** have been synthesised by cyclisation of amido(or thioamido) nitriles **249**, which are prepared from enamine **250** or substituted malononitrile **251**.[214, 215]





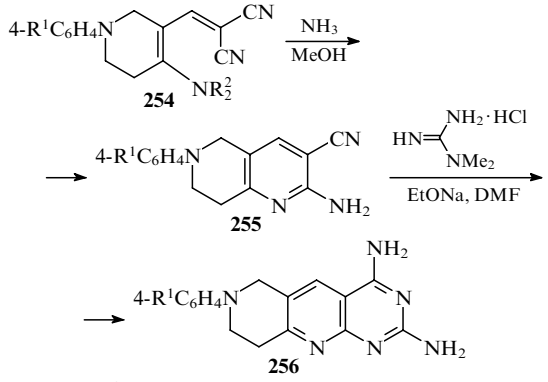
X = O, S.

On treatment with sodium ethoxide in ethanol, 1-methyl-2-dicyanomethylidenepiperidine-3-carbanilides **252** cyclise to give partially hydrogenated 1,6-naphthyridin-5(6*H*)-ones **253**.[216]



Ar = Ph, 4-ClC_6H_4, 3-MeC_6H_4.

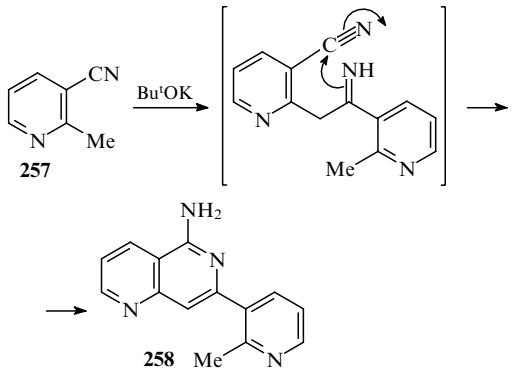
Ammonolysis of enamines **254**, obtained from 1-aryl-3-(2,2-dicyanovinyl)-4-piperidones affords 2-amino-6-aryl-3-cyano-5,6,7,8-tetrahydro-1,6-naphthyridines **255**, employed in the synthesis of pteridines **256**.[211]



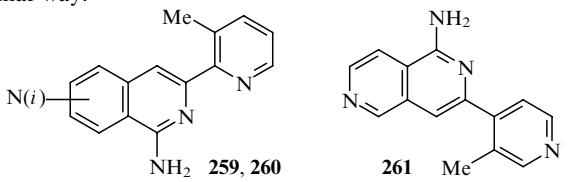
R^1 = Me, Et; R^2_2 = $(CH_2)_4$.

10. Thorpe dimerisation of cyanopicolines

Dimerisation of 2-methylnicotinonitrile (**257**) induced by potassium *tert*-butoxide and including intramolecular addition of the imine to the nitrile at the cyclisation stage gives rise to 5-amino-7-(2-methyl-3-pyridyl)-1,6-naphthyridine (**258**).[130]



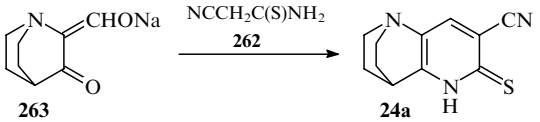
8-Amino-1,7-, 1-amino-2,6- and 1-amino-2,7-naphthyridines **259**–**261**, possessing efficient bactericidal and fungicidal activities, were prepared from the corresponding cyanopicolines in a similar way.[144]



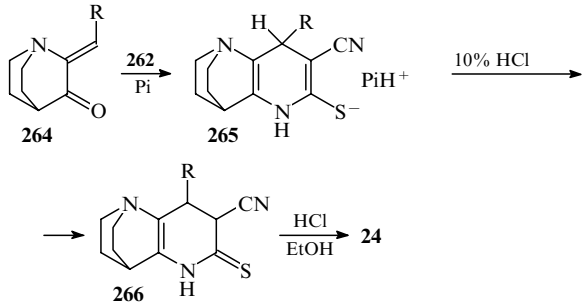
i = 6, 7.

11. Condensation of piperidones with cyanoacet(or thioacet)amides

The condensation of cyanothioacetamide **262** with the sodium salt of 2-formyl-3-quinuclidone **263** in ethanol in the presence of AcOH has resulted in the synthesis of 1,5-naphthyridine-2(1*H*)-thione **24a**.[106]

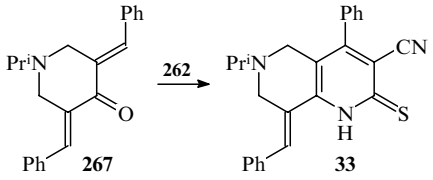


Cyanothioacetamide **262** condenses with 2-arylmethylidene-3-oxoquinuclidines **264** in the presence of piperidine to yield relatively stable salts **265**; in an acid medium, these products are converted into 3,4-dihydro-1,5-naphthyridinethiones **266**. Upon refluxing in an HCl–EtOH mixture, the compounds **266** are transformed into naphthyridinethiones **24**, which are also formed directly on refluxing the salts **265** in an ethanolic solution of HCl.

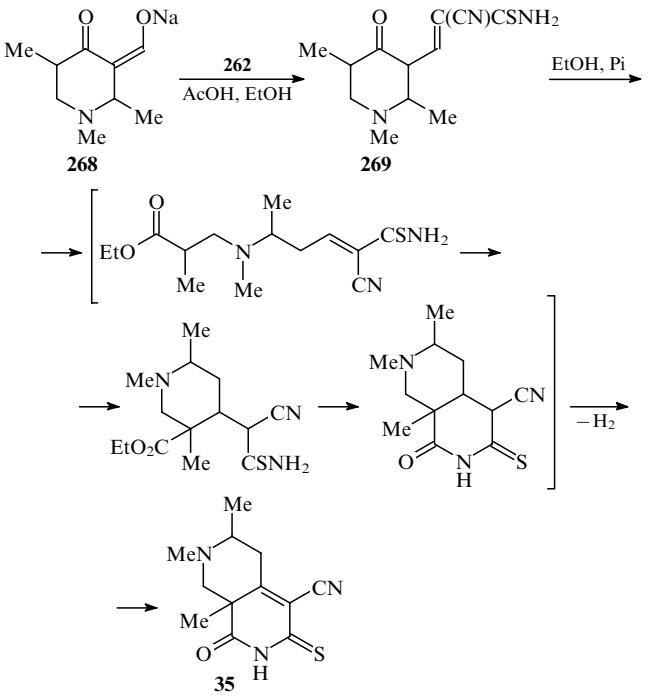


R = H, Ph, 4-FC_6H_4; Pi is piperidine.

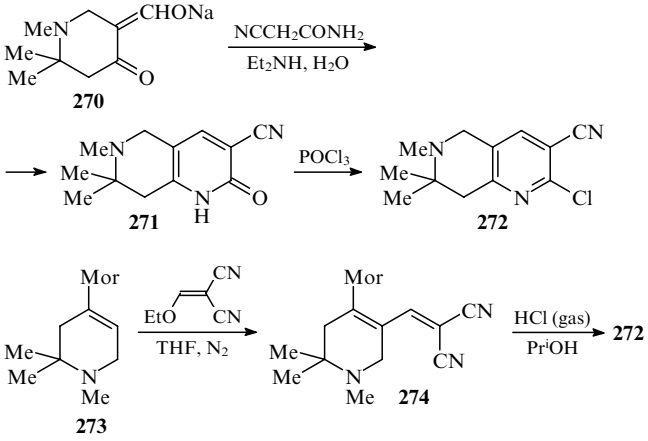
The partially hydrogenated 1,6-naphthyridinethione **33** has been synthesised by the reaction of 3,5-bis(phenylmethylidene)-1-isopropyl-4-piperidone **267** and the amide **262**.[107]



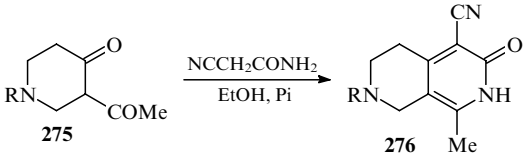
The reaction of the salt **268** with the amide **262** in ethanol in the presence of AcOH follows the Knoevenagel reaction route and affords adduct **269**, which recyclises when refluxed in ethanol in the presence of a catalytic amount of piperidine, giving rise to the the 2,7-naphthyridine **35**. The compound **35** is the product of a cascade type reaction comprising acidic cleavage according to Claisen, the Michael intramolecular addition, the interaction between the thioamide and ester groups and dehydrogenation.[110]



The cyclocondensation of piperidone **270** with cyanoacetamide in the presence of diethylamine gives 1,6-naphthyridinone **271**, which reacts with $POCl_3$ to give chloro derivative **272**.[217] The compound **272** was also prepared by condensation of enamine **273** with ethoxymethylidenemalononitrile followed by cyclisation of intermediate **274**.[217]



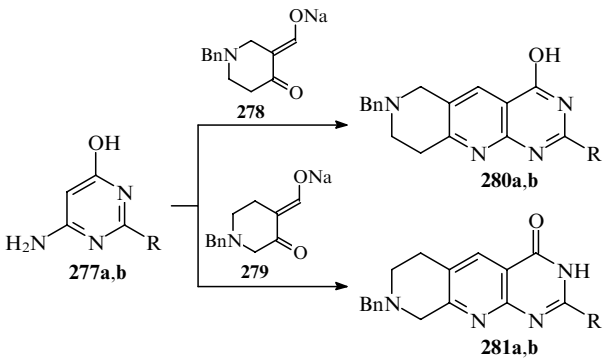
Refluxing of 1,3-dicarbonyl compounds **275** with cyanoacetamide in ethanol in the presence of piperidine gives 2,7-naphthyridine derivatives **276**, used as components of formulations for treatment of diseases of blood circulation organs.[218]



R = H, Alk, Ph, Ac, Bn, 4-pyridyl.

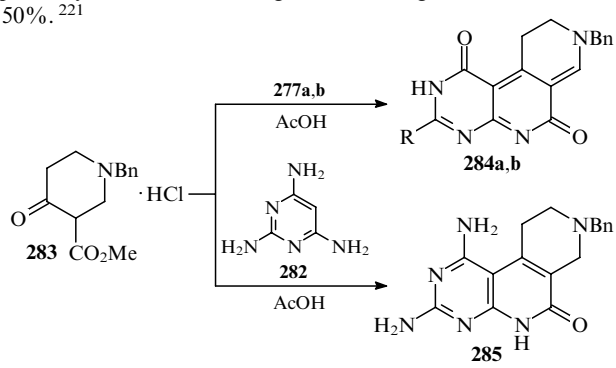
12. Cyclocondensation of piperidones with aminopyrimidines

When aminopyrimidines **277** are heated (100 °C, 3 h) with the salts of isomeric hydroxymethylidenepiperidones **278** and **279** in 85% orthophosphoric acid, substituted tetrahydropyrimido-[4,5-*b*]-1,6- (**280a**,**b**)[219] and -1,7-naphthyridines **281a**,**b** are formed;[220] they are potential antitumour remedies.

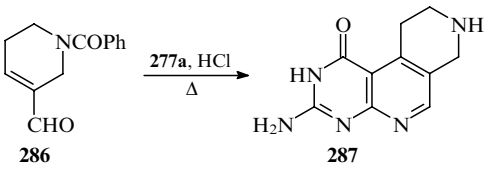


R = NH_2 (**a**), OH (**b**).

Refluxing of aminopyrimidines **277a**,**b** and **282** with methyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride **283** in glacial acetic acid provided the synthesis of pyrimido[4,5-*c*]-2,7-naphthyridin-6-ones **284a**,**b** and **285**. The compounds **284b** and **285** present in concentrations of 10^{-5} and 2×10^{-6} mol litre^{-1}, respectively, inhibit *in vitro* the growth of malignant leukemia cells by 50%.[221]

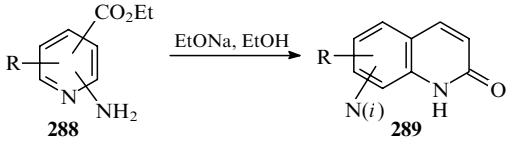


A similar condensation of the aminopyridine **277a** with hydrogenated 3-formylpyridine **286** in the presence of HCl in ethanol results in tetrahydropyrimido[4,5-c]-2,7-naphthyridine **287** mixed with its 7-benzoyl derivative.[219,222]

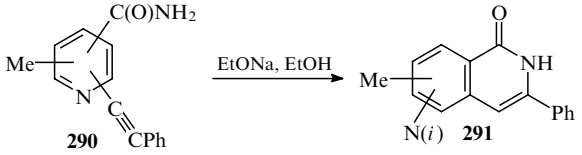


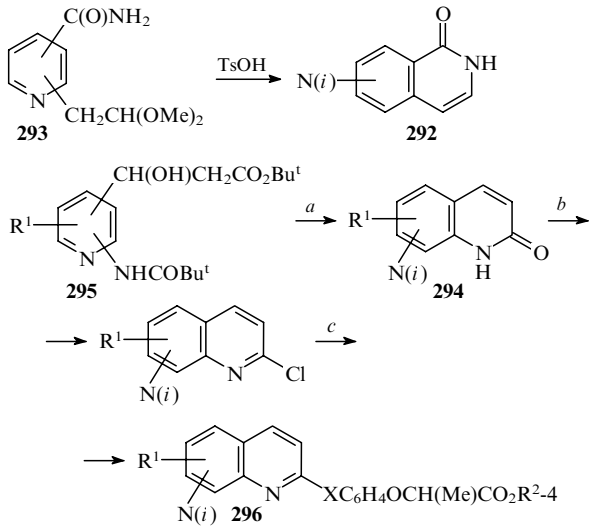
13. Other general methods for the synthesis of naphthyridines

Below we present the syntheses of naphthyridines starting from pyridine derivatives containing an amino (or protected amino) group and a carbonyl group or its synthetic equivalent in vicinal positions. Cyclisation is accomplished by treatment with basic or acidic reagents.

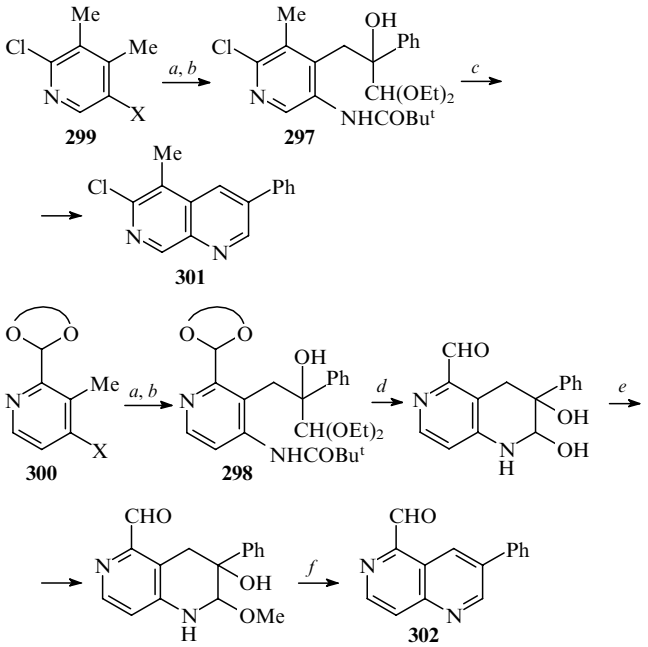


R = H, Me; *i* = 5–8.





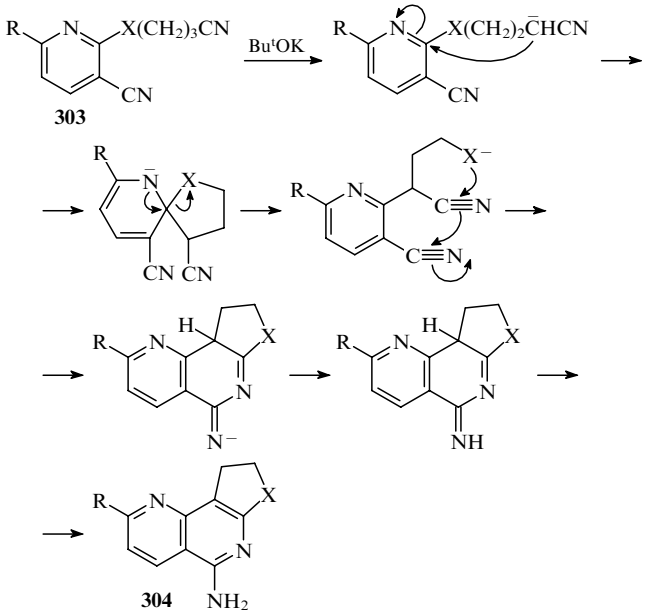
i = 6–8; R^1 = H, Me, Cl; R^2 = Alk; X = O, S; (*a*) 3 M HCl; (*b*) $POCl_3$, Δ; (*c*) 4-$HXC_6H_4OCH(Me)CO_2R^2$, K_2CO_3 or NaH, DMSO.



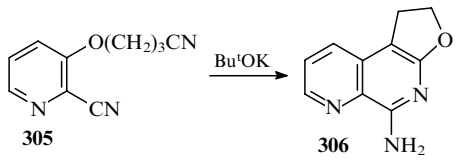
(*a*) Bu^nLi; (*b*) $(EtO)_2CHCOPh$; (*c*) HCl; (*d*) H_2SO_4; (*e*) MeOH, H_3PO_4; (*f*) diazabicycloundecene, dioxane, Δ.

Cyclisation of ethyl aminopyridineacrylates **288** in ethanol in the presence of sodium ethoxide has served as a route to N(1),N(*i*)-naphthyridin-2(1*H*)-ones **289**.[223] Cyclisation of ethynylpyridinecarboxamides **290** under similar conditions yields 1,6-, 1,7-, 2,6- and 2,7-naphthyridones **291**.[224] Naphthyridones **292** were prepared by refluxing vicinal (2,2-dimethoxyethyl)pyridinecarboxamides **293** with toluene-*p*-sulfonic acid in benzene.[224] N(1),N(*i*)-Naphthyridin-2(1*H*)-ones **294**, prepared by refluxing vicinal 2-*tert*-butoxycarbonyl-1-hydroxyaminopyridines **295** in dioxane in the presence of 3 M HCl, have been used to obtain naphthyridine derivatives **296**, which possess herbicidal and fungicidal properties and are efficient for the protection of cotton, soy-bean and sugar-cane crops.[225,226] Intramolecular cyclisation of substituted *tert*-butoxycarbonylaminopyridines **297** and **298**, synthesised from compounds **299** and **300** *via* a two-stage procedure, gives 1,7- (**301**) and 1,6-naphthyridines **302**.[227]

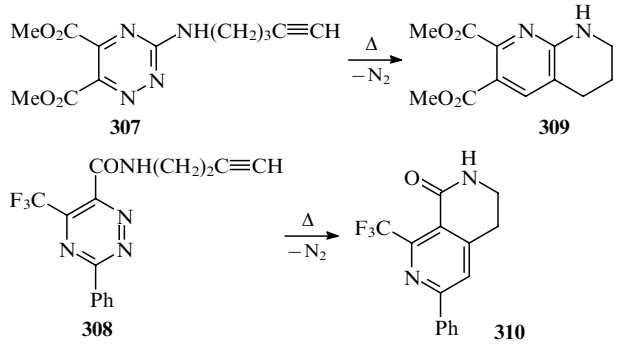
2-(3-Cyanopropyl-oxy or -thio)pyridine-3-carbonitriles **303** undergo an intramolecular nucleophilic rearrangement, similar to the Smiles rearrangement, being thus converted into fused 1,6-naphthyridines **304**.[228–230] A similar cyclisation of 2-pyridinecarbonitrile **305** gives rise to dihydrofuro[3,2-*f*]-1,7-naphthyridine **306**.[231]



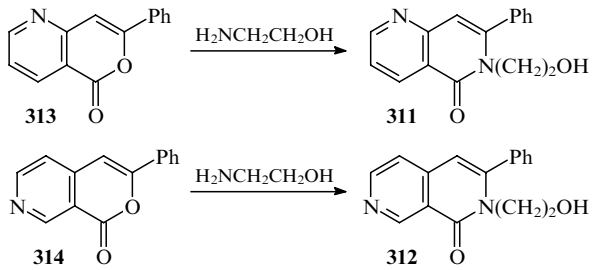
X = S, R = H; X = O, R = Me.



Substituted 1,2,4-triazines decompose on thermolysis with nitrogen evolution. Thermolysis of compounds **307** and **308**, having an ethynyl substituent in the side chain, yields substituted naphthyridines **309**[232] and **310**.[233]

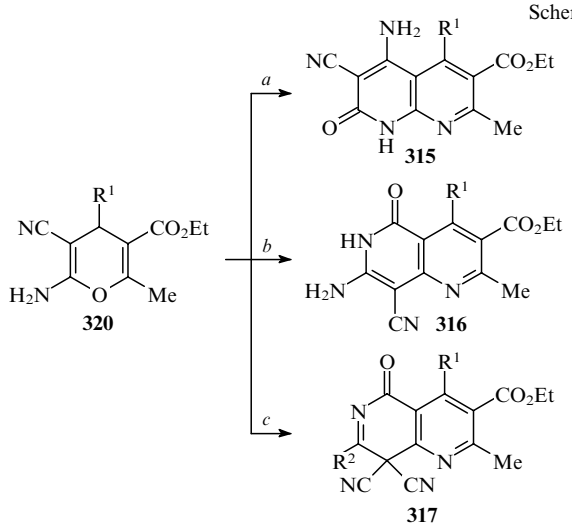


N-Hydroxyethyl-substituted 1,6- (**311**) and 2,7-naphthyridones **312** were prepared by refluxing the pyranopyridine isomers **313** and **314** with ethanolamine.[234]

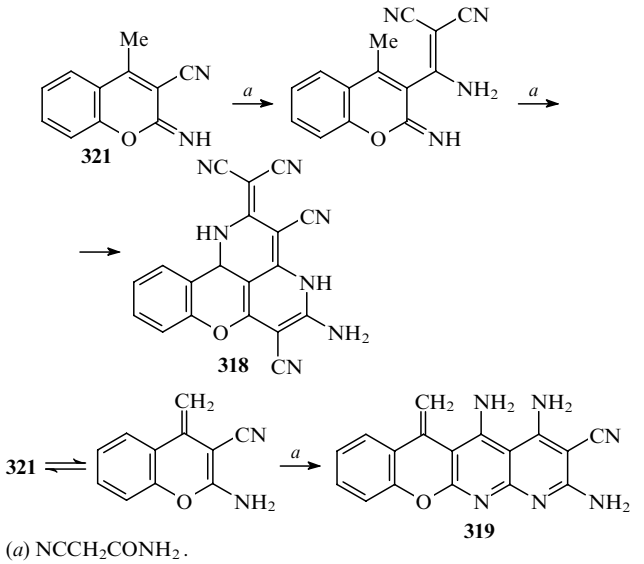


The synthetic routes to 1,8- (**315**) and 1,6-naphthyridones **316** and **317** and annelated systems **318** and **319** make use of the reactions of pyrans **320** and **321** with malononitrile or its derivatives. The reactions are carried out in ethanol in the presence of piperidine (Scheme 5).[235–237]

Scheme 5



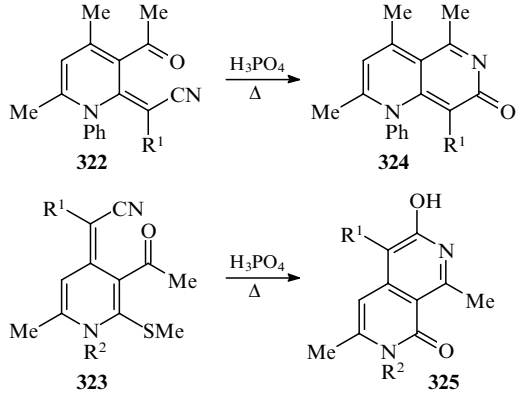
R^1 = 2-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4;
(*a*) $NCCH_2CONH_2$; (*b*) $CH_2(CN)_2$; (*c*) $R^2CH=C(CN)_2$; R^2 = Alk, Ar.



(*a*) $NCCH_2CONH_2$.

3-Acetyl-2-cyanomethylidenepyridine **322** and 3-acetyl-4-cyanomethylidenepyridine **323** cyclise on heating (130 °C, 30–45 min) in 85% orthophosphoric acid to give 1,6- (**324**) and 2,7-naphthyridinone derivatives **325** (Scheme 6).[238]

Scheme 6



R^1 = CN, CO_2Et; R^2 = Ph, 4-$MeOC_6H_4$.

V. Conclusion

The data surveyed here demonstrate that general and facile methods for the synthesis of diverse substituted naphthyridines are now available. Various naphthyridines can be synthesised under the same conditions using similar equipment. Various types of biological activity exhibited by many naphthyridine derivatives together with the ease of their preparation make these products attractive objects for the search for new highly effective medicinal preparations, which can be done using combinatorial synthesis.

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