Russian Chemical Reviews **70** (4) 299 – 320 (2001) © 2001 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2001v070n04ABEH000617

Pyridopyridines

V P Litvinov, S V Roman, V D Dyachenko

Contents

I.	Introduction	299
II.	1,5-Naphthyridines	299
III.	1,6-Naphthyridines	302
IV.	1,7-Naphthyridines	311
V.	2,6-Naphthyridines	313
VI.	2,7-Naphthyridines	314

Abstract. Studies on the development of procedures for the synthesis of five isomeric pyridopyridines, *viz*., 1,5-, 1,6-, 1,7-, 2,6- and 2,7-naphthyridines, their chemical properties and biological activities performed over the last 15 years are surveyed and systematised. The bibliography includes 223 references.

I. Introduction

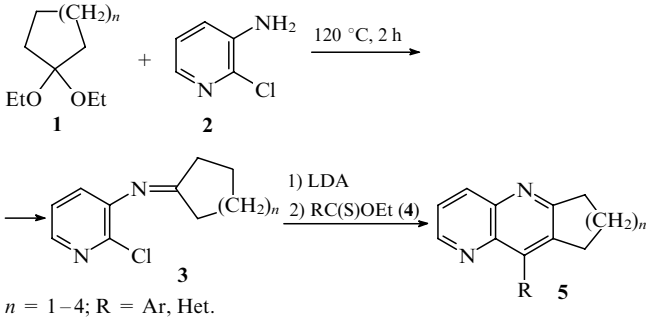
Pyridopyridines (diazanaphthalenes, napthyridines) are fused heterocyclic systems containing two nitrogen atoms in the adjacent rings. Naphthyridine derivatives attract interest because of the broad spectrum of their biological activities. These compounds are used in diagnostics and treatment of different human diseases (including HIV infection), agriculture, animal husbandry for external- and internal-parasite control, in industry as preservatives and components of lubricating coolants for metal processing, in analytical chemistry as ligands, *etc*.

Previously, we have considered general methods for the synthesis of naphthyridines, their structures and properties.[1] In the present review, we survey procedures for the synthesis of five isomeric pyridopyridines, *viz*., 1,5-, 1,6-, 1,7-, 2,6- and 2,7-naphthyridines, their chemical properties and biological activities. For convenience, the data are systematised according to the types of isomeric naphthyridines.

II. 1,5-Naphthyridines

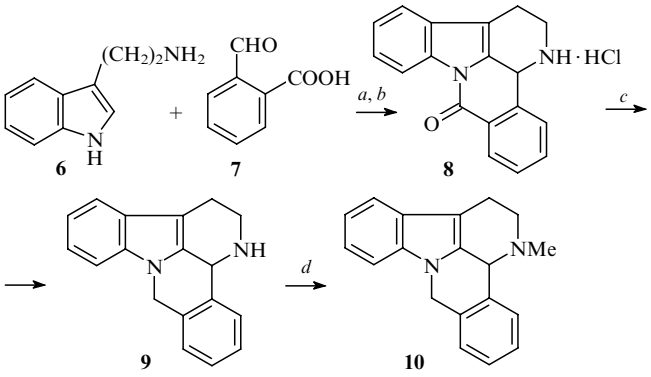
The major synthetic approach to the construction of the 1,5-naphthyridine system involves condensation of 3-aminopyridine derivatives with dicarbonyl compounds followed by the intramolecular reaction of the pyridine ring with the terminal carbonyl group under the action of acid catalysts to form a C–C bond. This approach serves as the basis for well-known syntheses according to Skraup, Friedländer, Knorr, *etc*.[1] Amino derivatives of pyridine,[2] indole,[3–6] and quinuclidine,[7] oximes of the isoquinoline series[8–10] and substituted anilines[11] were successfully used as substrates in these reactions.

Unlike the above-listed reactions, condensation of cycloalkanone diethyl acetals **1** with 3-amino-2-chloropyridine (**2**) afforded azomethines **3** whose successive treatment with lithium diisopropylamide (LDA) and thioesters **4** gave rise to aryl(hetaryl)cyclo(penta – octa)[*b*][1,5]naphthyridines **5**.[2]



n = 1–4; R = Ar, Het.

Tryptamine, tryptophan and their derivatives are widely used in the synthesis of indolo[3,2,1-*de*][1,5]naphthyridine derivatives. Thus refluxing of tryptamine (**6**) with 2-formylbenzoic acid (**7**) in alcohol followed by the addition of concentrated hydrochloric acid afforded hexahydrobenzo[*h*]indolo[3,2,1-*de*][1,5]naphthyridine hydrochloride (**8**) used as the starting compound in the synthesis of compounds **9** and **10**. The latter have an application in the treatment of oxygen deficiency.[3]

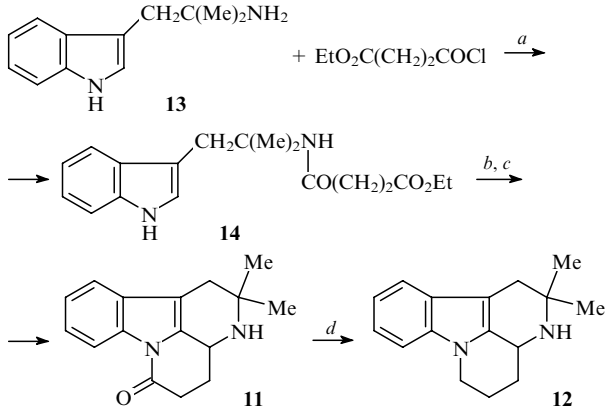


(*a*) EtOH, Δ, 2.5 h; (*b*) HCl; (*c*) $LiAlH_4$, $AlCl_3$;
(*d*) 37% CH_2O, $NaBH_3CN$, AcOH, MeCN, 20 °C, 2 h.

V P Litvinov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 135 88 37
S V Roman, V D Dyachenko T G Shevchenko Lugansk State Pedagogical Institute, ul. Oboronnaya 2, 348011 Lugansk, Ukraine.
Fax (38-064) 255 31 27. Tel. (38-064) 253 83 94

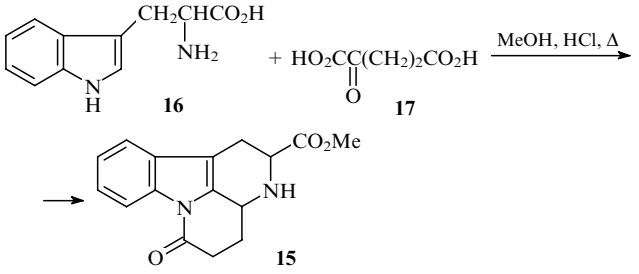
Received 27 July 2000
Uspekhi Khimii **70** (4) 343 – 367 (2001); translated by T N Safonova

1,5-Naphthyridine derivatives **11** and **12** prepared from α,α-dimethyltryptamine (**13**) and ethyl 3-chlorocarbonylpropionate are also used in the case of cerebral-vascular insufficiency and oxygen deficiency. Cyclisation of the intermediate **14** was carried out under the action of $POCl_3$ and KBH_4.[4]

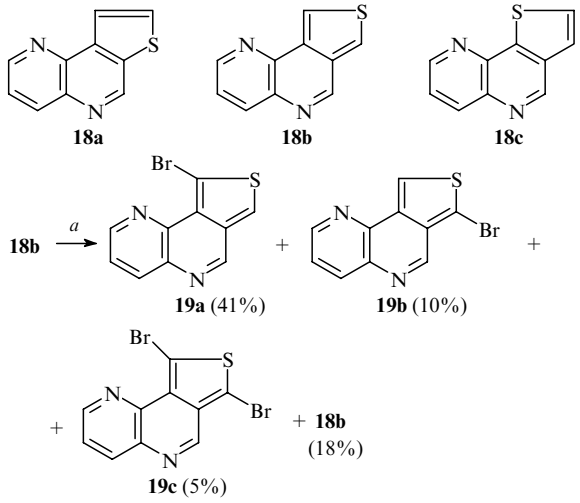


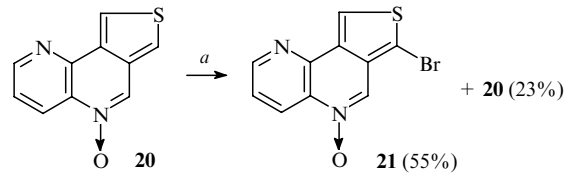
(*a*) Py, 20 °C, 1 h; (*b*) $POCl_3$; (*c*) KBH_4, EtOH – AcOH (5 : 1); (*d*) $LiAlH_4$, $AlCl_3$.

Indolonaphthyridine **15** was prepared by cyclocondensation of tryptophan (**16**) with 2-oxoglutaric acid (**17**) upon refluxing in methanol in the presence of HCl.[10]



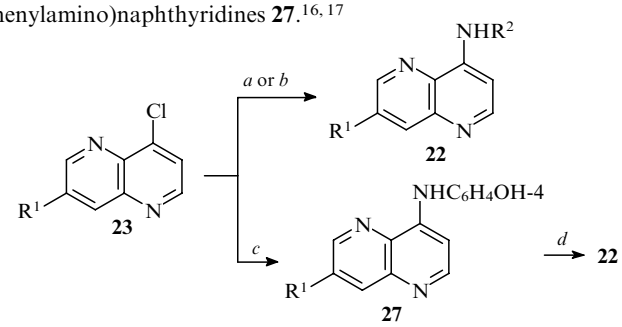
The chemical properties of 1,5-naphthyridines and the possibilities of their use for the preparation of biologically active compounds have been studied extensively. In particular, bromination of three isomeric thieno[*c*][1,5]naphthyridines **18a**–**c** and their *N*-oxides with tetrabutylammonium perbromide or bromine in the presence of $SOCl_2$ was investigated.[12] The reactions involving *N*-oxides proceed with higher regioselectivity. Thus bromination of thienonaphthyridine **18b** with tetrabutylammonium perbromide afforded a mixture of halogeno derivatives **19a**–**c**, whereas bromination of its *N*-oxide **20** under the same conditions gave rise to bromide **21** in 55% yield (23% of the initial compound remained unconsumed).[12]



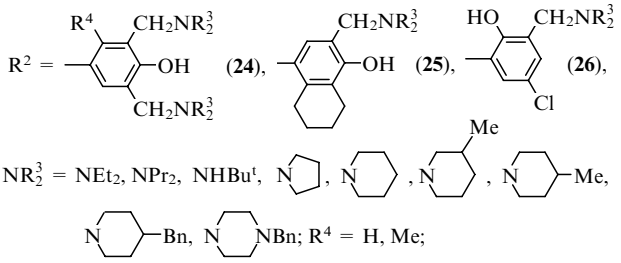


(*a*) 1.2 equiv. $Bu_4N^+Br_3^-$, $NaHCO_3$, CH_2Cl_2, 20 °C.

One of the recent major procedures used in the synthesis of biologically active 1,5-naphthyridines is based on the replacement of the halogen atom at position 4 of the naphthyridine ring.[13–23] Thus substituted 1,5-naphthyridin-4-ylamines **22** were prepared by the reactions of 4-chloro-1,5-naphthyridines **23** with aminophenols **24**–**26**[13–15] or by the Mannich reaction of 8-(4-hydroxyphenylamino)naphthyridines **27**.[16,17]



R^1 = H, Me, Cl, Br, CF_3;



NR^3_2 = NEt_2, NPr_2, $NHBu^t$,

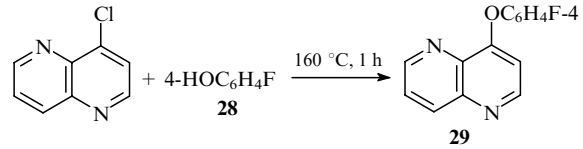
R^4 = H, Me;

(*a*) H_2NR^2, MeOH (EtOH), HCl, Δ; (*b*) $AcNHR^2$, MeOH (EtOH), HCl, Δ; (*c*) 4-$HOC_6H_4NH_2 \cdot HCl$, MeOH, Δ; (*d*) CH_2O, HNR^3_2, EtOH, Δ.

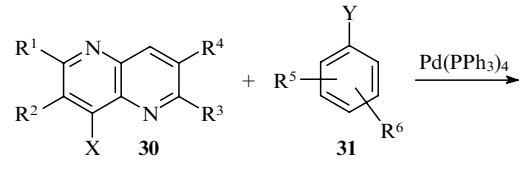
The compounds **22** exhibit antimalarial activity both *in vitro* and *in vivo*. This activity is less pronounced in the case of R^1 = Br or CF_3 and R^2 = Me or Et.[14,15]

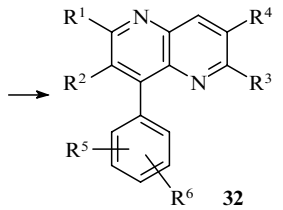
(7-Bromo-1,5-naphthyridin-4-yl)(piperidin-2′-yl)methanol, which is a potential antimalarial drug of a new type, was synthesised in four steps starting from 4,7-dibromo-1,5-naphthyridine.[22]

The reaction of 4-chloro-1,5-naphthyridine with 4-fluorophenol (**28**) afforded 4-(4-fluorophenoxy)-1,5-naphthyridine (**29**) exhibiting fungicidal and insecticidal activities.[23]



Cross-coupling of 1,5-naphthyridines **30** containing the bromine or iodine atom at position 4 with organotin, -silicon or -boron compounds **31** in the presence of $Pd(PPh_3)_4$ gave rise to aryl-substituted 1,5-naphthyridines **32** covered by a patent as herbicides.[24]

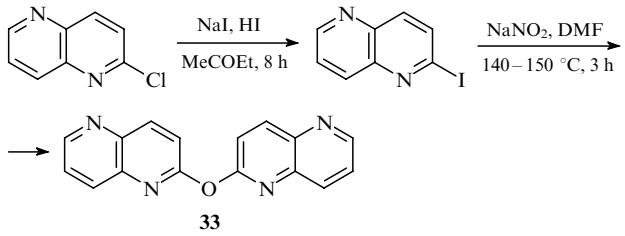




32

R^1 = Alk(C_1–C_4), OAlk, SAlk; R^2 = H, Me, F, Cl;
R^3–R^6 = H, Alk(C_1–C_4), OAlk, CN, Hal; X = Br, I;
Y = $SnMe_3$, $SiMe_3$, $B(OH)_2$.

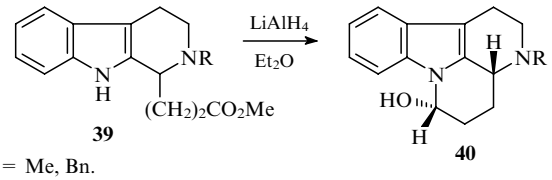
The chlorine atom in 2- or 4-chloronaphthyridines was replaced by the iodine atom under the action of NaI in the presence of hydroiodic acid yielding 2- or 4-iodo-1,5-naphthyridines, respectively.[25] It was noted[25] that treatment of 2-iodo-1,5-naphthyridine with $NaNO_2$ in DMF gave rise to 2,2′-bis(1,5-naphthyridyl) ether (**33**) in 44% yield, whereas an analogous reaction with 4-iodo-1,5-naphthyridine did not proceed.



33

In 6-chloronaphtho[1′,2′:4,5]thieno[2,3-c][1,5]naphthyridine (**34**), the chlorine atom is readily replaced by the amino or hydrazinoamino group and also is reduced to yield the corresponding 1,5-naphthyridine derivatives **35**–**37**. Under the action of ethyl orthoformate, the hydrazine **37** underwent cyclisation to give triazole **38**[26] (Scheme 1).

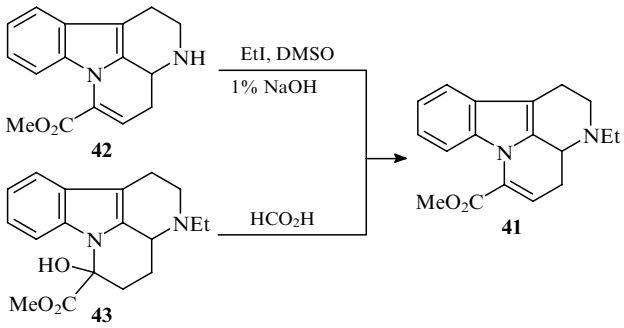
Reductive cyclisation of esters **39** afforded 1,5-naphthyridine derivatives **40**, which were dimerised under the action of acids.[27]



39 **40**

R = Me, Bn.

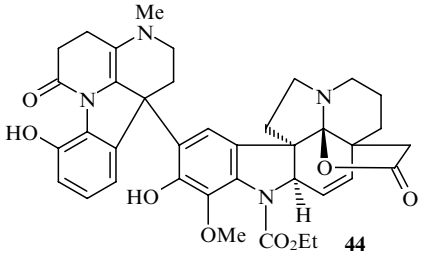
Methyl (±)-3-ethyl-2,3,3*a*,4-tetrahydro-1*H*-indolo[3,2,1-*de*]-[1,5]naphthyridine-6-carboxylate (**41**) possessing psychostimulating activity was prepared by alkylation of ester **42** with iodoethane in DMSO or by dehydration of hydroxy derivative **43**.[28]



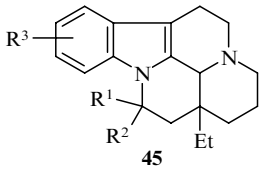
42 **43** **41**

1,5-Naphthyridine derivatives, like other isomeric pyridopyridines, were found in many natural substances and were used for the construction of a series of efficient medicines.

Recently, the previously unknown dimeric indole alkaloid cimiciduphytine (**44**) containing the 1,5-naphthyridine fragment[29] and derivatives of eburnane alkaloids **45** exhibiting hypotensive and pain-relieving activities have been isolated from naturally occurring sources. These compounds are suitable for the treatment of cerebral circulation disturbance.[30–35]



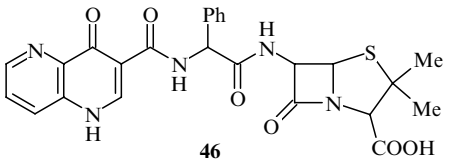
44



45

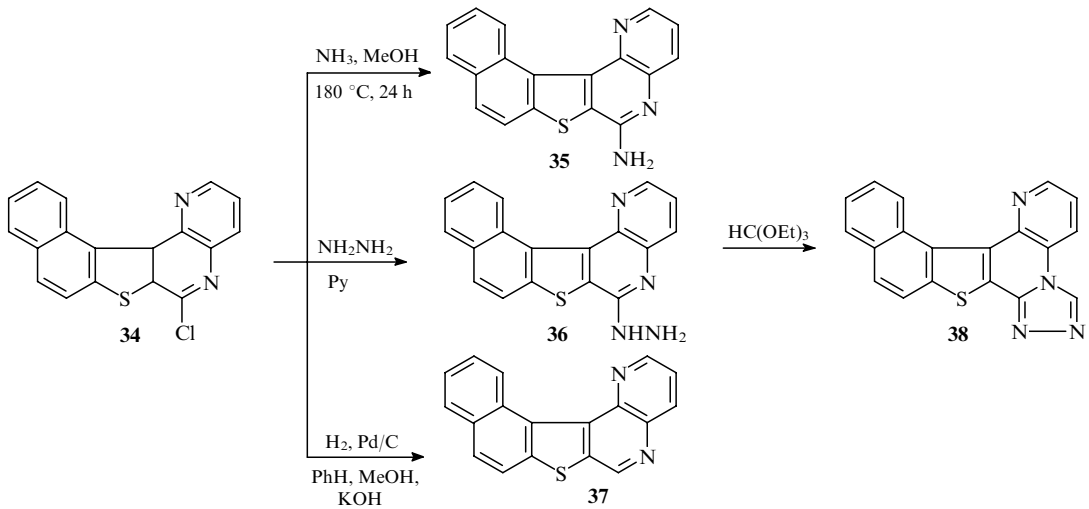
R^1 = H: R^2 = H, CO_2Me, CO_2Et, CH_2OH; R^1–R^2 = O;
R^3 = H, Cl, NO_2.

A derivative of penicillanic acid **46** was covered by a patent as an antibiotic.[36] Derivatives of hydroxy acid **47** were covered by a patent as anthelmintics.[37]

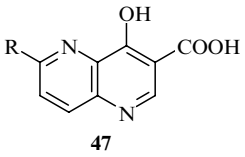


46

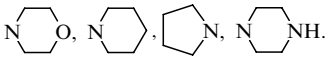
Scheme 1



34 **35** **36** **37** **38**

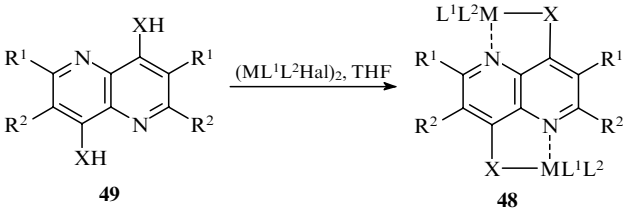


47

R = OEt, OPr, 

Derivatives of annelated benzoindolo-1,5-naphthyridines suitable for improvement of memory attenuated by drugs were described.[3,5] These are benzo[*b*][1,5]naphthyridines, which are analogues of inhibitors of neurokinin NK_1-receptors. Various 1,5-naphthyridine derivatives, in particular, 2-naphthyridinecarboxamide, possessing antiviral activity were also reported.[38].

Complexes **48** of Group IB or VIII metals with 1,5-naphthyridine derivatives **49** were synthesised.[39] The compounds **48** are used for the preparation of singlet oxygen. These compounds serve as sensitisers in photoinitiation of polymerases and electrophotography and as redox catalysts in organic reactions.[39]



49 **48**

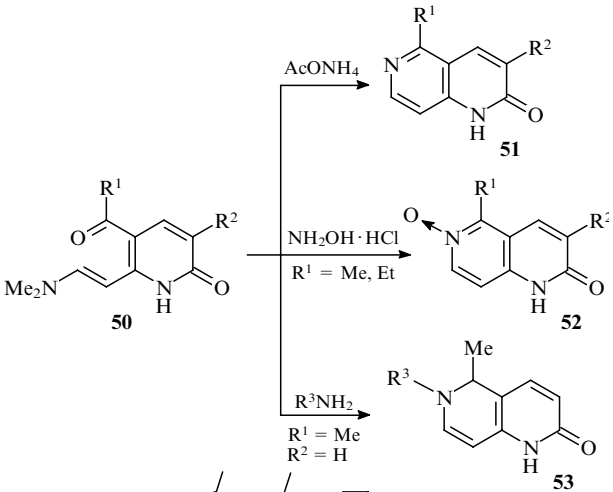
R^1, R^2 = H, Me, Et, cyclo-Alk(C_3–C_7); R^1–R^2 = $(CH_2)_n$, n = 3–6; X = O or S, M is Group IB or VIII metal; L^1, L^2 = Hal, NO, PPh_3, CN, CO.

The electronic structures and the UV spectral parameters of six isomeric formyl-substituted 4,6-benzo-1,5- and -1,6-naphthyridines were calculated.[40]

III. 1,6-Naphthyridines

Chemistry and biological activities of 1,6-naphthyridine derivatives were studied in much more detail than those of 1,5-, 1,7- and 2,7-naphthyridine derivatives. A wide variety of approaches to their syntheses are available.

One of the promising procedures for the synthesis of 1,6-naphthyridine derivatives involves functionally substituted pyridones as the starting compounds. Thus enamines **50** prepared from 6-formylpyrid-2-ones underwent cyclisation upon refluxing with ammonium acetate in DMF to give 1,6-naphthyridin-2-ones **51** in good yields.[41–47] *N*-Oxides **52** were prepared by cyclisation of the enamines **50** under the action of hydroxylamine hydrochloride.[42,45] The reactions of the compounds **50** with amines in methanol or DMF afforded 6-substituted 1,2,5,6-tetrahydro-1,6-naphthyridin-2-ones **53**.[48]

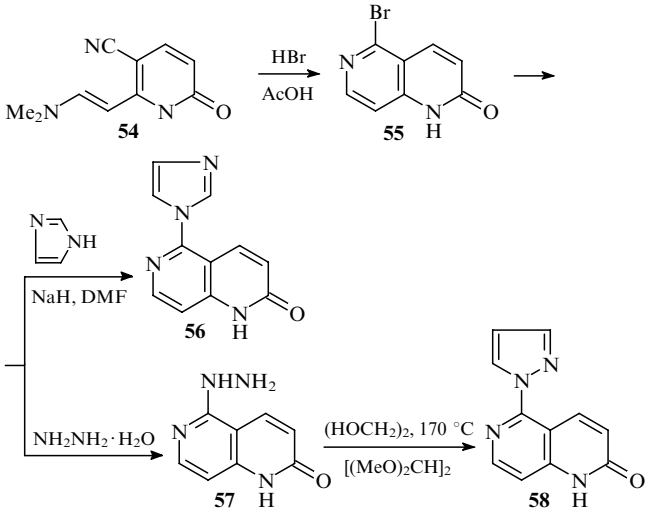


50 **51** **52** **53**

R^1 = Me, Et, Pr, Bu, Ph, ;

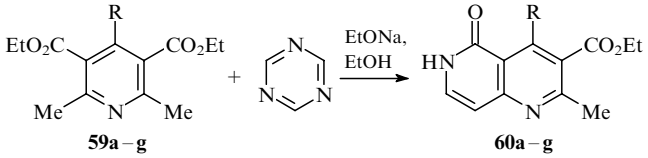
R^2 = H, Br, CN; R^3 = 4-$MeOC_6H_4$, NH_2, NMe_2.

Treatment of enamine **54** derived from 5-cyano-6-formyl-2-pyridone with gaseous HBr in AcOH gave rise to 5-bromo-1,6-naphthyridin-2-one (**55**). The bromine atom in the compound **55** is readily replaced by nitrogen nucleophiles. This fact was used in the synthesis of 1,6-naphthyridine derivatives **56**–**58**.[49–52] The compounds **51**, **52** and **55**–**58** exhibit cardiotonic activity.[41–52]



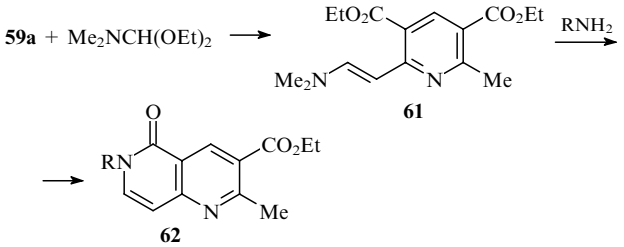
54 **55** **56** **57** **58**

1,6-Naphthyridin-5(6*H*)-ones **59a**–**g** were prepared by the reactions of pyridines **60a**–**g** with 1,3,5-triazine upon refluxing in ethanol in the presence of sodium ethoxide. The reaction of the compound **60a** with dimethylformamide diethyl acetal gave rise to enamine **61**. The reactions of the latter with amines upon refluxing in ethanol, DMF, *m*-xylene or pyridine afforded 6-substituted naphthyridinone derivatives **62**.[53,54] Refluxing of vicinal diamines **63** with enamine **61** yielded naphthyridinones **64**, which were converted into tetracyclic derivatives **65** under the action of $POCl_3$.[55]



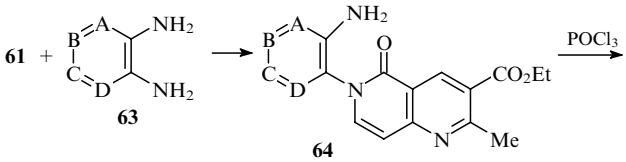
59a–**g** **60a**–**g**

R = H (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 2-$NO_2C_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**), 3-pyridyl (**g**).

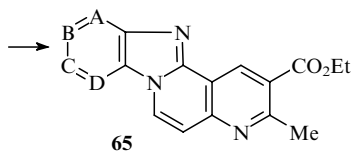


61 **62**

R = H, Ph, 2-FC_6H_4, 4-FC_6H_4, 3-$F_3CC_6H_4$, 2-$NH_2C_6H_4$.



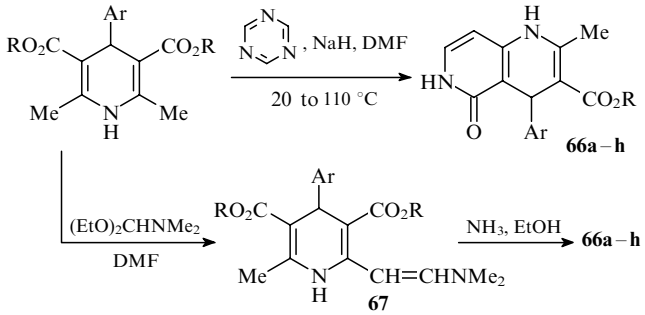
63 **64**



65

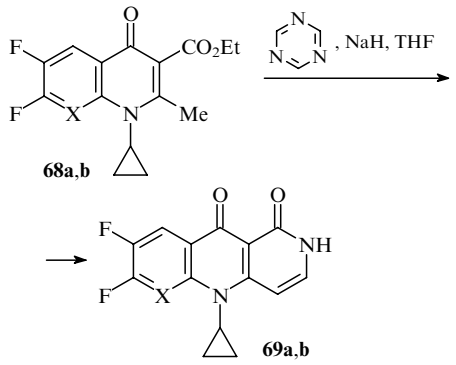
A = B = C = D = CH; A = B = C = CH, D = N; A = N, B = C = D = CH; A = C = D = CH, B = N; A = C = N, B = D = CH; A = C = CH, B = D = N.

The reactions of 1,4-dihydropyridines with 1,3,5-triazine in the presence of a base afforded 1,4-dihydro-1,6-naphthyridines **66a**–**h**. These compounds can also be prepared in two stages by the reactions of 1,4-dihydropyridines with dimethylformamide diethyl acetal followed by treatment of aminovinyl intermediates **67** with ammonia.[56] The compounds **66a**–**h** were covered by patents as agents promising in the treatment of cardiovascular diseases.[57–61]

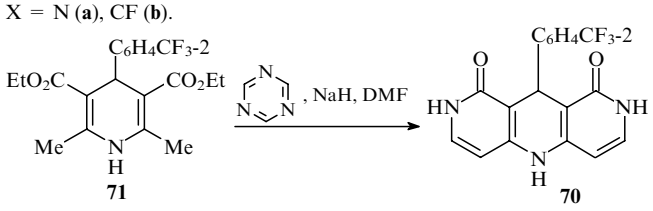


Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 2-$NO_2C_6H_4$ (**c**), 2-pyridyl (**d**), 2-thienyl (**e**), 2-FC_6H_4 (**f**), 2-$CF_3C_6H_4$ (**g**), 2-F-3-ClC_6H_3 (**h**);
R = Me, Et, Bu^t.

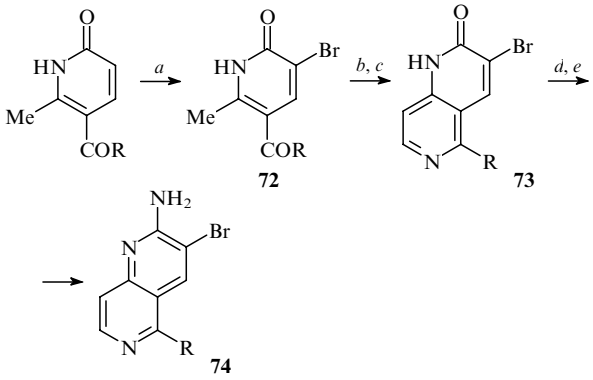
Substituted pyridones are widely used as the starting compounds in the synthesis of substituted 1,6-naphthyridines. Thus the reactions of 1,3,5-triazine with pyridones **68a**,**b** yielded annelated 1,6-naphthyridines **69a**,**b**. The tricyclic compounds **69** containing the cyclopropyl substituent were covered by patents as efficient antibiotics.[62] Pyrido[2,3-*b*][1,6]naphthyridine **70** prepared from 1,4-dihydropyridine **71** possesses spasmolytic activity and is used in the treatment of cerebral, cardiac and peripheral artery diseases.[63]



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

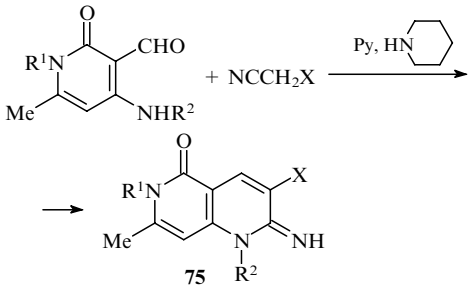


The reactions of 5-alkanoyl(aroyl)-6-methylpyridin-2(1*H*)-ones with *N*-bromosuccinimide in CCl_4 afforded bromides **72**. Successive treatment of the latter with $(Me_2N)_2CHBu^t$ (Bredereck's reagent) and ammonium acetate gave rise to 5-alkyl(aryl)-3-bromo-1,6-naphthyridin-2(1*H*)-ones **73** in high yields.[64] The compounds **73** were converted under the successive action of $POCl_3$ and ammonia into 5-alkyl(aryl)-2-amino-3-bromo-1,6-naphthyridines **74**, which are promising starting compounds for the preparation of new biologically active compounds.



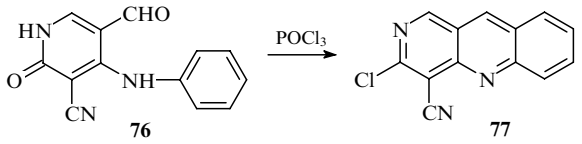
R = Me, Et, Pr^n, Bu^i, Ph, 4-$NO_2C_6H_4$;
(*a*) NBS (*N*-bromosuccinimide), CCl_4; (*b*) $(Me_2N)_2CHBu^t$, dioxane; (*c*) NH_4OAc, DMF; (*d*) $POCl_3$; (*e*) NH_3, EtOH.

The Knoevenagel reaction of substituted 4-amino-3-formylpyridin-2-ones with CH-acids in the presence of piperidine was used in the synthesis of 2-imino-1,6-naphthyridin-5(6*H*)-ones (**75**) possessing antitubercular activity.[65]

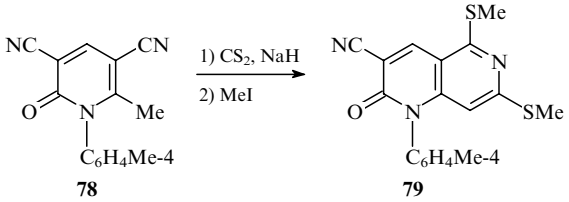


R^1, R^2 = $PhCH_2$, $Ph(CH_2)_2$; X = CN, CO_2H, CO_2Me, CO_2Et, 4-$NO_2C_6H_4$.

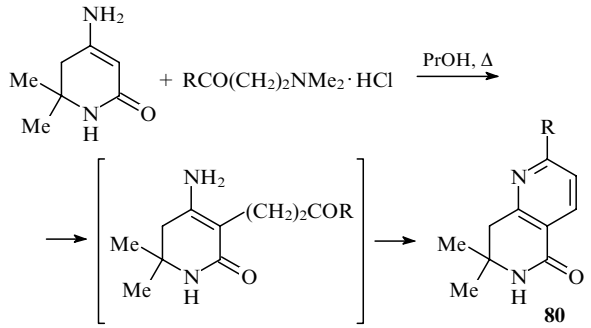
When heated with $POCl_3$, substituted pyridone **76** underwent cyclisation with simultaneous replacement of the 2-oxo group by the chlorine atom to give 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine **77**.[66,67]



The reaction of pyridone **78** with carbon disulfide and sodium hydride in benzene followed by methylation with iodomethane produced the 5,7-bis(methylthio)-1,6-naphthyridinone derivative **79**.[68]



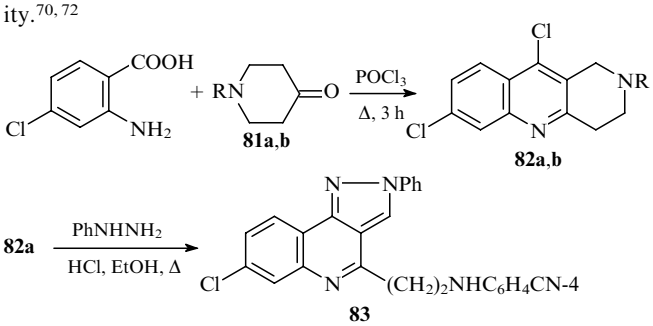
5,6,7,8-Tetrahydro-1,6-naphthyridin-5-ones **80** were synthesised by the reactions of 4-amino-5,6-dihydropyridin-2(1*H*)-one with amino ketone hydrochlorides.[69]



R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4.

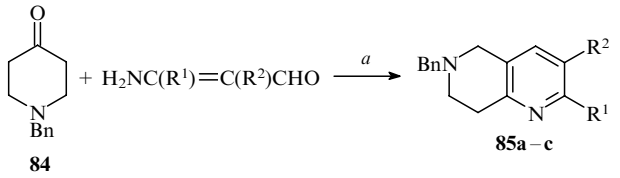
Piperidones are used as starting compounds in the synthesis of 1,6-naphthyridines. Thus the reactions of *N*-substituted piperidones **81a**,**b** with 2-amino-4-chlorobenzoic acid afforded 2-aryl(heteryl)tetrahydrobenzo[*b*][1,6]naphthyridines **82a**,**b**, which serve as inhibitors of interleukin 1 and were covered by patents as antiinflammatory agents.[70–72]

The reaction of the compound **82a** with phenylhydrazine in the presence of concentrated hydrochloric acid gave rise to pyrazolo[4,3-*c*]quinoline (**83**) exhibiting antiinflammatory activity.[70,72]



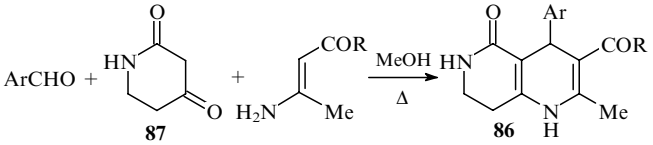
R = 4-NCC_6H_4 (**a**), pyrimidin-2-yl (**b**).

The reactions of *N*-benzylpiperidin-4-one (**84**) with 3-aminoacrolein and its homologues were used for the preparation of 5,6,7,8-tetrahydro-1,6-naphthyridines **85a**–**c**.[73]



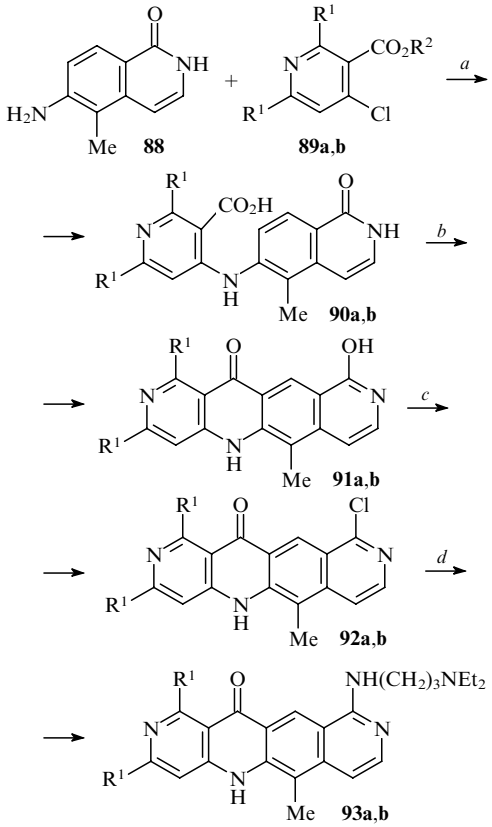
$R^1 = R^2 = H$ (**a**); R^1 = Me, R^2 = H (**b**); R^1 = H, R^2 = Me (**c**);
(*a*) NH_2 AcO^-, Et_3N, 120 °C, 24 h.

Partially hydrogenated 1,6-naphthyridines **86** were synthesised by the Hunch condensation of aromatic aldehydes with 2,4-dioxopiperidine (**87**) and derivatives of 3-aminocrotonic acid.[74] The compounds **86** were covered by a patent as drugs for the treatment of cardiovascular diseases.[75]



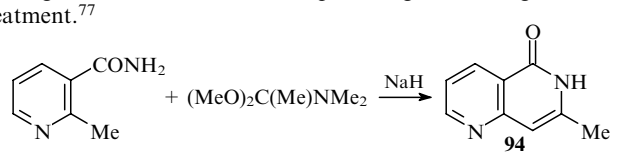
R = MeO, EtO, MeNH, Et_2N, $NH(CH_2)_2OH$.

The reactions of 6-amino-5-methylisoquinolin-1(2*H*)-one (**88**) with 4-chloronicotinic acid (**89a**) or ethyl 4-chloro-2,6-dimethylnicotinate (**89b**) afforded amino-substituted 6-aminoisoquinolines **90a**,**b**, which underwent cyclisation to form 5*H*-isoquinolino[6,7-*b*][1,6]naphthyridin-12-ones **91a**,**b**, respectively.[76] The latter were used in the synthesis of 10-substituted 1,6-naphthyridine derivatives **92a**,**b** and **93a**,**b**, which are analogues of 9-azaellipticine possessing antitumour activity. However, it appeared that the replacement of the pyrrole fragment in 9-azaellipticine by the 4-pyridone fragment led to a loss of biological activity.[76]

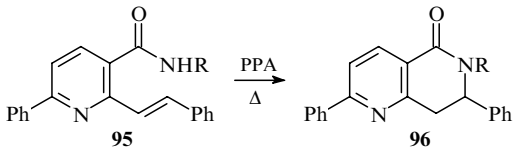


$R^1 = R^2 = H$ (**a**), R^1 = Me, R^2 = Et (**b**); (*a*) H_2SO_4, CF_3CO_2H; (*b*) H_2SO_4 or CF_3SO_3H; (*c*) $POCl_3$, PCl_5; (*d*) $NH_2(CH_2)_3NEt_2$.

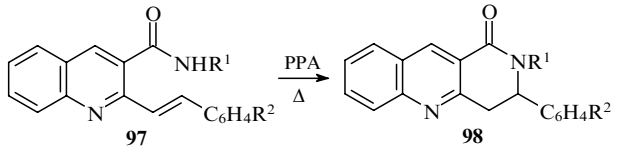
Pyridinecarboxylamides are widely used in the synthesis of 1,6-naphthyridines. Thus heating of a mixture of 2-methylnicotinamide with *N*,*N*-dimethylacetamide dimethyl acetal in the presence of NaH gave rise to 7-methyl-1,6-naphthyridin-5(6*H*)-one (**94**), which is used for eliminating harmful effects caused by ionising radiation or chemotherapeutic agents during tumour treatment.[77]



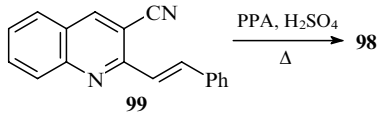
When heated in polyphosphoric acid (PPA), 6-phenyl-2-styrylnicotinamides (**95**) underwent cyclisation to form substituted 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridines **96**.[78] Analogously, benzo[*b*][1,6]naphthyridines **98** were prepared from amides of the quinoline series **97**.[78–80] Naphthyridine **98** ($R^1 = R^2 = H$) was also synthesised by cyclisation of 3-cyano-2-styrylquinoline **99** under the action of a mixture of polyphosphoric and sulfuric acids.[80]



R = CH_2=$CHCH_2$, iso-C_5H_{11}, Ph, 3-MeC_6H_4.



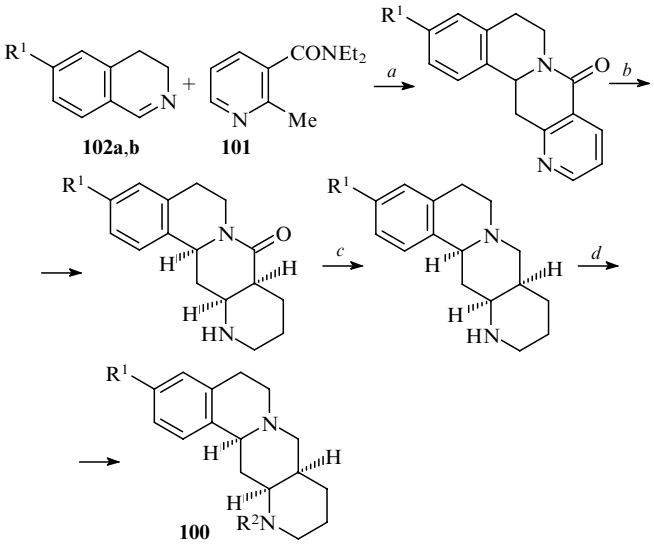
R^1 = H, Ph, Bn; R^2 = H, 4-MeO, 3-Br.



The reactions of *N*-substituted 2-chloro- or 4-chloronicotinamides with nitriles containing the active methylene group in the presence of bases were used for the preparation of amino derivatives of 1,6-naphthyridin-5(6*H*)-one or 2,7-naphthyridin-1(2*H*)-one, respectively.[81,82]

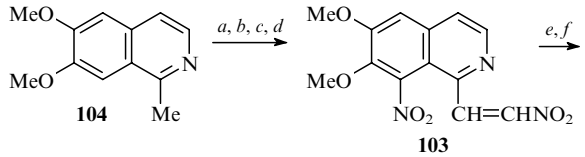
A procedure was developed for the synthesis of dodecahydroisoquinolino[2,1-*g*][1,6]naphthyridines **100** based on diethyl-2-methylnicotinamide (**101**) and 3,4-dihydroisoquinolines **102a**,**b**. The compounds **100** are highly efficient α_2-adrenoreceptor antagonists[83,84] and were covered by patents as drugs for the treatment of hypertonia, depression and diabetes, for inhibition of thrombocyte aggregation and for weight reduction.[85–90]

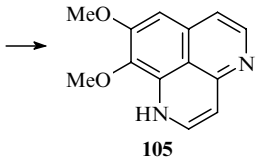
It should be noted that the structural analogue of α-yohimbine, *viz*., 6-methoxy-*N*-methylsulfonyl-6*H*-isoquinolino[2,1-*g*][1,6]naphthyridine (**100**, R^1 = MeO, R^2 = $MeSO_2$, the preparation RS-15385),[91] proved to be a very efficient drug in the treatment of impotence. A laboratory procedure for its preparation on a kilogram scale was developed.[92,93]



R^1 = H (**102a**), MeO (**102b**); R^2 = $MeSO_2$, $MeO(CH_2)_2SO_2$, $HO(CH_2)_2SO_2$, Bu^tNHSO_2, H_2NSO_2, Me_2NCO, $Cl(CH_2)_3SO_2$; (*a*) Pr^i_2NLi, THF, −40 °C; (*b*) H_2, Rh/Al_2O_3, AcOH; (*c*) $LiAlH_4$, THF, Δ; (*d*) R^2X (X = Cl, Br), CH_2Cl_2, Et_3N.

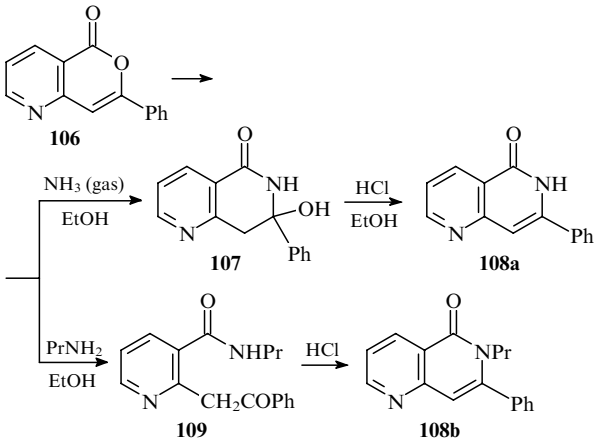
Reductive cyclisation of substituted isoquinoline **103**, which was prepared from 6,7-dimethoxy-1-methylisoquinoline (**104**) in four steps, was successfully used in the synthesis of 8,9-dimethoxy-1*H*-benzo[*d*,*e*][1,6]naphthyridine (aaptamine) (**105**). The latter compound was isolated from sea sponge *Aaptos aaptos* and exhibits sympatholytic and hypotensive activities.[94,95]



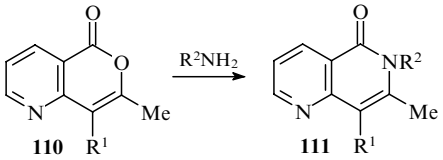


(*a*) HNO_3, −40 °C; (*b*) SeO_2, dioxane; (*c*) $MeNO_2$, Al_2O_3; (*d*) Al_2O_3, PhH, Δ; (*e*) Fe, AcOH, 20 °C, 2 h; (*f*) 90 °C, 45 min.

Pyranopyridines are convenient starting compounds in the synthesis of 1,6-naphthyridine derivatives. Thus, the reaction of 7-phenylpyrano[4,3-*b*]pyridin-5-one (**106**) with gaseous ammonia in ethanol was accompanied by the replacement of the oxygen atom of the pyran ring by the nitrogen atom to form hydroxynaphthyridine **107**. The latter was dehydrated with an alcoholic solution of HCl to give 7-phenyl-1,6-naphthyridin-5(6*H*)-one (**108a**). Treatment of pyranopyridine with propylamine led to the pyran ring opening to form 2-phenacyl-*N*-propylpyridine-3-carboxamide (**109**), which underwent cyclisation under the action of a 5% HCl solution giving rise to *N*-propyl-substituted naphthyridinone **108b**.[96]

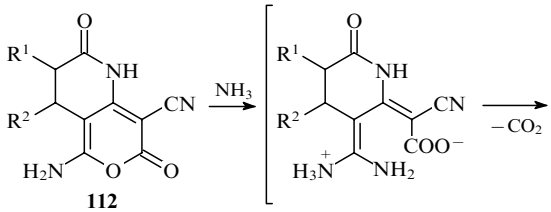


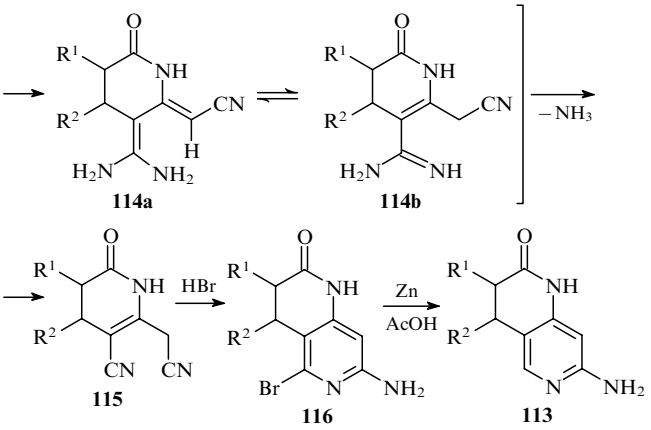
Analogous reactions of 7-methylpyrano[4,3-*b*]pyridines **110** with ammonia or aliphatic primary amines afforded 1,6-naphthyridinones **111**.[97]



R^1 = Ac, CO_2Et; R^2 = H, Me, Bu, $(CH_2)_2NH_2$, $(CH_2)_2OH$, $CH_2{=}CHCH_2$.

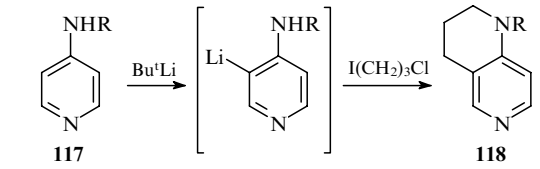
1,6-Naphthyridin-2(1*H*)-ones **113** were prepared from pyrano[4,3-*b*]pyridine-2,7-diones **112** by successive treatment with NH_3, HBr and Zn in acetic acid.[98] It was believed that the attack of the ammonia molecule on the C(5) atom led to the pyran ring opening. Subsequent decarboxylation afforded a tautomeric mixture of substituted tetrahydropyridines **114a**,**b**. Dinitrile **115** generated by elimination of the ammonia molecule underwent cyclisation under the action of HBr to form 1,6-naphthyridine derivative **116**. Dehydrobromination with Zn in acetic acid gave rise to the final products **113**.





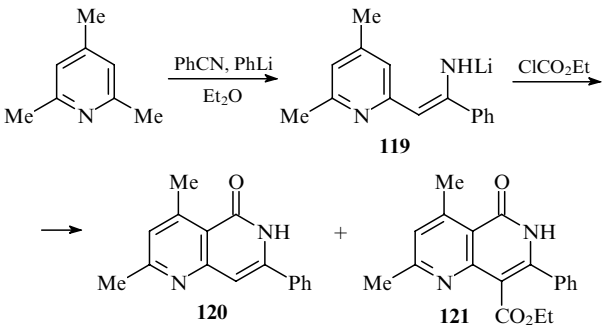
R^1, R^2 = H, Me, Ph.

Successive treatment of *N*-substituted 4-aminopyridines **117** with *tert*-butyllithium and 1,3-chloroiodopropane yielded tetrahydro-1,6-naphthyridines **118**.[99]

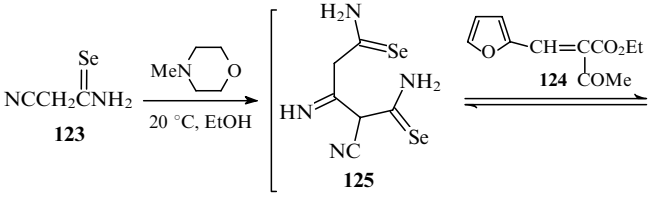


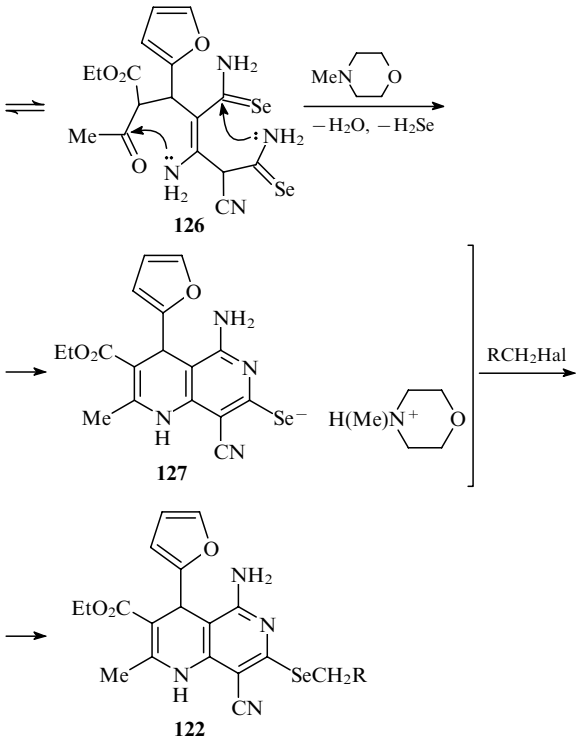
R = $COBu^t$, CO_2Bu^t.

The reaction of chlorocarbonic ester with the lithium derivative of enamine **119**, which was prepared by the reaction of 2,4,6-trimethylpyridine with benzonitrile and phenyllithium, afforded a mixture of 1,6-naphthyridin-5(6*H*)-ones **120** and **121**.[100]



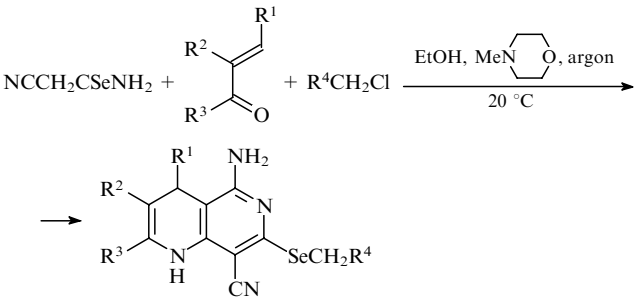
A convenient procedure was developed [101, 102] for the synthesis of 1,6-naphthyridine derivatives **122** containing the alkylselanyl substituent at position 7. Thus multicomponent condensation of cyanoselenoacetamide (**123**), 2-furfurylideneacetoacetic ester (**124**) and alkyl halides was carried out under the action of a twofold excess of *N*-methylmorpholine. The reaction involves the Thorpe dimerisation of the amide **123** yielding compound **125**, its reaction with a molecule of furfurylideneacetoacetic ester (**124**) to form adduct **126**, regioselective cyclocondensation of the adduct **126** producing substituted 1,4-dihydro-1,6-naphthyridine-7-selenolate (**127**) and alkylation of the selenolate **127** with alkyl halides giving rise to naphthyridines **122**.





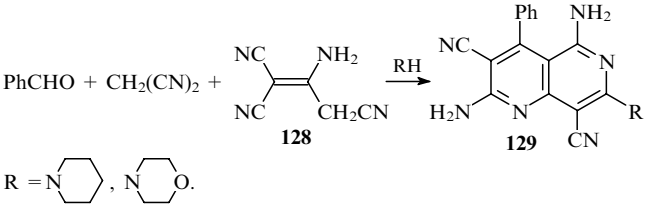
R = H, Me, Et, Pr, C_5H_{11}, CH_2Br, $(CH_2)_3Br$, $C(Me)=CH_2$, $HC=CH_2$, CO_2Et; Hal = I, Br, Cl.

This procedure also allows one to construct the naphthyridine system from other α,β-unsaturated carbonyl compounds under mild conditions.[103]



R^1–R^3 = H, Alk, Ar, Het, CN, COOH, COOAlk, COAr, COHet, $CONH_2$, CONHAr; R^4 = Alk.

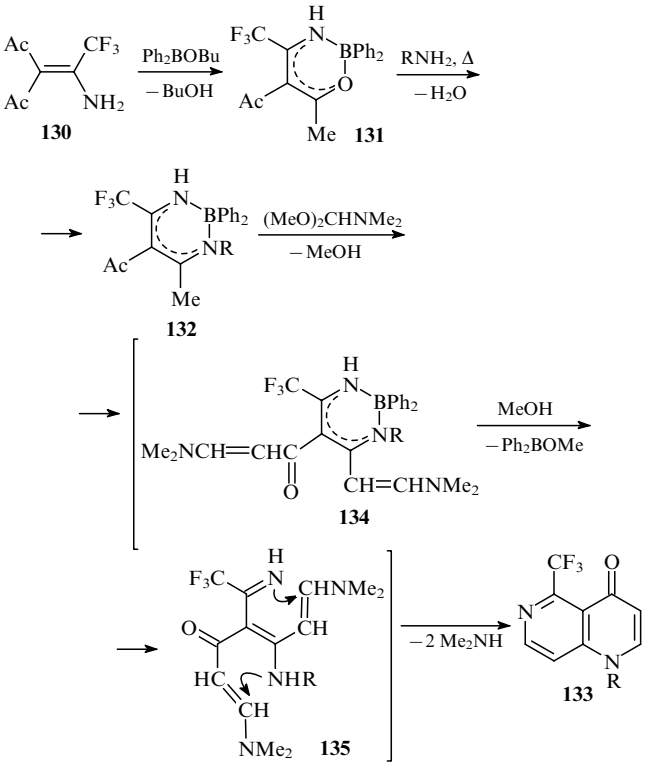
Multicomponent heterocyclisation of benzaldehyde with malononitrile and its dimer **128** in the presence of piperidine or morpholine was used for the construction of the 1,6-naphthyridine system **129**. Heterocyclisation was accompanied by the insertion of the cyclic-amine fragment into the molecule to form the compounds **129**.[104]



R =

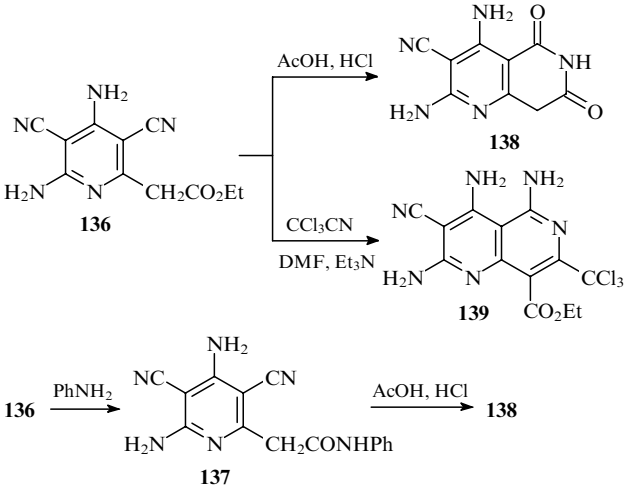
An ingenious method for the construction of the 1,6-naphthyridine system with the use of the 'chelate' methodology was developed.[105] Thus the reaction of 3-acetyl-4-amino-5,5,5-trifluoro-3-penten-2-one (**130**) with Ph_2BOBu afforded chelate complex **131** in which the oxygen atom was replaced by the nitrogen atom upon heating with primary amines. The resulting complexes

132 reacted with two equivalents of dimethylformamide dimethyl acetal to give 5-trifluoromethyl-1,6-naphthyridin-4(1*H*)-ones **133** in 77%–87% yields. It was believed [105] that the complexes **132** reacted with dimethylformamide dimethyl acetal to give condensation products at the methyl groups (**134**), which underwent deborylation with simultaneous cyclisation of intermediates **135** under the action of the methanol eliminated.

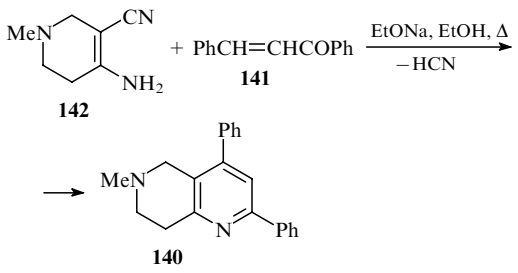


R = Bu, Bn.

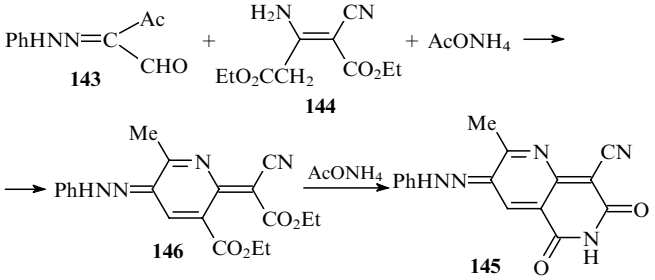
Ethyl (4,6-diamino-3,5-dicyano-2-pyridyl)acetate **136** or (4,6-diamino-3,5-dicyano-2-pyridyl)acetanilide **137** were converted into 1,6-naphthyridine-5,7(6*H*,8*H*)-dione **138** upon refluxing in acetic acid in the presence of HCl. Treatment of the ester **136** with trichloroacetonitrile in the presence of triethylamine afforded naphthyridine **139**.[106]



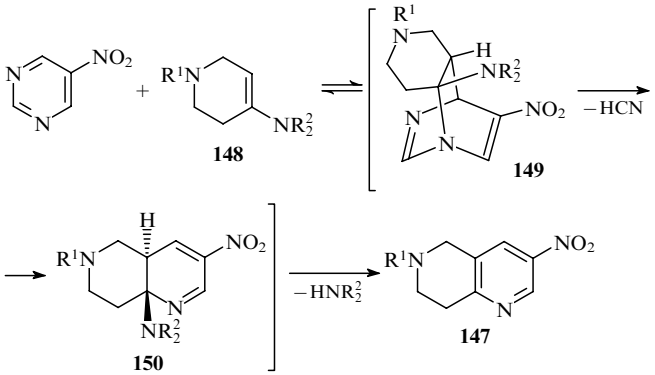
6-Methyl-2,4-diphenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**140**) was synthesised by cyclocondensation of benzylideneacetophenone (**141**) with enamino nitrile **142** in the presence of sodium ethoxide.[107]



Of other procedures for the synthesis of 1,6-naphthyridines, noteworthy is three-component cyclisation of 2,3-dioxobutanal phenylhydrazone (**143**) with diethyl 3-amino-2-cyanopent-2-enedioate (**144**) and ammonium acetate to form substituted 1,6-naphthyridine-5,7(3*H*,6*H*)-dione **145**. Polyfunctionalised pyridine derivative **146** was obtained as the intermediate in this reaction.[108]

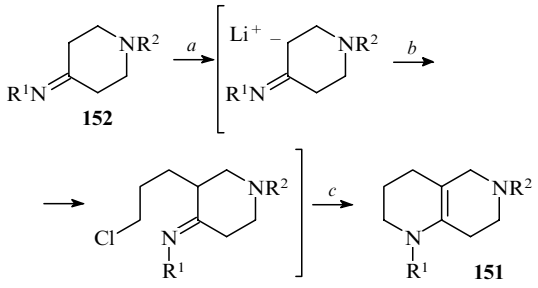


The synthesis of partially hydrogenated *N*-substituted tetrahydro-3-nitro-1,6-naphthyridines **147** involved diene condensation with the inversion of electrophilicity. 5-Nitropyrimidine reacted as the diene component with enamines **148**. Elimination of HCN from adducts **149** followed by elimination of pyrrolidine from intermediates **150** afforded the products **147**.[109]



R^1 = Me, Ac; NR_2^2 = .

A handy procedure for the one-pot synthesis of the previously unknown 1-substituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **151**, which are convenient building blocks and precursors of

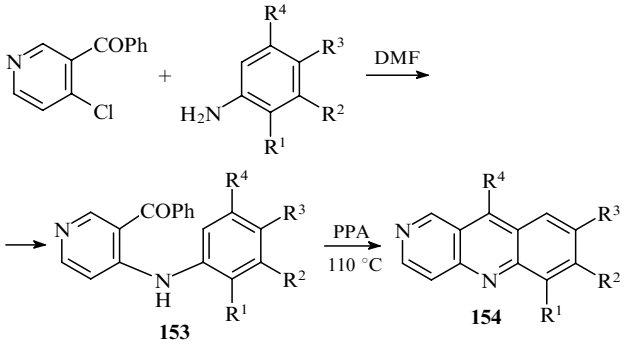


R^1 = Ph, CH_2Ph, (dl)-CH(Me)Ph, (*S*)-CH(Me)Ph; R^2 = Me, Bn, COPh; (*a*) LDA or Et_2NLi, THF, −30 °C, 30 min; (*b*) $Cl(CH_2)_3Br$, −78 °C; (*c*) Δ, 4 h.

biologically active compounds, was developed. The procedure involves metallation of imines **152** with lithium diisopropylamide or diethylamide followed by alkylation of the lithium derivatives with 1,3-bromochloropropane and intramolecular cyclisation of the resulting chloroalkylamines.[110]

2-Benzyl-1,6-dimethyl-3,10-di(methoxycarbonyl)-8-phenyldecahydro-1,6-naphthyridin-4-one was synthesised and its structure was confirmed by X-ray diffraction analysis.[111]

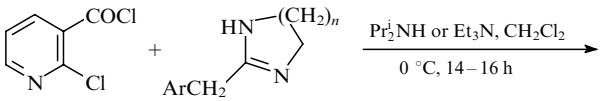
At the end of the section dealing with the synthesis of 1,6-naphthyridines, let us consider special procedures for the preparation of their annelated analogues. Thus a general procedure involves cyclisation of carbonyl derivatives of 4-chloropyridine with aromatic and heterocyclic amines under the action of acids. The reactions of 3-benzoyl-4-chloropyridine with substituted anilines afforded amine **153**, which underwent cyclisation under the action of polyphosphoric acid to form 1,6-naphthyridine derivatives **154** [112] (see also the synthesis of the compounds **91a**,**b** [76]).



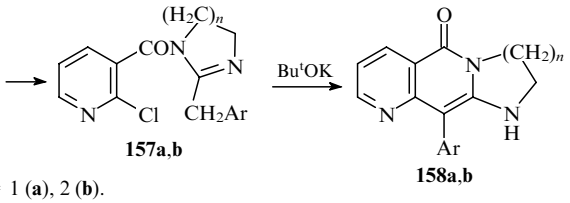
153 **154**

R^1, R^2 = H, OH, OMe, Cl; R^1-R^2 = CH=CH–CH=CH;
R^3 = H, OMe, NO_2; R^4 = H, OMe.

2-Chloronicotinoyl chloride (**155**) was used as the starting compound in the synthesis of heteryl-annelated 1,6-naphthyridines. Its reactions with 4,5-dihydro-1*H*-imidazolines (**156a**) or tetrahydropyrimidines (**156b**) gave rise to the corresponding *N*-acyl derivatives **157a**,**b**, which underwent cyclisation under the action of potassium *tert*-butoxide to yield imidazo- (**158a**) or pyrimido[1,2-*g*][1,6]naphthyridinones (**158b**), respectively. The compounds **158a**,**b** exhibit antiallergic and antiinflammatory activities.[113, 114]



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

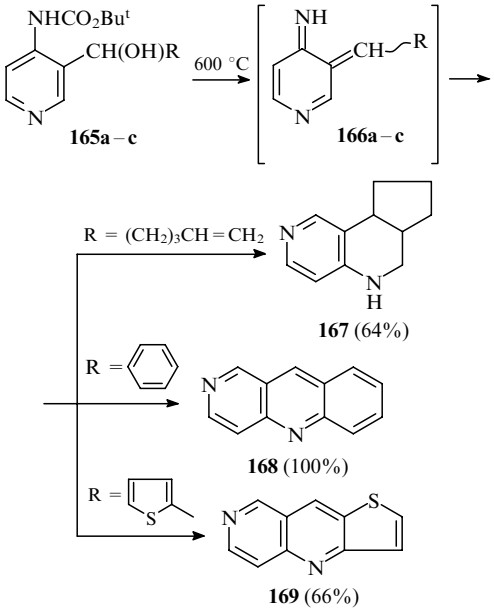


157a,**b** **158a**,**b**

n = 1 (**a**), 2 (**b**).

The reactions of 3-aminocoumarins **159** with 2-chloronicotinoyl chloride (**155**) or 2-chloro-3-formylquinoline (**160**) afforded *N*-acyl derivatives **161** or Schiff bases **162**, which were dehydrochlorinated under the action of bases with simultaneous cyclisation to give benzopyrano[3,4-*h*][1,6]naphthyridines **163** or **164**, respectively (Scheme 2).[115, 116]

Flash pyrolysis of aminopyridine derivatives **165a**–**c** gave rise to intermediates **166a**–**c** containing the heterodiene system. Intramolecular cyclisation of the latter involving the substituent R produced annelated naphthyridines **167**–**169**.[117]



165a–**c** **166a**–**c**

167 (64%)

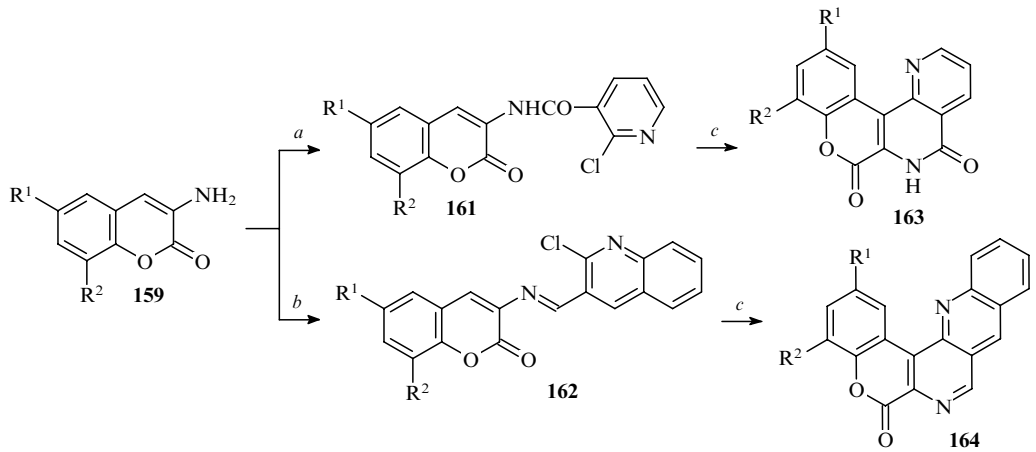
168 (100%)

169 (66%)

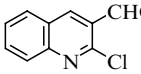
R = $(CH_2)_3CH=CH_2$ (**a**), Ph (**b**), 2-thienyl (**c**).

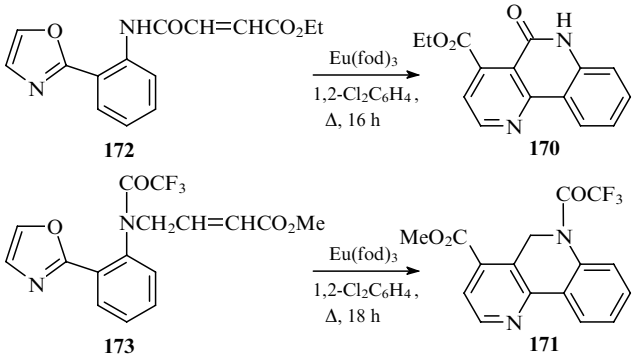
Dihydrobenzo[*h*][1,6]naphthyridines **170** and **171** were synthesised by Eu(fod)$_3$-catalysed intramolecular Diels–Alder cyclisation of the diene system of oxazoles **172** and **173**, respectively, with the double bond of the side-chain substituent.[118]

Scheme 2



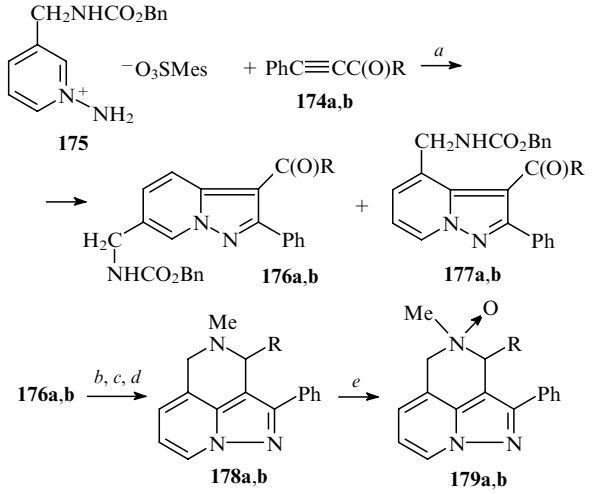
159 **161** **162** **163** **164**

R^1 = H, Br, Cl; R^2 = H, OMe, Br; (*a*) **155**, Et_3N, PhH, Δ, 8 h; (*b*)  (**160**), AcOH; (*c*) Py or $Et_3N-PdCl_2$.



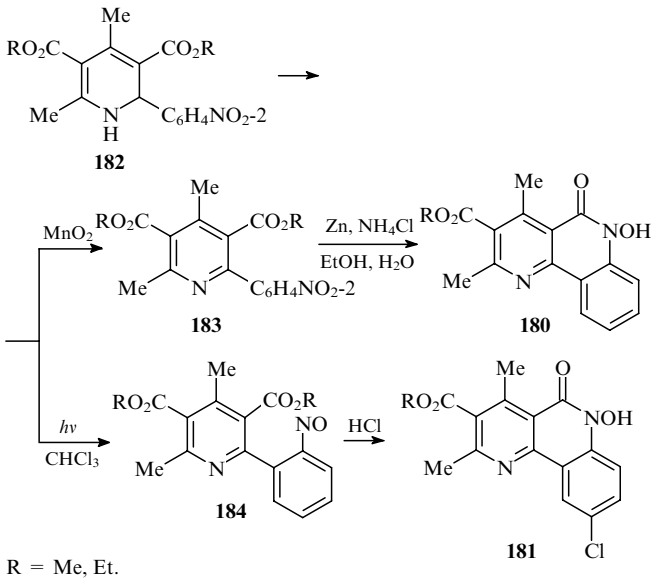
$Eu(fod)_3$ = $Eu[Bu^tC(O)CH_2C(O)(CF_2)_2CF_3]_3$.

1,3-Dipolar cycloaddition of 3-phenylpropynal (**174a**) or phenyl phenylethynyl ketone (**174b**) to the *N*-aminopyridinium salt **175** afforded a mixture of isomeric pyrazolo[1,5-*a*]pyridines **176a**,**b** and **177a**,**b**. Debenzylation of the compounds **176a**,**b** followed by successive treatment with formaldehyde and sodium cyanoborohydride gave rise to naphthyridines **178a**,**b**. Oxidation of the latter with *m*-chloroperbenzoic acid yielded *N*-oxides **179a**,**b**.[119]



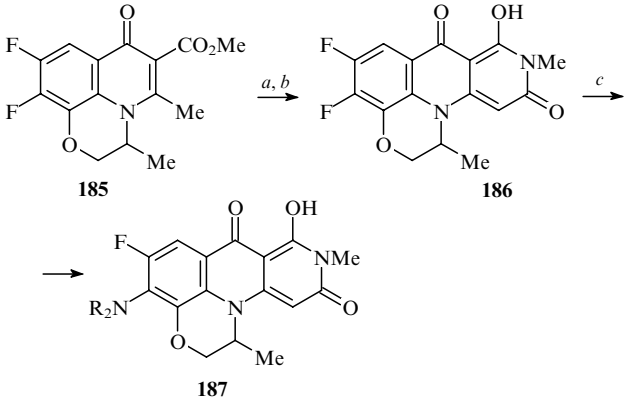
R = H (**a**), Ph (**b**); Mes = 2,4,6-$Me_3C_6H_2$; (*a*) K_2CO_3, MeCN; (*b*) 30% HBr, AcOH; (*c*) HCHO; (*d*) $NaBH_3CN$; (*e*) 3-$ClC_6H_4CO_2H$.

Dihydrobenzo[*h*][1,6]naphthyridines **180** and **181** can be prepared from 4,6-dimethyl-2-(2-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylic esters (**182**) according to two procedures, *viz*., by oxidation of the dihydro derivative **182** to form pyridinedicarboxylic ester **183** followed by reduction of the nitro group with simultaneous cyclisation or by storage of a solution of the compound **182** in chloroform in sunlight to give nitroso compound **184**, which undergoes cyclisation under the action of concentrated HCl.[120]



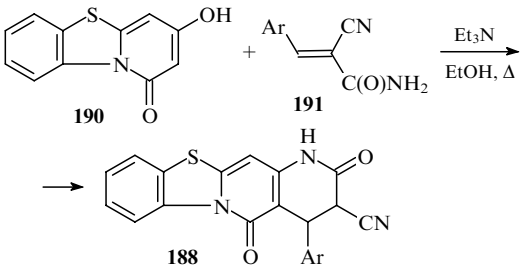
R = Me, Et.

Treatment of a solution of pyrido[1,2,3-*de*][1,4]benzooxazine **185** with a 60% NaOH solution in DMF followed by the addition of methyl isocyanate afforded the tetracyclic 1,6-naphthyridine derivative **186**. The reactions of the latter with substituted pyrrolidines or piperazines gave rise to amino derivatives **187**. The compounds **186** and **187** and their salts possess bactericidal properties.[121]

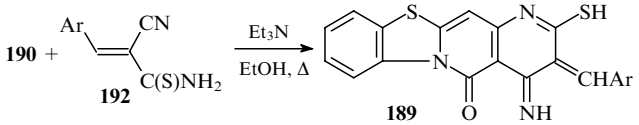


NR_2 are substituted pyrrolidinyls or piperazinyls;
(*a*) 60% NaOH, DMF; (*b*) MeNCO; (*c*) R_2NH, DMSO.

Amido and thioamido derivatives of α,β-unsaturated nitriles were used in the synthesis of annelated 1,6-naphthyridines. Thus substituted benzothiazolo[3,2-*g*][1,6]naphthyridin-5-ones (**188** and **189**) were prepared by refluxing 3-hydroxy-1*H*-pyrido-[2,1-*b*]benzothiazol-1-one (**190**) with arylmethylidenecyano(thio)-acetamides **191** and **192**, respectively, in ethanol in the presence of triethylamine.[122]

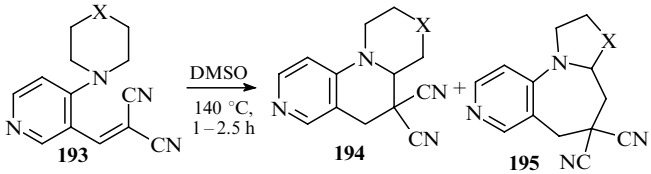


Ar = 4-$MeOC_6H_4$, 4-ClC_6H_4.



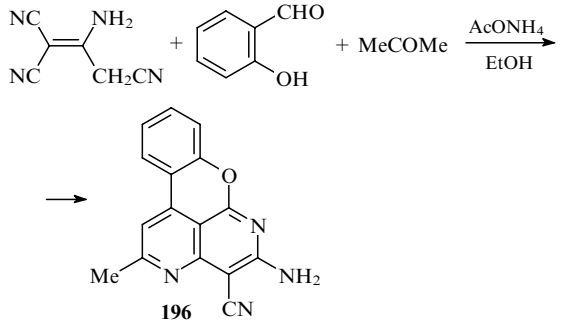
Ar = Ph, 4-$MeOC_6H_4$.

Thermal isomerisation of 3-(2,2-dicyanovinyl)-4-aminopyridines **193** in DMSO afforded a mixture of annelated 1,6-naphthyridines **194** and azepines **195**.[123]

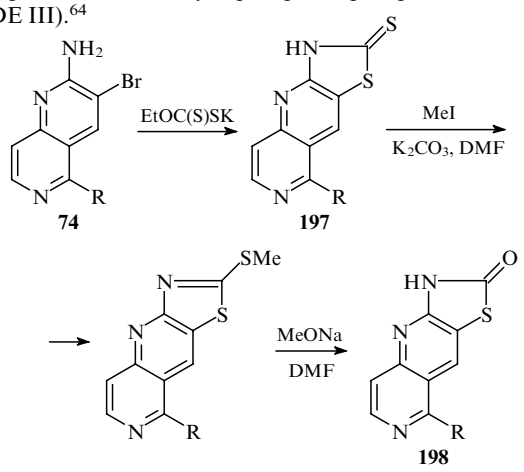


X = CH_2, NPh, O, S.

Of other procedures for the synthesis of annelated 1,6-naphthyridines, noteworthy is three-component condensation of the malononitrile dimer, salicylaldehyde and acetone giving rise to 1,6-naphthyridines **196**.[124]



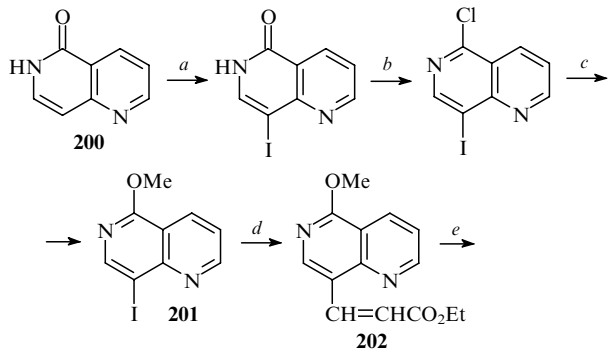
Considerable recent attention has been focused on procedures for modifications of 1,6-naphthyridine derivatives with the aim of searching for new biologically active compounds. Thus condensation of 2-amino-3-bromo-1,6-naphthyridines **74** with potassium *O*-ethyl xanthate in *N*-methylpyrrolidone afforded thiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thiones **197** whose subsequent methylation and hydrolysis of the methyl group in the presence of sodium methoxide afforded thiazolonaphthyridones **198** inhibiting adenosine-3′,5′-cyclophosphate phosphodiesterase (cAMP PDE III).[64]

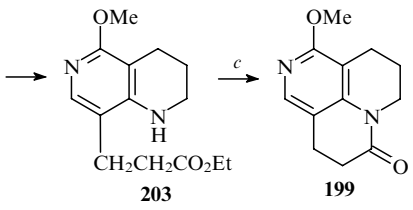


R = Me, Et, Pr^n, Bu^i, Ph, 4-$NO_2C_6H_4$.

The structural fragment of hydrogenated pyrido[3,2-*ij*]-1,6-naphthyridin-6-one **199** is present in the alkaloid matrine (sophocarpidine) found in dried roots of several plants belonging to the genus *Sophora*.

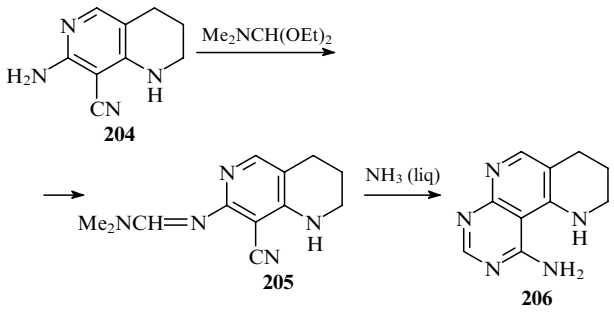
The compound **199** was synthesised from 1,6-naphthyridin-5(6*H*)-one (**200**) in six steps.[125] The key stage of the scheme consists in the Heck reaction of 8-iodo-5-methoxy-1,6-naphthyridine (**201**) with ethyl acrylate. Reduction of the double bond in the resulting derivative **202** and cyclisation of compound **203** under the action of sodium methoxide complete the synthesis.



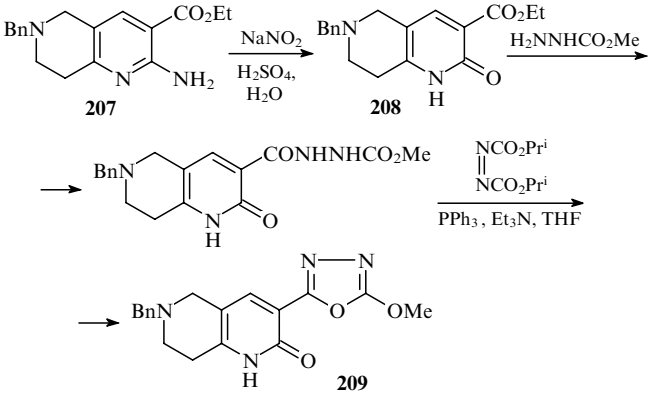


(*a*) I_2, 4M NaOH, 80 °C, 4 h; (*b*) $POCl_3$; (*c*) MeONa, MeOH; (*d*) $CH_2=CHCO_2Et$, $Pd(OAc)_2$, Et_3N, MeCN; (*e*) H_2, PtO_2, MeOH.

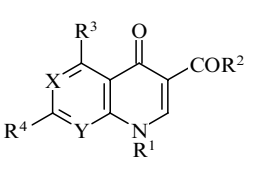
Condensation of 7-amino-8-cyano-1,2,3,4-tetrahydro-1,6-naphthyridine (**204**) with dimethylformamide diethyl acetal afforded azomethine **205**. Its treatment with ammonia gave rise to 1-amino-7,8,9,10-tetrahydropyrimido[4,5-*h*][1,6]naphthyridine (**206**).[126]



Diazotisation of the amine of the naphthyridine series **207** with a solution of sodium nitrite in 10% H_2SO_4 afforded naphthyridinone **208**, which was used as the starting compound in the synthesis of the antagonist of benzodiazepine receptors **209**.[127–129]

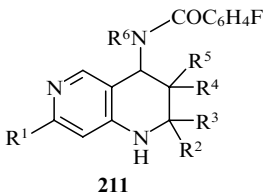


The compounds **210**, including 1,6-naphthyridine derivatives, as well as octahydronaphthyridines **211** are of interest from the pharmacological standpoint.[130–134] Thus the compounds **210** possess low toxicity and are used as components of drugs for prophylaxis and treatment of infectious diseases caused by various pathogenic bacteria.[130–133] Octahydronaphthyridines **211** are used in the treatment of depression or in cases of abstinence.[134]



210

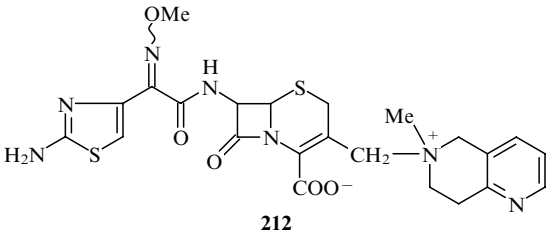
R^1 = H, Et, $(CH_2)_2OH$, $(CH_2)_2Cl$, $CH_2=CH$, cyclo-Alk; R^2 = OH, OAlk; R^3 = H, Hal, NH_2; R^4 = H, Alk, Hal; X, Y = N, CH



211

R^1 = H, Alk(C_1–C_6), CF_3, CN, NO_2; R^2, R^3 = H, Alk(C_1–C_4); R^2–R^3 = $(CH_2)_n$, n = 2–4; R^4 = H, Me, Et; R^5 = OPh, OBn, NO_2; R^6 = H, Alk(C_1–C_6)

The 1,6-naphthyridine fragment is present in the cephem molecule (**212**), which is active with respect to both gram-positive and gram-negative bacteria.[135]

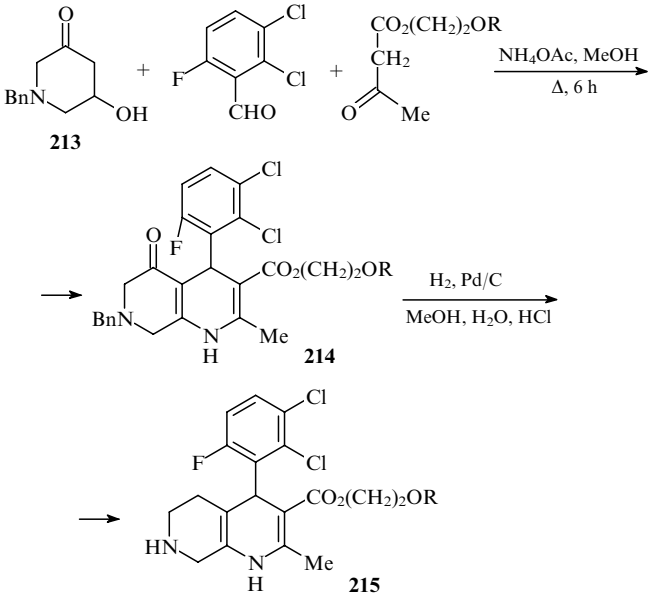


212

Recently, 1,4-dihydro-4-oxo-1,6-naphthyridine derivatives have also been covered by patents as antibacterial agents.[136] 1,4-Dihydro-5-isopropoxy-2-methyl-4-(2-trifluoromethylphenyl)-1,6-naphthyridine-3-carboxylic esters are efficient components of cytokinin inhibitors.[137] 1,6-Naphthyridine-2-carboxylamides were covered by patents as drugs used in the therapy and prophylaxis of cytomegalovirus infection.[138] 1,2,3,4,5,6,7,8-Octahydro-1,6-naphthyridine derivatives were covered by patents as anticonvulsive agents[139] and tachykinin NR_3-receptor antagonists.[140] Oxadiazolyl-substituted 1,6-naphthyridin-2-ones were covered by patents as benzodiazepine receptor antagonists.[141]

IV. 1,7-Naphthyridines

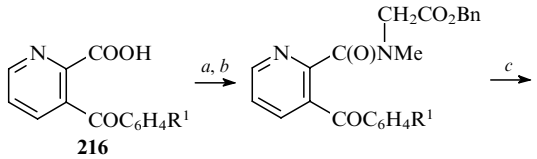
Among procedures for the synthesis of 1,7-naphthyridines, four-component condensation of 1-benzyl-3-hydroxy-5-piperidone (**213**) with 2,3-dichloro-6-fluorobenzaldehyde, acetoacetic esters and ammonium acetate giving rise to 1,4,5,6,7,8-hexahydro-1,7-naphthyridin-5-one-3-carboxylic esters **214** attracts attention due to its simplicity. The compounds **214** and their *N*-debenzylation products **215** exhibit hypotensive activity.[142, 143]



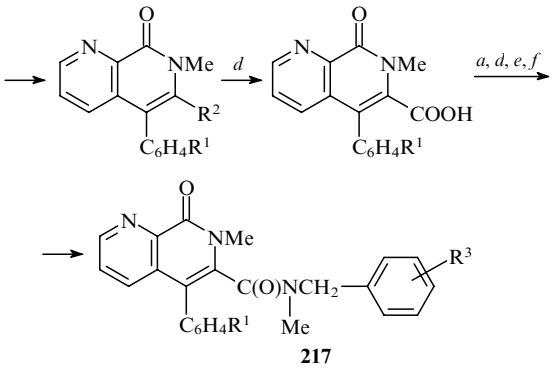
213 **214** **215**

R = Ph, 2,3-$Cl_2C_6H_3$.

3-Aroylpyridine-2-carboxylic acids **216** were used as the starting compounds for the preparation of 7-methyl-1,7-naphthyridin-8(7*H*)-one derivatives **217**, which are new strong neurokinin NK_1-receptor antagonists.[144]



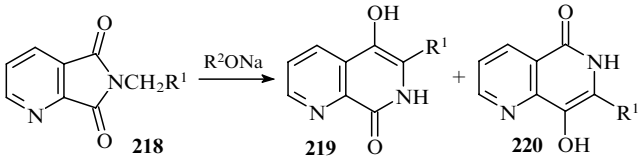
216



217

R^1 = H, 4-Me, 4-F; R^2 = CO_2CH_2Ph, CN, CHO, $CONH_2$;
R^3 = 3,5-$(CF_3)_2$, 2-MeO, 2-Cl, 2,5-Cl_2;
(*a*) $SOCl_2$, DMF, THF; (*b*) $BnCO_2CH_2NHMe \cdot HCl$, Et_3N, CH_2Cl_2;
(*c*) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhMe; (*d*) H_2, Pd/C, MeOH;
(*e*) $R^3C_6H_4CH_2NH_2$, Et_3N, CH_2Cl_2; (*f*) MeI, NaH, DMF.

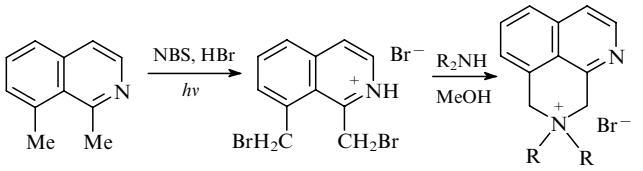
The reactions of *N*-substituted pyridine-2,3-dicarboxylimides **218** with sodium alkoxides afforded a mixture of 5-hydroxy-1,7-naphthyridin-8(7*H*)-ones **219** and 8-hydroxy-1,6-naphthyridin-5(6*H*)-ones **220**.[145]



218 **219** **220**

R^1 = CO_2Me, CO_2Et, CO_2Pr^i, COPh; R^2 = Me, Et.

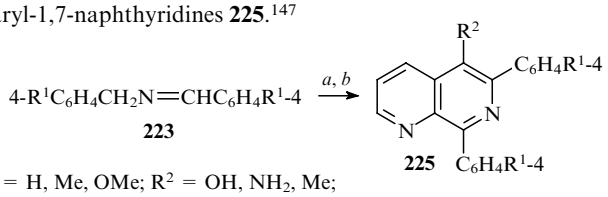
Treatment of 1,8-bis(bromomethyl)isoquinolinium bromide (**221**) prepared from 1,8-dimethylisoquinoline with secondary amines yielded *N*,*N*-dialkylbenzo[*de*][1,7]naphthyridinium bromides **222**.[146]



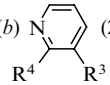
221 **222**

R = Me, Et, Pr^n, Pr^i.

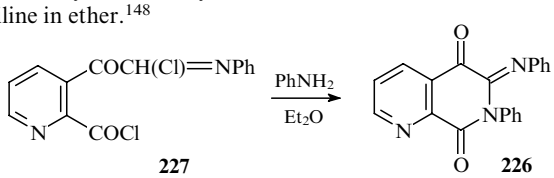
Condensation of the lithium salt, which was prepared by metallation of Schiff bases **223** with lithium diisopropylamide, with ethyl 3-acetyl-2-halogenonicotinates, 3-cyano-2-halogenopyridines or 3-acetyl-2-halogenopyridines **224** gave rise to 6,8-diaryl-1,7-naphthyridines **225**.[147]



223 **225**

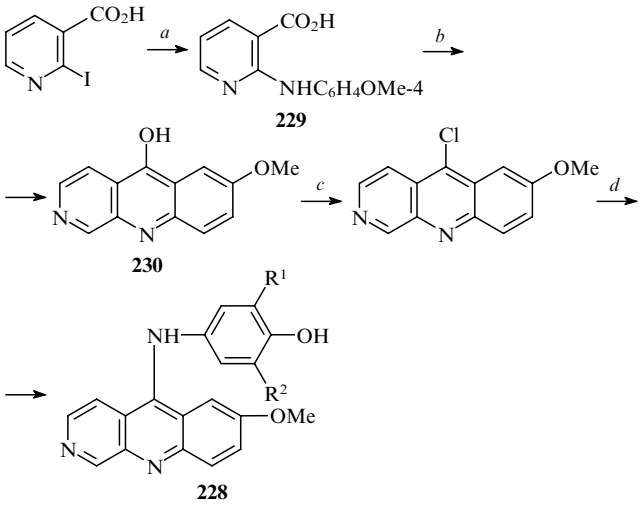
R^1 = H, Me, OMe; R^2 = OH, NH_2, Me;
(*a*) Pr^i_2NLi; (*b*)  (**224**), R^3 = CO_2Et, CN, COMe; R^4 = Cl, Br.

The imino derivative of tetrahydro-1,7-naphthyridinedione **226** was synthesised by the reaction of acid chloride **227** with aniline in ether.[148]



227 **226**

With the aim of searching for new antimalarial drugs among annelated 1,7-naphthyridines, compounds **228** were synthesised. Cyclisation of amino acid **229**, which was prepared from 2-iodonicotinic acid, under the action of $POCl_3$ in polyphosphoric acid afforded 10-hydroxy-2-methoxybenzo[*b*][1,7]naphthyridine **230**. The subsequent reactions with $POCl_3$ and then with aminophenols complete the synthesis. The preliminary assay of the biological activities of the compounds **228** demonstrated that these compounds are inferior to the well-known antimalarial agent pyronaridine.[149]



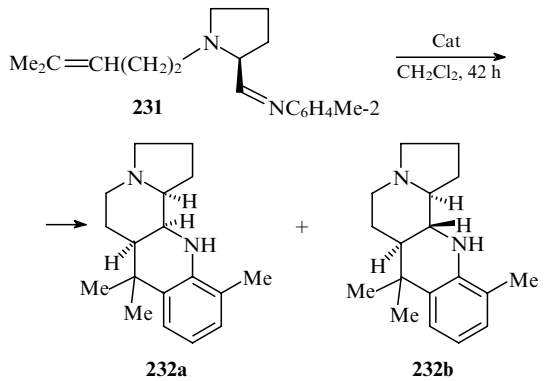
229 **230** **228**

R^1, R^2 = H, CH_2NEt_2;

(*a*) H_2N–C$_6$H$_4$–OMe; (*b*) $POCl_3$, PPA; (*c*) $POCl_3$;

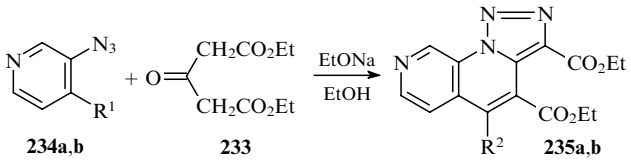
(*d*) H_2N–C$_6$H$_3$(R^1)(R^2)–OH.

Treatment of (*S*)-*N*-[*N*-(4-methylpent-3-enyl)pyrrolin-2-ylmethylidene]-*o*-toluidine (**231**) with Lewis acids ($FeCl_3$, $SnCl_4$, $AlCl_3$, $MeAlCl_2$, Me_2AlCl, $EtAlCl_2$, Et_2AlCl or $BF_3 \cdot OEt_2$) or Brønsted acids (CF_3COOH or TsOH) led to formal Diels – Alder heterocyclisation giving rise to 1,7-naphthyridines **232a**,**b** in yields of > 80%. The isomer ratio depends substantially on the nature of the catalyst used. In the case of monodentate Lewis acids of the $MeAlCl_2$ or $EtAlCl_2$ type, the *cis*-isomer **232a** was obtained as the major product (99%), whereas the reactions involving bidentate Lewis acids of the $SnCl_4$ type or Brønsted acids afforded predominantly the *trans*-isomer **232b** (87% – 99%).[150]



231 **232a** **232b**

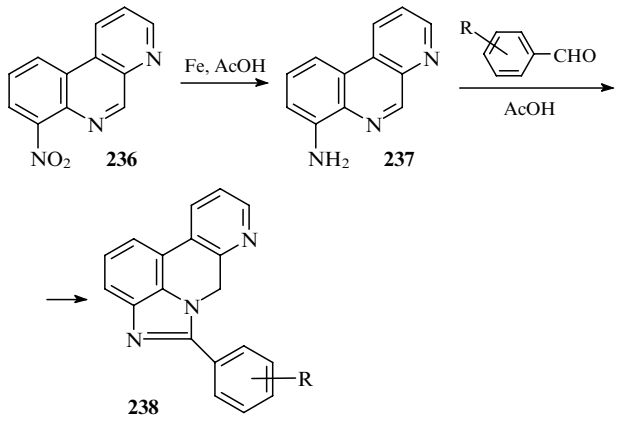
1,2,3-Triazolo[1,5-*a*][1,7]naphthyridines **235a**,**b** were synthesised by the reactions of diethyl acetone-1,3-dicarboxylate (**233**) with *ortho*-substituted azides of the pyridine series **234a**,**b**.[151]



234a,**b** **233** **235a**,**b**

R^1 = CN (**234a**), CO_2Et (**234b**); R^2 = NH_2 (**235a**), OH (**235b**).

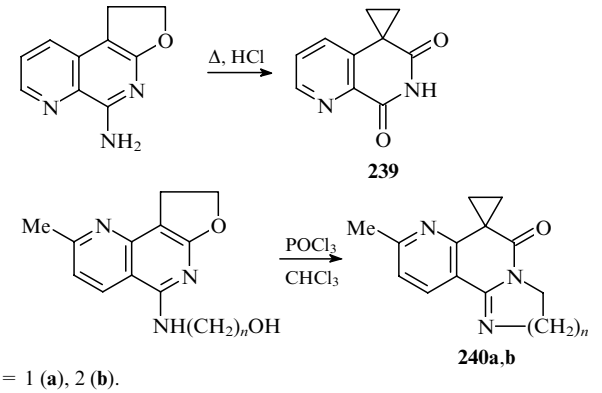
Reduction of 7-nitrobenzo[*f*][1,7]naphthyridine **236** with iron in 80% acetic acid gave rise to amine **237**, whose condensation with aromatic aldehydes afforded benzoimidazo[4,3-*fg*][1,7]-naphthyridines (**238**) exhibiting antibacterial and antifungal activities.[152, 153]



236 **237** **238**

R = H, Me, NO_2, Cl.

The rearrangement of amine of the 1,2-dihydrofuro[3,2-*f*]-[1,7]naphthyridine series produced naphthyridine derivative **239** containing the spirocyclopropane fragment.[154] The reactions of analogous 1,2-dihydrofuro[2,3-*h*][1,7]naphthyridine derivatives containing the hydroxyalkylamino group with $POCl_3$ afforded imidazo[2,1-*f*]- (**240a**) or pyrimidino[2,1-*f*][1,7]naphthyridinones (**240b**) bearing the spirocyclopropane fragment.[155]

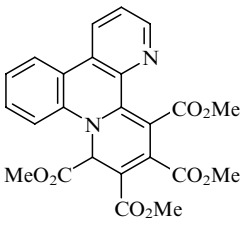


239 **240a**,**b**

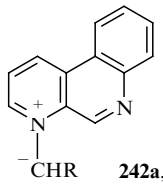
n = 1 (**a**), 2 (**b**).

The reactions of 5,8-dihalogeno-1,7-naphthyridines with potassium amide in liquid ammonia were demonstrated to give mixtures of aminohalogeno, monohalogeno and monoamino derivatives of 1,7-naphthyridines.[156]

The reactivity of 4,6-benzo[*h*][1,7]naphthyridine in the Diels – Alder reactions with maleic acid and dimethyl acetylenedicarboxylate was examined. In the former case, the corresponding quaternary salt was obtained, whereas the latter reaction afforded adduct **241**.[157] 6-Ethoxycarbonyl- (**242a**) and phenacylmethylides (**242b**) were used as 1,3-dipolar reagents in the reactions with methacrylic acid, methyl methacrylate, butyl vinyl ether, methyl vinyl ketone, maleic anhydride and dimethyl acetylenedicarboxylate.[157, 158]

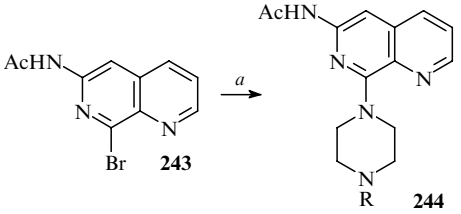


241



R = CO_2Et (**a**), PhCO (**b**). **242a,b**

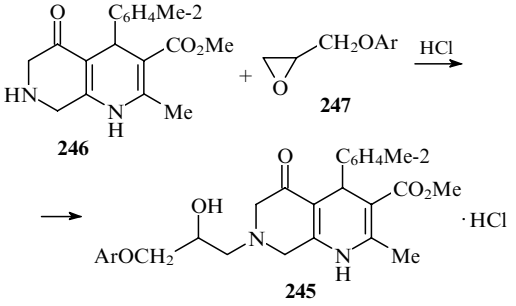
The reactions of 6-acetamido-8-bromo-1,7-naphthyridine (**243**) with substituted piperazines in the presence of NaH afforded 6-acetamido-8-(4-R-piperazin-1-yl)-1,7-naphthyridines **244** possessing antiinflammatory, antiarrhythmic, cardiotonic, vasodilator, broncholytic, diuretic and antichlolinergic activities.[159–162]



243 **244**

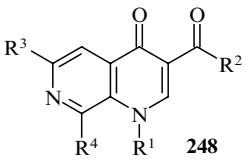
R = H, $(CH_2)_2OH$, CHO, Ar; (*a*)  NR, $EtO(CH_2)_2OH$, NaH.

Hydrochloride of the derivative of 1,7-naphthyridine-3-carboxylic acid **245**, which lowers high blood pressure, was prepared from compound **246** and oxirane **247** upon refluxing in MeOH followed by saturation of the reaction mixture with HCl.[163]



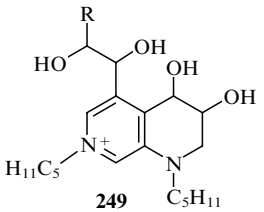
246 **247** **245**

1,7-Naphthyridone derivatives **248** were covered by patents as antibacterial agents.[164–166] Naphthyridinium derivatives **249** were covered by a patent as antidiabetic drugs.[167]



248

R^1 = H, Et, Bn; R^2 = OH, OAlk; R^3, R^4 = Hal, Me_2N, OAlk.



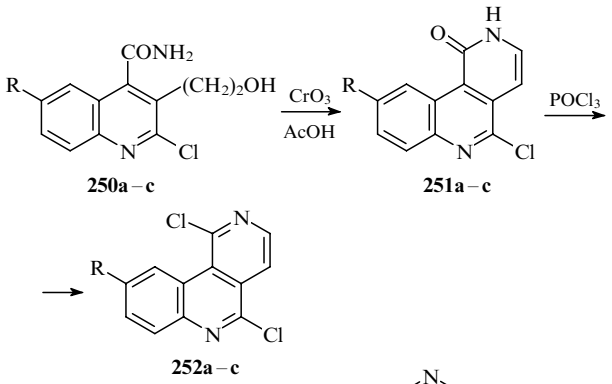
249

R = H, $HOCH_2CH(OH)$.

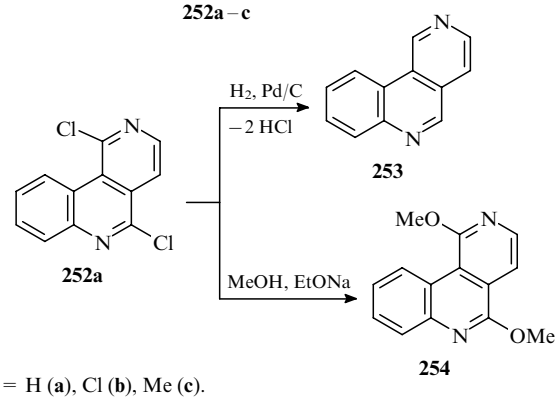
The data on different biological activities exhibited by a series of other 1,7-naphthyridine derivatives have also been reported in recent years.[157, 168–172]

V. 2,6-Naphthyridines

Judging from the number of papers published over the last 15 years, the chemistry of 2,6-naphthyridines attracted much less attention than that of 1,5-, 1,6- or 1,7-naphthyridines. Of the synthetic procedures developed over this period, noteworthy is oxidative cyclisation of 4-carbamoyl-3-(2-hydroxyethyl)quinolines **250a–c** under the action of CrO_3 in glacial AcOH giving rise to benzo[*c*][2,6]naphthyridines **251a–c**. The latter were used in the synthesis of 2,6-naphthyridine derivatives **252–254**.[173]



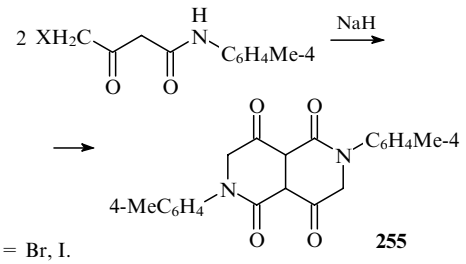
250a–c **251a–c** **252a–c**



252a **253** **254**

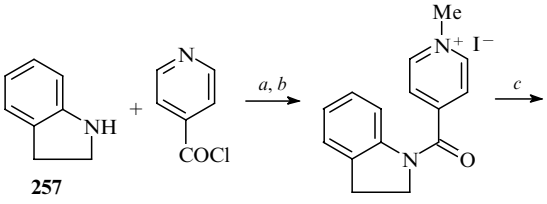
R = H (**a**), Cl (**b**), Me (**c**).

Treatment of toluidides of halogen-substituted acetoacetic acids with sodium hydride in dioxane led to intermolecular cyclisation to form completely hydrogenated 2,6-naphthyridinetetrone **255**.[174]

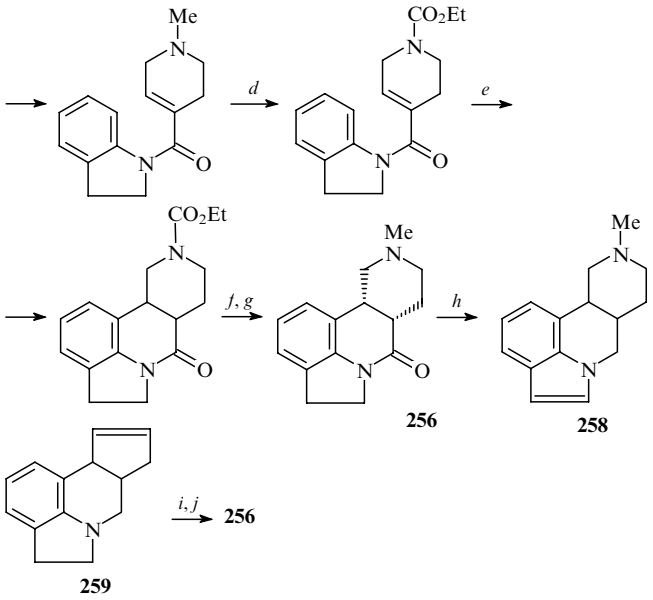


X = Br, I. **255**

Indolo[1,7-*bc*][2,6]naphthyridine **256** is a strong and selective antagonist of serotonin receptors of the 5-$HT_{2C/2B}$ subtypes possessing relatively weak affinity for 5-HT_{2A} subtype receptors.[175–177] The compound **256** was synthesised starting from indoline (**257**) and isonicotinoyl chloride.[175] Oxidation of the compound **256** with MnO_2 afforded indolonaphthyridine **258**. Yet another approach to the compound **256** involves oxidation of the double bond in compound **259** with ozone or osmium tetroxide followed by treatment with methylamine.[178] The indolonaphthyridines **256** and **258** were covered by patents as drugs for the treatment of appetite disturbance, obsessive states (phobia and depressions) and other diseases.[177, 178]

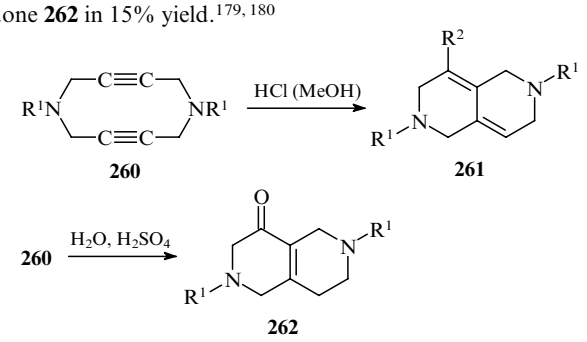


257



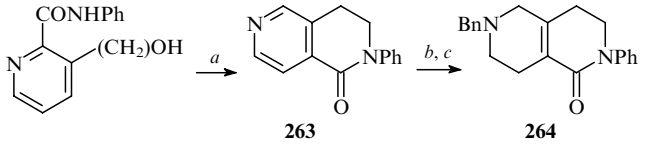
(*a*) Et_3N; (*b*) MeI; (*c*) $NaBH_4$; (*d*) $ClCO_2Et$; (*e*) *hv*; (*f*) AlH_3, THF; (*g*) (−)-di-*p*-tolyltartaric acid; (*h*) MnO_2; (*i*) O_3 (OsO_4); (*j*) $MeNH_2$.

The reactions of 1,6-dialkyl-1,6-diazacyclodeca-3,8-diynes **260** with different organic solvents (cyclohexa-1,4-diene, 9,10-dihydroanthracene or cyclooctane) as scavengers or with such reagents as HCl or MeOH proceed with high regioselectivity according to the Ad_E2 mechanism to give 1,2,3,5,6,7-hexahydro-2,6-naphthyridines **261** in quantitative yields. The reaction of the diyne **260** with H_2O in the presence of H_2SO_4 afforded naphthyridone **262** in 15% yield.[179, 180]



R^1 = Me, Et, Pr^i; R^2 = Cl, OMe.

Cyclisation of anilide of 3-(2-hydroxyethyl)pyridine-2-carboxylic acid occurred under the action of diethyl azodicarboxylate and Ph_3P. Subsequent treatment of the resulting 2,6-naphthyridine **263** with phenacyl bromide and then with sodium borohydride afforded octahydro-2,6-naphthyridine **264** covered by a patent as a medicine for prophylaxis and treatment of schizophrenia and depressions.[181]

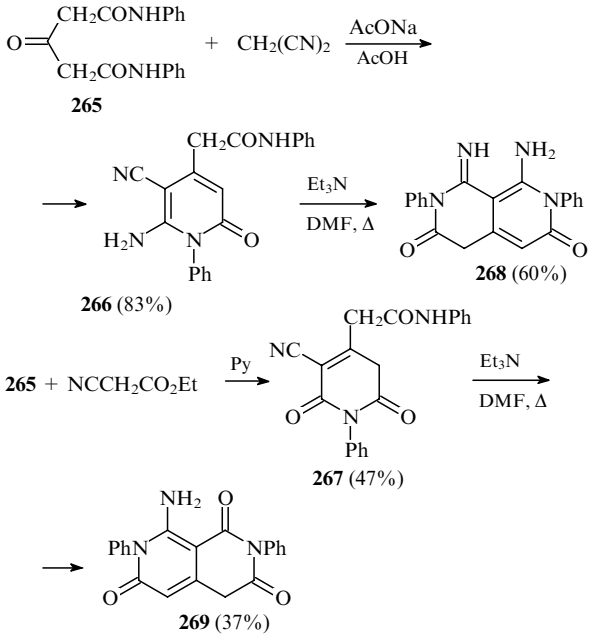


(*a*) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF; (*b*) BnBr, PhMe; (*c*) $NaBH_4$, MeOH.

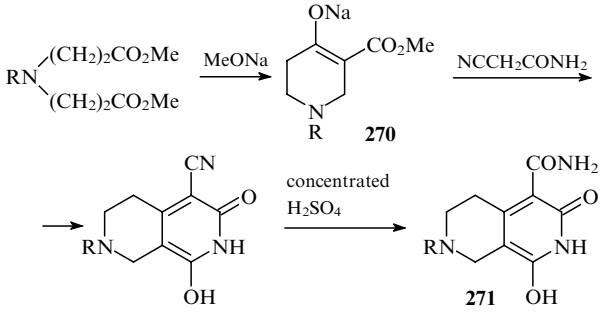
It was reported that 2-methoxy-12-methoxycarbonyl-2,6,8,9-tetrahydro-1*H*-indolo[7*a*,1*a*][2,6]naphthyridine isolated from seeds of *Erythrina melanacantha* Yarms can be used in the treatment of different forms of hypertonia and as an inhibitor of thrombocyte agglutination.[182]

VI. 2,7-Naphthyridines

Various approaches to the synthesis of 2,7-naphthyridines are available. Thus dianilide of 3-oxoglutaric acid **265** reacted with malononitrile in the presence of sodium acetate to give pyridone derivative **266**, whereas the reaction of the compound **265** with ethyl cyanoacetate in pyridine afforded tetrahydropyridinedione derivative **267**. The compounds **266** and **267** underwent cylcisation upon heating with triethylamine in DMF to form substituted 2,7-naphthyridine-3,6-diones **268** and **269**, respectively.[183]



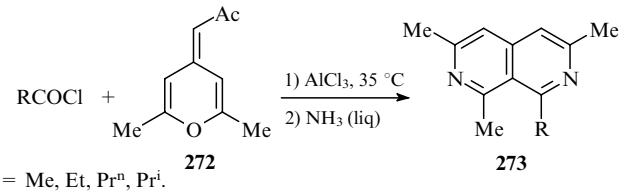
Dieckmann cyclisation of bis(2-methoxycarbonylethyl)alkylamines under the action of sodium methoxide gave rise to sodium salts of 4-hydroxy-3-methoxycarbonyltetrahydropyridines **270**. Condensation of the latter with cyanoacetamide afforded 4-cyano-1-hydroxy-5,6,7,8-tetrahydro-3-oxo-2,7-naphthyridines whose hydrolysis gave rise to 4-carbamoyl derivatives **271** exhibiting antiarrhytmic activity.[184]



R = Et, Bn.

One of procedures for the preparation of alkyl-substituted 2,7-naphthyridines involves acylation of alcohols, ketones or alkenes in the presence of $AlCl_3$ followed by treatment of the reaction mixture with ammonia. However, these reactions are not necessarily regioselective. Thus, the reactions of acetyl chloride with *tert*-butyl alcohol or isobutylene in the presence of $AlCl_3$ followed by treatment with NH_4OH gave rise to 1,3,6,8-tetramethyl-2,7-naphthyridine along with other reaction products.[185, 186]

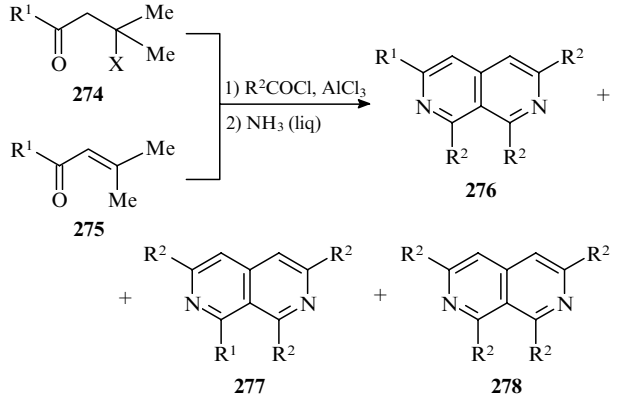
1-Alkyl-3,6,8-trimethyl-2,7-naphthyridines **273** were regioselectively prepared by the reactions of pyran **272** with an excess of fatty acid chlorides in the presence of $AlCl_3$ followed by treatment with liquid ammonia.[187]



272 **273**

R = Me, Et, Pr^n, Pr^i.

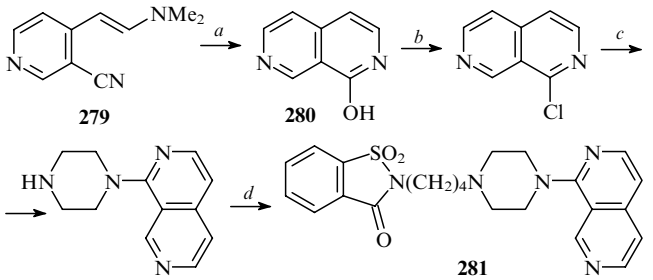
Acylation of ketones **274** or enones **275** in the presence of $AlCl_3$ proceeded nonselectively. Subsequent treatment with liquid ammonia afforded a mixture of 1,3,6,8-tetraalkyl-2,7-naphthyridines **276** and **277** along with symmetrically substituted naphthyridines **278** and picolines.[188]



274 **276** **275** **277** **278**

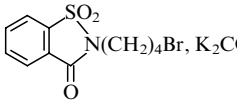
R^1, R^2 = Me, Et, Pr^i; X = OH, OMe.

Yet another reaction used in the synthesis of 2,7-naphthyridine derivatives involves intramolecular cyclisation of enamino nitriles under the action of acid catalysts. Thus compound **279** underwent cyclisation to form 1-hydroxy-2,7-naphthyridine (**280**), which was used in the synthesis of sedative agent **281**.[189]

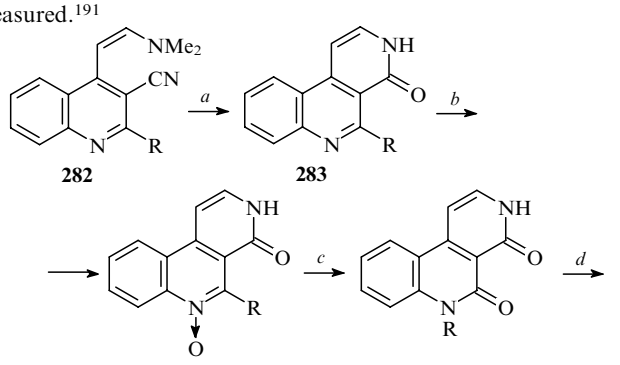


279 **280** **281**

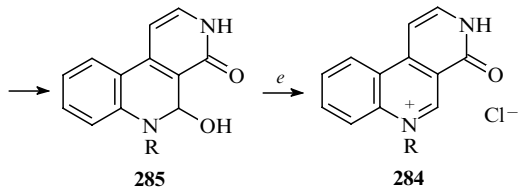
(*a*) 30% HBr, AcOH; (*b*) $POCl_3$; (*c*) HN NH, Bu^tOK, Bu^tOH;

(*d*) 

Analogous cyclisation of enamino nitrile **282** in polyphosphoric acid afforded benzo[*c*][2,7]naphthyridine **283**, which was converted into perlolinium chloride (**284**) [herbaceous alkaloid perloline (**285**)].[190] The mass spectra of the compound **285** were measured.[191]



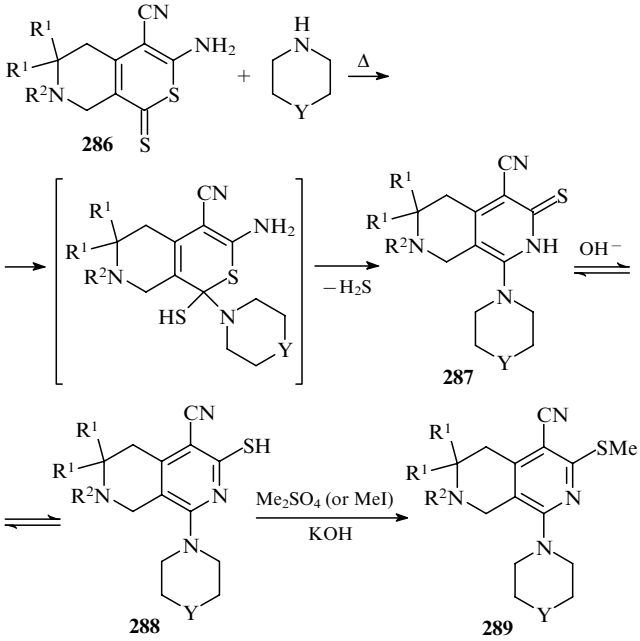
282 **283**



285 **284**

R = 3,4-$(MeO)_2C_6H_3$; (*a*) PPA; (*b*) 3-$ClC_6H_4CO_3H$; (*c*) *hv*, MeOH; (*d*) $[MeO(CH_2)_2O]_2AlH_2Na$; (*e*) HCl.

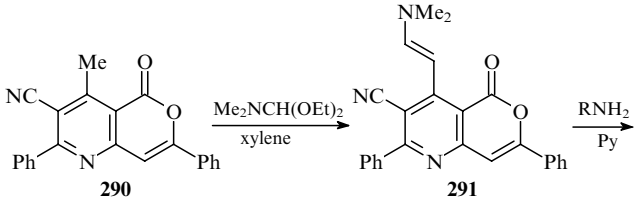
Yet another approach to the synthesis of 2,7-naphthyridines involves recyclisation of pyridinothiopyranothiones and pyridinopyranones. Thus recyclisation of thiopyranothiones **286** upon heating with morpholine, piperidine or piperazine in anhydrous ethanol proceeded through the nucleophilic attack of the amine on the thiocarbonyl group, the cleavage of the C(1)—S bond of the thiopyran ring and the rearrangement to form finally 2,7-naphthyridine-3(2*H*)-thiones **287**. It was demonstrated that the compounds **287** in the crystalline state exist in the equilibrium with the thiol form **288**. Their methylation with Me_2SO_4 or MeI in aqueous or ethanolic solutions of KOH produced thiomethyl derivatives **289** exhibiting antibacterial activity.[192]



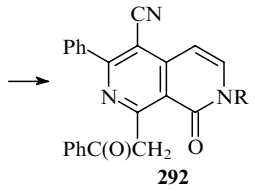
286 **287** **288** **289**

R^1 = H, Me; R^2 = Me, $CH_2CH{=}CH_2$; Y = O, CH_2, NH.

Condensation of substituted pyrano[4,3-*b*]pyridin-5-one **290** with dimethylformamide dimethyl acetal in xylene yielded enamine **291**, which underwent recyclisation to 2-alkyl-5-cyano-8-phenacyl-2,7-naphthyridin-1(2*H*)-ones **292** upon treatment with primary amines.[193] It was demonstrated that the change in the sequence of the addition of the reagents to the pyranone **292** (first, treatment with benzylamine and then condensation with dimethylformamide dimethyl acetal) resulted in 8-benzoyl-6-benzyl-3-cyano-4-(2-dimethylaminovinyl)-2-phenyl-1,6-naphthyridin-5(6*H*)-one (**293**).

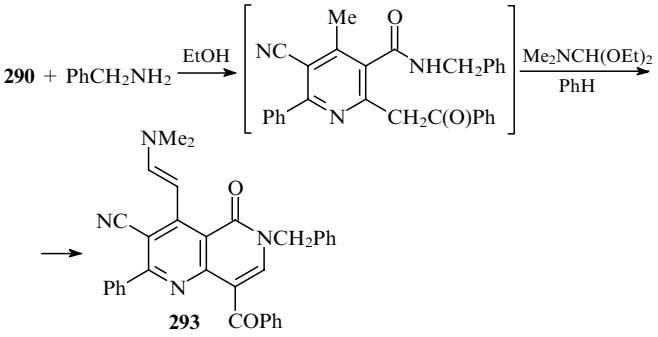


290 **291**



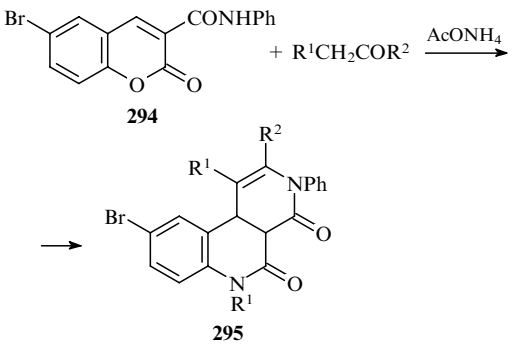
292

R = Pr, Bn.



293

The reactions of 3-(phenylcarbamoyl)coumarin (**294**) with ketones in the presence of ammonium acetate in ethanol at 20 °C or in the absence of a solvent at 170 °C yielded benzo[*c*][2,7]-naphthyridines **295**.[194]

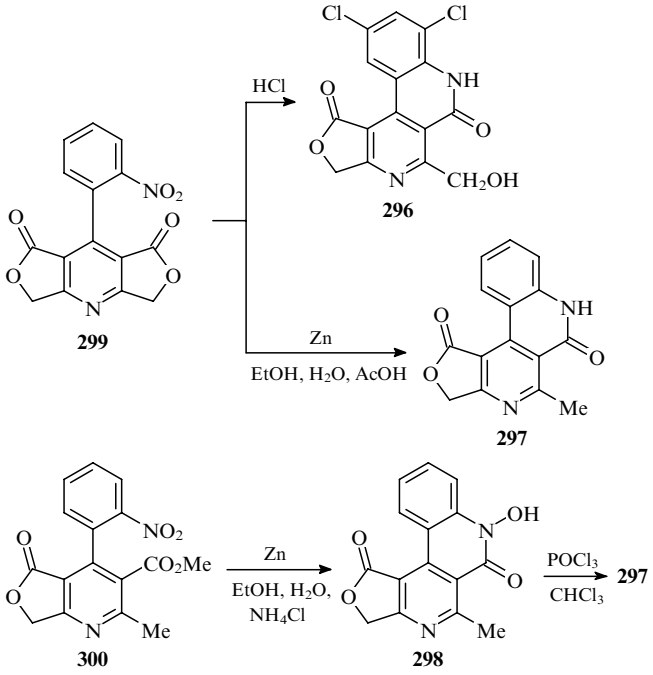


294

295

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

Fused tetrahydro-2,7-naphthyridine-1,6-diones (**296**–**298**) were also synthesised by reductive cyclisation of difuropyridine **299** and furopyridine **300**.[195]



296

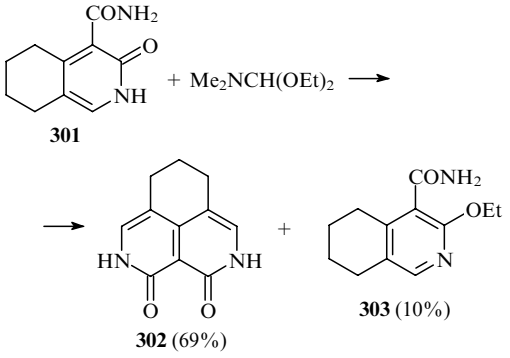
299

297

300

298

Annelated 2,7-naphthyridines were prepared according to a number of other approaches. Thus the reaction of hexahydro-3-oxoisoquinoline-4-carboxamide (**301**) with dimethylformamide diethyl acetal afforded a mixture of 4,5-trimethyl-1,2,7,8-tetrahydro-2,7-naphthyridine-1,8-dione (**302**) with another O-alkylation product **303**.[196]

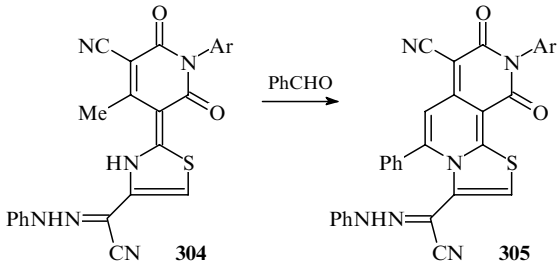


301

302 (69%)

303 (10%)

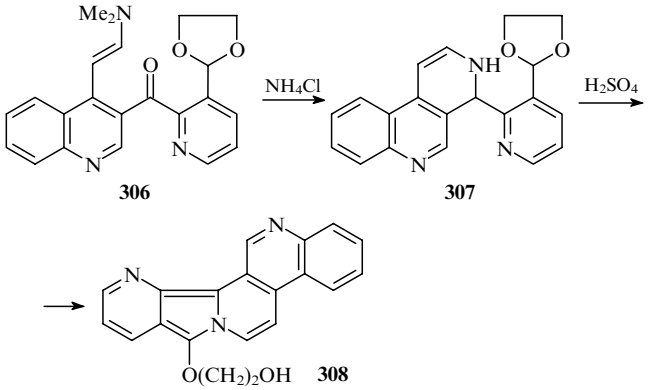
3-(2,3-Dihydrothiazol-2-ylidene)tetrahydropyridinedinone (**304**) underwent cyclocondensation upon treatment with benzaldehyde to form thiazolo[2,3-*a*][2,7]naphthyridine (**305**).[197]



304

305

Enamine **330** underwent cyclisation to give 2,7-naphthyridine **307** under the action of ammonium chloride. The compound **307** was converted into benzo[*f*]pyrido[2′,3′:3,4]pyrrolo[2,1-*a*]-[2,7]naphthyridine **308** on treatment with H_2SO_4.[198]

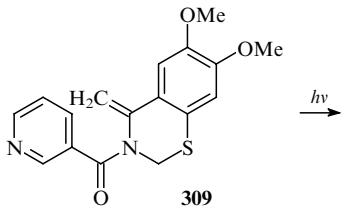


306

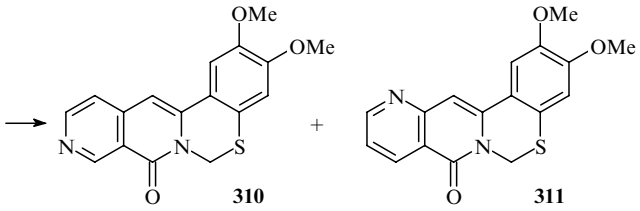
307

308

Photocyclisation (irradiation with a low-pressure mercury lamp, the power was 10 W, MeOH, N_2 atmosphere, 5 h) of 4-methylidene-3-nicotinoyltetrahydro-1,3-benzothiazine **309** gave rise to a mixture of isomeric 6*H*,8*H*-naphthyridino-1,3-benzothiazin-8-ones **310** and **311**.[187]

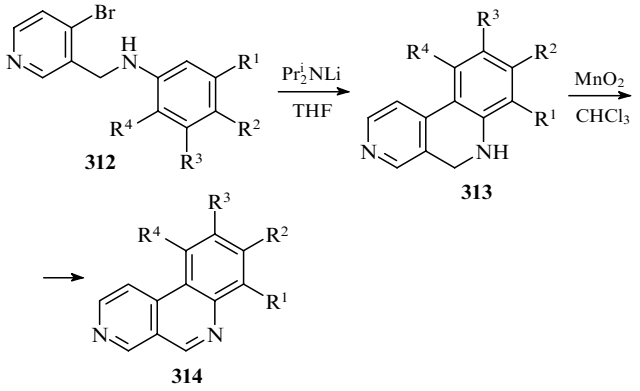


309



310 **311**

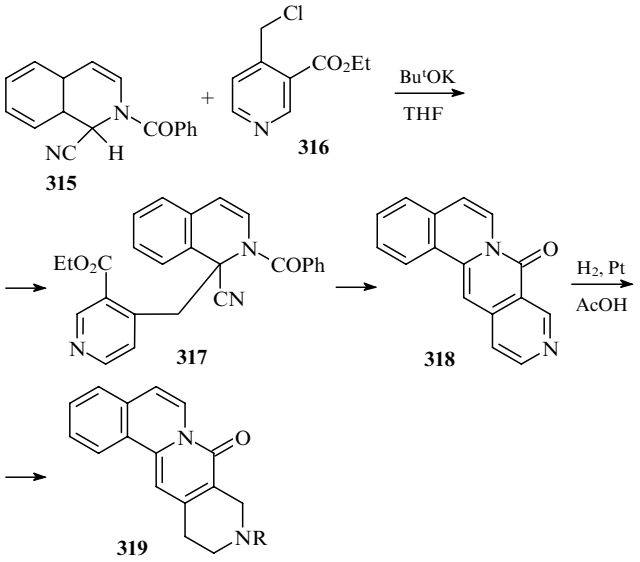
Intramolecular cyclodehydrobromination of substituted *N*-[(4-bromo-3-pyridyl)methyl]anilines **312** followed by dehydrogenation of intermediates **313** afforded benzonaphthyridines **314**.[199]



312 **313** **314**

R^1, R^2, R^3, R^4 = H, Me, OMe.

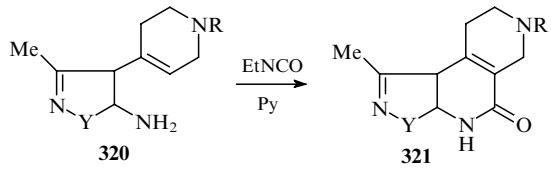
Treatment of isoquinoline derivative **315** with ethyl 4-chloromethylnicotinate **316** in the presence of Bu^tOK gave rise to isoquinoline derivative **317**, which underwent cyclisation to form isoquinolino[2,1-*b*][2,7]naphthyridin-8-one (**318**).[200] The latter was not reduced with $NaBH_4$ or $NaBH_3CN$ in AcOH or Ac_2O, though this compound in AcOH was converted into derivatives **319** upon hydrogenation with hydrogen over Pt.



315 **316** **317** **318** **319**

R = H, Ac.

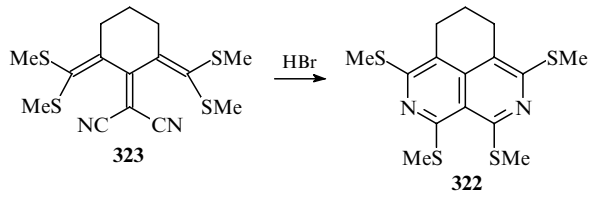
Refluxing of substituted heterylamines **320** with a threefold excess of ethyl isocyanate in pyridine gave rise to partially hydrogenated fused 2,7-naphthyridines **321**.[201]



320 **321**

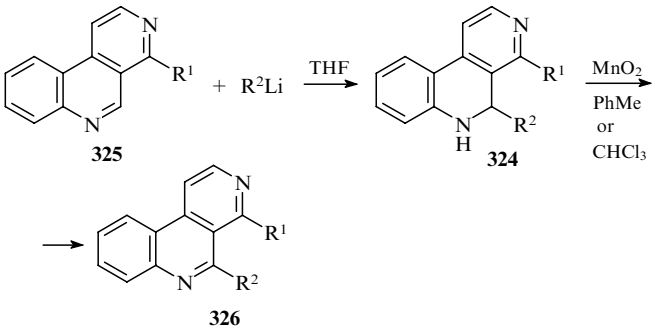
R = Me, Ac; Y = O, NMe.

An ingenious method for the preparation of annelated tetramethylthio-substituted 2,7-naphthyridine **322** is based on cyclisation of 2,6-bis[bis(methylthio)methylidene]cyclohexylidenemalononitrile (**323**) under the action of gaseous HBr.[202]



323 **322**

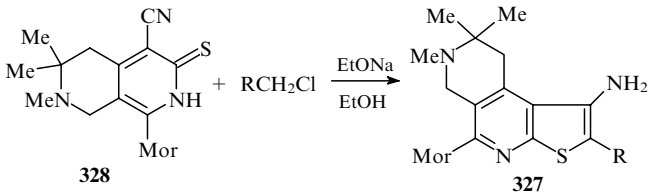
Dehydrogenation of 5,6-dihydro derivatives of 2,7-naphthyridines **324**, which were prepared by the addition of organolithium compounds to 4-substituted benzo[*c*][2,7]naphthyridines (**325**), afforded naphthyridines **326**.[203]



325 **324** **326**

R^1 = F, Cl, $CONPr^i_2$; R^2 = Bu, Ar, Het.

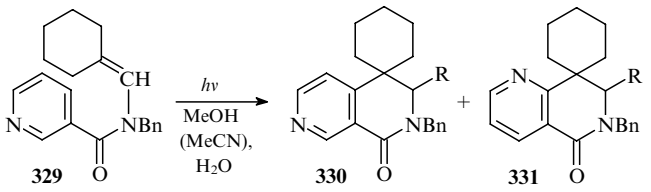
Substituted tetrahydrothieno[2,3-*c*][2,7]naphthyridines **327** were prepared by the reaction of naphthyridinethione **328** with derivatives of chloroacetic acid in ethanol in the presence of sodium ethoxide (the Thorpe–Ziegler reaction).Their neurotrophic properties were investigated.[204]



328 **327**

Mor = ; R = CN, $CONH_2$.

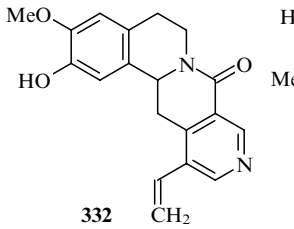
UV irradiation of *N*-aroyleneamide **329** in methanol or aqueous acetonitrile afforded a mixture of regioisomeric spirocycloadducts **330** and **331**. The solvent was not involved in the reaction performed in cyclohexane, and R = H in the compounds **330** and **331**.[205]



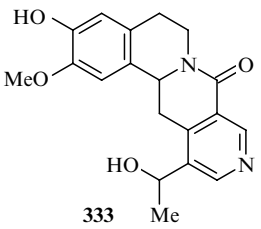
329 **330** **331**

R = OMe, OH.

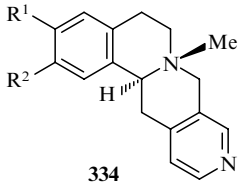
In a number of studies, the structural 2,7-naphthyridine fragment was found to be a component of alkaloids alangimaridine (**332**),[206] isoalamarine (**333**),[207] alamaridine (**334**) and *epi*-alamaridine,[208] nauclefine (**335**),[209,210] naulafine (**336**),[211] normalindine (**337**),[212] eudistones **338**,[213] cystodytins **339**–**341**,[214] kuanoniamines **342**,[215] meridine (**343**) possessing fungistatic activity,[216] alkaloids **344** and **345** exhibiting high antifungal and anticancer activities [217] and other biological compounds, such as sampangine (**346**) possessing antibacterial activity,[218,219] the biosynthetic precursor of camptothecin **347** exhibiting anticancer activity,[220] an analogue of olivecin **348** [221] and benzo derivatives **349** suitable for the treatment of asthma and lowering of blood pressure.[222] The data on antispasmodic activity of 2,7-naphthyridine derivatives were also reported.[223]



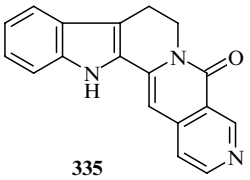
332



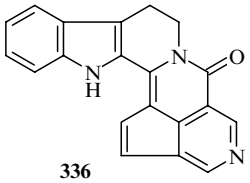
333



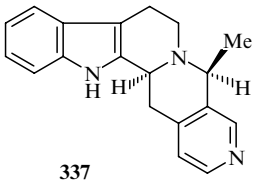
334



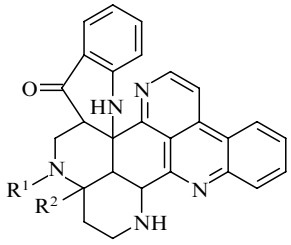
335



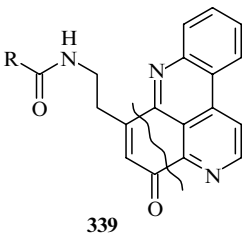
336



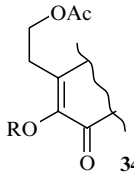
337



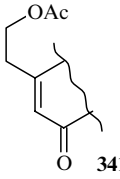
338



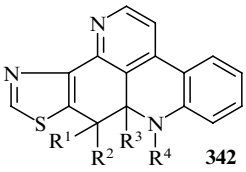
339



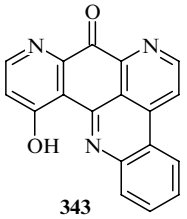
340



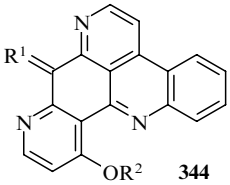
341



342

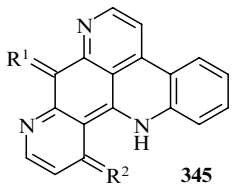


343

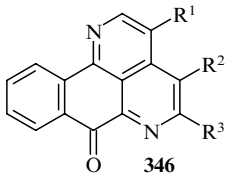


344

R^1 = O, S, NOAlk(Ar), R^2 = Alk

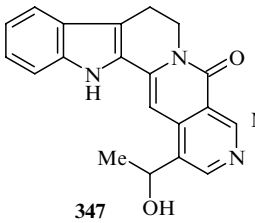


345

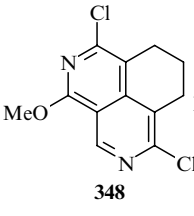


346

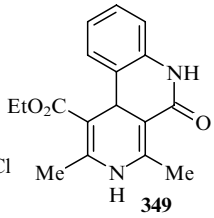
R^1, R^2 = O, S, NOAlk(Ar).



347



348



349

* * *

Analysis of the data on the synthesis, properties and biological activities of five isomeric pyridopyridines (1,5-, 1,6-, 1,7-, 2,6- and 2,7-naphthyridines) published over the last 15 years is indicative of a lively interest in different aspects of the chemistry of these heterocyclic systems. This interest is generally associated with the practical utility of their derivatives possessing a very broad spectrum of biological activities.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 99-03-32965).

References

1. V P Litvinov, S V Roman, V D Dyachenko *Usp. Khim.* **69** 218 (2000) [*Russ. Chem. Rev.* **69** 201 (2000)]
2. A Couture, E Deniau, P Grandclaudon, C Simion *Synthesis* 1227 (1993)
3. Fr. Appl. 2 548 667; *Chem. Abstr.* **103** 71 302 (1985)
4. Eur. P. 130 878; *Chem. Abstr.* **102** 220 856 (1985)
5. H Irikawa, Y Okumara *Bull. Chem. Soc. Jpn.* **60** 3797 (1987)
6. Eur. P. 327 426; *Chem. Abstr.* **114** 23 970 (1991)
7. G Viti, D Giannotti, R Nannicini, G Balacco, V Pestellini *Tetrahedron Lett.* **35** 5939 (1994)
8. US P. 4 652 567 (1987)
9. US P. 4 742 061 (1988)
10. US P. 4 7421 71 (1986)
11. WO PCT 9 818 795; *Chem. Abstr.* **128** 321 632 (1998)
12. J Malm, A B Hörfeldt, S Gronowitz *Heterocycles* **37** 331 (1994)
13. G B Barlin, S J Ireland *Aust. J. Chem.* **41** 1727 (1988)
14. G B Barlin, C Jiravinyu *Aust. J. Chem.* **43** 1175 (1990)
15. G B Barlin, C Jiravinyu *Aust. J. Chem.* **44** 151 (1991)
16. G B Barlin, W-L Tan *Aust. J. Chem.* **38** 905 (1985)
17. G B Barlin, W-L Tan *Aust. J. Chem.* **39** 51 (1986)
18. G B Barlin, S J Ireland, T M T Nguyen, B Kotecka, K H Rieckmann *Aust. J. Chem.* **47** 1143 (1994)
19. G B Barlin, S J Ireland, Ch Jiravinyu, Yan Jing-He *Aust. J. Chem.* **44** 677 (1991)
20. G B Barlin, W-L Tan *Aust. J. Chem.* **38** 459 (1985)
21. G B Barlin, W-L Tan *Aust. J. Chem.* **37** 2469 (1984)
22. G B Barlin, S J Ireland, C Jiravinyu, T M T Nguyen, B Kotecka, K H Rieckmann *Aust. J. Chem.* **46** 1695 (1993)
23. US P. 5 240 916; *Ref. Zh. Khim.* 13 O 85P (1995)
24. US P. 5 110 347; *Ref. Zh. Khim.* 3 O 274P (1994)
25. M Wozniak, M Tomula *Liebigs Ann. Chem.* 471 (1993)
26. R N Castle, S Pakray, G E Martin *J. Heterocycl. Chem.* **28** 1997 (1991)
27. A Achenbach, B Düthorn, R Waibel *Liebigs Ann. Chem.* 1159 (1992)
28. FR. P. 2 590 990; *Ref. Zh. Khim.* 15 O 118P (1988)
29. A A Adesomoju, M V Lakshmikantham, M P Cava *Heterocycles* **32** 1461 (1991)
30. Czech P. 216 622; *Ref. Zh. Khim.* 8 O 156P (1985)
31. Swiss P. 646 166; *Ref. Zh. Khim.* 14 O 167P (1985)
32. Fr. P. 2 562 894; *Ref. Zh. Khim.* 15 O 146P (1986)
33. BRD P. 3 409 185; *Ref. Zh. Khim.* 19 O 102P (1986)
34. Jpn. P. 60-248 688; *Ref. Zh. Khim.* 23 O 166P (1986)
35. L Czibula, A Nemes, G Visky, M Farkas, Z Szombathelyi, E Karpati, P Sohar, M Kessel, J Kreidl *Liebigs Ann. Chem.* 221 (1993)

36. BRD P. 279 887; *Ref. Zh. Khim.* 8 O 135P (1991)
37. Jpn. P. 59-93 080; *Ref. Zh. Khim.* 8 O 136P (1985)
38. WO PCT 99 29318; *Chem. Abstr.* **131** 44 810 (1999)
39. BRD P. 4 105 386; *Chem. Abstr.* **118** 82 835 (1993)
40. W Sliwa, B Minanowska *Pr. Nauk.-Wyzsza Szk. Pedagog. Czestochowa, Chem.* **1** 177 (1997); *Chem. Abstr.* **129** 175 215 (1998)
41. US P. 4 517 190 (1983)
42. US P. 4 532 247 (1983)
43. US P. 4 567 186 (1985)
44. US P. 4 559 347 (1984)
45. US P. 4 604 399 (1984)
46. US P. 4 650 806 (1985)
47. B Singh, G Y Lesher *J. Heterocycl. Chem.* **27** 2085 (1990)
48. B Singh *Synthesis* 279 (1992)
49. US P. 4 634 772 (1986)
50. US P. 4 657 915 (1986)
51. US P. 4 697 021 (1986)
52. US P. 4 716 170 (1986)
53. M Balogh, I Hermecz, G Naray-Szabo, K Simon, Z Meszaros *J. Chem. Soc., Perkin Trans. 1* 753 (1986)
54. M Balogh, I Hermecz, K Simon, L Pusztay *J. Heterocycl. Chem.* **26** 1755 (1989)
55. G Toth, A Kovacs, M Balogh, I Hermecz *J. Heterocycl. Chem.* **28** 497 (1991)
56. J Kleinschroth, K Mannhardt, J Hartenstein, G Satzinger *Synthesis* 859 (1986)
57. BRD P. 3 327 650; *Chem. Abstr.* 21 O 167P (1985)
58. BRD P. 3 431 303; *Ref. Zh. Khim.* 23 O 131P (1986)
59. BRD P. 3 502 790; *Ref. Zh. Khim.* 7 O 112P (1987)
60. BRD P. 3 605 743; *Ref. Zh. Khim.* 6 O 93P (1988)
61. BRD P. 3 602 655; *Ref. Zh. Khim.* 10 O 97P (1988)
62. Jpn. P. 477 488; *Ref. Zh. Khim.* 19 O 40P (1995)
63. BRD P. 3 609 785; *Ref. Zh. Khim.* 23 O 60P (1988)
64. B Singh, E R Bakon, G Y Lesher, Sh Robinson, P O Pennock, D C Bode, E D Pagani, R G Bentley, M J Connel, L T Hamel, P J Silver *J. Med. Chem.* **38** 2546 (1995)
65. I C Ivanov, E V Stoyanov, P S Denkova, V S Dimitrov *Liebigs Ann. Chem.* 1777 (1997)
66. N Z Tugusheva, L V Ershov, V G Granik, G Ya Shvarts, R D Syubaev, M D Mashkovskii *Khim.-Farm. Zh.* **20** 830 (1986) [a]
67. N Z Yalysheva, N P Solov'eva, V V Chistyakov, Yu N Sheinker, V G Granik *Khim. Geterotsikl. Soedin.* 1118 (1986) [b]
68. A W Erian, S M Sherif, A-Z A Alassar, Y M Elkholy *Tetrahedron* **50** 1877 (1994)
69. K-H Nietsch, R Troschütz, H J Roth *Arch. Pharm.* **318** 175 (1985)
70. US P. 4 748 246 SShA; *Chem. Abstr.* **109** 110 425 (1988)
71. US P. 4 751 305 (1987)
72. US P. 4 808 612; *Chem. Abstr.* **110** 231 609 (1989)
73. A Shiozawa, Y-i Ichikawa, C Komuro, S Kurashige, H Miyazaki, H Yamanaka, T Sakamoto *Chem. Pharm. Bull.* **32** 2522 (1984)
74. J B Sainani, A C Shah, V P Arya *Indian J. Chem.* **B34** 17 (1995)
75. BRD P. 3 502 831; *Ref. Zh. Khim.* 7 O 113P (1987)
76. C Rivalle, C Huel, E Bisagni *J. Heterocycl. Chem.* **26** 577 (1989)
77. US P. 5 391 554 (1992)
78. V I Sigova, M E Konshin *Zh. Obshch. Khim.* **54** 2083 (1984) [c]
79. S V Ukhov, M E Konshin *Khim. Geterotsikl. Soedin.* 238 (1989) [b]
80. S V Ukhov, M E Konshin *Khim. Geterotsikl. Soedin.* 92 (1992) [b]
81. A Nemazany, N Haider *J. Heterocycl. Chem.* **34** 397 (1997)
82. A Nemazany, N Haider *Electron. Conf. Heterocycl. Chem.* 1996; *Chem. Abstr.* **127** 205 495 (1997)
83. R D Clark, D B Repke, A T Kilpatrick, C M Brown, A C MacKinnon, R U Clauge, M Spedding *J. Med. Chem.* **32** 2034 (1989)
84. R D Clark, D B Repke, J Berger, J T Nelson, A T Klipatrick, C M Brown, A C MacKinnon, R U Clauge, M Spedding *J. Med. Chem.* **34** 705 (1991)
85. US P. 4 791 108 (1987)
86. Eur. P. 288 196; *Chem. Abstr.* **110** 173 210 (1989)
87. US P. 4 956 365 (1988)
88. US P. 4 960 891 (1989)
89. US P. 5 229 387 (1991)
90. US P. 5 231 181 (1991)
91. J C Rohloff, N H Dyson, J O Gardner, T V Alfredson, M L Sparacino, J Robinson III *J. Org. Chem.* **58** 1935 (1993)
92. I Hutton (Ed.) *Pharmacoproject* Vol. 13 (Richmond: PJB Publications, 1992) p. 648a
93. R D Clark, A D Michel, R L Whiting, in *Progress in Medical Chemistry* Vol. 23 (Eds G P Ellis, G B West) (Amsterdam: Elsevier, 1986) p. 1
94. P Balczewski, M K J Mallon, J D Street, J A Joule *J. Chem. Soc., Perkin Trans. 1* 3193 (1990)
95. Jpn. P. 59-48 482; *Ref. Zh. Khim.* 1 O 207P (1986)
96. N Nishiwaki, M Komatsu, Y Ohshiro *Synthesis* 41 (1991)
97. V K Jahalani, L P Ghalsasi, S P Acharya, R N Usgaonkar *Indian J. Chem.* **B28** 173 (1989)
98. P J Victory, J Teixido, J I Borrell, N Busquests *Heterocycles* **36** 1 (1993)
99. J N Reed, J Rotchford, D Strickland *Tetrahedron Lett.* **29** 5725 (1988)
100. P-L Compagnon, F Gasquez, T Kimny *Bull. Soc. Chim. Belg.* **95** 49 (1986)
101. V N Nesterov, V D Dyachenko, Yu A Sharanin, Yu T Struchkov *Izv. Akad. Nauk, Ser. Khim.* 437 (1996) [d]
102. V D Dyachenko, S V Roman, V P Litvinov *Izv. Akad. Nauk, Ser. Khim.* 121 (2000) [d]
103. S V Roman, V D Dyachenko, V P Litvinov, in *Organicheskii Sintez i Kombinatornaya Khimiya (Tez. Dokl. Mezhdunar. Konf.), Zvenigorod, 1999* [Organic Synthesis and Combinatorial Chemistry (Abstracts of Reports of the International Conference), Zvenigorod, 1999] P-58
104. S V Roman, V D Dyachenko, V P Litvinov *Khim. Geterotsikl. Soedin.* 1435 (1999) [b]
105. L S Vasil'ev, F E Surzhikov, O G Azarevich, V S Bogdanov, V A Dorokhov *Izv. Akad. Nauk, Ser. Khim.* 1510 (1994) [d]
106. R M Mohareb, S M Fahmy *Z. Naturforsch., B Chem. Sci.* **40** 1537 (1985)
107. J M Robinson, L W Brent, C Chau, K A Floyd, S L Gilham, T L McMahan, D J Magda, T J Motycka, M J Pack, A L Roberts, L A Seally, S L Simpson, R R Smith, K N Zalesny *J. Org. Chem.* **57** 7352 (1992)
108. I A El-Saaka *J. Chem. Res. (S)* 434 (1996)
109. A T M Marcelis, H C van der Plas *Tetrahedron* **45** 2693 (1989)
110. E L Gaidarova, A A Borisenko, T I Chumakov, A V Mel'nikov, I S Orlov, G V Grishina *Tetrahedron Lett.* **39** 7767 (1998)
111. T Siener, U Mueller, M Jansen, U Holzgrabe *Pharmazie* **53** 442 (1998)
112. R N Radinov, S D Simova, M A Haimova *Izv. Khim. Bulg. Akad. Nauk* **22** 144 (1989); *Ref. Zh. Khim.* 24 Zh 432 (1989)
113. R Friary, J H Schwerdt, V Seidl, F J Villani *J. Heterocycl. Chem.* **27** 189 (1990)
114. US P. 5 070 086 (1990)
115. K R Prasad, M Darbarwar *Synth. Commun.* **22** 2479 (1992)
116. K R Prasad, M Darbarwar *Org. Prep. Proced. Int.* **27** 547 (1995)
117. C W G Fishwick, R C Storr, P W Manley *J. Chem. Soc., Chem. Commun.* 1304 (1984)
118. J I Levin *Tetrahedron Lett.* **30** 2355 (1989)
119. Y Miki, O Tomii, M Utsunomiya, S Takemura, M Ikeda *Chem. Pharm. Bull.* **34** 3588 (1986)
120. K Görlitzer, C Heinrici *Arch. Pharm.* **321** 477 (1988)
121. Jpn. P. 491 090; *Ref. Zh. Khim.* 2 O 91P (1995)
122. S M Hussain, A M El-Reedy, T M Abdin *Gazz. Chim. Ital.* **118** 623 (1988)
123. V Ojea, I Muinelo, M C Figueroa, M Ruiz, J M Quintela *Synlett* 622 (1995)
124. J Svetlik, F Turecek, V Hanus *J. Chem. Soc., Perkin Trans. 1* 2053 (1988)
125. T Sakamoto, N Miura, Y Kondo, H Yamanaka *Chem. Pharm. Bull.* **34** 2018 (1986)
126. N I Smetskaya, A M Zhidkova, N A Mukhina, V G Granik *Khim. Geterotsikl. Soedin.* 1287 (1984) [b]
127. US P. 5 367 078 (1993)
128. US P. 5 424 433 (1994)
129. US P. 5 424 434 (1994)
130. Jpn. P. 58-7626; *Ref. Zh. Khim.* 2 O 123P (1985)
131. S Mishio, T Hirose, A Minamida, J-i Matsumoto, S Minami *Chem. Pharm. Bull.* **33** 4402 (1985)
132. US P. 5 180 719 (1991)
133. US P. 5 281 703 (1993)

134. WO PCT 94-12173; *Ref. Zh. Khim.* 3 O 76P (1996)
135. Jpn. P. 59-219 292; *Ref. Zh. Khim.* 1 O 184P (1986)
136. A Belicova, M Seman, V Milata, D I Ilavsky, L Ebringer *Folia Microbiol.* (*Prague*) **42** 193 (1997); *Chem. Abstr.* **127** 63 024 (1997)
137. Jpn. P. 10 182 462; *Chem. Abstr.* **129** 153 228 (1998)
138. WO PCT 97-34 894; *Chem. Abstr.* **127** 318 884 (1997)
139. WO PCT 98-54 184; *Chem. Abstr.* **130** 38 370 (1999)
140. WO PCT 99-00 388; *Chem. Abstr.* **130** 110 251 (1999)
141. WO PCT 99-03 857; *Chem. Abstr.* **130** 125 079 (1999)
142. US P. 4 596 873 (1985)
143. US P. 4 618 678 (1985)
144. H Natsugari, Y Ikeura, Y Kiyota, Y Ishichi, T Ishimaru, O Saga, H Shirafuji, T Tanaka, I Kamo, T Doi, M Otsuka *J. Med. Chem.* **38** 3106 (1995)
145. M Blanco, M G Lorenzo, I Perillo, C B Schapira *J. Heterocycl. Chem.* **33** 361 (1996)
146. A Niimi, Y Nagao, Y Abe, T Misono *Chem. Express* **6** 45 (1991)
147. A Couture, P Grandclaudon, C Simion, P Woisel *J. Chem. Soc., Perkin Trans. 1* 2643 (1995)
148. L Capuano, W Hell, C Wamprecht *Liebigs Ann. Chem.* 132 (1986)
149. P-E Zhu, Ch Chen *Pharm. Ind.* **19** 55 (1989); *Ref. Zh. Khim.* 5 O 120 (1990)
150. F Linkert, S Laschat, M Knickmeier *Liebigs Ann. Chem.* 985 (1995)
151. R K Smalley, M Teguiche *Synthesis* 654 (1990)
152. M Paluszewski, W Sliwa *Aust. J. Chem.* **46** 1115 (1993)
153. Pol. P. 167 956; *Ref. Zh. Khim.* 20 O 46P (1996)
154. T Hirota, T Matsushita, K Sasaki, S Kashino *Heterocycles* **41** 2565 (1995)
155. K Sasaki, A S S Rouf, T Hirota *J. Heterocycl. Chem.* **33** 49 (1996)
156. M Wozniak *Pol. J. Chem.* **62** 305 (1988)
157. B Bachowska, T Zujewska *Pol. J. Chem.* **70** 1324 (1996)
158. G Matusiak *Aust. J. Chem.* **52** 149 (1999)
159. Jpn. P. 62-30 780; *Ref. Zh. Khim.* 2 O 83P (1988)
160. US P. 4 690 924 (1986)
161. Jpn. P. 63-48 277; *Ref. Zh. Khim.* 15 O 88P (1989)
162. US P. 4 866 176; *Ref. Zh. Khim.* 17 O 69P (1990)
163. US P. 4 551 534 (1984)
164. S Radl, P Hradil *Collect. Czech. Chem. Commun.* **56** 2420 (1991)
165. P Hradil *Cesk. Farm.* **41** 55 (1992)
166. P Hradil *Cesk. Farm.* **41** 194 (1992)
167. Eur. P. 563 797; *Chem. Abstr.* **120** 106 978 (1994)
168. WO PCT 97-03 074; *Chem. Abstr.* **126** 199 561 (1997)
169. WO PCT 97-48 368; *Chem. Abstr.* **128** 88 786 (1998)
170. WO PCT 98-18 796; *Chem. Abstr.* **128** 321 633 (1998)
171. Jpn. P. 10 109 989; *Chem. Abstr.* **129** 16 149 (1998)
172. Y Ikeura, T Ishimaru, T Doi, M Kawada, A Fujishima, H Natsugari *Chem. Commun.* 2141 (1998)
173. P Rajamanickam, P Shanmugam *Synthesis* 541 (1985)
174. N S Ibrahim, K U Sadek, S I Aziz, M H Elnagdi *Z. Naturforsch., B Chem. Sci.* **40** 129 (1985)
175. J Nozulak, H O Kalkam, P Floersheim, D Hoyer, P Scoeffter, H R Buerki *J. Med. Chem.* **38** 28 (1995)
176. H Mühle, J Nozulak, J Cercus, E Küsters, U Buetler, G Penn, W Zaugg *Chimia* **50** 209 (1996)
177. BRD P. 473 550; *Chem. Abstr.* **117** 111 583 (1992)
178. BRD P. 4 027 018; *Ref. Zh. Khim.* 2 O 76P (1993)
179. R Gleiter, J Ritter *Angew. Chem., Int. Ed. Engl.* **33** 2470 (1994)
180. J Ritter, R Gleiter *Liebigs Ann. Chem.* 1179 (1997)
181. Br. P. 2 299 582; *Ref. Zh. Khim.* 12 O 64P (1997)
182. BRD P. 3 336 194; *Ref. Zh. Khim.* 10 O 13P (1986)
183. A M El-Reedy, M K A Ibrahim, S M Hussain, H H Moharram *J. Prakt. Chem.* **331** 745 (1989)
184. E G Paronikyan, S N Sirakanyan, A S Noravyan, T O Asatryan, K Zh Markaryan, R A Aleksanyan *Khim.-Farm. Zh.* **30** (6) 13 (1996) [a]
185. C H Erre, C M A Roussel *Bull. Soc. Chim. Fr., Pt. 2* 449 (1984)
186. F A Selimov, O G Rutman, U M Dzhemilev *Izv. Akad. Nauk SSSR, Ser. Khim.* 688 (1986) [d]
187. C Roussel, A Merier, M Gartier *J. Org. Chem.* **52** 2935 (1987)
188. C H Erre, C M A Roussel *Bull. Soc. Chim. Fr., Pt. 2* 454 (1984)
189. US P. 4 859 671 (1988)
190. A B Ridley, W C Taylor *Aust. J. Chem.* **40** 631 (1987)
191. G Dannhardt, K K Mayer, L Steindl *Chem. Ztg.* **109** 139 (1985)
192. E G Paronikyan, G V Mirzoyan, A S Noravyan, D A Avakimyan, Yu Z Ter-Zakharyan *Khim.-Farm. Zh.* **27** (11) 29 (1993) [a]
193. V A Dorokhov, A Yu Yagodkin, V S Bogdanov, S V Baranin *Izv. Akad. Nauk, Ser. Khim.* 1079 (1997) [d]
194. M Y El-Kady, G H Sayed, A M El-Gendy, M El-Sherif *Egypt. J. Chem.* **28** 63 (1985)
195. K Görlitzer, U Bartke, E Schmidt *Arch. Pharm.* **324** 105 (1991)
196. L T Guss, L V Ershov, V G Granik *Khim. Geterotsikl. Soedin.* 1696 (1987) [b]
197. R M Mohareb, H F Zohdi, S M Sherif, W W Wardkhan *Tetrahedron* **50** 5807 (1994)
198. F Bracher *J. Heterocycl. Chem.* **30** 157 (1993)
199. C F Nutailis, S R Marsh *J. Heterocycl. Chem.* **29** 971 (1992)
200. E Reimann, H Bened *Arch. Pharm.* **327** 539 (1994)
201. G Winters, A Sala, A de Paoli, V Ferri *Synthesis* 1052 (1984)
202. GDR P. 279246; *Ref. Zh. Khim.* 18 O 75P (1991)
203. C Cochennec, P Rocca, F Marsais, A Godart, G Queguiner *J. Chem. Soc., Perkin Trans. 1* 979 (1995)
204. E G Paronikyan, G V Mirzoyan, A S Noravyan, E M Arzanunts, R S Sukasyan, I S Sarkisyan, I M Nazaryan, I A Dzhagatspanyan *Khim.-Farm. Zh.* **31** (10) 34 (1997) [a]
205. J-C Gramain, Y Troin, D Vallee-Goyet *Tetrahedron* **47** 7301 (1991)
206. Jahangir, M A Brook, D B MacLean, H L Holland *Can. J. Chem.* **65** 2362 (1987)
207. U S Chowdhury *Tetrahedron* **46** 7893 (1990)
208. E Reimann, H Renz *Monatsh. Chem.* **125** 1397 (1994)
209. Jahangir, M A Brook, D B MacLean, H L Holland *Tetrahedron* **43** 5761 (1987)
210. R Vohra, D B MacLean *Heterocycles* **39** 445 (1994)
211. D B Repke Jr, M A Brook, R D Clark, J T Nelson *Heterocycles* **27** 2289 (1988)
212. A W Rey, W A Szarek, D B MacLean *Heterocycles* **32** 1143 (1991)
213. H-Y He, D J Faulkner *J. Org. Chem.* **56** 5369 (1991)
214. M A Ciufolini, N E Byrne *J. Am. Chem. Soc.* **113** 8016 (1991)
215. G P Gunawardana, F E Koehn, A Y Lee, J Clardy, H-Y He, D J Faulkner *J. Org. Chem.* **57** 1523 (1992)
216. P J McCarthy, T P Pitts, G P Gunawardana, M Kelly-Borges, S A Pomponi *J. Natur. Prod.* **55** 1664 (1992); *Ref. Zh. Khim.* 13 E 80 (1993)
217. US P. 5 182 287 (1991)
218. US P. 5 128 344 (1990)
219. US P. 5 227 383 (1991)
220. B K Carte, C DeBrosse, D Eggleston, M Hemling, M Mentzer, B Poehland, N Troupe, J W Westley, S M Hecht *Tetrahedron* **46** 2747 (1990)
221. L Mathew *J. Indian Inst. Sci.* **72** 345 (1992); *Ref. Zh. Khim.* 19 Zh 209 (1993)
222. US P. 4 478 834; *Ref. Zh. Khim.* 13 O 168P (1985)
223. E G Paronikyan, S N Sirakanyan, R G Paronikyan, A S Noravyan, in *Khimiya Fiziologicheski Aktivnykh Soedinenii (Tez. Dokl. Vsesoyuz. Konf.), Chernogolovka, 1989* [The Chemistry of Physiologically Active Compounds (Abstracts of Reports of the All-Union Conference), Chernogolovka, 1989] p. 193

[a] — *Chem. Pharm. J. (Engl. Transl.)*
[b] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[c] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[d] — *Russ. Chem. Bull. (Engl. Transl.)*