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Benzo[*b*]naphthyridines

A S Ivanov, N Z Tugusheva, V G Granik

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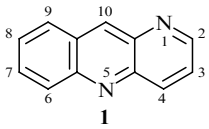
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Abstract. The published data on the methods for the synthesis, properties and applications of benzo[*b*]naphthyridines are analysed and generalised. The main attention is focused on biologically active compounds of the benzo[*p*]naphthyridine series. The bibliography includes 140 references.

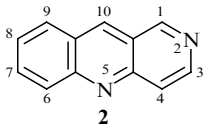
I. Introduction

Benzo[*b*]naphthyridines **1** – **4** can be regarded as aza derivatives of acridines. By virtue of their planar linear structures, benzo[*b*]-naphthyridines attract keen attention of investigators as promising antitumour agents, *viz*., intercalators.† The number of publications devoted to the synthesis and analysis of biochemical and pharmacological properties of representatives of this class of heterocycles is steadily increasing. However, no reviews specially devoted to benzo[*b*]naphthyridines exist so far. Several papers published before 1986 were considered in a review.[1] Some novel data on benzonaphthyridines were included into more recent reviews [2–4] devoted to naphthyridines. In this study, we made an attempt to generalise and systematise all published data on the methods for the synthesis and properties of benzo[*b*]naphthyridines (hereinafter referred to for the sake of brevity as benzonaphthyridines). The review encompasses the literature published in the period from 1980 to 2004. Wherever necessary, some earlier papers are included for a more logical and consistent presentation of the material. Special attention is given to the description of methods for the synthesis of benzonaphthyridine derivatives which present interest for medicinal chemistry with due regard to the state-of-the-art and trends.

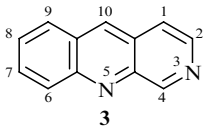
The structural formulas of all the four isomeric benzo[*b*]naphthyridines **1** – **4** containing 1,5-, 1,6-, 1,7- or 1,8-naphthyridine skeletons are given below.



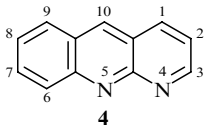
1



2



3



4

II. Physicochemical properties

Relative nucleophilicities of the nitrogen atoms in the peripheral pyridine ring of 6-methylbenzo[*b*]naphthyridines **5** – **8** upon their interactions with MeI in DMSO have been studied.[5] To this end, the relative methylation rates of compounds **5** – **8** with respect to pyridine (k_1/k_{Py}) were measured by the competitive reaction method (Table 1). The presence of a methyl group in the benzene ring near the nitrogen atom in the central ring in the compounds under study prevents the reaction from occurring at the acridine nitrogen atom; the reactivities of compounds **5** – **8** decrease in the following order: 1,8-naphthyridine > 1,6 > 1,7 > 1,5 (see ‡).[5,6] High reactivity of benzo[*b*][1,8]naphthyridine (**5**) is attributed [5] to the proximity of the lone pairs of the N(1) and N(10) atoms involved in transition state **9** upon quaternisation of N(1). However, in the case of the benzo[*b*][1,5]-isomer **8** the reaction at N(1) is hindered by the H(10) atom in the *peri*-position.[6,7]

Such an interpretation seems to be reasonable enough, but it fails to provide an explicit answer to the question why the methylation rates of all benzonaphthyridines fit in the above-mentioned series. In our opinion, this problem requires an analysis of all initial and hypothetical transition states realised in the processes under consideration. For compound **5**, stabilised hypothetical transition state **9** is rather plausible despite certain instability of the initial state resulting from the interaction of the electron pairs at N(4) and N(5). A combination of these two factors leads to a general decrease in the free activation energy and

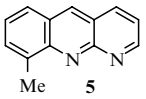
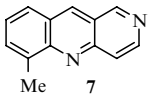
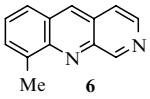
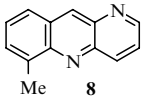
A S Ivanov, N Z Tugusheva, V G Granik Federal State Unitary Enterprise 'State Scientific Centre on Antibiotics', ul. Nagatinskaya 3a, 117105 Moscow, Russian Federation. Fax (7-495) 231 42 38, tel. (7-495) 231 42 93, e-mail: a.ivan@mail.ru (A S Ivanov), tel. (7-495) 231 42 84 (N Z Tugusheva), (7-495) 231 42 83, e-mail: vggranik@mail.ru (V G Granik)

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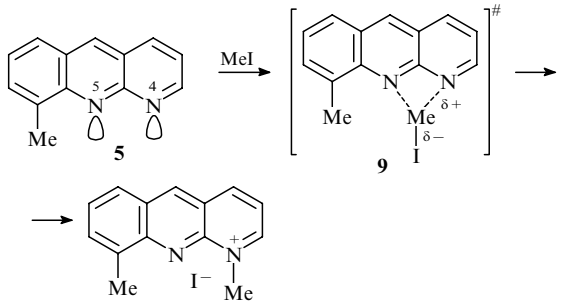
† Intercalation entails insertion of compounds between base pairs of DNA; the complex formed is stabilised by van der Waals forces. Intercalation prevents unwinding of DNA chains and, as a consequence, their normal functioning.

‡ Hereinafter, the isomers bear the numbers corresponding to those used to denote naphthyridines.

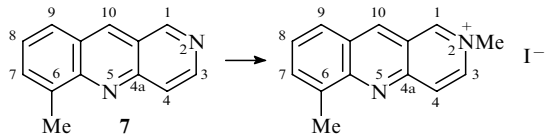
Table 1. Relative methylation rates of compounds **5**–**8** in comparison with pyridine.

Compound	Isomer	k_1/k_{Py}	Compound	Isomer	k_1/k_{Py}
 Me **5**	1,8	0.325	 Me **7**	1,6	0.265
 Me **6**	1,7	0.169	 Me **8**	1,5	0.010

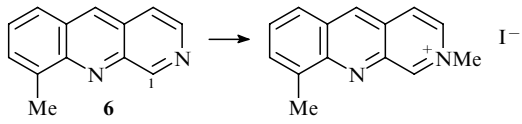
thus determines the highest methylation rate of this particular isomer.



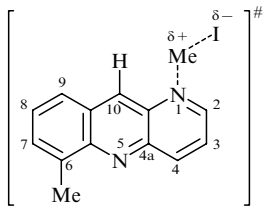
The methylation rate of the 1,6-isomer **7** is comparable with that of the isomer **5**.



The absence of conjugation between the electron-withdrawing double bond C(4a)=N(5) and the nitrogen atom at position 2 of compound **7** favours the electrophilic attack at this nitrogen atom in comparison with other benzonaphthyridines (except for compound **5**). Neither stabilisation of the initial state nor destabilisation of the transition state take place in this case. The methylation rate of the 1,7-isomer **6** is even lower, since the conjugation between two double bonds C=N results in stabilisation of the initial state and destabilisation of the transition state.

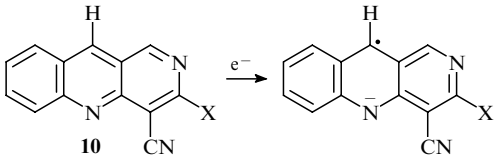


This finding provides a rationale for the decrease in the methylation rate of compound **6** in comparison with other isomers considered above. Methylation of the tricycle **8** is controlled by the same factors. There exists yet another factor responsible for the lowering of the reactivity of 1,5-naphthyridine (**8**) in comparison with the isomer **6**. The transition state of compound **8** can be presented as follows:



Apart from destabilisation induced by the electron-withdrawing effect (conjugation) of the C(4a)=N(5) bond, the stability of the transition state is adversely affected by yet another factor, *viz*., the nonbonding interaction between the N(1)···Me and C(10)–H bonds in *peri*-positions. It is this contributing evidence that sheds additional light on the lower (in comparison with the isomeric compound **6**) methylation rate of the tricycle **8**.

The electroreduction of 3-substituted 4-cyanobenzo[*b*][1,6]-naphthyridine derivatives **10** in DMF was studied by polarography.[8] It was found that the first step of this reaction includes transfer of one electron to position 10 (analogously to reduction of acridine), which is consistent with the appearance of one-electron waves on the polarograms. It was found also that an increase in the electron-donor properties of the substituents at position 3 causes a shift of polarographic half-wave reduction potentials to negative values, *i.e*., hinders reduction of the tricycles **10**.



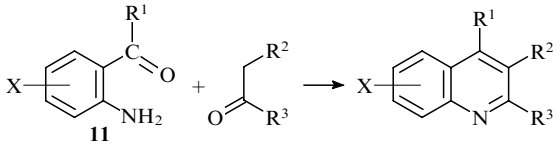
X = NR^1R^2, SR^1; R^1, R^2 = Alk, Ar.

III. Methods for synthesis

The most general approaches to the synthesis of benzonaphthyridines are based on the methods used for the closure of the pyridine ring in the course of quinoline synthesis. The use of the Friedlander and Pfitzinger reactions and the synthesis based on arylaminopyridines enable the preparation of derivatives with functional groups at different positions of the tricyclic system.

1. Friedlander reaction and its modifications

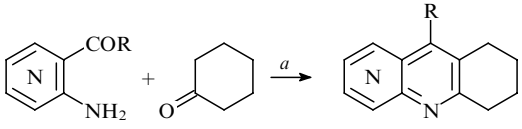
The Friedlander reaction is the most general and well-developed approach to the synthesis of various benzo[*b*]naphthyridines. It is based on the reaction of *o*-aminoaryl(hetaryl)carbonyl compounds with methylene ketones.[9]

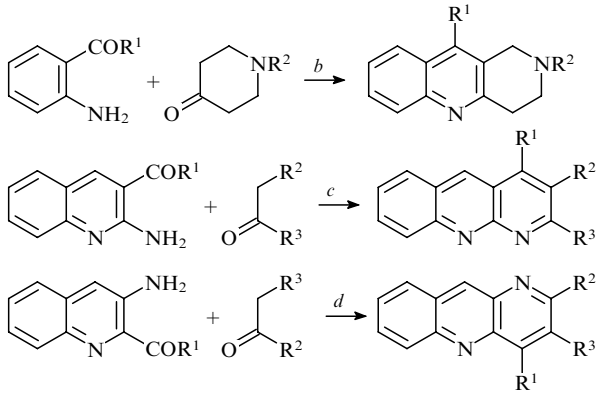


The Niementowski (R^1 = OH) and Pfitzinger (R^1 = CO_2H) reactions are essentially very similar to the Friedlander reaction (the Pfitzinger reaction is more extensively used for the preparation of benzo[*b*][1,6]naphthyridines).

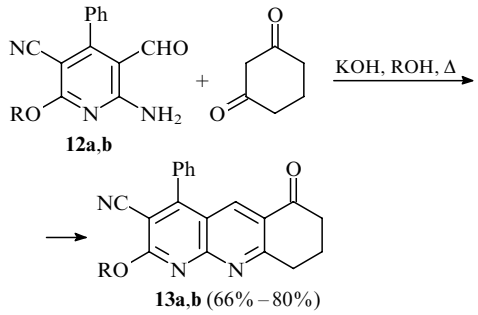
The classical variant of the Friedlander reaction makes use of *o*-aminobenzaldehydes and basic catalysts (KOH, NaOH, piperidine, *etc*.), but this reaction can also be carried out in the absence of these catalysts. However, attempts to synthesise quinolines from less reactive *o*-aminobenzophenones under alkaline conditions are not always successful. In this case, the carbonyl group is activated by acids [HCl, H_2SO_4, TsOH, polyphosphoric acid (PPA), *etc*.]. Very often, the reaction is carried out by refluxing in AcOH in the presence of catalytic amounts of H_2SO_4 (the so-called Fehnel modification [10]).

The formation of a pyridine ring in this reaction enables the synthesis of tricyclic benzonaphthyridines. This can be accompanied by the closure of both the central (routes *a* and *b*) and peripheral pyridine rings (routes *c* and *d*).

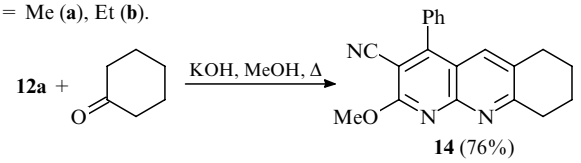




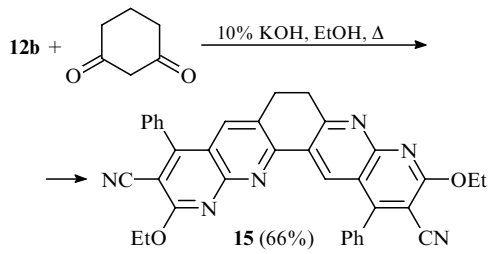
Substituted 2-amino-3-formylpyridines **12a**,**b** are involved in the Friedlander reaction with cyclohexane-1,3-dione and cyclohexanone under conditions of basic catalysis giving rise to the 1,8-naphthyridine derivatives **13a**,**b** and **14**. Cyclisation of cyclohexane-1,3-dione occurs much more smoothly due to higher CH-acidity of the methylene fragment.[11,12]



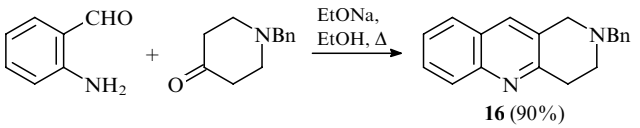
R = Me (**a**), Et (**b**).



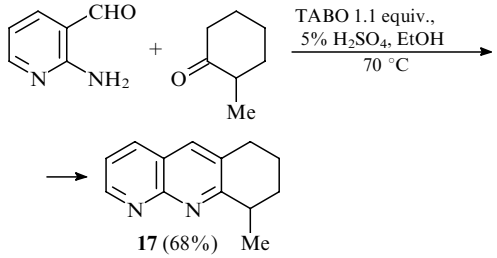
If *o*-aminoaldehyde is used in excess, the reaction with cyclohexane-1,3-dione does not stop at the formation of benzonaphthyridine **14**, but proceeds further eventually resulting in the pentacyclic product **15**.[12]



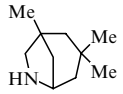
Shiozawa *et al.*[13] used 4-piperidones as ketone components in the synthesis of 2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (**16**).



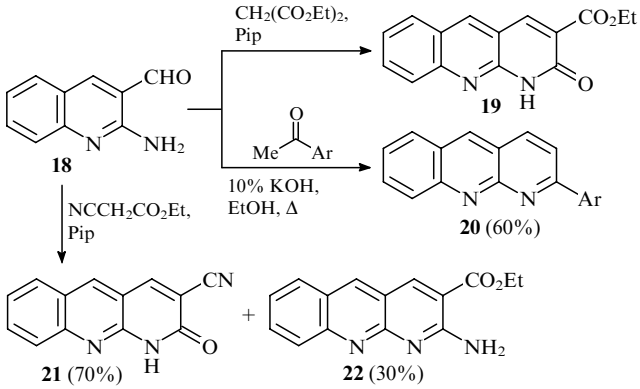
The reaction of 2-amino-3-formylpyridine with 2-methylcyclohexanone in the presence of 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) as the basic catalyst produced tetrahydrobenzo[*b*][1,8]naphthyridine **17**.[14] In earlier studies,[15] such conversion has been achieved by heating the reactants with sodium *tert*- butoxide in *tert*-butyl alcohol; the yield of naphthyridine **17** was 84%. Apparently, TABO is the catalyst of choice for the Friedlander reaction both by virtue of its high catalytic activity and optimum selectivity. This circumstance is of special importance in those cases where unsymmetrical ketones are used.[14]



TABO =

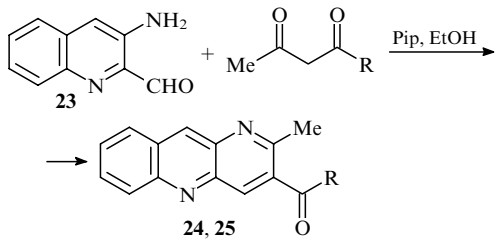


The Friedlander synthesis based on aminoformylquinolines was successfully used for the preparation of benzo[*b*][1,5]naphthyridines and benzo[*b*][1,8]naphthyridines.[16] Thus 2-amino-3-formylquinoline **18** was introduced into base-catalysed cyclocondensation with diethyl malonate and aryl methyl ketones to give the corresponding benzo[*b*][1,8]naphthyridines **19** and **20** in good yields. The reaction with ethyl cyanoacetate gave a mixture of naphthyridines **21** and **22**.



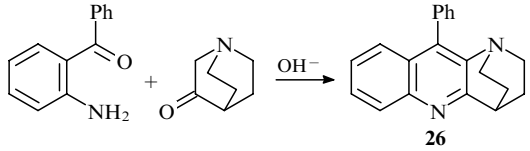
Pip is piperidine.

3-Aminoquinoline-2-carbaldehyde (**23**) reacts with acetylacetone in the presence of piperidine to give 3-acetyl-2-methylbenzo[*b*][1,5]naphthyridine (**24**). The condensation of compound **23** with ethyl acetoacetate under identical conditions involves only the ketone carbonyl group, 3-ethoxycarbonyl-2-methylbenzo[*b*]-[1,5]naphthyridine (**25**) being the only reaction product.[16]

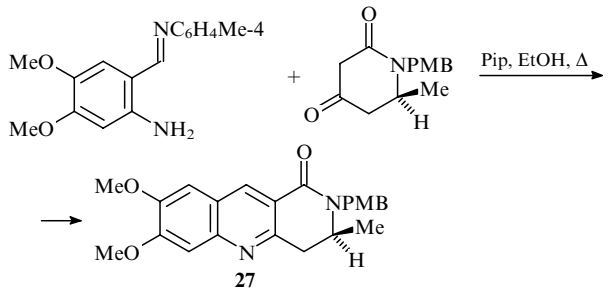


R = Me (**24**, 74%), OEt (**25**, 70%).

2-Aminobenzophenone reacts with quinuclidin-3-one under basic catalysis to give the benzo[*b*][1,5]naphthyridine derivative **26**.[17]



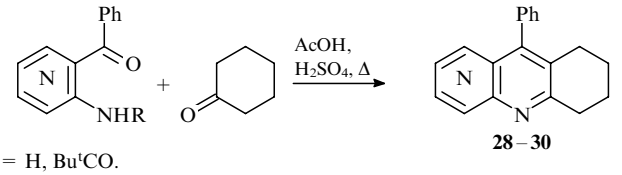
The Borsche modification of the Friedlander synthesis [18], *i.e.*, the replacement of the aldehyde group with the azomethine fragment, enables the reaction to occur without complications due to low stability of substituted 2-aminobenzaldehydes at elevated temperatures. This reaction was used in the synthesis of benzonaphthyridine **27**.[19]



27

PMB is $CH_2C_6H_4OMe$-4.

The reactions of *vic*-aminobenzoylpyridines or *vic*-(pivaloylamino)benzoylpyridines with cyclohexanone were used in the synthesis of the corresponding tricyclic derivatives of 1,6- (**28**), 1,7- (**29**) and 1,8-naphthyridine (**30**) (70% – 99% yields).[20–22]

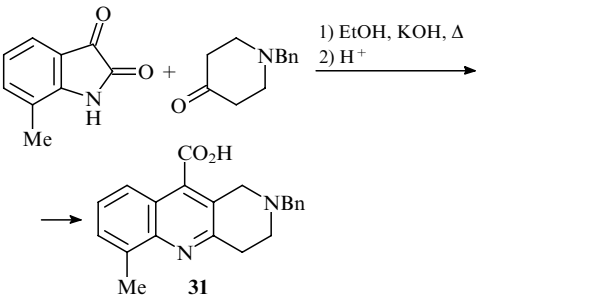


28 – 30

R = H, Bu^{t}CO.

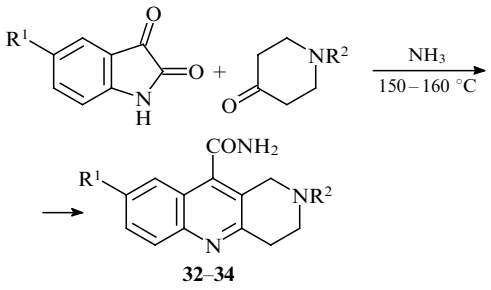
The Pfitzinger reaction [23] involves condensation of isatine and its derivatives with methylene ketones in the presence of bases (KOH, NaOH, *etc.*), which convert isatine into isatinates. The latter, being *o*-aminocarbonyl compounds, react further with ketones according to the Friedlander reaction.

Thus the use of 4-piperidone derivatives as a carbonyl component in the Pfitzinger reaction enables the one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines in good yields. For example, refluxing of 7-methylisatine with 1-benzylpiperidin-4-one in ethanolic KOH affords 1,2,3,4-tetrahydrobenzo[*b*][1,6]-naphthyridine-10-carboxylic acid (**31**).[24]



31

The synthesis of benzo[*b*][1,6]naphthyridine derivatives containing an amide group at position 10 by the Pfitzinger reaction is carried out in the presence of ammonia or ammonium salts. Thus derivatives of 2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]napththyridine-10-carboxamide (**32**) and 1,2,3,4-tetrahydro-2-ethoxycarbonylbenzo[*b*][1,6]naphthyridine-10-carboxamide (**33**) were prepared by passing ammonia through the reaction mixture containing 5-substituted isatines and 1-benzylpiperidin-4-one or 1-ethoxycarbonylpiperidin-4-one, respectively, in ethylene glycol at 150 – 160 °C.[25] The reaction of isatine with 1-*tert*-butoxycarbonylpiperidin-4-one proceeds in a similar fashion: heating in DMF with ammonium acetate affords 2-*tert*-butoxycarbonyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine-10-carboxamide (**34**) in 50% yield.[26]

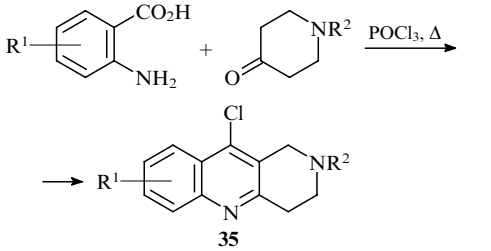


32–34

R^1 = H,Cl, F, OMe; R^2 = Bn (**32**), CO_2Et (**33**), CO_2Bu^t (**34**).

The approach employed in the synthesis of benzonaphthyridines, *i.e.*, reactions of substituted anthranilic acids and *o*-aminonitriles with cyclic ketones, is very similar to that underlying the Friedlander reaction. It is noteworthy that cyclisation reactions involving nitrile groups produce various amino derivatives of benzonaphthyridines (*i.e.*, aza analogues of 9-aminoacridines) that present substantial interest for biological investigations.

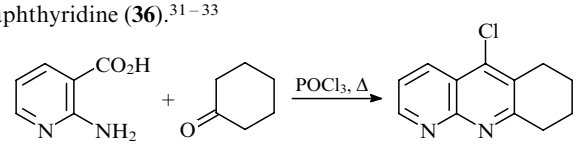
Heating of substituted anthranilic acids with *N*-alkyl- and *N*-arylpiperidin-4-ones in $POCl_3$ gave 2-substituted 10-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **35**.[27–30]



35

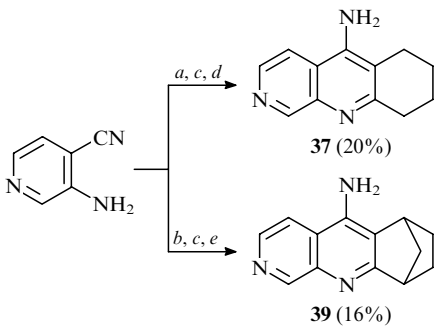
R^1 = H, Alk, NO_2, Hal; R^2 = Alk, Ar.

Analogously, heating of 2-aminonicotinic acid with cyclohexanone and $POCl_3$ affords 5-chloro-6,7,8,9-tetrahydrobenzo[*b*][1,8]-naphthyridine (**36**).[31–33]



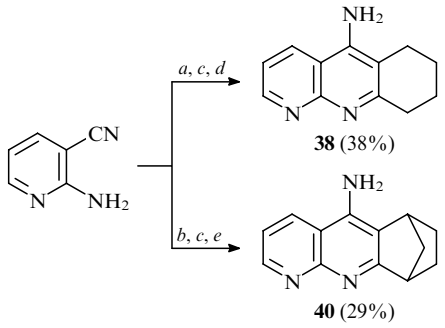
36 (86%)

The synthesis of aminobenzonaphthyridines by reactions of *vic*-aminonitriles with cyclic ketones is of importance because it provides an approach to tetrahydro derivatives of 9-aminoacridine (aza analogues of the pharmaceutical tacrine). Heating of the reactants with Lewis acids ($ZnCl_2$, $AlCl_3$, $TiCl_4$) affords complexes, which are decomposed by treatment with bases (NH_4OH, aqueous NaOH). Thus reactions of 3-amino-4-cyanopyridine and 2-amino-3-cyanopyridine with cyclohexanone and $TiCl_4$ in dichloroethane give the corresponding 5-amino-6,7,8,9-tetrahydrobenzo[*b*]naphthyridines **37** and **38**. The tetracyclic 1,7- and 1,8-naphthyridine derivatives **39** and **40** were successfully synthesised,



37 (20%)

39 (16%)

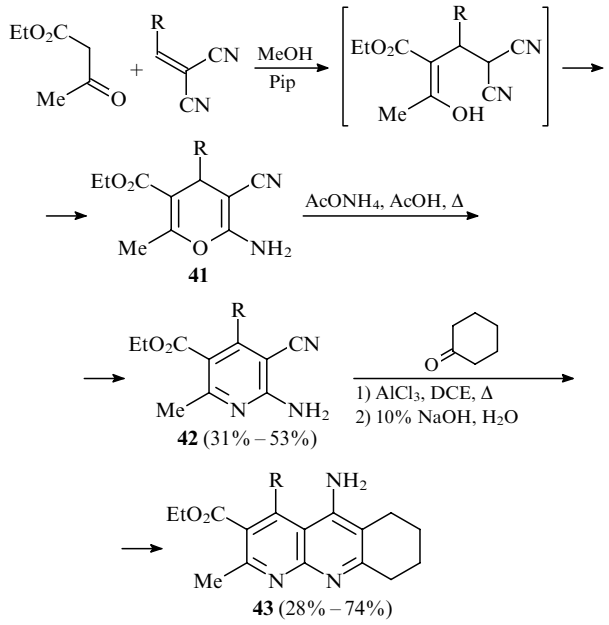


(*a*)  ; (*b*)  ; (*c*) $TiCl_4$, 1,2-dichloroethane (DCE);

(*d*) 5% NaOH, H_2O; (*e*) 15% NaOH, H_2O.

although in lower yields, by the reactions of these compounds with norcamphor, which has a more rigid (in comparison with cyclohexanone) carbon skeleton.[34]

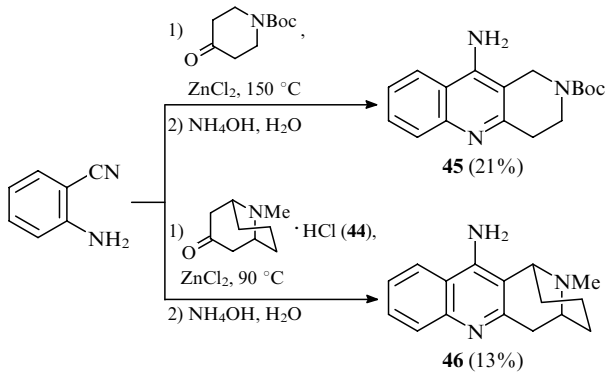
Pyrans **41** derived from ethyl acetoacetate and arylmethylidenemalononitriles underwent recyclisation under the action of ammonium acetate in acetic acid to yield the pyridine derivatives **42**. The resulting compounds containing cyano and amino groups in *vic* positions are involved in cyclocondensation with cyclohexanone in refluxing dichloroethane in the presence of $AlCl_3$ to give the tricyclic 1,8-naphthyridine derivatives **43**.[35,36]



R = Ph, C_6H_4OMe-4, C_6H_4OMe-3, $C_6H_3(OMe)_2$-3,4, C_6H_4F-4, C_6H_4Cl-4, $C_6H_4NO_2$-3.

Cyclocondensation of 2-amino-4,6-diarylnicotinonitriles with cyclohexanone in the presence of $ZnCl_2$ gave 10-amino-1,3-diaryl-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridines in 57% – 65% yields.[37]

In the presence of $ZnCl_2$, anthranilonitrile reacts with cyclic ketones, such as 1-*tert*-butoxycarbonylpiperidin-4-one and pseudopelletierine hydrochloride (**44**), to give the corresponding 1,6-naphthyridine derivatives **45** and **46**.[26,30]



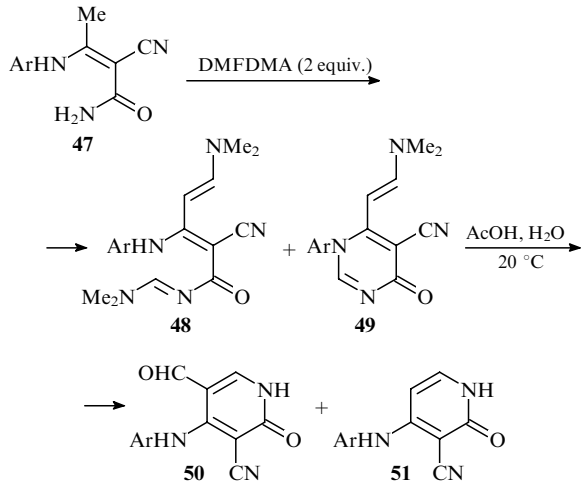
Boc = CO_2Bu^t.

2. Cyclisation of arylaminopyridines

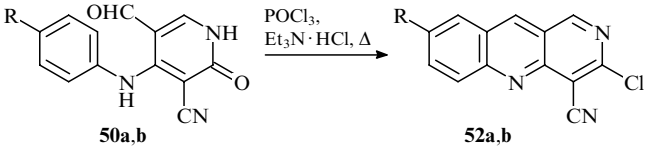
An efficient approach to the design of the benzonaphthyridine system is based on the synthesis involving arylaminopyridines whose aryl rings (less frequently, the pyridine ring) contain a group capable of providing intramolecular cyclisation. Arylaminopyridines are usually prepared by the replacement of good leaving groups in pyridine derivatives with arylamines as well as by the Ullman reaction.

a. Cyclisation involving carbonyl groups of aldehydes, ketones and esters

N,*N*-Dimethylformamide dimethyl acetal (DMFDMA) reacts with *N*-aryleneamines **47** involving both the amide and reactive methyl groups to give mixtures of dieneamidine **48** and 1-arylpyrimidinones **49**.[38] Because of low stability of dieneamidines **48**, the resulting mixtures are subjected to acid hydrolysis in aqueous AcOH without separation; this resulted in mixtures of the corresponding formylpyridones **50** and pyridones **51**. The former can be easily isolated due to their lower solubility. Special studies have demonstrated that formylpyridones can be produced only from dieneamidines **48**, whereas hydrolysis of pyrimidinones **49** yields exclusively pyridones **51**.

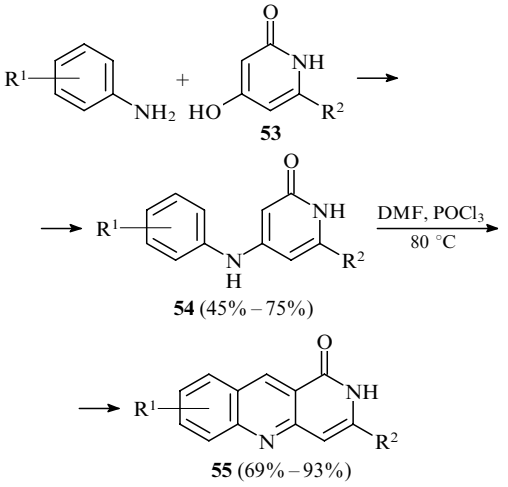


Cyclisation of 4-arylamino-3-cyano-5-formylpyridones **50a,b** under the action of $POCl_3$ in the presence of $Et_3N \cdot HCl$ afforded 3-chloro derivatives of benzo[*b*][1,6]naphthyridine **52a**,**b**.[38,39]



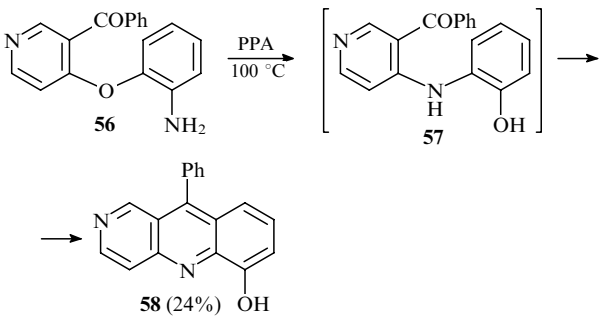
R = H (**a**), Me (**b**).

The reactions of arylamines with pyridones **53** give the corresponding 4-arylaminopyridones **54**. This reactions can be performed in the presence of the corresponding arylamine hydrochloride.[40,41] Compounds **54** undergo regioselective formylation at position 3 activated by the arylamino group followed by cyclisation to give the corresponding benzo[*b*][1,6]naphthyridines **55** substituted in the benzene ring and at position 3.[40,42]

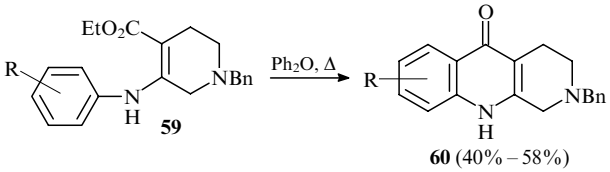


R^1 = H, 3-Cl, 3-OMe, 2,5-Me_2; R^2 = H, Me.

4-(2-Aminophenoxy)-3-benzoylpyridine (**56**) is unstable in both the solid state and in solution and is gradually isomerised into anilinopyridine **57** as a result of the O → N-Smiles rearrangement.[43] Heating of compound **56** in PPA leads to the rearrangement and subsequent cyclisation to give 6-hydroxy-10-phenylbenzo[*b*][1,6]naphthyridine (**58**).[44]



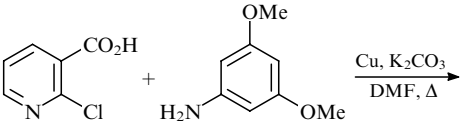
Heating of compounds **59** in diphenyl ether leads to its cyclisation to form benzo[*b*][1,7]naphthyridines **60**.[45]

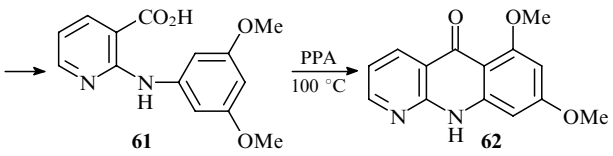


R = 2-Cl (**59**), 4-OMe (**59**); 6-Cl (**60**), 8-OMe (**60**).

b. Cyclisation involving the carboxy group

The Ullman reaction was used in the synthesis of 2-(3,5-dimethoxyphenyl)aminonicotinic acid (**61**), which underwent cyclisation to form benzo[*b*][1,8]naphthyridinone **62** as a result of heating in PPA.[46]

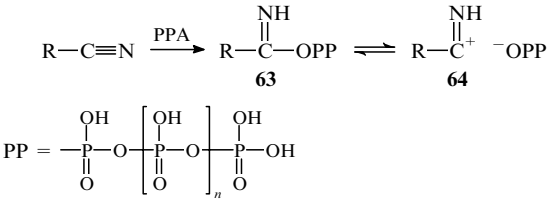




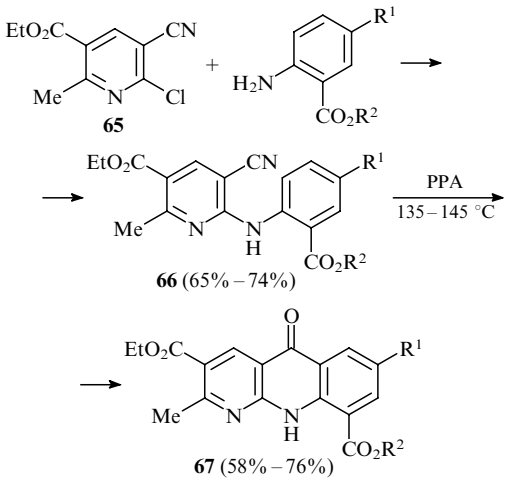
Other benzo[*b*][1,8]naphthyridinone derivatives were prepared analogously from arylaminonicotinic acids.[47,48]

c. Cyclisation involving the nitrile group

Heating of starting compounds with strong acids is one of the most efficient procedures for the closure of the pyridine ring involving the nitrile group. Thus PPA can add to the nitrile group to give compounds **63**.[49] The latter can exist in equilibrium with iminocarbenium ions **64**, which are much more electrophilic than the starting imidoyl polyphosphates **63**.[50]



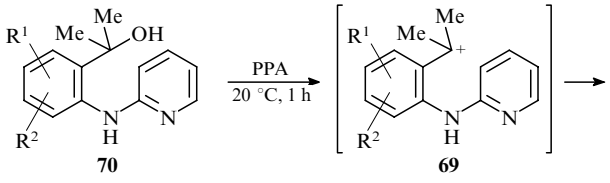
Concentrated H_2SO_4 and H_3PO_4 capable of activating the nitrile group through protonation can be used instead of PPA. However, the disadvantage of the use of PPA and H_2SO_4 is that protonated amino derivatives produced upon cyclisation often undergo hydrolysis to give the corresponding oxo derivatives. Thus the reaction of substituted 2-chloro-3-cyanopyridine **65** with arylamines gives the corresponding 2-arylamino-3-cyanopyridines **66**. Heating of the latter in PPA leads to their cyclisation to form benzo[*b*][1,8]naphthyridinones **67**.[51]

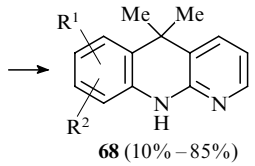


R^1 = H, Me; R^2 = H, Me, Et.

d. Cyclisation involving carbocations

5,10-Dihydro-5,5-dimethylbenzo[*b*][1,8]naphthyridine derivatives (**68**) were prepared by intramolecular cyclisation of the carbocations **69** generated *in situ* from alcohols **70** under the action of PPA.[52]





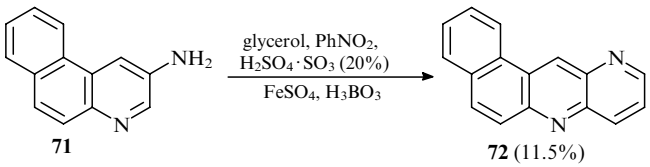
68 (10% – 85%)

R^1 = H, Hal, OMe, OEt; R^2 = H, Cl, Me.

3. Annulation of the pyridine ring to the quinoline system

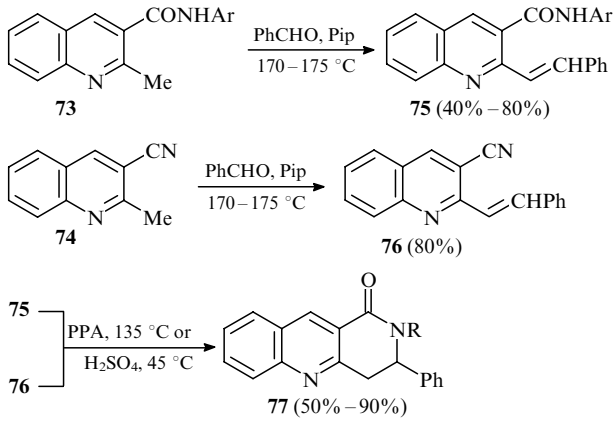
Annulation of the pyridine ring to substituted quinolines can be used as an alternative approach to the design of the benzonaphthyridine system.

Benzonaphthyridines can be prepared by the Skraup synthesis.[53] Thus annulated benzonaphthyridine **72** was synthesised starting from 2-aminobenzo[*f*]quinoline **71**. This reaction was carried out in the presence of an oxidant (nitrobenzenesulfonic acid) formed *in situ* upon the reaction of nitrobenzene with oleum.[54]



71 **72** (11.5%)

N-Arylamides (**73**) and nitriles (**74**) of 2-methylquinoline-3-carboxylic acid reacted with aromatic aldehydes on heating in *p*-xylene in the presence of piperidine as a base.[55, 56] The β-arylvinyl derivatives **75** and **76** formed upon heating in PPA underwent cyclisation to form 3-phenyl-1-oxo-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines **77**.[55, 56]



73 **75** (40% – 80%)

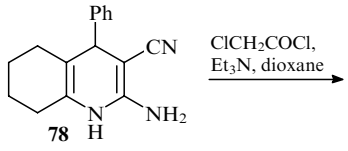
74 **76** (80%)

75 / **76** **77** (50% – 90%)

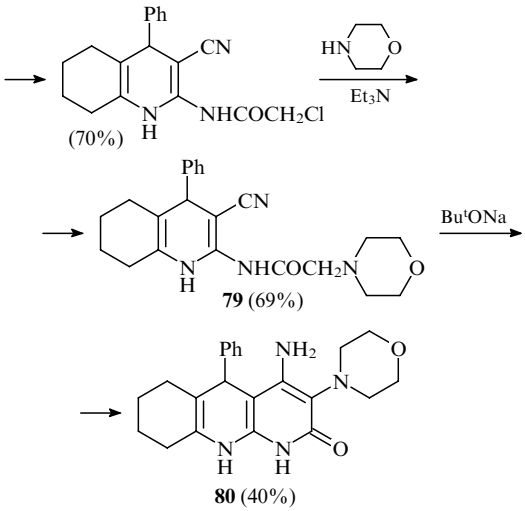
R = Ar, H.

Analogous cyclisation of 8-benzylidene-2-styryl-5,6,7,8-tetrahydroquinoline-3-carboxanilide giving rise to 6-benzylidene-2,3-diphenyl-1-oxo-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine was performed by heating in PPA (80% – 84% P_2O_5) at 135 °C.[57]

Acylation of 2-amino-3-cyanohexahydroquinoline (**78**) with chloroacetyl chloride followed by the reaction with morpholine affords the morpholinoacetyl derivative **79**. Cyclisation of the latter under the action of sodium *tert*-butoxide yields benzo[*b*][1,8]naphthyridinone **80**.[58]

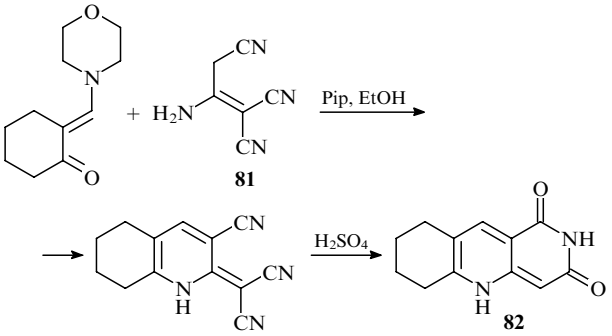


78



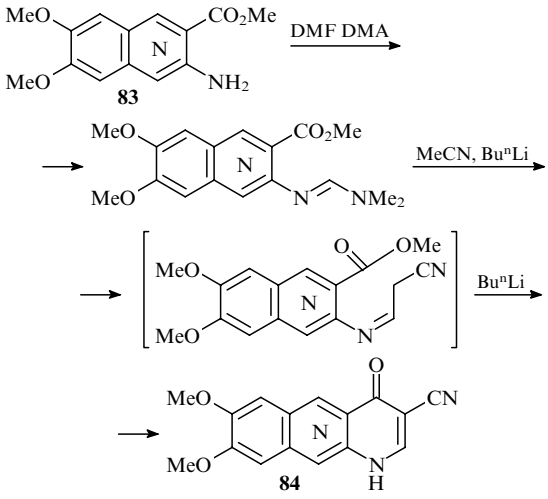
(70%) **79** (69%) **80** (40%)

The piperidine-catalysed reaction of morpholinomethylenecyclohexanone with the malononitrile dimer **81** and subsequent heating of the product in concentrated H_2SO_4 gave the benzo[*b*][1,6]naphthyridine derivative **82**.[59]



81 **82**

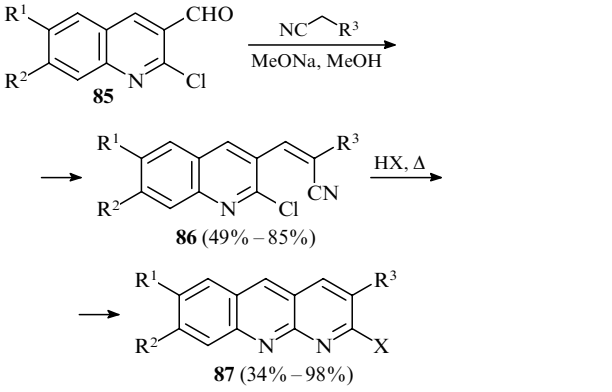
Dimethoxyquinolines **83** containing the *vic*-amino and methoxycarbonyl groups were transformed into benzo[*b*][1,5]- and benzo[*b*][1,8]naphthyridinone derivatives **84** in two steps. The reactions of quinolines **83** with the DMF acetal gave amidines whose reactions with acetonitrile and n-butyllithium include nucleophilic substitution of the dimethylamino group for the acetonitrile anion and the Thorpe – Ziegler cyclisation. Butyllithium acted as a base abstracting the proton from the reactive methylene group and thus providing the closure of the pyridine ring.[60]



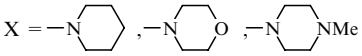
83 **84**

Condensation of 2-chloro-3-formylquinolines **85** with substituted acetonitriles in MeOH in the presence of MeONa yields the 2-chloro-3-cyanovinyl derivatives **86**.[61] The latter react with

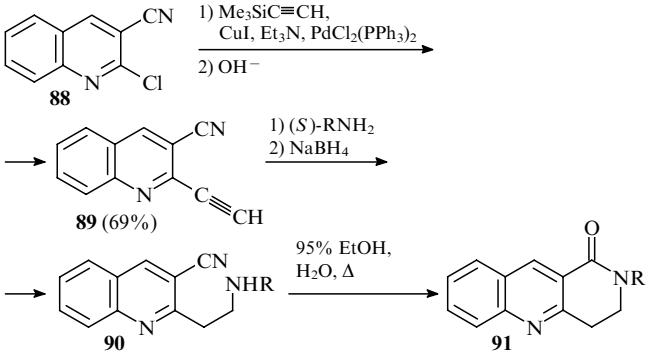
secondary amines resulting in smooth cyclisation giving rise to the 2-aminobenzo[*b*][1,8]naphthyridine derivatives **87**.



$R^1 = R^2 = H$, OMe; $R^3 = C_6H_4Cl$-4, SC_6H_4Cl-4;

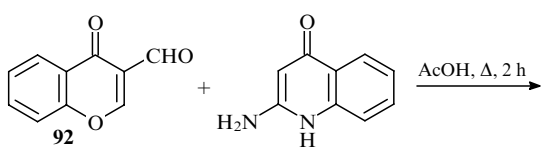
X = 

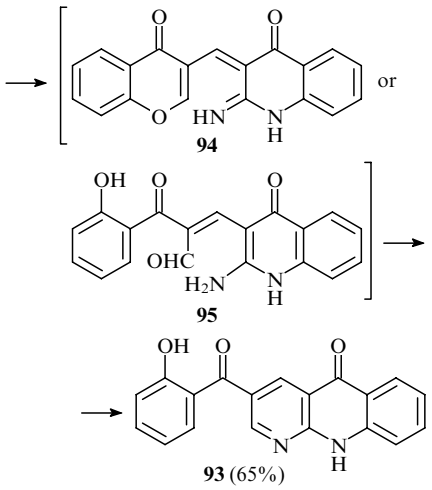
2-Chloro-3-cyanoquinoline (**88**) and trimethylsilylacetylene are involved in the Sonogashira reaction catalysed by Pd^0 that is generated from $PdCl_2(PPh_3)_2$ during the reaction. Subsequent elimination of the trimethylsilyl group in an alkaline medium gives rise to 3-cyano-2-ethynylquinoline **89**. The addition of (*S*)-phenylalaninol to the latter compounds and subsequent reduction of the double bond yield the amine **90**, whose refluxing in aqueous ethanol results in intramolecular cyclisation at the nitrile group and hydrolysis to give lactam **91** (the yield over two steps is 52%).[62]



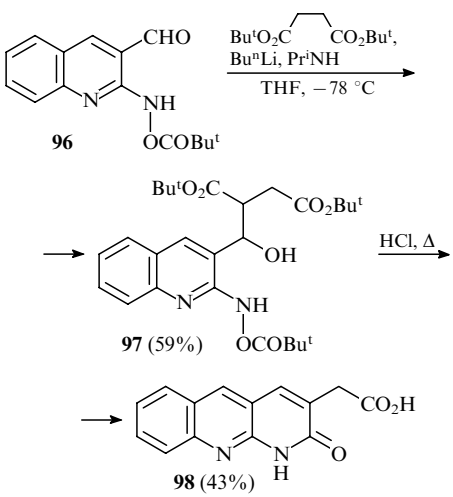
R = $CH(CH_2OH)CH_2Ph$.

3-Formylchromone (**92**) containing three electrophilic centres, *viz*., C(2), C(4) and CHO, reacts with 2-amino-1*H*-quinolin-4-one to give benzo[*b*][1,8]naphthyridinone **93**.[63] It is suggested [63] that 2-aminoquinolin-4-one in which position 3 is activated by the electron-donating amino group similarly to the β-position in enamines can undergo condensation at both the aldehyde group (which seems to be a more preferable route) and the C(2) atom of chromone **92** to give the intermediates **94** or **95**, respectively. In both cases, cyclisation of the addition products **94** and **95** gives benzonaphthyridinone **93**.[63]

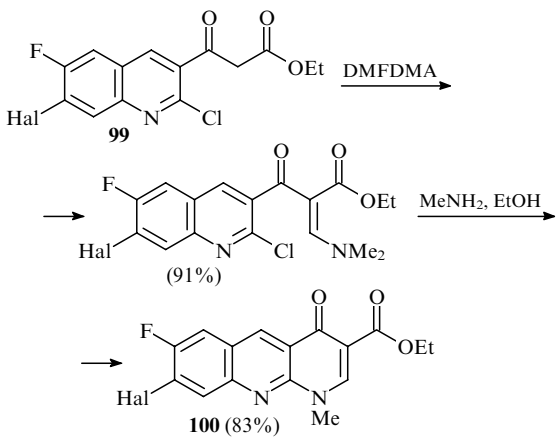




Condensation of compound **96** with di-*tert*-butyl succinate in the presence of Bu^nLi yields a mixture of the corresponding diastereomeric alcohols **97** in 59% yield. Refluxing of these alcohols with HCl in dioxane leads to elimination of the protective *tert*-butyloxycarbonyl group and cyclisation to form 3-carboxymethylbenzonaphthyridine **98**.[64]



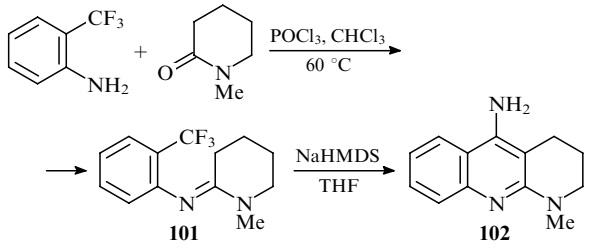
Condensation of compounds **99** with dimethylformamide dimethyl acetal gave enamine. Transamination of the latter with methylamine resulted in the replacement of chlorine at position 2 of the quinoline ring and cyclisation to form the benzo[*b*][1,8]-naphthyridine derivative **100**.[65–67]



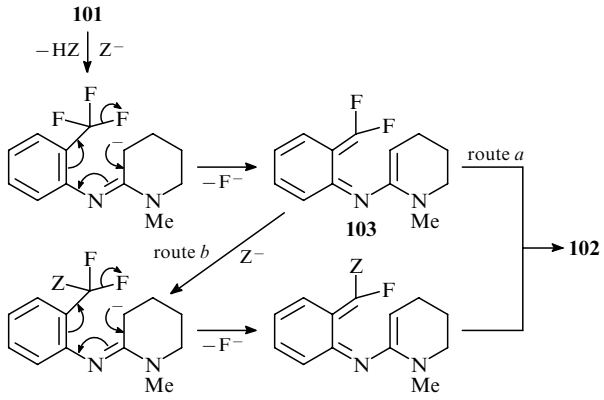
4. Syntheses involving *ortho*-quinomethane intermediates

Syntheses of heterocycles involving intermediates having *o*-quinomethane or *o*-quinomethane imide structures (hereinafter referred to as quinomethanes) offer an original approach to the design of the benzonaphthyridine system. The literature term azaxylylenes is, in our opinion, inappropriate as a synonym for *o*-quinomethane imides.

Amidine **101**, which was prepared by the reaction of 2-trifluoromethylaniline and the *N*-methylpiperidin-2-one complex with $POCl_3$, reacted with sodium hexamethyldisilazide (NaHMDS) to give the tricyclic product **102**.[68]

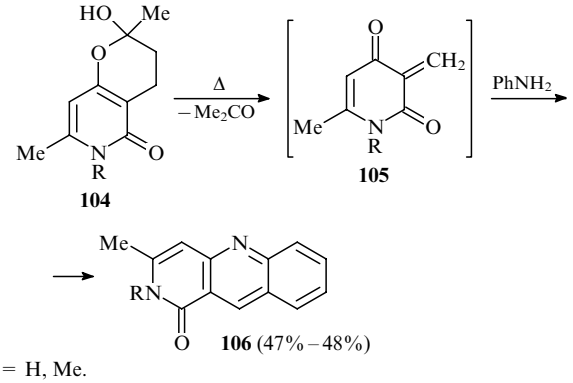


In terms of the cyclisation mechanism proposed in,[68] the anion formed as a result of proton abstraction from amidine **101** under the action of a base loses the fluoride anion to give quinomethane **103**. Its cyclisation giving rise to the target tricyclic product **102** can occur by two different pathways: (*a*) through the electrocyclic reaction with subsequent nucleophilic substitution of fluorine for the amino group followed by aromatisation and elimination of HF; (*b*) through the addition of the Z^- anion and elimination of the fluoride anion to give the target product **102**.



$Z^- = {}^-N(SiMe_3)_2$.

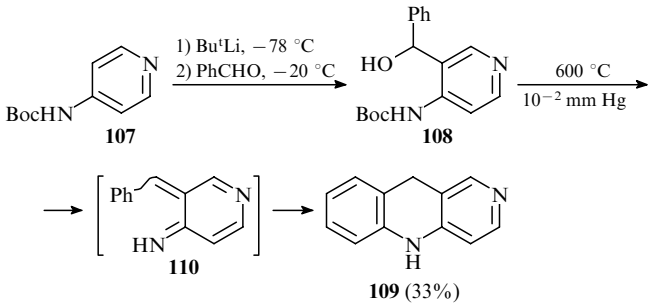
Hemiacetals **104** derived from the corresponding 4-hydroxypyridin-2-ones can be used as a source of quinomethanes.[69,70] Heating of hemiacetals **104** leads to elimination of acetone to form quinomethane intermediates **105**, which react with aniline to give the tricyclic products **106**.



R = H, Me.

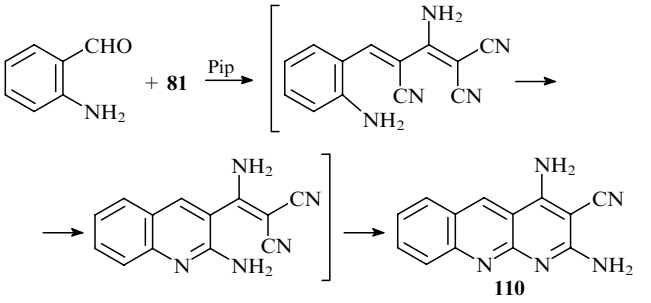
Tetracyclic derivatives of 1,6-naphthyridine were synthesised with the use of hemiacetals derived from 3-hydroxyquinolones as a source of quinomethanes. Elimination of acetone in this reaction was confirmed by the formation of the corresponding 2,4-dinitrophenylhydrazone.

Directed *ortho*-lithiation of 4-*tert*-butoxycarbonylaminopyridine (**107**) and subsequent reactions of the lithium derivative with aldehydes yield alcohol **108**, which is further transformed into the benzo[*b*][1,6]naphthyridine derivative **109** by flash vacuum pyrolysis (FVP). Apparently, quinomethane intermediate **110** is involved in the formation of tricyclic product **109**.[71]

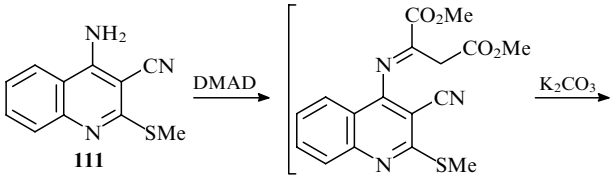


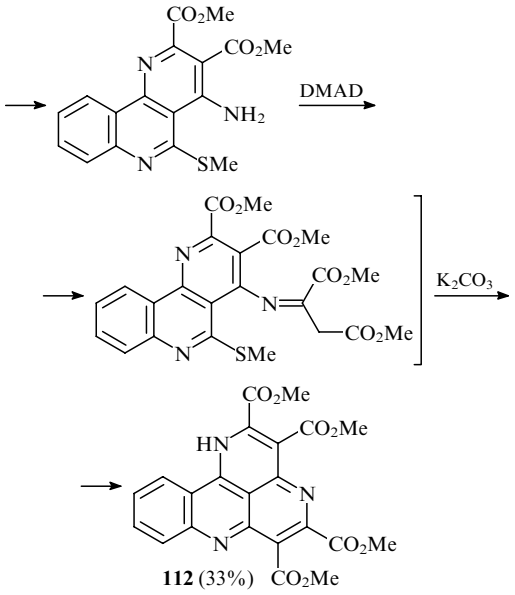
5. Domino reactions

Domino reactions involve two or more transformations giving rise to new bonds (as a rule, C−C bonds). These reactions proceed under identical conditions without the addition of supplementary reagents or catalysts. Noteworthy, each subsequent reaction is triggered by a functional group generated in the previous step.[72] Only a few examples of the synthesis of benzonaphthyridines by domino reactions are known. Thus the piperidine-catalysed reaction of 2-aminobenzaldehyde with the malononitrile dimer **81** gives 1,3-diamino-2-cyanobenzo[*b*][1,8]naphthyridine (**110**).[73]



4-Amino-3-cyano-2-methylthioquinoline (**111**) reacts with two molecules of dimethyl acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 or $K_3PO_4 \cdot H_2O$ to give tetramethyl 1*H*-quinolino[2,3,4-*de*][1,6]naphthyridine-2,3,5,6-tetracarboxylate (**112**).[74] The mechanism of this reaction can be presented as follows: the addition of DMAD to the amino group, proton abstraction from the activated methylene group under the action of a base and, finally, cyclisation involving the nitrile group. The addition of the second DMAD molecule to the amino group of the naphthyridine derivative thus formed is followed by cyclisation involving the activated methylene group and the replacement of the good leaving group MeS.

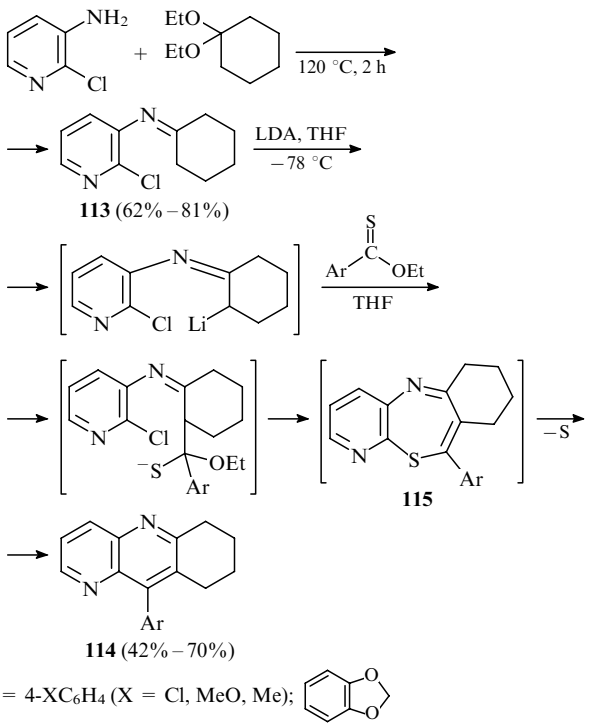




6. Other transformations of heterocycles producing benzo[*b*]naphthyridines

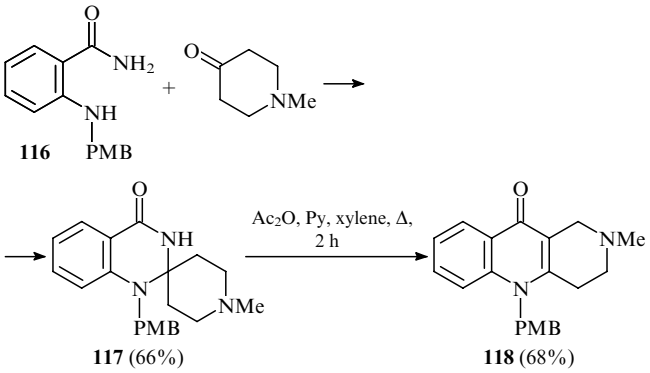
The synthesis of benzonaphthyridine derivatives by recyclisation of other heterocyclic systems is an efficient approach to the synthesis of compounds many of which are otherwise inaccessible.

The ability of 8π-electron systems containing divalent sulfur to be transformed into more stable aromatic compounds in the course of thermal rearragement accompanied by the removal of sulfur from the ring is well known.[75] This principle underlies the synthesis of benzo[*b*][1,5]naphthyridine derivatives generated *in situ* from the corresponding fused 1,4-thiazepines. Thus the reaction of 3-amino-2-chloropyridine with cyclohexanone diethyl ketal gives imine **113**. Lithiation of the latter with lithium diisopropylamide (LDA) and subsequent treatment with ArC(S)OEt afford 10-aryl-6,7,8,9-tetrahydrobenzo[*b*][1,5]naphthyridines **114**. In all probability, this reaction entails sequential addition of the lithiated imine to ArC(S)OEt, closure of the 1,4-thiazepine ring and extrusion of sulfur from the 8π-electron system of the intermediate **115** giving finally benzonaphthyridines **114**.[76] Apparently, this approach can be used in the synthesis of both 1,5-naphthyridines and other isomers.

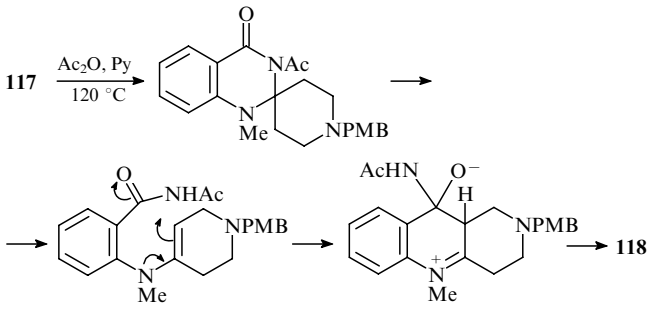


Ar = 4-XC$_6$H$_4$ (X = Cl, MeO, Me);

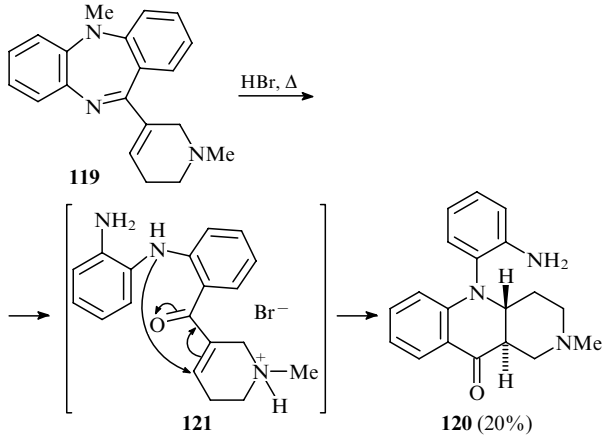
The reaction of *N*-(4-methoxybenzyl)anthranilamide (**116**) with *N*-methylpiperidin-4-one yielded spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolinone)] (**117**), whose refluxing with acetic anhydride and pyridine in xylene led to recyclisation to form benzonaphthyridine **118**.[77]



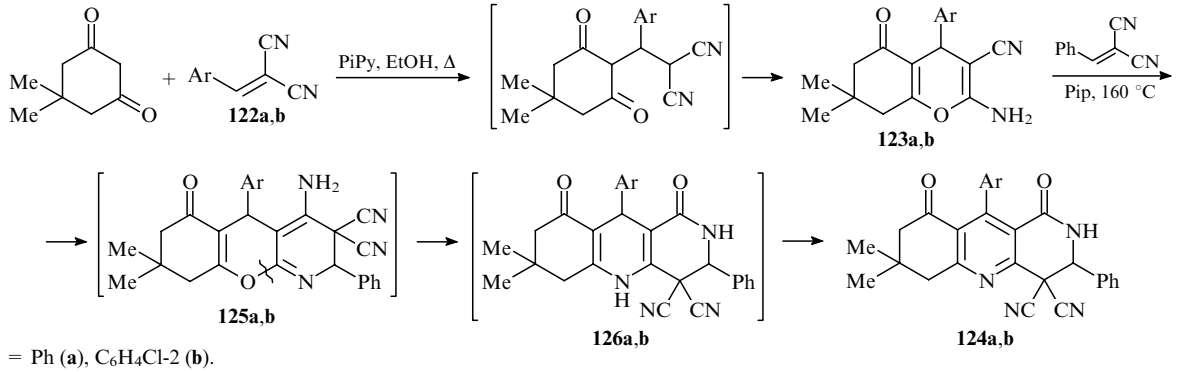
Earlier study has shown[78] that *N*(3)-substituted and *N*(1),*N*(3)-disubstituted spiro compounds that are structurally similar to quinazoline **117** do not react under these conditions. At the same time, the spiro compound in which both atoms in the quinazoline ring are devoid of substituents was transformed into quinazolone. The benzonaphthyridine structure was prepared exclusively from *N*(1)-substituted compounds.[78] Based on these findings, a mechanism for the rearrangement of compounds **117** into **118** has been proposed. Its first step involves acylation of the lactam NH group.



Heating of diazepine **119** in 40% HBr leads to demethylation along with recyclisation to give benzo[*b*][1,6]naphthyridinone **120**. It may be assumed that hydrolytic cleavage of the diazepine ring in acidic media affords the intermediate **121** which contains an α,β-



Scheme 1

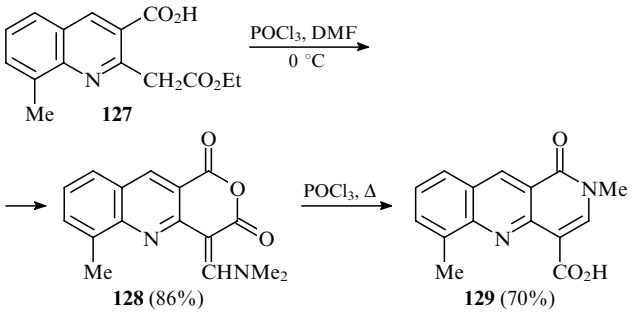


Ar = Ph (**a**), C_6H_4Cl-2 (**b**).

unsaturated ketone fragment. This compound is transformed into the *trans*-isomer **120** through the intramolecular Michael addition involving the NH group and the β-carbon atom of the acryloyl fragment.[79]

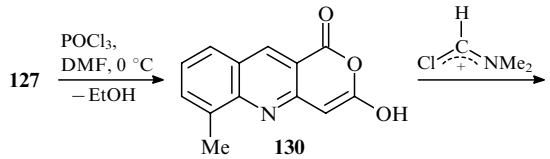
Arylmethylidenemalononitriles **122a**,**b** react with dimedone to give Michael addition products which undergo spontaneous cyclisation to form 4*H*-pyrans **123a**,**b**. Reactions of the latter with benzylidenemalononitrile in the presence of catalytic amounts of piperidine at 160 °C afforded benzonaphthyridines **124a**,**b**.[80] In the authors' opinion, this reaction proceeds *via* the intermediate formation of compounds **125a**,**b** and **126a**,**b**. An analogous rearrangement concomitant with the formation of 1,6-naphthyridine derivatives has been reported.[81] It is noteworthy that this reaction is accompanied by aromatisation of the 1,4-dihydropyridine fragment (Scheme 1).

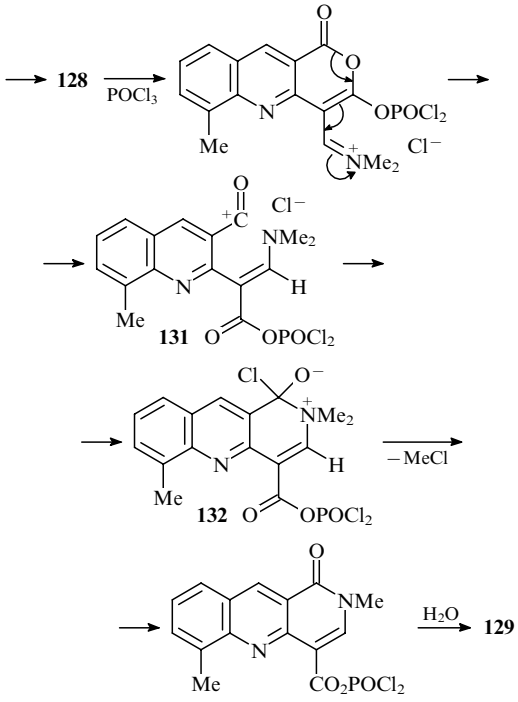
Ethyl (3-carboxy-8-methylquinolin-2-yl)acetate (**127**) undergoes cyclisation to form 4-dimethylaminomethylidene-6-methyl-4*H*-pyrano[4,3-*b*]quinoline-1,3-dione (**128**) by the Vilsmeier reaction. Heating of the latter with $POCl_3$ results in its transformation into 1,2-dihydro-2,6-dimethyl-1-oxo-benzo[*b*][1,6]naphthyridine-4-carboxylic acid (**129**).[82]



128 (86%) **129** (70%)

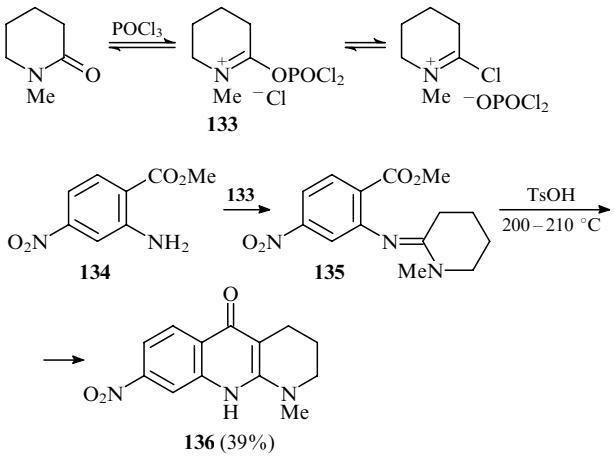
An analogous $POCl_3$-induced transformation has been described for homophthalic acid and its methyl ester.[83] Based on these data, the following reaction mechanism for the synthesis of benzonaphthyridine **129** can be proposed. Cyclisation of dicarboxylic acid **127** into anhydride **130** is followed by electrophilic addition of the Vilsmeier reagent to form enamino anhydride **128**. *o*-Acylation of the latter with $POCl_3$ and cleavage of the C–O bond yield the acylium cation **131**, which can undergo cyclisation involving the dimethylamino group to give the intermediate **132**. Subsequent elimination of MeCl and hydrolysis afford benzonaphthyridine **129**.





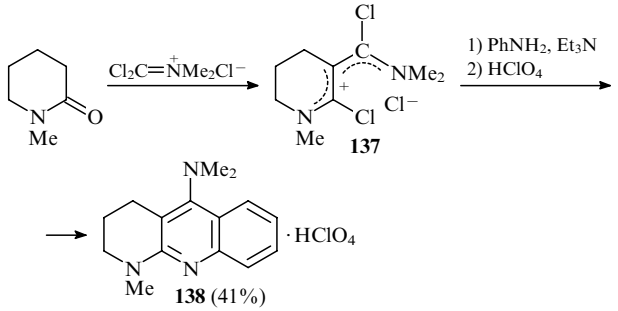
7. Other methods

The reaction of the *N*-methylpiperidin-2-one–$POCl_3$ complex (**133**) with the methyl 4-nitroanthranilate (**134**) gives amidine **135**. Heating of the latter in the presence of TsOH results in cyclisation to form benzonaphthyridinone **136**. Analogous cyclisation takes place in the Friedlander reaction.[84]

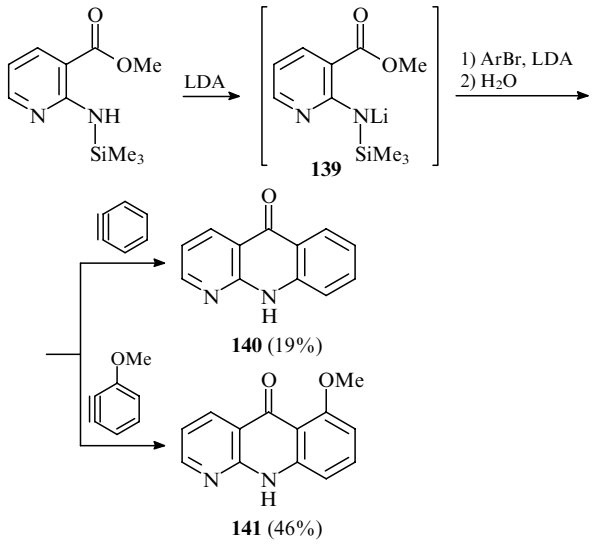


The addition of *N*,*N*-dimethyldichloromethyleneimmonium chloride to *N*-methylpiperidin-2-one gives the salt **137**. The reaction of the latter with aniline proceeds selectively and is

accompanied by the replacement of chlorine at the C(2) atom followed by cyclisation to form benzonaphthyridine **138**.[85,86]

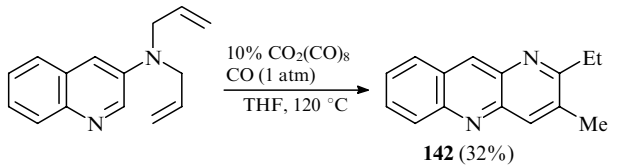


A procedure for the synthesis of benzonaphthyridines based on cycloaddition of arynes to 1,4-dipolar compounds was developed. The *N*-lithium derivative of methyl 2-(trimethylsilylamino)-nicotinate **139** reacts with dehydrobenzene, which is generated *in situ* from bromobenzene in the presence of a base, under mild conditions to give benzo[*b*][1,8]naphthyridinone **140**. 6-Methoxybenzonaphthyridinone **141** was isolated as the only product from 3-methoxydehydrobenzene derived from 3-bromoanisole.[87] High regioselectivity of this reaction testifies that the process occurs by a concerted mechanism.[88]

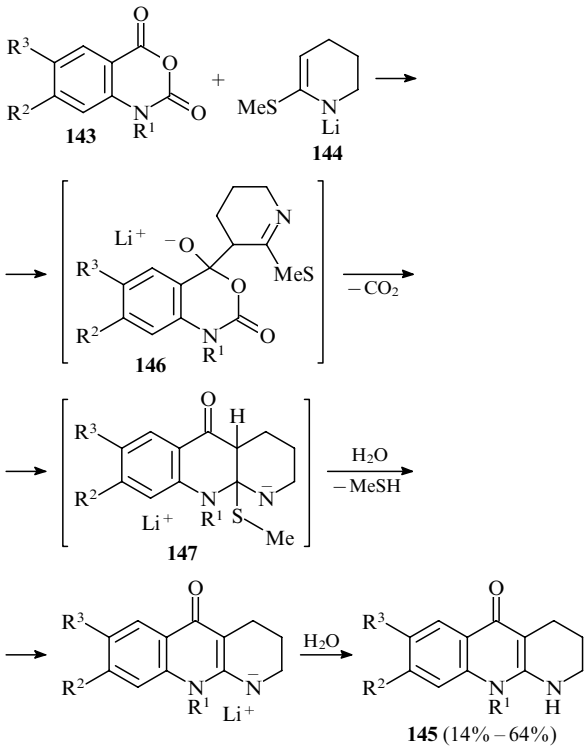


Ar = Ph, $MeOC_6H_4Br$-3.

The conversion of 3-(*N*,*N*-diallylamino)quinoline into the benzo[*b*][1,5]naphthyridine derivative **142** was carried out under a CO atmosphere using $Co_2(CO)_8$ as a catalyst. Analogously, *N*,*N*-diallylaniline is transformed under the action of CO and $Co_2(CO)_8$, the mechanism of transfer of the allylic groups between the substrate molecules being confirmed for this process.[89]

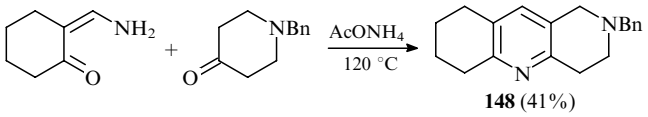


The reaction of *N*-alkylisatic anhydrides **143** with the lithium derivative of enamine **144** was used for the preparation of benzo[*b*][1,8]naphthyridinones **145**.[90] Presumably, the addition of enamine **144** to the C(4)-carbonyl group of isatic anhydride derivatives gives the intermediates **146**, which can be further transformed into the tricyclic derivatives **147** with elimination of the CO_2 molecule. After elimination of MeSH, these compounds are transformed into benzonaphthyridinones **145**.[90]

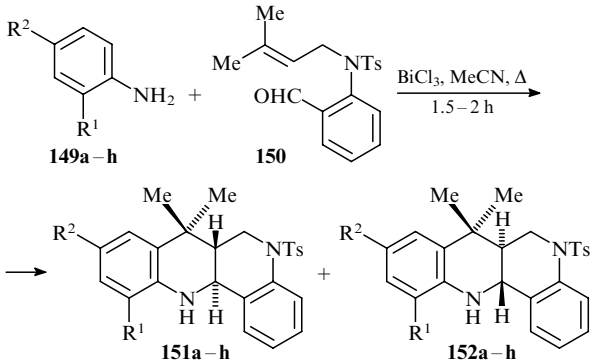


R^1 = Me, Bn; R^2 = H, Cl; R^3 = H, Me.

1,2,3,4,6,7,8,9-Octahydrobenzo[*b*][1,6]naphthyridine (**148**) was synthesised starting from 2-aminomethylidenecyclohexanone, 1-benzylpiperidin-4-one and ammonium acetate.[13]



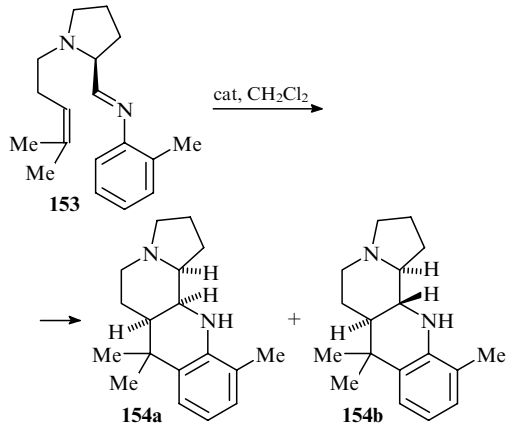
A procedure was proposed for the synthesis of dibenzo[*b*,*h*]-[1,6]naphthyridines based on the $BiCl_3$-catalysed hetero-Diels–Alder reaction involving the aryl ring as a component of the diene system.[91] Cyclisation of aldimines generated *in situ* from anilines **149a–h** and the *N*-allylic derivative of *o*-aminobenzaldehyde **150** affords a mixture of the diastereomers **151a–h** and **152a–h** in a 1 : 1 ratio in 90%–96% yields.[92]



R^1 = R^2 = H (**a**); R^1 = Me, R^2 = H (**b**); R^1 = Br, R^2 = Me (**c**);
R^1 = H: R^2 = OMe (**d**), Cl (**e**), F (**f**), Me (**g**);
R^1 = OH, R^2 = H (**h**).

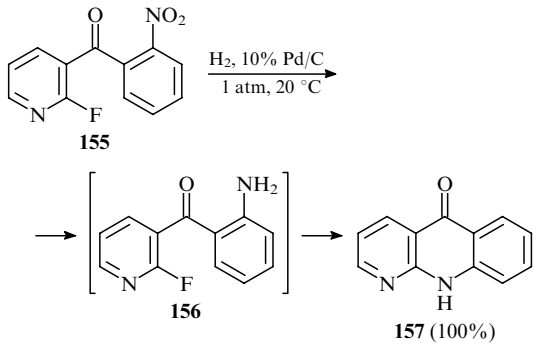
Cyclisation of (*S*)-*N*-(1-(4-methylpent-3-enyl)pyrrolidin-2-ylmethylidene)toluidine (**153**), which is catalysed by Lewis and Brönsted acids ($FeCl_3$, $SnCl_4$, $BF_3 \cdot Et_2O$, TsOH, CF_3CO_2H, $SnCl_4$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $MeAlCl_2$, Me_2AlCl), yields tetracyclic decahydro-7,7,4-trimethylindolizino[3,4-*b*]quinolines **154a**,**b** (79%–84% total yields). Only two out of four possible

isomers are formed under these conditions. The ratios of the isomeric products depend on the coordination number of the acidic catalyst. Monodentate Brönsted and Lewis acids as well as octahedral bidentate Lewis acids yield predominantly the *trans*,*trans*-product **154b**, whereas tetrahedral aluminium Lewis acids give the *cis*,*cis*-product **154a**.[93]

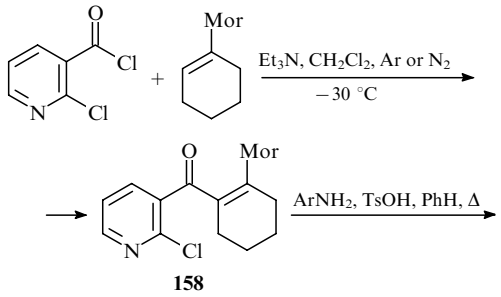


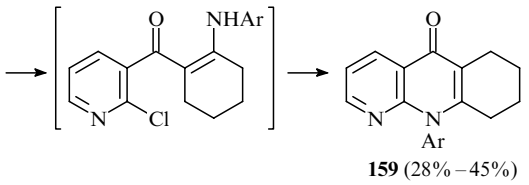
A stepwise mechanism involving the imino group was proposed for cyclisation of compound **153**. Within the framework of this mechanism, complete inversion of the configuration occurs due to the presence of the nitrogen atom in the pyrrolidine ring capable of complex formation.[93]

Reduction of 2-fluoro-3-(2-nitrobenzoyl)pyridine (**155**) by hydrogen over Pd/C yields the amino derivative **156**, which undergoes spontaneous cyclisation to give benzonaphthyridinone **157**.[22]



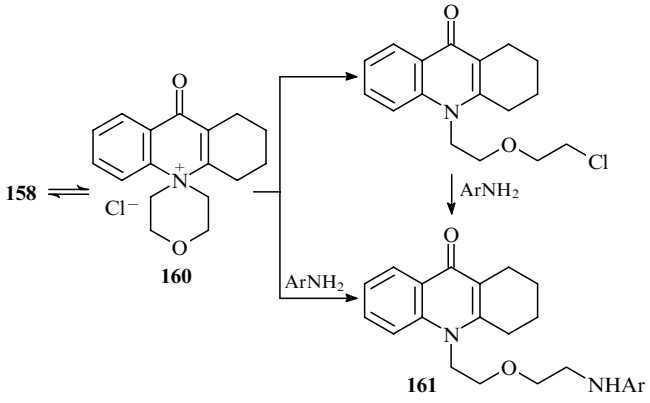
Addition of 2-chloronicotinoyl chloride to morpholinocyclohexene yields enamino ketone **158**, which is involved in the reactions with arylamines accompanied by cyclisation to form the 1,8-naphthyridine derivatives **159**.[94] It is of note that this process occurs both through transamination of the enamino ketone **158** with arylamine followed by cyclisation and replacement of chlorine at position 2 of the pyridine ring and through the primary replacement of chlorine by the arylamine fragment with subsequent intramolecular transamination and elimination of morpholine.





Mor is  ; Ar = XC_6H_4 (X = 3-MeO, 3-Cl, 2-Cl, 3-NO_2), 3-Py.

Moderate yields of the target products **159** are partly due to hydrolysis of enamines and a side process involving cyclisation of enamino ketone **158** to give the spiro intermediate **160**. Treatment of the latter with nucleophilic reagents eventually results in its conversion into the acridine derivatives **161** containing an *N*-alkyl substituent.[94]



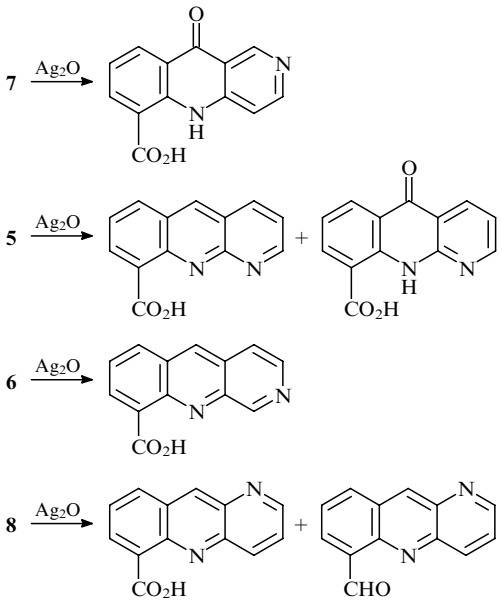
IV. Chemical properties

The chemical properties manifested by benzonaphthyridines are equally characteristic of acridine derivatives and the corresponding naphthyridines.

1. Oxidation and dehydrogenation

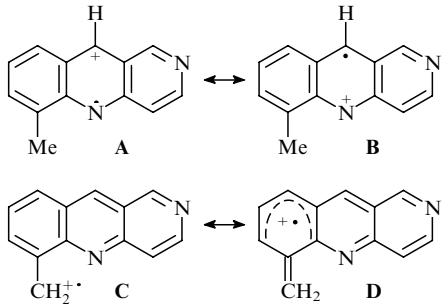
This section contains information concerning oxidation of benzonaphthyridines and their di- and tetrahydro derivatives that yields fully aromatic tricycles.

Four isomeric 6-methylbenzo[*b*]naphthyridines **5**–**8** were treated with a basic solution of silver oxide at 20 °C for 30 min. The structures of the reaction products were established by ^{1}H NMR spectroscopy. The processes associated with such



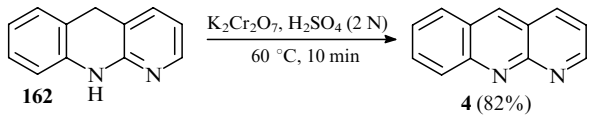
oxidation were found to depend on the structures of isomeric substrates. The methyl group can be oxidised to the formyl group (compound **8**) or the carboxy group (for all isomers).

The abilities of compounds **5**–**8** to be oxidised can be compared using oxidation at position 10 as a criterion. The reactivities of the isomeric compounds change in the following order: **7** (1.6) > **5** (1.8) > **6** (1.7) > **8** (1.5).[5] The difference in stability of the radical cations **A**–**D** generated upon oxidation of the isomeric compounds **5**–**8** can in principle be regarded as the determining factor.

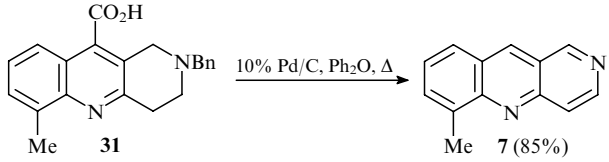


However, this experimental material is insufficient for adequate interpretation of the available data.[5] Therefore, in this review we simply cite the results of investigations.

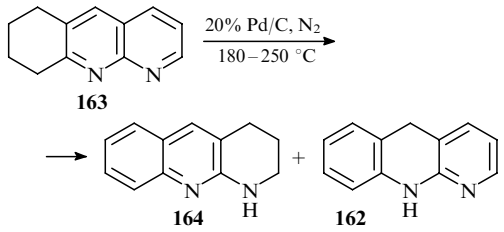
5,10-Dihydrobenzo[*b*][1,8]naphthyridine (**162**) is rapidly oxidised under the action of a chromic mixture to give benzo[*b*][1,8]-naphthyridine (**4**).[24]



Debenzylation, decarboxylation and dehydrogenation of benzonaphthyridine **31** were successfully combined by refluxing with 10% Pd over activated carbon in diphenyl ether.[24]

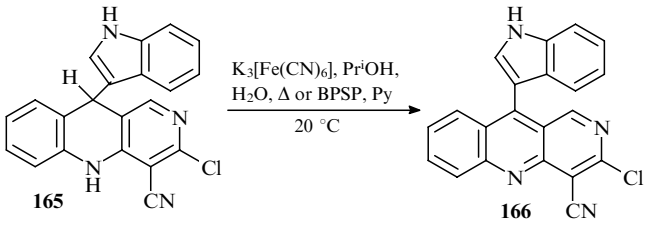


However, an attempt to perform dehydrogenation of 6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**163**) by heating over 20% Pd/C gave a mixture of compounds **164** and **162**. The product **162** was obtained as the major one at higher temperatures.[95]

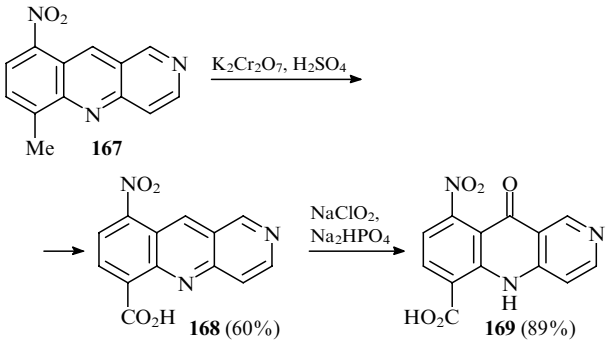


Dehydrogenation of 6-methyl-6,7,8,9-tetrahydrobenzo[*b*]-[1,5]naphthyridine achieved by heating with 10% Pd/C in biphenyl afforded a fully aromatic tricycle in 76% yield.[15]

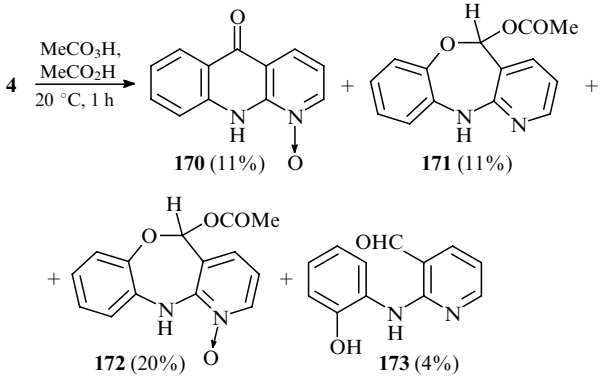
Potassium ferricyanide or bispyridine silver(I) permanganate (BPSP) was used as an oxidant for the transformation of 5,10-dihydrobenzo[*b*][1,6]naphthyridine **165** into the corresponding aromatic heterocycle **166**.[96]



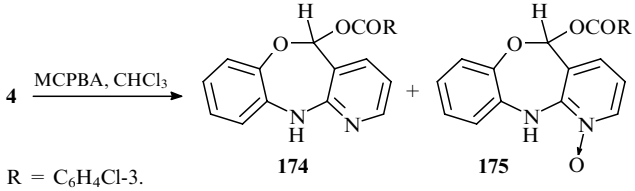
Oxidation of 6-methyl-9-nitrobenzo[*b*][1,6]naphthyridine (**167**) by a chromic mixture occurred at the methyl group without affecting position 10 and yields 9-nitrobenzo[*b*][1,6]naphthyridine-6-carboxylic acid (**168**). The latter was oxidised with sodium chlorite at 20 °C for 4 days to give the 10-oxo derivative **169**.[24]



Oxidation of benzonaphthyridines by peroxy acids is often accompanied by transformations of the heterocyclic system. Thus oxidation of benzo[*b*][1,8]naphthyridine (**4**) with peracetic acid occurred at the nitrogen atom of the peripheral pyridine ring to yield *N*-oxide **170**.[93] This was concomitant with competitive reactions yielding the oxazepine derivatives **171** and **172** and aldehyde **173**. The latter seems to be formed as a result of opening of the oxazepine ring in the compound **171**.[93] The reactions of 1,8-naphthyridine[97] and acridine[98] with peroxy acids were not accompanied by expansion of the pyridine ring to the oxazepine ring. However, oxidation of acridine by perbenzoic and *m*-chloroperbenzoic (MCPBA) acids yielded a mixture of acridine *N*-oxide and 2-(2-hydroxyanilino)benzaldehyde analogous to compound **173**.

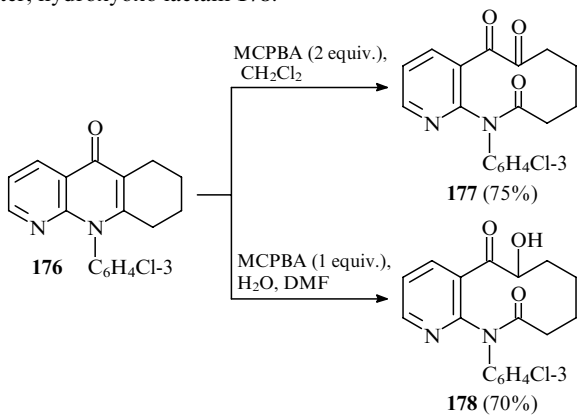


Oxidation of benzo[*b*][1,8]naphthyridine (**4**) by MCPBA gives a mixture of the products **174** and **175**; their ratio depends on the reaction temperature.

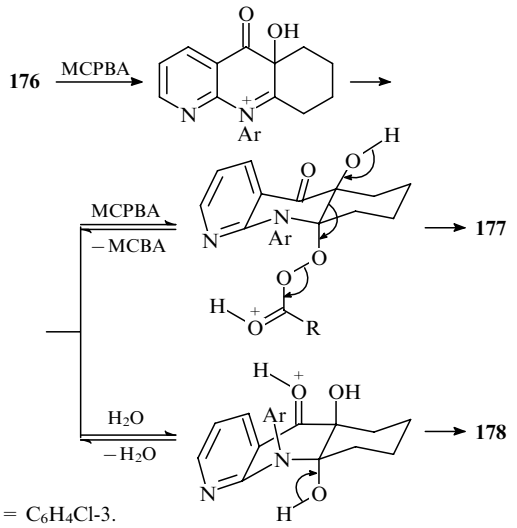


R = C_6H_4Cl-3.

Benzonaphthyridinone **176** is oxidised by MCPBA in non-aqueous media to give dioxo lactam **177** or, in the presence of water, hydroxyoxo lactam **178**.[99]

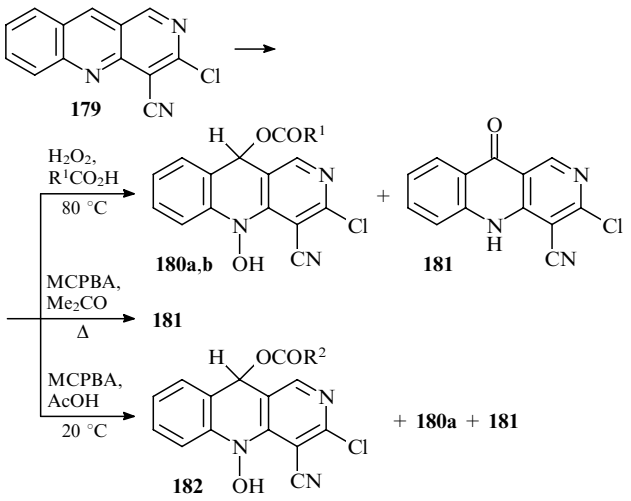


A mechanism for oxidative cleavage of benzonaphthyridinone **176** has been proposed that involves the formation of lactams **177** and **178** in the presence and absence of water.[99]



Ar = C_6H_4Cl-3.

Oxidation of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**179**) by hydrogen peroxide in acetic or propionic acid afforded the corresponding ethers **180a**,**b** and a small amount of the 10-oxo derivative **181**.[100] Oxidation of the compound **179** by MCPBA in aqueous AcOH at 20 °C gave the acyloxy derivative **182** and trace amounts of the products **180a** and **181**. This reaction performed in refluxing acetone gave the 10-oxo derivative **181** as the only product.[96]



R^1 = Me (**a**), Et (**b**); R^2 = C_6H_4Cl-3.

Most probably, the transformation of the starting compound **179** into the acyloxy derivatives **180a**,**b** and **182** under the action of MCPBA occurs *via* N(5)-oxidation (oxidation of the nitrogen atom in the peripheral pyridine ring is hindered due to the presence of electron-withdrawing substituents). The resulting N(5)-oxide intermediate readily add acyloxy anions and water to give the products **180a**,**b**, **181** and **182**.

The mechanisms of action of NADH-containing coenzymes in stereospecific biochemical reactions formed the basis of the biomimetic approach to the design of novel chiral NADH mimetic agents of the benzo[*b*][1,6]naphthyridine series. The derivatives **183a**–**f** (Table 2) were used for stereoselective reduction of the oxo groups of methyl mandelate and 2-benzoylpyridine.[101]

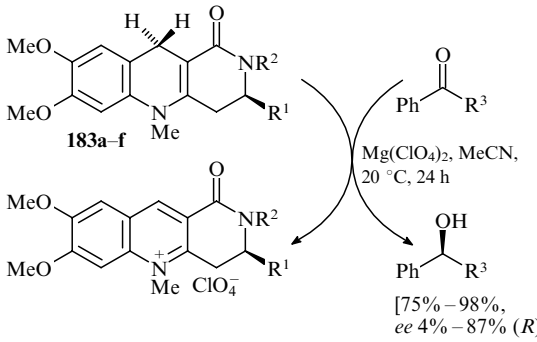
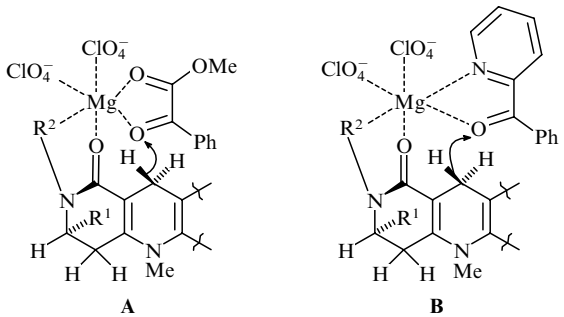


Table 2. Reduction of the oxo groups of methyl mandelate and 2-benzoylpyridine by compounds **183a**–**f**.[101]

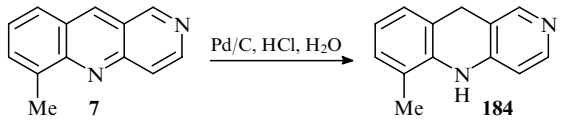
Reagent	R^1	R^2	R^3	Yield (%)	*ee* (R) (%)
183a	Me	Bn	CO_2Me	95	4
183b	Me	$(CH_2)_2OMe$	CO_2Me	98	71
183c	Me	$(CH_2)_3OH$	CO_2Me	90	81
183d	Me	$(CH_2)_2OH$	CO_2Me	81	86
183e	Ph	$(CH_2)_2OH$	CO_2Me	90	84
183f	Me	$(CH_2)_2PO(OEt)_2$	CO_2Me	91	87
183b	Me	$(CH_2)_2OMe$	2-Py	90	30
183c	Me	$(CH_2)_3OH$	2-Py	95	84
183d	Me	$(CH_2)_2OH$	2-Py	85	35

The data listed in Table 2 suggest that the compounds **183f** (*ee* 87%) and **183c** (*ee* 84%) are stereoselective reagents of choice for reduction of methyl mandelate and 2-benzoylpyridine, respectively. Both reactions were carried out in the presence of $Mg(ClO_4)_2$, which is thought to be involved in the formation of the triple **183a**–**f**–Mg^{2+}–substrate complexes (**A** and **B**).[101]

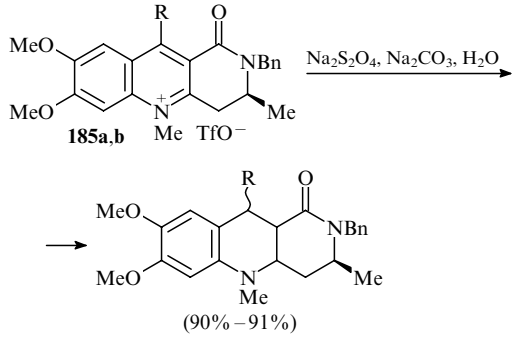


2. Reduction and hydrogenation

Treatment of 6-methylbenzo[*b*][1,6]naphthyridine (**7**) with hydrochloric acid in the presence of Pd/C is accompanied by reduction of the central ring to form the derivative **184**.[24]



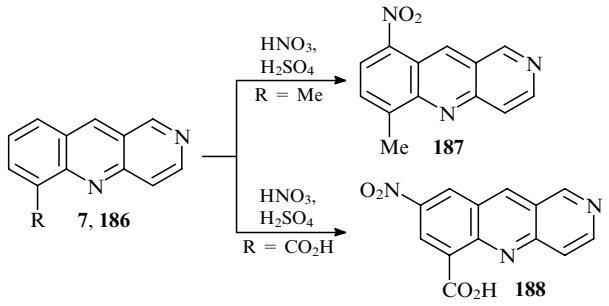
As expected, reduction of benzonaphthyridinium salts occurs more smoothly than reduction of the corresponding bases. Sodium dithionite was used for reduction of the benzonaphthyridinium salts **185a**,**b** at 20 °C.[62, 101]



R = H (**a**), Me (**b**).

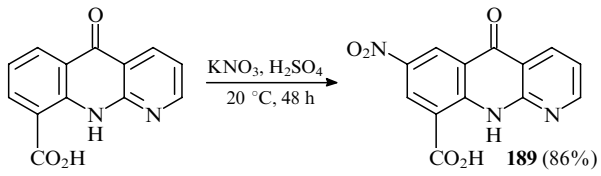
3. Substitution reactions

Data on the electrophilic substitution in benzonaphthyridines are scarce. It is known that nitration of benzonaphthyridines by a $HNO_3-H_2SO_4$ mixture occurs exclusively in the benzene ring. Thus nitration of 6-methyl-(**7**) and 6-carboxybenzo[*b*][1,6]naphthyridines (**186**) gives the corresponding 9-nitro (**187**, 78%) and 8-nitro derivatives (**188**, 82%).[24]

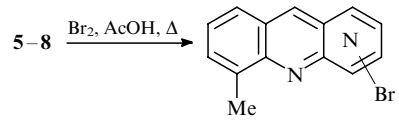


Nitration of 9-methylbenzo[*b*][1,8]naphthyridine (**5**) and 6-methylbenzo[*b*][1,5]naphthyridine (**8**) occurs analogously. In these reactions, the nitro group is also attached to the benzene ring in the *para* position with respect to the methyl substituent.[15]

Nitration of 5,10-dihydro-9-carboxy-5-oxobenzo[*b*][1,8]-naphthyridine by a nitrating mixture at 20 °C gave the 7-nitro derivative **189**.[102]



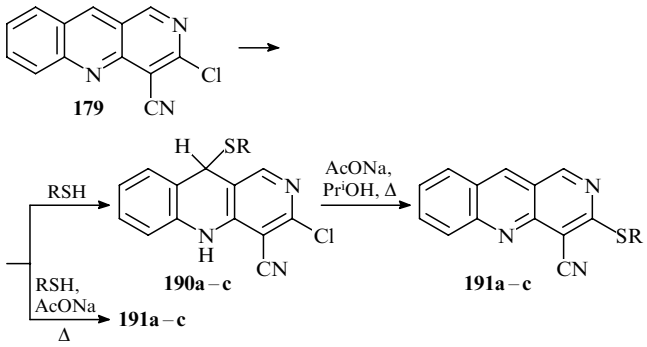
At the same time, isomeric 6-methylbenzo[*b*]naphthyridines **5**–**8** are brominated at the peripheral pyridine ring in the β-position with respect to the nitrogen atom (rather than at the benzene ring).[5]



This reaction pathway cannot be explained in terms of the electrophilic substitution mechanism [aromatic $S_E(AE)$]. In this case, the behaviour of benzonaphthyridines **5**–**8** is similar to that of quinoline and isoquinoline. Bromination of the latter in weakly acidic media also occurs at the pyridine ring in the β-position with respect to the nitrogen atom rather than at the benzene ring. The mechanism for bromination of these compounds, which entails nucleophilic addition–elimination [$S_N(AE)$], was proposed.[103]

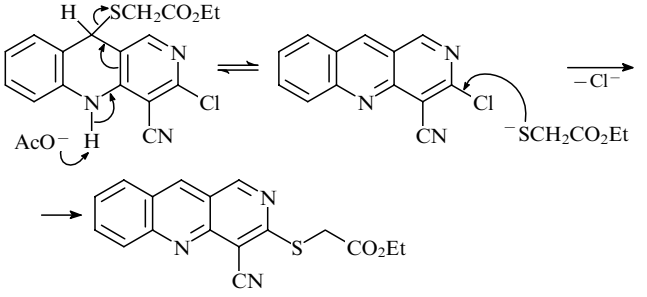
Nucleophilic substitution of hydrogen (S_N^H) is widely used in the synthesis of heterocycles and for the introduction of various substituents into π-electron-deficient heterocycles.[104–107] The S_N^H reactions were well studied for benzo[*b*][1,6]naphthyridine derivatives in which position 10 is depleted of electrons as a result of the unidirectional electron-withdrawing effect of both nitrogen atoms. The latter created a prerequisite for the nucleophilic addition at this position.

In the absence of bases, 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine (**179**) adds thiols at position 10 to give stable products **190a**–**c** even at 20 °C. The reaction of the compound **179** with thiols in the presence of a basic catalyst (AcONa) yields sulfides **191a**–**c**.[100] Reversibility of the addition of thiols to the tricyclic compound **179** can be illustrated by the following experiment. Heating of compound **190b** with sodium acetate as a base in isopropyl alcohol resulted in its conversion into sulfide **191b**.



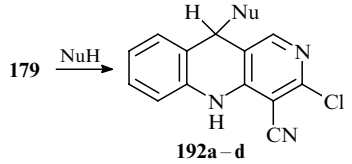
R = Ph (**a**), CH_2CO_2Et (**b**), $CH_2CONHPh$ (**c**).

Evidently, the reaction involves abstraction of the NH proton and elimination of the thiolate anion under the action of a base followed by slower, albeit irreversible substitution of chlorine at position 3 for the thiol residue.[100]

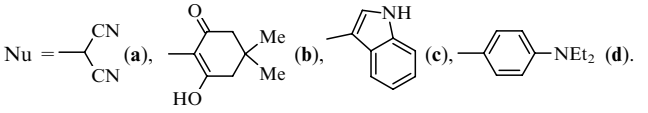


The reaction of benzonaphthyridine **179** with various C-nucleophiles yielded the addition products **192a**–**d** at position 10. Compounds with strong C–H-acidic properties, such as malononitrile and dimedone, and electron-rich aromatic compounds,

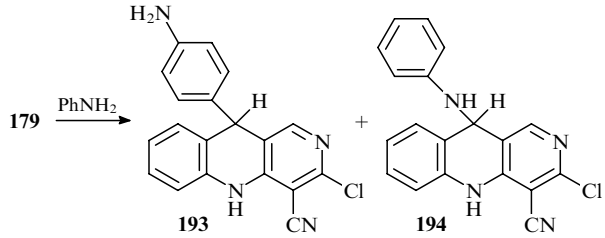
such as indole and *N*,*N*-diethylaniline, were used as C-nucleophiles.



192a–d

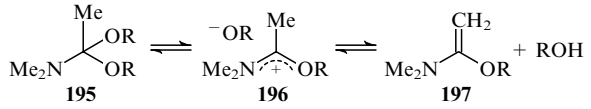


The reaction of benzonaphthyridine **179** with aniline gave a mixture of C–C- (**193**) and C–N-addition (**194**) products. Thus aniline manifested dual reactivity by reacting with the substrate both as a C- and N-nucleophile.



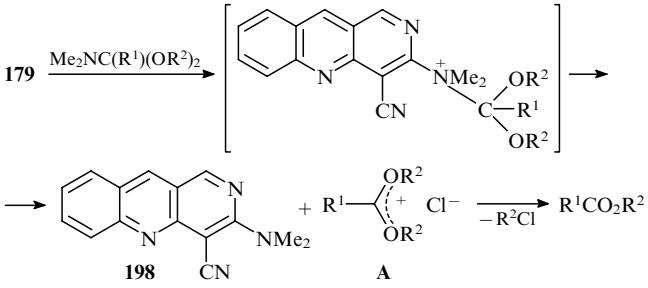
At the same time, reactions of compound **179** with more basic arylamines, *e.g.*, *p*-toluidine and *p*-anisidine, and aliphatic alkyl- and dialkylamines were accompanied by the replacement of chlorine at position 3.[8, 100]

Dimethylacetamide acetals, which can acts as C-nucleophiles due to equilibrium between amidoacetals **195**, their ionised forms **196** and α-alkoxy enamines**197**, were studied as nucleophilic reagents in a reaction with the tricyclic compound **179**.



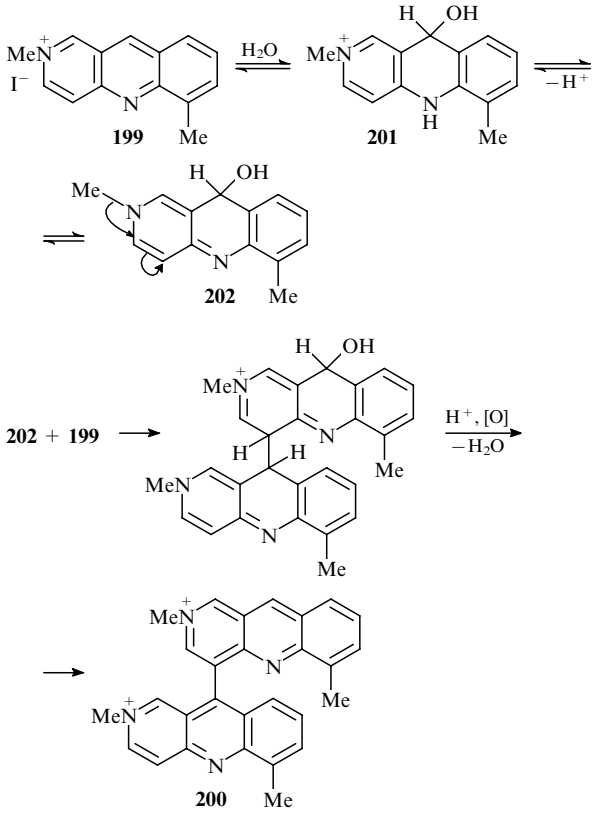
R = Me, Et.

However, the reactions of compound **179** with acetals **195** gave the 3-dimethylamino derivative **198** as the only product.[96] The latter was also synthesised by the reaction of the chloro derivative **179** with dimethylformamide dimethyl acetal, which excludes its involvement in the reactions with α-alkoxy enamine **197**. Evidently, the latter reaction involves hetarylation of amidoacetals by the compound **179**. The reaction of enamine **197** with DMF diethyl acetal results in elimination of ethyl acetate (identified by GLC) due to dealkylation of the diethoxycarbenium ion A, which is produced upon arylation and then easily splits the corresponding alkyl halide.



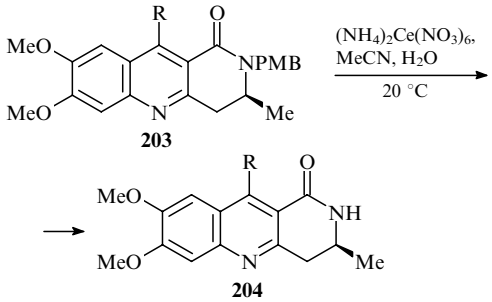
R^1 = H, Me; R^2 = Me, Et.

2,6-Dimethylbenzo[*b*][1,6]naphthyridinium iodide (**199**) in DMSO is easily dimerised to form compound **200**. The structure of the latter was established by X-ray diffraction analysis. Dimerisation is markedly accelerated in the presence of water. Apparently, water can add to the cation **199** to give pseudobase **201**. The latter can be deprotonated to give the intermediate **202**. The dimer is formed through the addition of the intermediate **202** at electron-deficient position 10 of the cation **199**. Subsequent elimination of water and oxidation afford the dication **200**.[5]



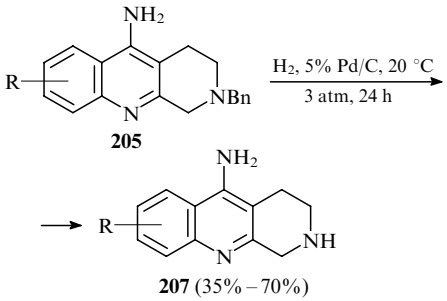
4. Deacylation and dealkylation

Considering that many synthetic processes produce benzonaphthyridines containing alkyl or acyl substituents at the pyridine nitrogen atom, it is necessary to get a better insight into the mechanism of their elimination. Thus the acyl group of tetrahydrobenzo[*b*][1,6]naphthyridines is easily eliminated under conditions of acid or alkaline hydrolysis to give deacylation products in nearly quantitative yields.[30] The protective 4-methoxybenzyl group in compounds **203** can smoothly be removed under oxidative conditions; this affords debenzylation products **204** in good yields.[19]

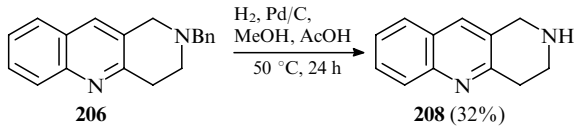


R = H (72%), Me (67%).

The benzyl group in compounds **205** and **206** is not activated by electron-donating substituents and it was removed by hydrogenation over Pd/C. This approach was used for the preparation of the debenzylated tetrahydro derivatives of benzo[*b*][1,7]-(**207**) (see Ref. 45) and benzo[*b*][1,6]naphthyridines **208**.[30]



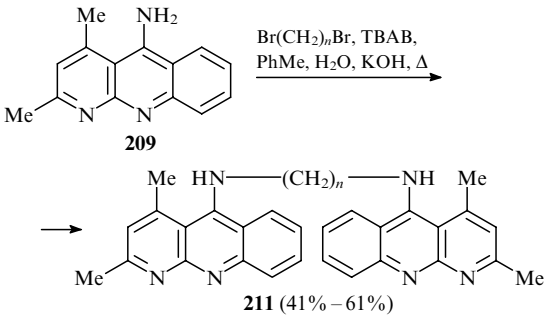
R = 7-F, 7-OMe, 8-F, 8-OMe.



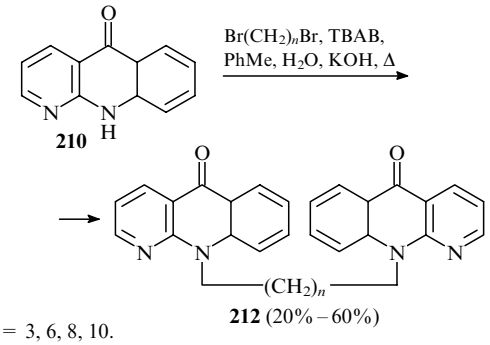
5. Synthesis of bis(benzo[b]naphthyridines)

Biological (mostly antitumour and antiacetylcholinesterase) properties of dimeric derivatives of acridine and its aza analogues, *viz*., benzo[*b*]naphthyridines, have been studied extensively in the past decade. Reactions of the corresponding 10(5)-chlorobenzonaphthyridines with alkylenediamines or reactions of alkylene dihalides with the corresponding 10(5)-aminobenzonaphthyridines are used in the synthesis of bis(aminobenzonaphthyridines). However, the yields of the target products are rather low.

The tricyclic compounds **209** and **210** were used as the starting reagents in the synthesis of *N*,*N*′-bis(benzo[*b*][1,8]naphthyridin-5-yl)-α,ω-alkylenediamines **211** and α,ω-bis(5,10-dihydro-5-oxobenzo[*b*][1,8]naphthyridin-10-yl)alkanes **212.** These reactions were carried out under phase-transfer catalysis conditions using tetrabutylammonium bromide (TBAB) as a catalyst.[108]



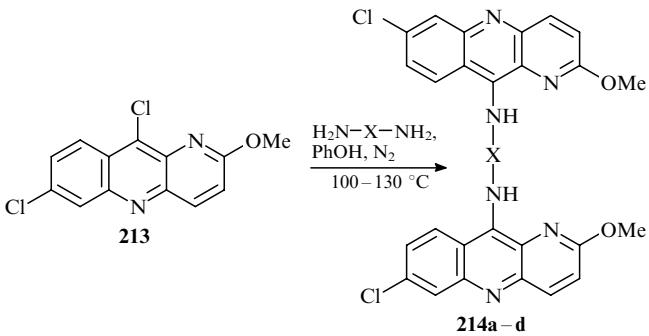
n = 3, 6, 8, 10.



n = 3, 6, 8, 10.

The synthesis of a series of *N*,*N*′-bis(6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-5-yl)-α,ω-alkylenediamines containing polymethylene chains of different length was also documented.[31–33].

Dimeric benzo[*b*][1,5]naphthyridines **214a – d** were synthesised by the reactions of 7,10-dichlorobenzonaphthyridine **213** with di- and polyamines.[109]



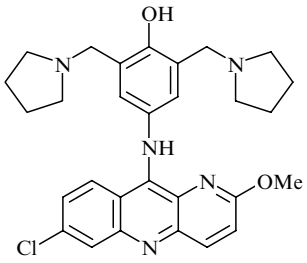
X = $CH_2CH(OH)CH_2$ (**a**), $(CH_2)_3NH(CH_2)_3$ (**b**), $(CH_2)_4NH(CH_2)_3$ (**c**), $(CH_2)_3NH(CH_2)_4NH(CH_2)_3$ (**d**).

Aminobenzonaphthyridines linked to other heterocycles through a flexible chain are synthesised in a similar way.[26,110]

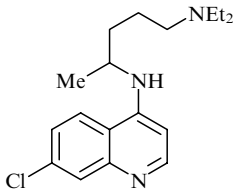
V. Biological activity

1. Antimicrobial activity

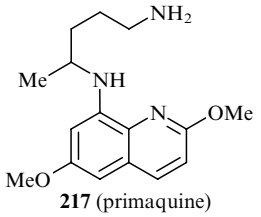
The Chinese antimalarial drug pyronaridine (**215**) is related to the class of benzo[*b*][1,5]naphthyridine derivatives. Its preclinical trials demonstrated its safety and high activity against *Plasmodium falciparum* and *P. vivax*.[111,112] The clinical efficiency of pyronaridine against the chloroquine (**216**) resistant strain of *P. falciparum*, *P. ovale* and *P. malariae* was established in studies with human volunteers from Thailand and Cameroon.[113–115] The antimalarial activities of pyronaridine and other drugs were compared in *vitro* studies on clinically isolated malarial strains obtained from Cameroon, Gabon and Senegal.[116–120] An HPLC procedure for measuring pyronaridine levels in human blood plasma samples and in different drug forms has been developed.[121] *In vitro* studies demonstrated synergism between pyronaridine **215** and primaquine **217**.[116]



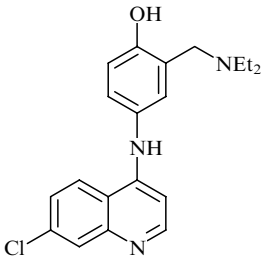
215 (pyronaridine)



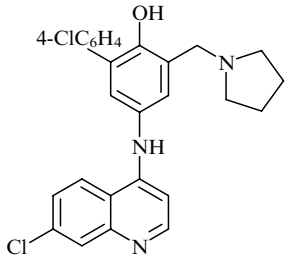
216 (chloroquine)



217 (primaquine)



218 (amodiaquine)



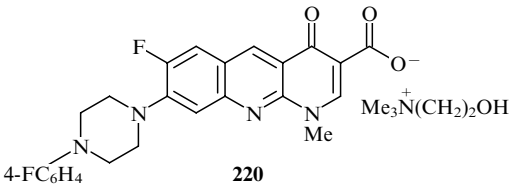
219 (tebuquine)

A more long-lasting pharmacological effect of pyronaridine in comparison with amodiaquine (**218**), tebuquine (**219**) and other antimalarial drugs related to the group of Mannich monobases

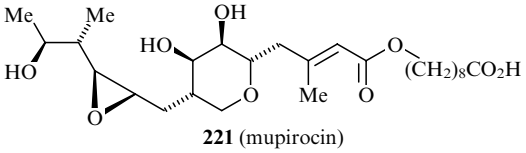
can be attributed to its higher lipophilicity and, as a consequence, higher ability to be accumulated in tissues.[122]

Drug	Distribution coefficient in octanol–water (log*P*)	
	pH 5.0	pH 7.4
Pyronaridine	−0.88	0.34
Amodiaquine	−1.16	0.93
Tebuquine	0.99	1.08

A series of benzo[*b*][1,8]naphthyridine-based antimicrobial agents highly active against multiresistant Gram-positive pathogens, including *Staphylococcus aureus* (MRSA), have been synthesised. These substances did not exhibit cross-resistance against the major classes of antimicrobial drugs (quinolones, β-lactams, *etc.*). The 50% inhibitory concentration (IC_{50} = 0.25–2 mg litre^{-1}) was established *in vitro* for the most reactive compound, RP60556A (**220**); its *in vivo* activity upon topical use in a model of skin infection (*Staphylococcus aureus*) in guinea pigs was found to be similar to that of mupirocin (**221**).[65]



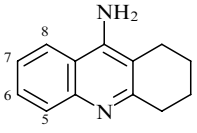
220



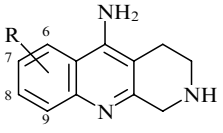
221 (mupirocin)

2. Anticholinesterase activity

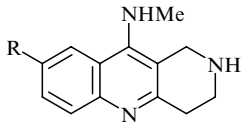
The use of drugs related to the class of acetylcholinesterase inhibitors (tacrine, amiridine) is chronologically the earliest and most well-developed approach to the use of adjuncts to control an attack of neurodegenerative diseases (*e.g.*, Alzheimer's disease).[123, 124] The disadvantage of this class of medicinal drugs is that they are low selective acetylcholinesterase (AChE) inhibitors (compared to butyrylcholinesterase (BChE) inhibition), which evokes undesirable side effects. A series of investigations are devoted to the synthesis of tricyclic aza analogues of tacrine (**222**) and analysis of their anticholinesterase properties. 1,7-Naphthyridine **223**,[34, 45, 125] 1,6-naphthyridine **224** (see Ref. 25) and 1,8-naphthyridine **225** derivatives were synthesised and studied.[35] The IC_{50} values of compounds **223** lie in the range 0.06 (R = 8-Cl)–0.5 (R = 8-OMe) mM, the tacrine activity being 0.19 mM. The presence of a substituent at position 8 (corresponding to position 6 of tacrine) improves the inhibiting properties.[45] 1,6-Naphthyridines **224** have much lower affinity for the enzyme in comparison with tacrine. The IC_{50} of the most efficient of those, *viz.*, (R = H), was = 0.86 mM, *i.e.*, about four times lower in comparison with tacrine.[25] Naphthyridine **225** approached tacrine in terms of anti-AChE activity, but strongly exceeded it in selectivity (AChE/BChE).[35, 36] Compounds of the type **225** also manifested the properties of L-type calcium channel blockers.[36]



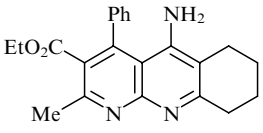
222 (tacrine)



223
R = H, 7-F, 8-F, 6-Cl, 7-Cl, 8-Cl, 7-OMe, 8-OMe



224



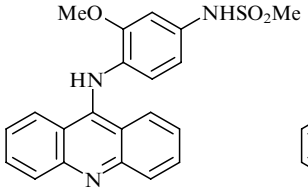
225

R = H, F, Cl, OMe

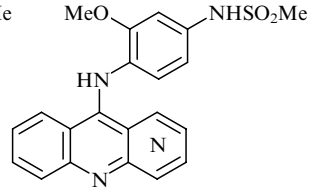
Compounds exhibiting a higher AChE inhibition level *in vitro* and higher [in comparison with tacrine (**222**)] anti-AChE selectivity with respect to butyrylcholinesterase (BChE) were identified among other dimeric tetrahydroacridine derivatives (tacrine analogues) and 5,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine derivatives. The optimum length of the polymethylene bridge was 7 methylene units.[31]

3. Antitumour activity

Antitumour activity of 9-aminoacridine derivatives is closely connected with the intercalation characteristic of many planar ionisable systems. The drug amsacrine (**226**) (see Ref. 126) is an example.



226 (amsacrine)

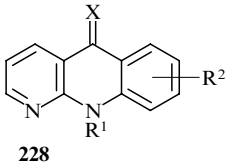


227

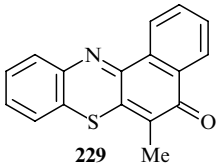
A series of compounds the acridine system in which was modified by the insertion of an additional nitrogen atom into the benzene ring have been synthesised in an attempt to search for novel promising medicinal drugs endowed with antitumour activities. The same approach was used in the synthesis of amsacrine aza analogues **227**.[127]

The antitumour properties of benzonaphthyridines have also been studied. Some of these compounds manifested antitumour properties *in vitro* [32, 47, 102, 109, 127] and *in vivo*.[102] Dimeric intercalators based on *N*,*N*′-bis(benzonaphthyridine)-α,ω-alkylenediamines manifested higher (in comparison with monointercalators) DNA binding constants.[108, 109] If the chains contained 7–10 methylene fragments, double intercalation took place.

The benzo[*b*][1,8]naphthyridine derivatives **228** were studied as modulators of multidrug resistance (MDR). These compounds were tested *in vitro* on mouse T-lymphoma cells after transfection (artificial transfer of genetic information) of the MDR1 gene into eukaryotic cells with the help of purified DNA. The effects of compounds **228** were compared to those of 6-methyl-5-oxobenzo[*a*]phenolthiazine (**229**) and 9-[2-(diethylamino)ethylamino]-2,7-dimethoxyacridine (**230**). The majority of the tested substances killed MDR tumor cells more effectively than the reference compounds **229** and **230**.[128]

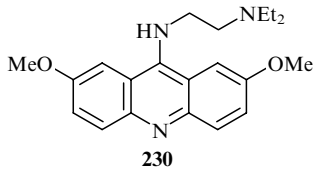


228



229

X = O, NH; R^1 = OMe;
R^2 = $R^3_2N(CH_2)_n$ (R^3 = Alk, Ar; *n* = 2, 3).



230

4. Anti-inflammatory activity

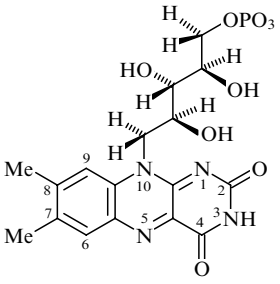
10-Substituted 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines manifested remarkable activities as interleukin-1 inhibitors and were patented as anti-inflammatory drugs.[28, 29]

Several neurokinin A antagonists, which represent 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine derivatives, were patented as remedies against diseases associated with tachykinin receptors and as preventives.[30]

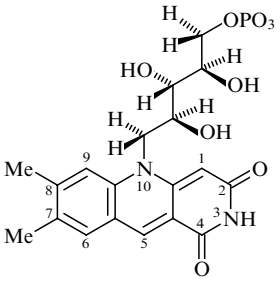
3-Amino derivatives of 4-cyanobenzo[*b*][1,6]naphthyridine relieved the spasmogenic effect of bradykinin in experiments with isolated segments of guinea pig ileum; however, these compounds manifested significantly lower activities when the experiments were carried out on whole animals.[129]

5. Other biological characteristics

In some papers devoted to the study of the cofactor properties of modified flavins, benzo[*b*][1,6]naphthyridine derivatives were considered as 1,5-dideaza analogues of alloxazine and isoalloxazine. Bio-isosters of flavins, such as compound **231**, were used to simulate the activities of flavin-dependent enzymes and to elucidate the structural properties essential for the manifestation of cofactor effects.[130, 131]

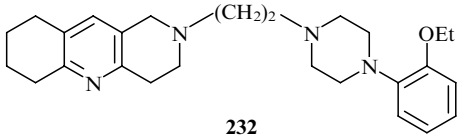


Flavin mononucleotide (FMP)

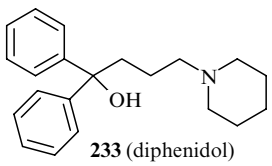


231

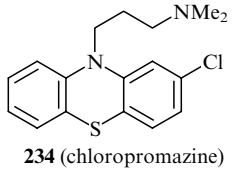
6-[ω-(4-Aryl-1-piperazinyl)alkyl]-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridines **232** manifested high antivertigo and anti-emetic activities.[132–135] A close QSAR – activity relationship was established for *ortho*-substituted arylpiperazine derivatives.[135] Compound **232** (NK 422; difumarate) was chosen as a promising antivertigo drug[134] and manifested a stronger (in comparison with diphenidol[136] and chlorpromazine[137]) anti-emetic effect.



232



233 (diphenidol)



234 (chloropromazine)

A series of acridines and their aza derivatives (in total, 71 compounds) were tested as Ca^{2+}-dependent inhibitors of protein kinase from wheat embryos. Benzo[*b*][1,5]naphthyridine derivatives containing basic and neutral substituents at position 4 manifested the highest activity.[138]

The ability of the 10-aminobenzo[*b*][1,5]naphthyridine compounds, fragments in which are linked together through flexible chains, to inhibit replication of the prions PrP^{Sc} was studied §.

§ Prions are abnormal forms of ordinary cellular proteins that are thought to be causatives of many severe infectious diseases, *e.g.*, Creuztfeld–Jacob's disease (degenerative neurological disorder).[139]

However, the activities of such bisbenzonaphthyridines appeared to be lower than those of the corresponding bisacridines.[140]

VI. Conclusion

This review is a generalisation of the published data on the synthesis and properties of benzo[*b*]naphthyridines. The data reviewed suggest that a search for novel compounds endowed with unique biological properties is the main trend of research in this area. Indeed, some experimental findings corroborate the conclusion that such a search can be both successful and constructive. The discovery of pyronaridine, the first representative of this class of compounds manifesting high clinical efficiency, is the first step in this direction. In-depth studies into antitumour activities of some benzo[*b*]naphthyridine derivatives, their ability to inhibit acetylcholinesterase and to suppress replication of prions are currently of paramount importance. The search for novel biologically active substances among compounds of the benzo[*b*]naphthyride series demands additional experiments aimed at the functionalisation of this type of tricyclic compound through the insertion of various pharmacophores able to enhance their biological properties.

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