Contents

Advances in the Chemistry of Naphthyridines

V.P. Litvinov

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Preface

This volume opens with an overview of tautomeric equilibria involving substituents (such as OH, NH_2, SH) in six-membered heterocycles provided by B. Stanovnik and M. Tišler (University of Ljubljana, Slovenia) together with O. Denisko (CAS, Columbus, Ohio) and your editor. The chapters update reviews which appeared in earlier volumes of this series and brings this complex and important subject up to date.

In the second chapter, M. Yus and F. Foubelo (University of Alicante, Spain) survey the introduction of additional ring atoms into heterocycles to provide homologated analogues, by a reductive ring opening–electrophilic attack–cyclization sequence. This is followed by a review of the applications of tetrahydrofolate models in organic synthesis authored by K. Singh and H. Singh (Guru Nanak Dev University, Amritsar, India).

The volume closes with a detailed up-to-date account of the chemistry of naphthyridines authored by V.P. Litvinov (Zelinsky Institute, Moscow).

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The Tautomerism of Heterocycles: Substituent Tautomerism of Six-Membered Ring Heterocycles

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I. Substituent Tautomerism of Six-Membered Ring Heterocycles: General Discussion

The first detailed survey of the prototropic tautomerism of heteroaromatic compounds appeared in four chapters that were published in 1963, in Volumes 1 and 2 of "Advances in Heterocyclic Chemistry." In 1976, a monograph entitled "The Tautomerism of Heterocycles" was issued as Supplement 1 to "Advances in Heterocyclic Chemistry" (76AHCS1) to update the work published in 1963. Later on, a review dealing with the annular tautomerism of monocyclic six-membered rings (01AHC(81)253) discussed the literature data on the subject reported in 1976–2001. A series of reviews on ring-chain tautomerism of five- and six-membered ring heterocycles was published recently (85MI1, 95AHC(64)251, 96AHC(66)1, 03EJOC3025).

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This chapter is a part of an endeavor to provide a further update covering work on substituent tautomerism of six-membered heterocycles that has appeared since 1976. The most significant development since 1976 is the enormous emphasis on the computational studies. Recent advances in computer technology in combination with increasingly accurate quantum-chemical methods allow studies of systems of up to 50 atoms on standard personal computers at relatively high levels. Computational chemistry has become increasingly important in traditional heterocyclic chemistry. A short review on tautomerism of functionalized heterocycles with emphasis on investigation methods and quantum-chemical calculations was published in 1991 (91H(32)329). It was later followed by an excellent review on recent advances in computing heteroatom-rich five- and six-membered ring systems (01AHC(81)2). A comprehensive review on the general overview and methodology of heteroaromatic tautomerism studies (00AHC(76)1) appeared recently discusses the generalized approach to the tautomerism phenomenon and its studies using theoretical, physical spectroscopic, non-spectroscopic, and chemical methods.

The effect of introduction of an additional heteroatom (88ZOR1799), inductive substituents (90ZOR1793), mesomeric substituents (88ZOR1806), and effect of benzannulation (90ZOR1387) on the position of the tautomeric equilibrium of azines with various functional groups were investigated by PMO semiempirical calculations. It was shown that the transition from pyridine to analogous 2-pyrimidine or 2-pyrazine derivatives should shift the equilibrium toward the aromatic form (hydroxy, mercapto, amino, etc.), whereas the transition to 4-pyrimidine or 3-pyridazine analogs favor the ylidene form (oxo, thioxo, imino, etc.). The fraction of the aromatic form can also be increased by introduction of a mesomeric or inductive-accepting substituents into the *para*-position to the tautomeric groups or inductive-donating substituents into the *meta*-positions. None of the effects studied depends on the type of the tautomeric group. A general discussion of various substituent tautomeric interconversions in azines including the thermodynamics of the transformations, the substituent and the solvent effects and suggested mechanisms was published in 1990 (90UK268).

The UV-induced phototautomeric studies revealed that substitution of the exocyclic oxygen atom in azinones and diazinones with sulfur causes the relative stabilization of the fully aromatic form; this trend was confirmed by theoretical *ab initio* calculations performed at the SCF + MBPT(2) level with the DZP basis set (92JPC6250). The potential role of zwitterionic forms in a tautomeric equilibrium of hydroxy- and mercapto-substituted heterocycles and, thus, the importance of taking them into consideration have been emphasized by aromaticity index-based theoretical studies (92T7857, 94H(37)249). The differences between the aromaticity indices, calculated from crystallographic data for a range of oxo (or thiono) tautomers of substituted azines, and those for the corresponding hydroxy (mercapto) tautomers lead to values for changes in resonance energies accompanying tautomerization, which are closely parallel to those measured for the same process in aqueous solution.

The molar fractions of oxo (thiono) and hydroxy (thiol) tautomers for a series of monohydroxy- and monomercapto-substituted pyridines, quinolines, and acridines were calculated from the acid–base constants of these compounds at the isoelectric points in an amphiphilic medium (80ZOR1499).

II. Compounds with One Potentially Tautomeric Functional Group

A. Oxo–Hydroxy Tautomerism

The summary of theoretical studies of oxo–hydroxy tautomerism of various heterocycles by AM1, MNDO-PM3, and MNDO semiempirical methods has been published (91JCC17).

In a review article (91H(32)127) the concept of heterocyclic aromaticity has been presented, summarized, and applied to discussion of tautomerism for a series of hydroxy-substituted azines. Later, the tautomerism of 2(1*H*)-pyridone, 2(1*H*)-pyrimidone, 2(1*H*)-pyrazinone, 4-pyrimidone, and 3(2*H*)-pyridazinone in low-temperature inert gas matrices has been investigated by means of IR spectroscopy. It was found that the relative stability of the oxo and hydroxy tautomers of these compounds depends in a systematic way on the relative position of the lactam group and the second nitrogen atom in the ring (92JPC6250).

1. *2-Hydroxypyridines*

The prototropic tautomerism of 2-hydroxypyridine (**1** ⇌ **2**) is frequently considered as a prototype for oxo–hydroxy tautomerization processes in heterocycles, which resulted in comprehensive studies of this heterocycle by a wide variety of theoretical and experimental methods.

1 **2**

The traditional evaluation of tautomeric equilibria by comparison of the pK_a values of the conjugate acids of the tautomeric system and the fixed-form model compounds has been continued, although spectroscopic and other methods have been used complementary. These estimates are based on assumptions that the cations resulting from protonation and the methylated derivatives all have the common structure.

a. Gas-Phase Tautomerism. Much attention has been devoted to gas-phase tautomerism of 2-hydroxypyridine. The gas-phase basicities of 2(1*H*)-pyridone and its 6-chloro analog were reported in order to provide estimates of the prototropic equilibrium between the hydroxy and oxo form (79JA1361, 80JA5222). Studies of tautomeric equilibria in the gas-phase by UV and IR spectroscopy have shown that for these compounds the major tautomers are the hydroxy forms. The determined K_T constants (NH/OH) were 0.4 ± 0.25 (by UV) or 0.5 ± 0.3 (by IR) for 2-hydroxypyridine and 0.05 for 6-chloro-2-hydroxypyridine (76JA171). More recent FT-IR studies of 2-hydroxypyridine, isolated in Ar matrix at 303 K, gave the similar equilibrium constant values ((91CPL(187)532, 94JST(322)113, 95JPC14967).

The predominance of the hydroxy tautomer in the gas phase for 2-hydroxypyridine has been confirmed by photoelectron spectroscopy, although a rather significant

amount of the oxo form, in contrast to the 3- and 4-isomers, has also been detected (77JCS(P2)1652). The enthalpy difference, associated with the prototropic equilibrium, was determined by photoelectronic spectra in the temperature range from 50 to 440 °C and found to be $\Delta H^0 = -0.6$ kcal/mol (79TL2585). The investigation of structural isomers and proton-transfer phenomena of the 2-hydroxypyridine system in the cation ground state has been performed by zero kinetic energy photoelectron spectroscopy to give the adiabatic ionization energies of 68 137 and 72 093 cm^{-1} for 2(1*H*)-pyridone and 2-hydroxypyridine, respectively. In addition, no spectroscopic evidence for fast proton transfer from the hydroxy form to the pyridine form in the D_0 state has been obtained from the analysis of the spectral line width (95JPC8608). The O_{1S} and N_{1S} binding energies, obtained by X-ray photoelectron spectroscopy, were used to calculate the equilibrium constant at 130 °C providing $K_T = 0.48 \pm 0.05$ in favor of the hydroxy tautomer (80JA1174).

The tautomerism of 2-hydroxypyridine in the gas phase has also been studied by microwave spectroscopy using both a conventional spectrometer and a jet-cooled millimeter-wave spectrometer. The spectra attributable to both (*Z*)-hydroxy tautomer and 2-pyridinone were observed in all cases, the relative abundance being 3:1 in favor of the hydroxy form. No (*E*)-hydroxy isomer has been detected (93JPC46). The increased stability of the *cis*-hydroxy tautomer compared to the *trans*-isomer is confirmed by CNDO/2 calculations ($\Delta E = 0.64$ kcal/mol), whereas the semiempirical "effective pair correlation energy" method favors the *trans*-isomer by 0.69 kcal/mol (90BCJ2981).

The kinetic energy release associated with the decomposition of metastable ions has been used to differentiate between the hydroxypyridines and their pyridone tautomers in the gas phase. The hydroxy forms were found to be favored for 2-hydroxypyridines (88JCS(P2)347).

Measuring the intensity of the OH and NH stretching vibrations in the IR spectra of 2-hydroxypyridine in the range from 428 to 533 K in the gas phase allowed for determination of ΔH and ΔS for the equilibrium. The oxo–hydroxy tautomeric ratio in Ar or N_2 matrices has been estimated as 1:2.80 and 1:2.99, respectively. A similar ratio of tautomers has been observed also in the gas phase (92JPC1562). IR has also been used as a quantitative tool to determine the association of pyridone dimer (96MI1).

Various calculation methods have been used to predict the tautomeric equilibrium in the gas phase. The AM1 semiempirical method has been widely used (89JCR(S)56, 89JOC6030, 89JST(184)179, 91CPL(187)532, 93JCC371, 98JPC(B)1787, 00KG1342), providing the values for the relative stability of tautomers ($\Delta E = -0.4$ kcal/mol in favor of the (*Z*)-hydroxy tautomer) in good qualitative agreement with the experimental values. Similar results were obtained using MNDO procedure with full geometry optimization ($\Delta E = -0.4 - 0.5$ kcal/mol) (81JST(86)85). The results of high level *ab initio* molecular orbital studies, using basis sets up to 6−31 + G** with electron correlation included at the second-order Moller–Plesset perturbation and quadratic interaction with singles and doubles leves (92JA1645), and calculations at the TZV2P basis sets with electron correlations at the QCISD(T) level (93JCS(P2)861, 93JPC46) were even in a better agreement with the experimental data ($\Delta E = -0.64 - 0.7$ kcal/mol). Slightly higher free-energy difference ($\Delta E = -1.3$ and -1.1 kcal/mol) was predicted by CCSD and QCISD methods (92CPL(203)46) and MNDO/4−21 method (86JST(148)45), respectively. However, the calculation results are greatly dependent on the method and the

basis set used. For example, the GAUSSIAN80 series of programs using minimal (STO-3g), extended (3-21G and 6-31G), and polarization (6-31G*) basis sets (82JA5347), the semiempirical MINDO/3 method (79IJQC(16)1141, 87JA6283), MINDO – forces MO method (85ZN(A)1278) and density functional theory with the B3LYP functionals (94CPL(220)129, 96JST(376)325) overestimate the stability of the oxo tautomer ($\Delta E = 0.3$, 3.1, 3.7, and -0.06 kcal/mol, respectively), whereas the 3-21G split-valence basis set (82JCS(CC)685, 83JA3568), *ab initio* SCF/6–31 + + G** method (94JST(322)113), coupled-cluster method (89CPL(161)73), and CNDO/2 method (79IJQC(16)1141) overestimate the stability of the hydroxy form ($\Delta E = -10.4$, -2.7, -3.5, and -31.0 kcal/mol, respectively). Calculations at the HP, MP2, MP3, and MP4 levels gave ΔE ranging from $+0.4$ to -2.62 kcal/mol (94JST(312)201, 99JOM(575)39), whereas those obtained by SCF method at several different levels ranged from $+2.0$ to -1.0 kcal/mol (88JA2353). The semiempirical "Effective Pair Correlation Energy" method favors the oxo tautomer over the hydroxy form by 2.7 kcal/mol (90BCJ2981). The tautomerization constants, calculated from IR intensities by DFT and HF methods, are in good agreement with experimental and theoretical predictions (94JST(322)113, 99JST(484)215). The mean values obtained from DFT and HF methods are 0.46 and 0.51, respectively. The DFT predictions are closer to the experimental data, reported for gas-phase equilibrium from UV, IR, matrix isolation IR, and photoelectron spectroscopy studies.

A semiempirical study of prototropic equilibria of 2(1*H*)-pyridone in the ground and first excited electronic states was reported. The results for the ground electronic state are generally comparable with those obtained by refined *ab initio* computations, except for a significant overestimation of energy barriers for intermolecular proton transfer (93JCS(P2)697).

Theoretical studies at varying levels of approximation (CNDO/2, NDDO, MINDO/2, MINDO/3, MNDO, and STO-3G methods) have been carried out in order to predict the tautomerization energy ΔH° (80CPL(69)537, 83JA3568). In all the cases the stability of the hydroxy form is strongly overestimated.

Theoretical calculations have also been performed to estimate the potential energy barrier for the tautomeric interconversion. The energy of the transition state depends on the method of calculation and was calculated to be 26.0 (AM1 method) (00KG1342), 31.4 (SCF level) (93JCC1429), 49 (3-21G method) (84CPL(107)330), and from 43.4 to 51.9 kcal/mol (STO-3G, DZP1, and DZP2 methods) (90CPL(171)475, 95IJQC(56)645). This energy level is so high that direct interconversion including classical intramolecular proton transfer is excluded. Thus, two possible transformation pathways have been suggested: (a) direct proton transfer through a tunneling mechanism (90CPL(171)475), and (b) concerted tautomerization in the cyclic dimers (92JST(277)313, 94JST(312)157).

The total energies of dimers were calculated on SCF + MBPT(2) level, and the hydroxy–hydroxy dimer is found to be the most stable in the gas phase (92JST(277)313). The relative energies of oxo–oxo and oxo–hydroxy dimers were calculated to be 0.7 and 2.5 kcal/mol, respectively. The AM1 and *ab initio* B3LYP/6–31 + G** calculations predicted the higher stability of the self-associated oxo dimers (89JST(184)179, 02JOC1515). The energy difference between hydroxy–hydroxy and oxo–oxo forms agrees well with the energy difference between the oxo and hydroxy monomers in the

gas phase and in the matrix deposit, which suggests that in the gas phase and in a matrix the equilibrium really occurs between cyclic dimers.

Tautomeric equilibria of oxo–oxo, hydroxy–hydroxy, as well as oxo–hydroxy dimers, mediated by the conjugated dual hydrogen-bonding (CDHB) formation have been studied by *ab initio* molecular orbital calculations up to the 6–31 + G** basis set at the Moller–Plesset level. The result in the combination with the semi-empirical solvation free-energy calculation reasonably predicts the relative free energy and consequently the tautomeric equilibria between 2(1*H*)-pyridone and 2-hydroxypyridine, their corresponding dimers and complex in the gas phase as well as in solution. The results also indicate that the strength of dual hydrogen bonding resonantly affects the 2(1*H*)-pyridone and 2-hydroxypyridine electronic structures upon the CDHB formation, resulting in an additional stabilization energy (97JPC(B)9119). The correlation energy term is stabilizing for the associative process of monomeric and dimeric tautomers (90BCJ2981).

Calculations at the SCF/(mixed basis set) level suggest the tautomerization barrier between the dimers to be 10.7–14.3 kcal/mol, which is about three times smaller than the potential energy barrier for a single proton transfer in monomers (84CPL(107)330, 94JST(312)157). The presence of the dimers of 2-hydroxypyridine in the gas phase was confirmed by IR spectra (01SA(A)2659).

The substituent effects on the prototropic tautomerism of monosubstituted (00PJC1283) and polyhalogenated (99PJC1863) 2-hydroxypyridines in the gas phase have been estimated by semiempirical AM1 calculations.

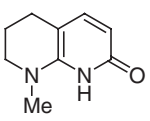
b. Solution Tautomerism. ^{17}O chemical shifts were found to be highly sensitive probes in the studies of keto–enol tautomerism due to the sensitivity of these shifts to the coordination of the oxygen atom. This method was successfully used for studying the tautomeric equilibrium of 6-substituted 2-pyridones in a solution (92JPC7895). Another NMR criterion, used for estimation of the tautomeric equilibrium in 2-hydroxypyridines, is based on $^{3}J_{(CH)}$ values for the C–N–CH, C–N = CH, and C = N–CH structural elements (83OMR20).

It was found that the relative ratio of the tautomers strongly depends on the 6-substituent with the significantly larger fraction of the hydroxy form for 6-chloro and 6-amino derivatives than that for the unsubstituted and 6-methyl analogs. Determination of the tautomeric equilibrium constant by means of IR and UV spectroscopy showed that the fraction of the oxo tautomer, measured in the same solvent, increases in the following order of the 6-substituents: Cl < Br < MeO < H (78TL2221, 80TL3359, 02MI198). The optimized SCF energies confirmed the experimental findings (91JCS(P2)799, 92JPC7895). This shift of the tautomeric equilibrium toward the less polar hydroxy form, even in protic solvents, such as water and octanol, on introduction of electron-withdrawing substituents, especially in the 6-position, has also been confirmed by UV spectroscopic studies (02MI198) and by comparison between calculated and experimental lipophilicity values (00BMCL909).

3-Nitro-2-pyridone exists predominantly in the keto form in DMSO-d_6 at 30 °C (91MRC878), whereas a mixture of both tautomers was found for 3,5-dinitro-2-pyridone (99JOM(575)39). Tautomerism of 3-formyl-2(1*H*)-pyridone was investigated by UV-photoelectron, UV-visible, and ^{1}H and ^{13}C NMR spectroscopy (81T2663). ^{1}H and

^{13}C NMR studies of a number of 2-hydroxy- and 2,3-dihydroxypyridine derivatives showed that these compounds exist as 2-oxo tautomers in a DMSO solution (90JCS(P2)1215).

The effects of various non-tautomeric amino substitutents and of cyano group on the position of the tautomeric equilibrium were studied by UV, IR, and mass spectroscopy (78KG793). Although all the studied compounds **3–6** exist predominantly in the oxo form in polar solvents and in hydroxy form in non-polar solvents, the presence of the 3-cyano group or inclusion of the amino substituent into the annelated ring leads to the shift in the equilibrium favoring the hydroxy form.



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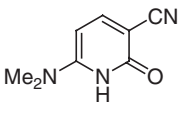

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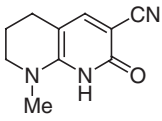

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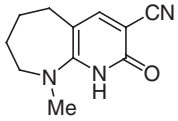

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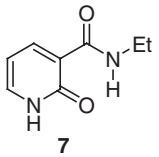
A comparison of the ^{1}H and ^{13}C NMR spectra for a series of *N*- and *O*-acyl substituted 2-hydroxypyridines allows unambiguous distinction between isomeric N- and/or O-substituted derivatives on the basis of ^{13}C chemical shifts and, thus, use of this method as a tool for tautomeric equilibrium studies (84T4067). ^{1}H–^{1}H coupling constants are used to determine the major tautomeric structure in 2(1*H*)-pyridone/2-hydroxypyridine equilibrium (83JST(94)163).

Interesting substituent effects were observed for the tautomeric interconversions of 3-ethylaminocarbonyl-2(1*H*)-pyridone **7** and 3-ethoxycarbonyl-2(1*H*)-pyridone **8**. Compound **7** exists exclusively in the lactam form, either monomeric or dimeric, and cooling, heating, or addition of methanol induce minimal changes. The relative stabilization of the lactam form is suggested to be due to the intramolecular hydrogen bonding between the lactam carbonyl and amide NH group. On the other hand, **8** exists as a mixture of both tautomers in $CHCl_3$, with the lactam concentration increasing on complexation with methanol and on cooling, which shift the monomer–dimer equilibrium (98JCS(P2)937).



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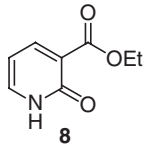

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Solvent effects on the prototropic equilibrium of several 2-pyridones, such as 6-methoxy- or 6-chloro-2-pyridone, have been studied by determination of their equilibrium constant in multiple solvents using UV spectroscopy (78JA3961, 78TL2221, 80JOC1347, 80TL3359, 04JPC(A)6117). In all the cases, transition to more polar solvents shifted the equilibrium toward the lactam tautomers. The preferential hydration of lactam tautomers by one water molecule to form cyclic monohydrates, which could contribute to the interconversion mechanism, has also been suggested (78TL2221). When the equilibrium is greatly in favor of the oxo form, the minor hydroxy tautomers can be directly observed in fluorescence spectra, when the excitation near the absorption maximum of the pyridinol form (about 270 nm) was

used, allowing for determination of the tautomer ratios (84JCS(CC)435, 85JCS(P2)1423). Values for both self-association and prototropic equilibrium constants of variously substituted 2-hydroxypyridines have been determined in different solvents (80JOC1354), and it was shown that in the concentrated solutions these compounds exist as cyclic dimers with degree of association depending on the solvent and steric requirements of the hydroxypyridine.

The mole fraction of the hydroxy form of unsubstituted 2-hydroxypyridine was determined to be 0.08 in acetone and 0.04 in methanol using the ^{14}N NMR spectroscopy (76T1065) and one bond and long range ^{13}C–^{1}H coupling constants (75OMR244). The predominance of the oxo tautomer in nitromethane was determined by comparison of its basicities and titration curves with those of its N- and O-fixed derivatives (78ZOB2358). 3-Methoxycarbonyl-2-hydroxypyridine exists as a mixture of the hydroxy (10–70%) and oxo forms (30–90%) in ethers with the tautomer ratio depending on the solvent polarity (78CPB1415). The hydroxy tautomer is favored in dioxane and diethyl ether, whereas the oxo tautomer predominates in isopropyl ether and butyl ether. The similar dependence of the equilibrium position on the solvent polarity was observed for 5-chloro-2-pyridone, which exists mainly in the oxo form in CCl_4, $CHCl_3$, and cyclohexane solutions, but as an equimolar mixture of hydroxy and oxo tautomers in dioxane (86SA(A)1289). An extensive $NH\cdots O=C$ intermolecular association was observed in CCl_4 and chloroform by IR spectroscopy.

The position of the tautomeric equilibrium could be determined by the combination of the solvent and substituent effects. For example, methyl 2-hydroxy-6-methylnicotinate exists in non-polar solvents mainly in the hydroxy form, stabilized by intramolecular hydrogen bonding with the methoxycarbonyl group. The introduction of a hydrogen-bonding solvent, such as methanol, leads to predomination of the thermally stable oxo tautomer participating in the intermolecular hydrogen bonding (90JPC3639).

Interestingly, although 6-diethylamino-2-hydroxypyridine exists primarily in the hydroxy form at ambient temperature, its ^{1}H NMR spectrum in THF-d_8 is temperature-dependent indicating the presence of two distinct species at $-118\,^{\circ}C$, the phenomenon being attributed to solvated hydroxypyridine monomer – pyridone dimer interconversion (91JA721). Hydroxypyridine dimer and pyridone monomer were not detected.

The concentration dependence of FTIR and UV spectra of 2-hydroxypyridine and its 6-chloro analog was measured in chloroform and CCl_4 in order to elucidate their tautomeric equilibrium and determine the association constants (96MI1). For unsubstituted 2-hydroxypyridine, the hydroxy monomer or dimer was not detected in both solvents, and the equilibrium existed exclusively between oxo monomer and dimer. In contrast, for 6-chloro-2-pyridone both monomeric hydroxy (about 72%) and oxo (about 28%) forms were observed in chloroform. Increase in the substrate concentration led to decrease in the content of the monomeric species in favor of relevant dimers. In CCl_4, 6-chloro-2-hydroxypyridine was found to exist mainly in hydroxy monomer – hydroxy dimer equilibrium.

The UV spectrum of 2-hydroxypyridine in decane at the concentration of 10^{-5} M is indicative of the predominance of the oxo tautomer, the amount of the hydroxy form, if detectable, does not exceed 10% (76JA8284). However, at lower concentrations or higher temperatures (110–130 °C) the hydroxy tautomer becomes readily

detectable. This phenomenon is also readily explained by the tendency of 2-pyridone to form stable dimers, broken up on heating or extreme dilution.

Temperature-jump experiments were performed with aqueous solutions of 2-chloro-2(1*H*)-pyridone and its 6-methoxy analog. It was suggested that due to the proximity of the functional groups a direct proton-transfer mechanism without intermediate ionic dissociation contributes efficiently to the interconversion rate (77JA4438). Studies of 2(1*H*)-pyridone and its 6-methoxy derivative using the temperature-jump relaxation spectrophotometry (78JA7055, 79JA2423) in water/propylene carbonate solvent system suggested that tautomeric interconversion partly involves a bifunctional water-catalyzed proton transfer. A combination of kinetic and UV spectral data indicates the formation of stoichiometric hydrates which inhibit substrate dimerization. The same behavior has been observed for several other 2(1*H*)-pyridones investigated. The predominance of the lactam forms of 2(l*H*)-pyridone and 2-piperidinone in aqueous solution diminishes considerably in solvents of lower polarity (76TL2685).

The jump-relaxation technique has also been used to study the influence of temperature on the position and on the dynamics of the tautomeric equilibrium of 6-methoxy-2(1*H*)-pyridone in neutral water, which was shown to be an essentially a pH-independent process. The equilibrium and activation parameters obtained indicate that the interconversion mechanism is ionic rather than concerted and involves the anionic form of the substrate in a cyclic transition state, in which at least two solvent molecules would temporarily ensure a hydrogen bond connection between the sites which undergo tautomerism (83JCS(P2)979).

The dynamics of the molecular rotation of 2-pyridone in toluene, carbon tetrachloride, methanol, and water have been investigated at 305 K by ^{13}C and ^{2}H NMR spectroscopy. Both chemical shifts and relaxation times show that it forms stable hydrogen-bonded complexes in methanol and in water, reorienting as a complete unit and taking with it two solvent molecules. These solvated species are stable within the liquid-state temperature range, and reorient according to the hydrodynamic law as indicated by the ^{14}N line width measurements (85MRC460).

The mechanism of 2-hydroxypyridine tautomeric interconversion has been studied by supersonic jet expansion (89JPC643). The absence of the emission from the lactam tautomer in the dispersed emission spectra suggests that the excited-state intramolecular proton transfer (ESIPT) does not occur in the single molecule. Binding energies and structures of 2-hydroxypyridine clusters with water and ammonia were estimated. The binding energies for water clusters of lactim were found to be smaller in the ground state than in the excited state, whereas the opposite is true for the lactam.

The tautomeric equilibrium in solution could be shifted by changes in the physical conditions or by additives increasing the medium polarity or complexing with the tautomeric substrate. For example, the equilibrium constant K_T = (oxo)/(hydroxy) for unsubstituted 2-hydroxypyridine interconversion in supercritical fluids (1,1-difluoroethane at 403 K) increases 4-fold for a pressure increase of 40 bar and, thus, can be adjusted over a continuum from gas-phase values to those encountered in polar solvents isothermally over a relatively small pressure change (89JPC4297). An increase in the temperature of a substituted 2-pyridone in aq. THF shifts the equilibrium toward the hydroxy form (02MI198).

In addition to stoichiometric associations with water, associations with alcohols (78CPB1403), carboxylic acids (80JCS(P2)620), and alkali metal cations (78JA7055) have been shown to favor the lactam tautomers. Addition of methanol or *n*-butanol favors the lactam forms, which is explained as a result of an association of two molecules of alcohol with one molecule of the corresponding pyridine derivative (78CPB1403). On the other hand, addition of tetrabutylammonium halides in polar aprotic solvents shifts the equilibrium toward the lactim form, at least for 2-hydroxypyridines with an electron-attracting substituent at position 6. The interactions are the strongest with tetrabutylammonium chloride and change in the order $Cl^- > Br^- > I^-$. The effect is attributed to the specific anion binding (80JA401). The content of 2-pyridone dimer in acetonitrile solution could be decreased by the addition of sodium perchlorate as a result of cation binding to the oxygen atom (78JA7055). Complexation of tautomeric mixture of 3,5-dinitro-2-hydroxypyridine with gold shifts the equilibrium completely toward the oxo tautomer (99JOM(575)39).

IR and UV absorption spectroscopy of 6-chloro-2(1*H*)-pyridone/acetic acid mixtures in carbon tetrachloride at room temperature indicated lactim–acid and lactam–acid heterodimer formations, preferential association being with the lactam tautomer. In the presence of acetic acid, the proportions of monomeric pyridone species diminish (80JCS(P2)620).

Unsubstituted 2-hydroxypyridine has been selected as a model compound for theoretical studies of solvent effects. The medium dependence of the tautomeric equilibrium of 2-hydroxypyridine was calculated in cyclohexane and chloroform by AM1 and PM3 semiempirical methods (93JCC371, 96JPC4269), in acetonitrile and water using Monte-Carlo statistical mechanics simulation (98JPC(B)1787) and in chloroform, cyclohexane, and acetonitrile using self-consistent reaction field (SCRF) theory (96JPC16141). The free energy of solvation of the oxo tautomer in chloroform was found to be more favorable than that of the hydroxy form (96JPC4269), the solvent effect being attributed to the electrostatic interactions. The free energy changes, calculated using 6–31 + G** basis set with electron correlation included at the second order Moller–Plesset perturbation, were 0.36 and 2.32 kcal/mol in cyclohexane and acetonitrile, in a very good agreement with the experimental values (0.33 and 2.96 kcal/mol, respectively) (92JA1645). The solvation free energies in cyclohexane and water, calculated both for monomers and three possible dimers using semiempirical PM3-SM3 and PM3-SM4 solvation models, predicted the lactam monomer to be the most stable in both solvents, although the 2-pyridone dimer is to be considered at higher concentrations (97JPC(B)9119). Calculations at the SCRF level showed the linear dependency of the tautomeric equilibrium constant on the solvent polarity as measured by the Kosower *Z* parameter, in agreement with the experimental findings. At the HF level, 2-hydroxypyridine is favored over the oxo form in cyclohexane and this trend is inverted in chloroform. In more polar acetonitrile, the equilibrium is predicted to shift further to the oxo tautomer (96JPC16141). In contrast, INDO parametrized MO calculations including the solvation model predicted the rapid increase in the relative proportion of the hydroxy form with the increase in polarity, contradicting the experimental results (87JST(158)69). The theoretical studies of solvent effects have also been carried out for 6-chloro-2-hydroxypyridine in water and in carbon tetrachloride (91JCS(P2)799).

The SCRF approach was also used to study the solvent effects on thermodynamics and kinetics of tautomerization of 2-hydroxypyridine in aq. solution and confirmed that the oxo tautomer is favored due to stabilization by the solvent interaction (95IJQC(56)645). The participation of a water molecule in the process of interconversion was rationalized by means of CNDO/2 method (81TL775). The tautomeric equilibrium constant in water was calculated using the combination of the AM1 method with inclusion of the solvent reaction field; the results are in a good agreement with the experimental findings (89JOC6030, 90JPOC332). *Ab initio* molecular orbital studies using 3-21G and 6-31G* basis sets were reported for the tautomeric equilibrium of 2-hydroxypyridine monohydrate – 2-pyridone monohydrate (93IJQC(46)183). On hydration with one molecule of water, both hydroxy and oxo tautomers are stabilized by 8.6 and 9.1 kcal/mol, respectively (85JST(120)73). The effect of second molecule of water on thermodynamics and kinetics of tautomerization is significant. In particular, the energy barrier is increased by about 1 kcal/mol and the oxo form is further stabilized by ~2.5 kcal/mol, which is sufficient to account quantitatively for enhanced stability of the lactam tautomer (84JCS(CC)1310, 95JPC15062). The inclusion of additional water molecules is likely to have a little effect due to small differences in the dipole moments of dihydrated tautomers. The hydration effect upon the tautomeric equilibrium of 2-hydroxypyridine has also been studied using the recently proposed coupled reference interaction site model/molecular dynamics solvation method (04JPC(B)19043), which provided the solvation free energy differences between tautomers in the range of −3.96 to −3.80 kcal/mol, in a good agreement with the experimental value of −4.3 kcal/mol.

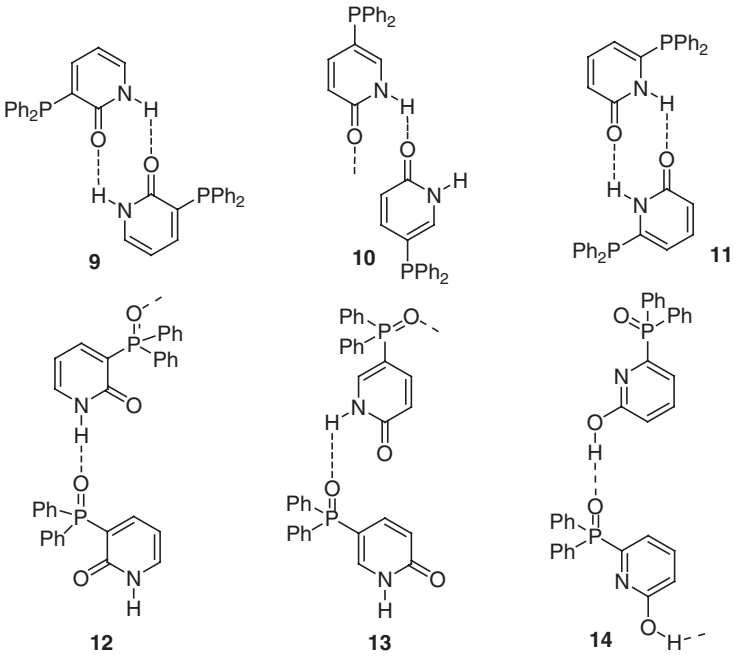
The activation energy in water was calculated to be 28.8–51.5 kcal/mol depending on the method used (84JCS(CC)1310, 95IJQC(56)645). The proton-transfer barrier was also calculated to be 13.5 kcal/mol for 2-pyridone dihydrate (3-21G method) (84JCS(CC)1310), 23.4 kcal/mol for 2-pyridone monohydrate (STO-3G method) (85JST(120)73), and 12.5 kcal/mol for 2-pyridone monohydrate (DFT (B3LYP)) (95JPC15062). The nature of the transition state is intermediate between that expected for a fully concerted and for a sequential proton-transfer mechanism (84JCS(CC)1310). The possibility of fine-tuning the tautomeric equilibria by the formation of a hydrogen-bonded complexes with guest molecules, other than water, possessing bifunctional hydrogen bonds, was confirmed by *ab initio* MO calculations (97JPC(B)9119).

The lactim–lactam tautomerism of 2(1*H*)-pyridone *via* non-dissociative proton-transfer mechanisms has been investigated using *ab initio* MO methods. Stationary points on the potential energy surfaces for proton transfer by three types of mechanisms have been obtained: (i) an intramolecular mechanism, (ii) tautomeric interconversion within a self-associated dimer, and (iii) a mechanism involving one or two water molecules as a bifunctional catalyst. Mechanisms (ii) and (iii) were found to be more energetically favorable than the first one. The consideration of large supermolecules (bulk solvent) was suggested to be unlikely to affect the energetics dramatically (87JCS(P2)617).

c. Solid-State Tautomerism. Solid-state Raman spectra of 2-hydroxypyridine at the temperatures from 51 to 295 K indicate that the oxo tautomer predominates over this

temperature range. No variations in the tautomeric equilibrium with temperature or pressure change were observed (94JST(324)83). 6-Hydroxy-2-pyridinecarboxylic acid exists in the solid state in the tautomeric equilibrium with the oxo-tautomer, the latter being preferred. The molecules form dimers connected by two N–H···O hydrogen bonds (98AX(C)1491). 4-Benzoyloxy-5-chloro-2-pyridone exists exclusively as the oxo tautomer in the solid state (93CPB1498). X-ray analysis showed that in the 2(1*H*)-pyridone/lauric acid complex 2-pyridone exists in a dimeric oxo form similar to that found in solution, although non-complexed 2-pyridone exists in the polymeric oxo form in the solid state (96MI1).

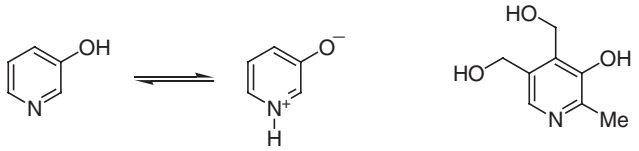
Single-crystal X-ray analyses of regioisomeric 2-oxopyridyl phosphines and phosphine oxides **9**–**14** exhibited three kinds of molecular aggregations: bimolecular aggregates, chiral one-dimensional structures, and achiral one-dimensional structures. Thus, in **9** and **11**, two molecules of 2(1*H*)-pyridone aggregate so as to construct a cyclic dimer, whereas the crystals of **10**, **12**, and **13** are constructed with chiral or achiral one-dimensional chains like those of unsubstituted 2(1*H*)-pyridone. Interestingly, the phosphine oxide **14** exists in the solid state in the hydroxy form with the OH proton participating in the one-dimensional chain (00JOC6917).



2. *3-Hydroxypyridines*

Unsubstituted 3-hydroxypyridine and its 2-methyl analog were shown to exist in aq. solutions in equilibrium between the neutral form **15a** and zwitterion **15b**, the latter being hydrated by two molecules of water, which stabilize the electrical charges

(78TL2221). The mechanism of this proton transfer was also investigated using the temperature-jump relaxation technique (77JA4438). 3-Hydroxypyridine tautomerism has also been studied by magnetic circular dichroism spectroscopy (80BCJ3069).



15a **15b** **16**

The substituent effect on the equilibrium of 3-hydroxypyridines has been investigated by ^{1}H and ^{13}C NMR spectroscopy (90JST(221)299) and UV spectroscopy (89KG1094). It was shown that the equilibrium in 2-halo-substituted 3-hydroxypyridines is shifted toward the zwitterionic form **15b**, whereas 6-methyl- and 5-chloro-substituted derivatives exist exclusively in the enol form **15a**. No bipolar form was detected for 2-benzyl- or 2-*tert*-butyl-substituted 3-hydroxypyridines in $CHCl_3$, DMSO, or alcohols. In neutral aqueous solution, all 3-hydroxypyridines studied existed as mixtures of hydroxy and zwitterionic forms, the ratio being dependent on the nature and the position of the substituent.

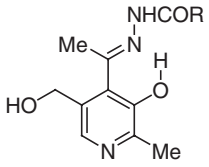
The solvent effects have been studied by ^{14}N NMR spectroscopy revealing the predominance of the hydroxy form for 3-hydroxypyridine in acetone/methanol = 2:1 (**15a**:**15b** = 0.96:0.04) and in methanol (**15a**:**15b** = 0.97:0.03) (76T1065). The preference for the enol form was also observed in nitromethane (78ZOB2358). The gradual increase of water content in the methanol solutions of 3-hydroxypyridine changes the tautomeric ratio from almost exclusive hydroxy tautomer (methanol) to nearly equimolar mixture of hydroxy and zwitterionic forms (water) (73B5377). Interestingly, complexation of 3-hydroxypyridine with β-cyclodextrin in water markedly affects the tautomeric equilibrium shifting it toward the less polar hydroxy tautomer **15a** (94MI13). The tautomeric constant $K_T = 0.53$ was obtained under these conditions compared to $K_T = 1.1$ in the absence of β-cyclodextrin.

Thermodynamic values of the ionization constants and tautomeric equilibrium constants of 3-hydroxypyridine **15** and pyridoxine **16** were determined in dioxane-water at 25 °C. Tautomeric equilibrium constants K_T, calculated from UV/visible spectra, were found to be 1.10 for 3-hydroxypyridine and 3.92 for pyridoxine in dioxane–water (84JCS(P2)2047) and 2.3 for pyridoxine in water (73B5377). The minor changes in K_T values of 3-hydroxypyridine, measured in phosphate buffers with different concentrations, indicates small variations of the activity coefficient of the dipolar form with the ionic strength (84JCS(P2)2047). A potentiometric method has been used to determine the thermodynamic equilibrium constants for the macroscopic ionization processes of 4-formyl-3-hydroxy-2,5-dimethylpyridine (5-deoxypyridoxal) in water–dioxane mixtures at temperatures ranging from 10 °C to 50 °C (97MI1021).

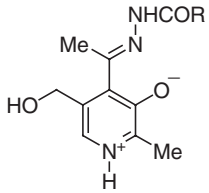
A remarkable temperature dependence of the ^{13}C NMR and ^{15}N NMR chemical shifts of 3-hydroxypyridine in D_2O (pD = 7.0) (93MRC552) and pyridoxine in water (pH = 7.0) (00JOC2716) was observed and explained by thermally induced equilibrium

shift between the hydroxy and dipolar forms. The observed average ^{13}C and ^{15}N chemical shifts at different temperatures were used to estimate the thermodynamic parameters of these equilibria providing $\Delta H = -4.3$ kcal/mol for 3-hydroxypyridine and $\Delta H = -5.6$ kcal/mol for pyridoxine. Another method for individual measurement of "microequilibrium" constants, based on spectral measurements as the function of temperature, was developed and applied to 3-hydroxypyridine tautomeric equilibrium (97AC1642).

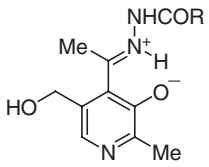
A series of pyridoxal aroylhydrazones **17** has been synthesized and studied by UV, IR, and ^1H NMR spectroscopy. In absolute methanol, these hydrazones exist in the neutral form **17a**, however, gradual addition of water to the methanol solution results in the appearance of new bands in the UV spectra, indicating the formation of zwitterionic tautomer **17b**. In aqueous solution, the equilibrium is greatly shifted toward **17b** rather than earlier proposed ketoenamine **17c**. The dipolar species **17b** are stabilized by intermolecular hydrogen bonding with water molecules (92JCS(P2)213).



17a



17b



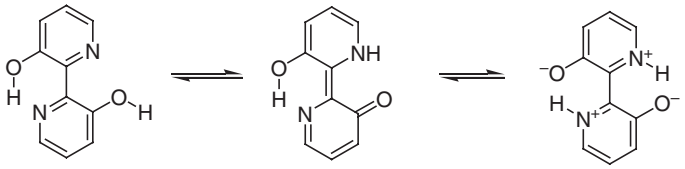
17c

R = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Theoretical studies of 3-hydroxypyridine at varying levels of approximation have been carried out in order to predict the enthalpy of tautomerization using CNDO/2, NDDO, MINDO/2, MINDO/3, MNDO, and STO-3G methods (80CPL(69)537). The predominance of the hydroxy tautomer in the gas phase (96JPC16141) and in low-temperature argon matrices (95JPC14967) was predicted ($\Delta E = -13.1$ kcal/mol). The solvent dependence of the tautometic equilibrium has been studied by means of SCRF theory. The log K_T in cyclohexane, chloroform, and acetonitrile was found to be linearly dependent on the solvent polarity as measured by Kosower Z parameter. Although this trend is similar for all regioisomeric hydroxypyridines, 3-hydroxypyridine demonstrates more significant solvent effects owing to bigger difference in the dipole moments of the tautomeric forms. An almost equal amount of hydroxy and dipolar tautomers is predicted for 3-hydroxypyridine in aqueous solution (96JPC16141). The hydrogen-bond interaction of 3-hydroxypyridine with water was investigated using a combined experimental matrix isolation FTIR spectrum and theoretical *ab initio* method (95JPC14967).

The relative stabilities of three tautomeric forms of 2,2′-bipyridyl-3,3′-diol **18** were calculated using the semiempirical AM1 and MNDO-PM3 and *ab initio* (4-31G basis set) methods (96IJQC(57)721). The dienol tautomer **18a** was found to be the most stable by all methods. Keto–enol tautomer **18b** is the second, less stable than **18a** by 12–16 kcal/mol. The tautomerization process in several electronic states has been

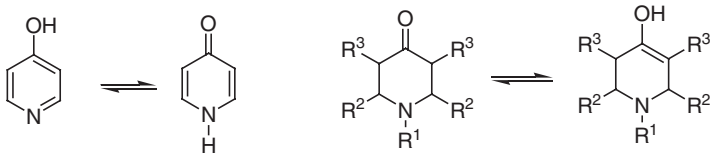
investigated theoretically by the semiempirical PM3 method. Although this compound exists in the ground electronic state in the dienol form, the calculations showed that three energy maxima should exist in photoelectron spectra corresponding to dienol, diketo, and enol(keto) forms. Tautomerism is thus driven by stepwise rather than concerted proton transfer. However, the proton transfer is governed by significant activation barriers both in ground and in excited electronic states, which prevent the experimental observation of any but dienol form (95JCS(P2)1141). It has been established that the solvent may participate in the interconversion mechanism or that it may influence the relative stabilities of the tautomeric species. The effect of water, which makes dienol and diketo tautomers equally stable, is not observed for other polar or non-polar solvents, where the dienol form is always the more stable one (96JST(368)17).



18a **18b** **18c**

3. *4-Hydroxypyridines*

Studies of tautomeric equilibria (**19**⇌**20**) in the gas phase by UV and IR spectroscopy have shown that unsubstituted 4-hydroxypyridine exists almost exclusively in the hydroxy form ($K_T = (NH/OH) < 0.1$) (76JA171). This conclusion was later confirmed by photoelectron spectroscopy studies (77JCS(P2)1652).



19 **20** **21a** **21b**

The substituent effect on the tautomeric equilibrium in solution has been studied using experimental pK_a values and UV spectra (in water at 20 °C) of several 4(1*H*)-pyridones and their N- and O-fixed derivatives. It was concluded that most of the factors affecting the tautomerism of 4(1*H*)-pyridones are due to the electronic effect, including steric effect, of the substituents in the 2-position. Thus, the proportion of the hydroxy form increases on introduction of an electron-withdrawing group into the 2-position. For example, 5-methoxy-4(1*H*)-pyridones with a methyl, hydroxymethyl, and methoxymethyl groups in the 2-position exist essentially in the pyridone form; however, 2-methoxycarbonyl-substituted derivative exists as a mixture of hydroxy and oxo form in water (77BCJ710). The effect of substituents in the 3-position

is much less pronounced (81RTC30). 3-Nitro-4-hydroxypyridine exists predominantly in the oxo form in DMSO-d_6 solution (91MRC878). Whereas 3,5-dibromo-4-hydroxypyridine exists in the pyridone form, the introduction of two additional bromine atoms leads to the shift in the tautomeric equilibrium, so 2,3,5,6-tetrabromo-4-hydroxypyridine exists primarily as the hydroxy tautomer (78KG70).

Substituent-dependent keto–enol tautomerism was also observed for 4-piperidinones **21** (91ZN(B)1237). When $R^1 = H$, Me, the ketones **21a** are more stable than enols **21b**, and 2,6-*cis*-substituted ketones are more stable than 2,6-*trans*-substituted ketones. The introduction of an ester group into the 3-position shifts the keto–enol equilibrium toward the enol form.

The solvent effects on the tautomeric equilibrium of 4(1*H*)-pyridone and 2,6-di-*t*-butyl-4(1*H*)-pyridone was studied by UV spectroscopy in solvents of different polarity, and the almost linear dependence of the proportion of the 4-pyridone form, which is dominant in aqueous solution, with the solvent polarity as measured by Kosower *Z* values has been established (76JCS(P2)1428). From the ^{14}N NMR spectra of unsubstituted 4-pyridone, the molar fraction of the oxo tautomer was found to be 0.83 in acetone and 0.90 in methanol (76T1065). In nitromethane, the parent 4-pyridone also exists primarily in the oxo form (78ZOB2358). Comparison of the UV spectra of 5-hydroxy-2-hydroxymethyl-4(1*H*)-pyridone and its N-substituted derivatives in neutral, acidic, and alkaline solutions showed that the neutral species and the conjugate acids of these compounds exist in the pyridone and hydroxypyridine form, respectively. The conjugate base may exist in both forms (79BCJ107). The tautomeric equilibrium of 3,5-dinitro-4-hydroxypyridine, which exists in THF predominantly in the 4-pyridone form, can be completely shifted to the hydroxy tautomer on complexation with gold (99JOM(575)39).

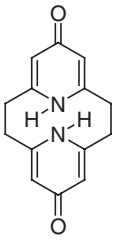
There is an extensive self-association of 4(1*H*)-pyridone in chloroform and in cyclohexane, which shifts the tautometic equilibrium toward the oxo tautomer. Less than 30% of the compound is estimated to be monomeric in these solvents, whereas 4-pyridone is monomeric in acetonitrile. The 6.1 kcal/mol self-association energy in chloroform is sufficient to dominate the position of the prototropic equilibrium (78JOC177). Values for both self-association and prototropic equilibrium constants of variously substituted 4-hydroxypyridines have been determined in different solvents (80JOC1354), and it was shown that in the concentrated solutions these compounds form oligomers (in contrast to 2-pyridones forming cyclic dimers) with degree of association depending on the solvent and steric requirements of the hydroxypyridine.

Temperature-jump experiments were performed with aqueous solutions of 2-chloro-4(1*H*)-pyridone and 2,6-di(methoxycarbonyl)-4(1*H*)-pyridone (chelidamic acid dimethyl ester). It was suggested that when the tautomeric functional group is remote, tautomeric interconversion occurs through intermediate ionization and dissociation followed by ion recombination (77JA4438).

The tautomeric equilibrium of 2,6-bis(2′-pyridyl)-4-hydroxypyridine in solution and in the solid state was evaluated using IR, variable temperature ^1H and ^{13}C NMR spectroscopy and X-ray crystallography. It was shown that less polar hydroxy tautomer is the predominant species in the gas phase, whereas in the solid state both species are present in 1:1 ratio and form a dimeric structure held together by strong

C = O···H–O bond between the tautomers. In the solution, the polar oxo form is predominant but not exclusive, and the ratio of tautomers depends on the polarity and hydrogen bonding ability of the solvent as well as temperature (99JCS(P2)2789). In contrast, the regioisomeric 2,6-bis(4′-pyridyl)-4-hydroxypyridine exists exclusively in the hydroxy form even in the polar solvents, such as DMSO, with was explained by steric interactions of all three heterocyclic rings and intramolecular C–H···N hydrogen bonding.

Pyridinophane **22** exists in the solid state in the 4(1*H*)-one form with molecules linked by water molecules to form infinite, hydrogen-bonded layers (91JCS(CC)860). Interestingly, the crown ether **23** exists in the solid state exclusively as oxo tautomer, whereas the related crown ether **24** – in its hydroxy form (85JCS(CC)749).



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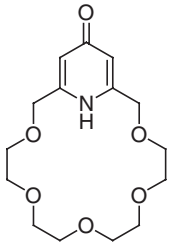

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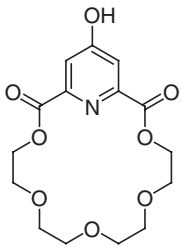

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Calculations at the 6-31G**/3-31G level (82JA5347, 82JCS(CC)685, 83JA3568), by the MP2/6-31G** method (99JOM(575)39), by MINDO/3 method (79IJQC(16)1141), and by MINDO–Forces MO method (85ZN(A)1278) indicated that 4-hydroxypyridine is more stable than 4(1*H*)-pyridone in the gas phase ($\Delta E =$ −2.4–3.6, −5.3, −4.0, and −3.9 kcal/mol, respectively) and in argon matrix ($\Delta E =$ −5.2 kcal/mol) (95JPC14967). The stability of the oxo tautomer is overestimated by AM1 method (89JCR(S)56, 89JOC6030, 89JST(184)179). The introduction of electron-accepting nitro groups into the heterocyclic ring further stabilizes the oxo tautomer (99JOM(575)39). The substituent effects on the prototropic tautomerism of monosubstituted (00PJC1283) and polyhalogenated (99PJC1863) 4-hydroxypyridines in the gas phase have also been estimated by semiempirical AM1 calculations.

AM1 and PM3 semiempirical calculations were applied to estimate the solvent effects on the tautomeric equilibrium of 4-hydroxypyridine in the gas phase and in solution. The calculated tautomeric equilibrium constants for the gas phase, cyclohexane and chloroform are in good agreement with the experimental data (93JCC371). The solvent dependence of the tautomeric equilibrium has also been studied using SCRF theory (96JPC16141). The log K_T in cyclohexane, chloroform, and acetonitrile were found to be linearly dependent on the solvent polarity. The free energy of solvation of the oxo tautomer in chloroform was found to be more favorable than that of the enol form ($\Delta E_{solv} = -1.8$–2.9 kcal/mol) (96JPC4269).

The hydrogen bond interactions of 4-hydroxypyridine with water were investigated using a combined experimental matrix isolation FTIR spectra and theoretical *ab initio* method (95JPC14967). *Ab initio* (6-31++G**) calculations of 1:1 complexes of 4-hydroxypyridine with water indicated that only two of five possible

complexes, namely OH···OH_2 and N···HO–H types, should occur in detectable amounts in argon matrices (94JST(322)113). This conclusion was confirmed by experimental IR spectra. The combination of the AM1 method with inclusion of the solvent reaction field was used to determine the equilibrium constant of 4-hydroxypyridine in aqueous solution; the value obtained was in a good agreement with experimental data (89JOC6030, 90JPOC332). The relative stabilities of five isomeric complexes of 4-hydroxypyridine with water were estimated by *ab initio* SCF calculations (93MI13). A semiempirical potential, obtained from *ab initio* calculations, was used in the study of multiple solvation of 4-hydroxypyridine tautomers with up to 92 molecules of water (85JA7569).

4. *Quinolines and Benzologues*

The effect of benzannulation on the position of the tautomeric equilibrium has been evaluated using the PMO semiempirical calculations (90ZOR1387) and revealed the following trends: (a) the transition from 2-hydroxypyridine to 2-hydroxyquinoline and 1-hydroxyisoquinoline leads to increased stability of the oxo tautomer; (b) transition from 2-hydroxypyridine to 3-hydroxyisoquinoline shifts the equilibrium toward the hydroxy tautomer; and (c) the relative stability of the oxo tautomer of 1-hydroxyisoquinoline is higher compared to that of 2-hydroxyquinoline. These theoretical results are in good agreement with the experimental data.

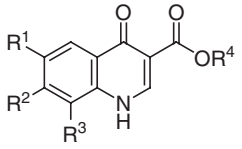
Early gas-phase calometric measurements showed that the 2-hydroxyquinoline is more stable than 2-quinolone by 0.3 kcal/mol. The small difference in relative energies of these tautomers has been confirmed by the two-photon time-of-flight mass spectrometry (TOFMS), fluorescence excitation spectra and dispersed emission spectra of 2-hydroxyquinoline, which indicated the presence of both oxo and hydroxy tautomers in the supersonic jet expansion (87JPC6610). The presence of the 4-hydroxyquinoline form in the gas phase is confirmed by low- and high-resolution mass spectrometry, and supported by B3LYP gas-phase calculations (02JCS(P2)2159). On the other hand, photoelectron spectra of 2(1*H*)- and 4(1*H*)-quinolinone provided no evidence for existence of the hydroxy tautomer in the vapor phase (81LA366).

The kinetic energy release associated with the decomposition of metastable ions has been used to differentiate between the hydroxyquinolines and the corresponding tautomeric quinolinones in the gas phase. The 2-hydroxyquinolines were shown to exist in both forms, whereas the other monohydroxyquinolines exist only in the hydroxy forms (88JCS(P2)347). In the solid state, 2(1*H*)-quinolinone and its 8-acetoxy analog exist exclusively in the lactam form (82CPB1488). The mass-spectra of 4-methoxy-2-hydroxyquinoline are consistent with the presence of both oxo and hydroxy forms in the gas phase, with the latter predominating (86JST(147)351).

Prototropic tautomerism of 4(1*H*)-quinolone-3-carboxylic acid derivatives **25** has been studied with particular emphasis on the influence of the ring substituents on the equilibrium. The techniques used include UV, ^{1}H-NMR, ^{13}C-NMR (solution), and ^{13}C-NMR CP/MAS (solid state) (92T6135).

Self-association, observed for 4(1*H*)-pyridones, is significantly suppressed by 2,6-substitution in the ring, so 3-decyl-2,8-dimethyl-4(1*H*)-quinolinone is essentially

monomeric in chloroform solution as measured by vapor pressure osmometry (78JOC177). Studies of the tautomeric equilibria of 3-decyl-2,8-dimethyl-4(1*H*)-quinolinone, 2-(dimethylamino)-4(1*H*)-quinolinone, and azacycle-fused 4-quinolones **26** (X = NMe; Y = $(CH_2)_n$; $n = 1-3$; $R^1 = R^2 = H$) in solvents of different polarity by UV and IR spectroscopy demonstrated that the proportion of the oxo form, which is dominant in aqueous or ethanol solutions, falls roughly linearly with the solvent polarity as measured by Kosower *Z* values (76JCS(P2)1428, 80KG349). Interestingly, no solvent effect on the tautomerism of 4(1*H*)-quinolone has been observed. The dependence of the solvent effect on the heterocyclic ring substitution has been confirmed by UV studies of substituted 4-quinolones in various solvents (81RTC30). Thus, whereas monosubstituted ester **25** ($R^1 = R^2 = R^3 = H$; $R^4 = Et$) and 3-cyano-4-quinolinone exist in water, DMSO, MeOH, MeCN, $CHCl_3$, and benzene predominantly as oxo tautomers showing only minor variations with the solvent change, the equilibrium of **25** ($R^1R^2 = OCH_2O$; $R^3 = H$; $R^4 = Et$) is more sensitive with the fraction of the oxo tautomer decreasing with diminishing solvent polarity.



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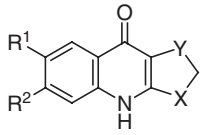

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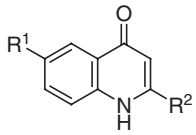

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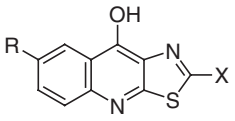
NMR studies of 2-substituted 4-quinolones **27** (R^1 = H, Me, OMe; R^2 = OMe, SMe, NMe_2) showed the predominance of the 4-hydroxy tautomers in DMSO-d_6 solution and of 4-oxo tautomers in $CDCl_3/CD_3OD$. In the last case, the H/D exchange takes place at the C-3 position in several days at ambient temperature indicating that the less favorable and not directly observed 3H-tautomer also participates in the equilibrium (99JOC3608). The structure of the potentially tautomeric 2-aryl-3-bromoquinolin-4(1*H*)-ones were studied using spectroscopic (^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy), X-ray crystallographic methods and quantum chemical calculations (PCM-B3LYP). These compounds were found to exist both in solution and in the solid state as the oxo tautomers (02JCS(P2)2159).

Tetrahydrofuran-fused 4-quinolinones **26** (X = O; Y = CH_2; R^1, R^2 = H, Cl) exist in alcohol solutions as oxo tautomers, possibly bonded to an alcohol molecule *via* both heterocyclic oxygen and nitrogen atoms. In dioxane, the equilibrium in **26** (X = O; Y = CH_2; R^1 = H; R^2 = H, Cl) is shifted toward the hydroxy form, whereas no changes are observed for **26** (X = O; Y = CH_2; R^1 = Cl; R^2 = H). Interestingly, the two former compounds exist in the solid state in the hydroxy form, while the latter – in the oxo form (84KG376).

According to their IR, ^{13}C, and ^{15}N NMR spectra, thiazole-fused 4-hydroxyquinolines **28** (R = H, F, Me; X = Cl, SMe, SO_2Me) exist exclusively in the hydroxy form in solution; the preference of the hydroxy tautomer is confirmed by the AM1 semiempirical calculations ($\Delta E = 3.4$ kcal/mol for **28** (R = H; X = SMe)) (96T11929).

Fused 2-hydroxyquinoline **29** exists in benzene, chloroform, dioxane, and ethanol in the hydroxy form (81ZOR803). On the addition of water or lower aliphatic carboxylic acids, the oxo form also appears reaching 75% in acetic acid. The introduction of bromine at the 3-position reduces the content of the lactam form in acetic acid to 45%, whereas the introduction of chlorine at position 6 reduces it to 60%. The introduction of the amino group at position 6, however, shifts the equilibrium in the opposite direction.



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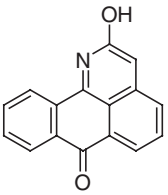

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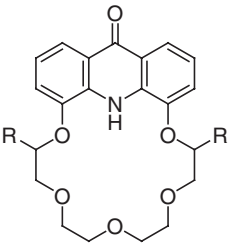

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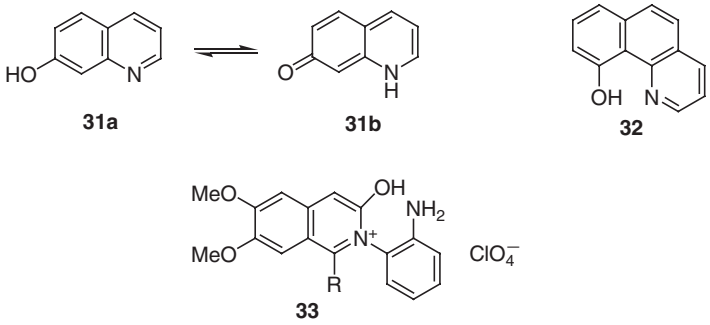
According to UV and IR spectroscopy, the unsubstituted acridone exists in the vapor phase and in water predominantly in the oxo form (K_T = (NH/OH) > 10 in the gas phase) (76JA171). Acridone crown ethers **30** (R = Me, *i*-Bu) also prefer the oxo tautomeric form in MeCN solution; however, on complexation with Pb^{2+} the shift of the tautomeric equilibrium toward the hydroxy form associated with intermolecular interactions and strong hydrogen bonding is observed (04T(A)1487).

Aromatic resonance energy differences were determined for 2-hydroxyquinoline and 4-hydroxyquinoline and found to be 2.45 and 1.3 kcal/mol, respectively (92T7857). The geometries, relative stabilities and proton affinities for the different tautomers of 2-, 3-, and 4-hydroxyquinolines have been calculated with full geometry optimization using AM1, PM3, and MNDO methods. The reported results are somewhat contradictory. AM1 and PM3 calculations predict the higher stability of the hydroxy (92T6135) or oxo form of 2-hydroxyquinoline (02JST(594)185), whereas the MNDO method favor the hydroxy form. Almost all methods favor the hydroxy form of 3-hydroxyquinoline both in gaseous and aqueous phases. For 4-hydroxyquinoline, AM1 and MNDO calculations indicate the predominance of the hydroxy form in gas phase as well as in aqueous solution, whereas the PM3 method favors the keto form in the gas phase (02JST(594)185). The semiempirical and functional density calculations predicted the negligible energy difference between tautomers of 4-quinolone in the gas phase (02JCS(P2)2159). The predominant hydroxy tautomer is predicted for 4-oxoquinoline-3-carboxylic acid and its ethyl ester with differences in relative stabilities of the tautomers being larger than that for the unsubstituted 4(1*H*)-quinolinone (92T6135). Semiempirical MNDO calculations with geometry optimization, carried out for 4-substituted 2-quinolones, showed the predominance of the hydroxy tautomer in each case, although the relative stability difference between the tautomers was found to be smaller than that for the 2-hydroxypyridine analogs. The substituent in the 4-position does not effect significantly the equilibrium position. The results of the calculations were confirmed by UV absorption studies (82ZN(A)1276).

The enthalpy difference between the keto and enol forms of 7-hydroxyquinoline **31** has been measured by using the time-resolved thermal lens techniques. The large differences obtained, 3400 cm^{-1} in the ground state and 4200 cm^{-1} in the excited singlet state, indicate the predominance of the enol form **31a** in the ground state and the keto form **31b** in the excited state (89JA3824). When 7-hydroxyquinoline is excited in dry chloroform, MeCN, or DMF, only enol emission is observed. However, both enol and keto tautomer emission is detected in the presence of an alcohol or water, the intensity of the keto emission increasing with increase in the concentration of the proton donor (83CPL(96)509). The kinetics of this tautomerization in methanol and alcohol-containing cyclohexane solutions have been studied by picosecond fluorescence spectroscopy (82CPL(85)317, 89JCS(F2)39). The stabilization of the ground-state keto tautomer has been observed in Ar matrices (93CPL(207)513) and mixed methanol/argon matrices (92CPL(204)96) at 10 K. The stabilized tautomer has been ascribed to the isolated dimer complex or to the **31** – $(MeOH)_2$ bridged complex, respectively. The dimer concentration can be increased by photolysis or by an increase in the deposition temperature.



31a **31b** **32** **33**

The double proton-transfer reactions of 7-hydroxyquinoline with water at both gates of cyclodextrins have been studied (98CPL(296)335). It was shown that whereas in neutral water both tautomers coexist (85% of **31a** and 15% of **31b**; $K_T = 5.7 \pm 1$), addition of β-cyclodextrin results in their conversion into the encapsulated hydroxy tautomer thus shifting the tautomeric equilibrium entirely to **31a**.

7-Hydroxyquinoline structure has been calculated using RHF/6-31G(d,p) basis set at 298 K. The association enthalpy for cyclic dual hydrogen-bonded dimer was found to be less exothermic (by 0.67 kcal/mol) than that of the linear dimer, so the cyclic dimer formation is disfavored. Thermodynamics of self-association and hydrogen-bonded complexes in various non-polar solvents has been studied by means of absorption and emission spectroscopy and theoretical approaches. Specific hydrogen-bonding sites have been determined in the complexes of 7-hydroxyquinoline incorporated with guest molecules possessing either a proton-donating or -accepting site. A proton-transfer mechanism incorporating the rotational diffusion dynamics of guest molecules is proposed (99JPC(A)1939).

The excited-state keto–enol tautomeric interconversion has been observed for 1-hydroxybenzo[h]quinoline **32** in non-polar solvents (cyclohexane, methylcyclohexane, benzene), acetonitrile, and water at ambient temperature (92CPL(193)151, 96JPC17059,

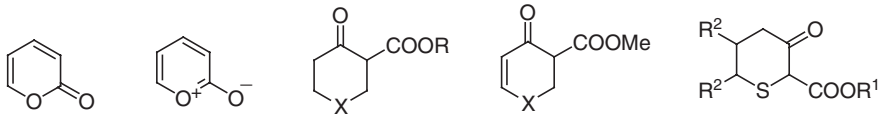
01JPC(A)1731, 02JPC(A)5967). The dynamics of the ESIPT in various solvents and the substituent effects have been studied.

Proton-transfer tautomerism mediated by the CDHB effect in the ground state as well as in the excited state has been studied in 3-hydroxyisoquinoline. In cyclohexane, upon increasing concentration or addition of guest molecules possessing the bifunctional hydrogen-bonding property, spectral and dynamic analyses indicate the existence of equilibria between various proton-transfer tautomers, including lactim monomers, lactim dimers (or 1:1 lactim/guest complexes), and lactam/lactim complexes (or 1:1 lactam/guest complexes). The lactim dimer was calculated to be the most stable species, in agreement with experimental observations. The equilibrium constants among each species have been determined. The results conclude that the CDHB formation and its strength play the key role in fine-tuning the ground-state equilibria toward the lactam form. Upon excitation, the lactim CDHB complexes undergo a rapid proton-transfer reaction, resulting in a unique oxo emission. Drastically different excited-state relaxation dynamics between the oxo dimer and oxo/hydroxy complex have been observed (98JPC(B)1053).

According to their IR and UV spectra, 1-halo-3-hydroxyisoquinolines exist in the solid state predominantly in the lactim form. 1-Unsubstituted 3-hydroxyisoquinolines exist in methanolic solution at 20 °C in the lactim–lactam equilibrium with 48–58% of the lactam form (74LA1802). 1-Alkyl-3-oxo-6,7-dimethoxy-*N*-(2′-aminophenyl)isoquinoline perchlorates **33** were found to exist in the lactim form shown with a hydrogen bond between the amino and hydroxy groups (76KG238).

5. *Other Heterocyclic Compounds with One Heteroatom*

2-Pyranones and 4-pyranones are mesomeric species (e.g., **34a** ↔ **34b**), although these compounds have been classified as non-aromatic on the basis of their magnetic susceptibility measurements, chemical reactivity, and calculated aromaticity indices (84CHEC(3)632). In transition from 4-pyranone to thiopyran-4-one, higher-frequency shifts of ring protons are observed, probably indicating the increased ring currents and greater aromaticity.



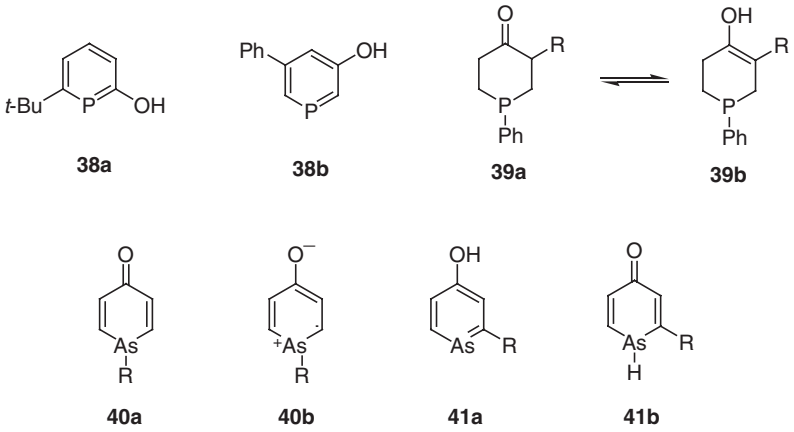
34a **34b** **35** **36** **37**

Of all the partially reduced thiopyranone derivatives, the enol forms are detected only for dihydro- and tetrahydrothiopyran-4-ones and tetrahydrothiopyran-3-ones with a sp^3-carbon bound alkoxycarbonyl substituent adjacent to the potentially tautomeric carbonyl group (81T2633, 86JCS(P2)1887). Thus, esters **35** (X = SO, SO_2; R = Me, Et) and **36** (X = SO_2) exist exclusively or predominantly in the enol form in $CDCl_3$ solution, whereas **35** (X = S; R = Me) and **36** (X = S) as mixtures of enol and keto forms and **36** (X = SO) – only in the keto form. In the solid state, **36** (X = S, SO) exist exclusively in the keto form, while **36** (X = SO_2) – in the enol form.

Tetrahydrothiopyran-3-ones **37** ($R^1 = Et$; $R^2 = H$) exist in solution in an equilibrium of the keto and enol forms with about 68–69% of the enol form (81T2633). Their cyclohexane-fused analogs **37** ($R^1 = Me$; $R^2_2 = (CH_2)_4$) favor the enol form stabilized with intramolecular hydrogen bonding in the solid state and in $CHCl_3$ or CCl_4 solution. Upon addition of an acid to the enol solution, however, the equilibration takes place giving a mixture of both forms (74% of enol form) (94ACSA417).

UV and ^1H NMR spectra of phosphabenzenes **38a** (89TL5245) and **38b** (77TL3445), and 4-hydroxyarsabenzene (75AG(E)710) indicate their phenolic structure; no evidence for a betaine form has been found in these cases. The dependence of the tautomeric equilibrium in phosphorinanes **39** (R = CN, COOMe) on the substituent R, solvent and temperature has been evaluated (77DOK858). For **39** (R = COOMe), the enol form **39b** predominates independent of the solvent; the keto fraction slightly increases with increase in the temperature. In contract, the keto form **39a** predominates for **39** (R = CN) in all solvents studied with fraction of the enol form increasing in the polar solvents.

According to their ^1H NMR and IR spectra, the 1-substituted arsacyclohexadienone **40a** ↔ **40b** is mesomeric (76TL4143). These compounds undergo an arsacyclohexadienone-phenol rearrangement to give the 2-substituted derivatives that exist as phenolic compounds **41a** (77TL3449) or in an equilibrium of **41a** and **41b** tautomers (78TL1471).

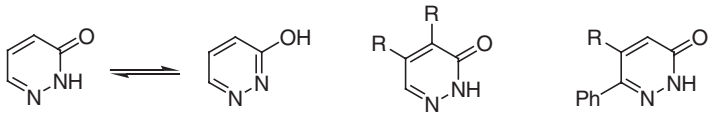


6. *Pyridazines, Cinnolines, and Phthalazines*

Semiempirical AM1 studies of the effect of an additional heteroatom on the tautomeric equilibrium position showed that transition from 2-hydroxypyridines to 3-hydroxypyridazines should shift the equilibrium toward the oxo form (88ZOR1799). Later, semiempirical (AM1, MNDO, and MINDO/3) and *ab initio* (3-21G basis set) calculations were performed for unsubstituted 3-hydroxypyridazine (90JST(206)295). Whereas *ab initio* methods correctly predicted the greater stability of the oxo

tautomer, semiempirical methods erroneously favored the hydroxy tautomer, the error being the smallest for the AM1 method.

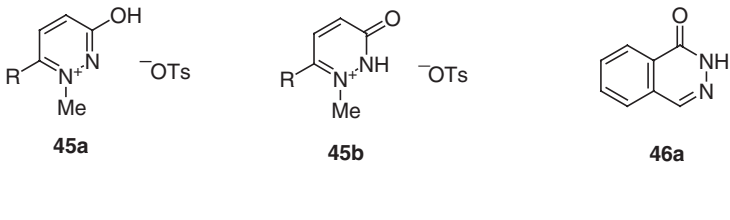
Tautomerism of unsubstituted 3-pyridazinone in low temperature inert gas matrix has been investigated by means of IR spectroscopy (90SA(A)1087, 92JPC6250). In accordance with the theoretical calculations, only oxo tautomer **42a** was observed after the deposition of the matrix. The hydroxy tautomer, however, was produced photochemically by UV irradiation of the matrix. Aromatic resonance energy difference for tautomers of 3-hydroxypyridazine was calculated to be 4.7 kcal/mol (92T7857).



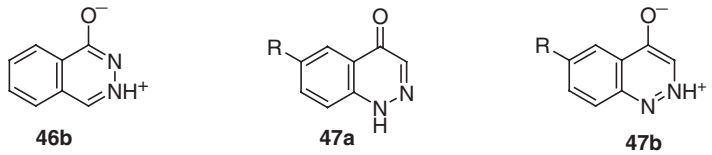
42a **42b** **43** **44**

Lactam–lactim tautomerism of pyridazinones **43** (R = H, Cl) in solution and in the solid state has also been studied by IR spectroscopy (97JST(408)467). It was shown that in the solid state or chloroform solution these compounds exist in the lactam form shown. In dioxane, however, the concentration-dependent oxo-hydroxy equilibrium was observed. The existence of the oxo tautomer in the form of a cyclic dimer was confirmed by charge distribution calculations. The relative stabilities of oxo and hydroxy tautomers of substituted pyridazinones **44** (R = H, CHO, CN, SO_2Me, NH_2, OEt) were calculated by the HF/3-21G method (02T2389). The lactam tautomer was predicted to be predominating in all the cases in spite of a significant effect of the nature of the R substituent on the tautomeric equilibrium. 6-(4-Bromophenyl)-3-hydroxypyridazine exists as oxo tautomer in a neutral medium and as deprotonated hydroxy tautomer in strongly alkaline medium; the experimental findings were confirmed by MO calculations (94RRC991).

IR and ^{1}H NMR data have been used to study tautomerism in the pyridazine, cinnoline, and phthalazine series. For hydroxypyridazines **45** (R = H, Me), the lactim structures **45a** rather than the lactam structures **45b** were assigned. Although only lactam forms **46a** and **47a** were observed in the phthalazine **46** and cinnoline **47** series, the presence of betaines **46b** and **47b** as minor components was suggested on the basis of the chemical reactivity of these compounds (75JCS(P1)1506).



45a **45b** **46a**

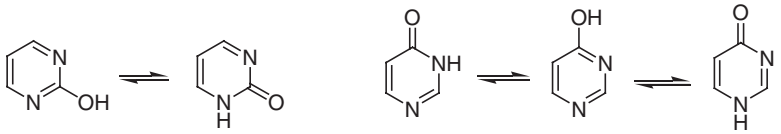


46b **47a** **47b**

Studies of tautomerism of 1(2*H*)-phthalazinone using UV, IR, and ^{1}H NMR spectroscopy suggest that this compound exists predominantly in the lactam form in DMSO-d_6 and in water and the contributions of the lactim and zwitterionic structures are minor (77JCS(P2)1184).

7. *Pyrimidines and Quinazolines*

2-Hydroxypyrimidine can potentially exist in two tautomeric forms **48a** and **48b** (three isomers are possible for unsymmetrically substituted 2-hydroxypyrimidines), whereas three potential tautomers **49a**, **49b**, and **49c** could be involved into tautomeric interconversions of 4-hydroxypyrimidine. As in many (especially, early) reports, the exact form for the oxo tautomer of 4-hydroxypyrimidine was not identified, it will be referred just as oxo tautomer.



a. Gas-Phase Tautomerism. 2- and 4-Hydroxypyrimidine were studied in gas phase by means of UV and IR spectroscopy. Whereas 2-hydroxypyrimidine exists primarily in the hydroxy form ($K_T = <0.1$ (NH/OH)), the reverse is true for 4-hydroxypyrimidine that exists predominantly in the oxo form ($K_T = 1.8 \pm 1.0$ (NH/OH)) (76JA171). The gas-phase prototropic tautomerism of 2-hydroxy- and 4-hydroxypyrimidine and a series of their monosubstituted derivatives (substituted at C-4 and C-2 positions, respectively, by NH_2, OH, SH, and SMe groups) were studied in detail. The *ab initio* Hartree–Fock method, the many-body perturbation theory, and the coupled cluster method with the double ζ Gaussian basis augmented with polarization functions support experimentally derived conclusions that 2-hydroxypyrimidine exists in the gas phase, low-temperature gas matrix or in the weakly polar environment almost exclusively in the hydroxy form ($K_T = 0.01$ at $T = 500$ K) (89MI1650, 90JPC7021, 92JPC6250). The strong predominance of the hydroxy form was also observed for halo- and methyl-substituted 2-hydroxypyrimidines in low-temperature argon matrix and in the gas phase (80JST(62)47, 81IJQC(20)573, 86JST(140)235). A coexistence of hydroxy and oxo forms with a clear predominance of the hydroxy form was found for *S*-methyl 4-thiouracil vapor ($K_T = 0.17$), whereas 4-hydroxypyrimidine and *S*-methyl 2-thiouracil exist in the gas phase as a nearly equimolar tautomeric mixture ($K_T = 1.08$) (90JCS(P2)871, 90JPC7021, 92JPC6250, 94JST(322)113). *Ab initio* calculations using the 6-31G** basis set (90JCS(P2)871) and semiempirical AM1 calculations (89JCS(P2)1507) slightly overestimate the stability of the oxo tautomer of *S*-methyl 2-thiouracil predicting it to be more stable by 1.64 kcal/mol, while semiempirical MNDO method erroneously predict the highest stability of the hydroxy tautomer (89JCS(P2)1507). In low-temperature gas matrices,

the oxo tautomer of *S*-methyl 2-thiouracil predominates with $K_T = (oxo)/(hydroxy) = 1.2–1.5$, whereas predominance of the hydroxy form was observed for *S*,6-dimethyl 4-thiouracil ($K_T = 0.5$) (88JST(176)137, 90JA2147).

The oxo–hydroxy equilibration of halo- and methyl-substituted 4-pyrimidinones in low-temperature argon matrix was confirmed by high-resolution IR spectra (80JST(62)47, 81IJQC(20)573, 87JST(158)275). The 3*H*-oxo form **49a** was ascribed to the oxo tautomer of 4-hydroxypyrimidine (90SA(A)61). On increasing the polarity of the environment, e.g., by increasing the concentration of the hydroxypyrimidine in the matrix (86JST(140)235) or by addition of water to the matrix (98JPC(A)8157), the shift of the equilibrium toward the oxo form was observed. The tautomerization constant is also slightly dependent on the activity of the matrix gas with the keto tautomer favored in the more active matrix. The introduction of a substituent at the 5- or 6-position does not significantly effect the equilibrium, whereas an additional methyl group at the 2-position does (80JST(62)47).

UV-light-induced intramolecular proton transfer was observed in argon, xenon, and neon matrix-isolated 4-hydroxypyrimidine (88JST(175)91, 90SA(A)61, 92JPC6250). This photoenolization involves only monomeric molecules (the phenomenon has not been observed in concentrated matrices) and has been used to separate the IR spectra of the tautomers. No influence of the matrix environment of the tautomeric ratio was observed.

The electron impact mass spectra of N-unsubstituted 4-pyrimidinones indicate the predominance of the two oxo tautomers compared to the hydroxy form (90OMS115).

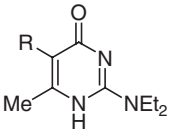
Both semiempirical AM1, PM3, PCILO, MNDO, MINDO/3 (79IJQC(16)1141, 80CPL(69)537, 85IJQC(27)567, 87JA6283, 94MI113, 99JST(458)217), and *ab initio* calculations (84JST(110)183, 87JA6283, 96JST(376)375, 98JPC(A)8157) were used to estimate relative stabilities of 2- and 4-hydroxypyrimidines. For 2-hydroxypyrimidine, *ab initio* calculations at the 6-21G* basis set (84JST(110)183) and at HF/6-31G(d,p) level and semiempirical AM1 and MNDO calculations (99JST(458)217) correctly predict the predominance of the hydroxy tautomer, whereas the opposite results were obtained using *ab initio* calculations with 3-21G basis set (84JST(110)183, 87JA6283) and semiempirical MINDO/3 method (79IJQC(16)1141, 87JA6283). Variable β-SCF-CI calculations predict the predominance of the oxo tautomers for both 2- and 4-hydroxypyrimidines (73CPB1474). The predominance of the hydroxy tautomer of *S*-alkyl 4-thiouracil in the gas phase was confirmed by SCF/3-21G* calculations (90JA1504), in good agreement with the experimental data.

All the semiempirical methods greatly overestimated the stability of the hydroxy tautomer of 4-hydroxypyrimidine (80CPL(69)537). *Ab initio* calculations at the HF/6-31G(d,p) level indicated a very small difference between the most stable hydroxy tautomer **49b** (*Z*-conformer) and 3*H*-oxo tautomer **49a** ($\Delta E = 0.37$ kcal/mol) (96JST(376)375), which is supported by experimental findings discussed above. 1*H*-Oxo tautomer **49c** was found to be less stable than **49b** by 11.0 kcal/mol. The position of the tautomeric equilibrium was not significantly affected by the heterocyclic ring substitution (94MI113). *Ab initio* calculations correctly predict the coexistence of 3*H*-oxo (**50b**) and hydroxy tautomers for substituted 4-hydroxypyrimidine **50** (R = *n*-Pr) in the gas phase; the 1*H*-oxo tautomer **50a** was found to be less stable by about

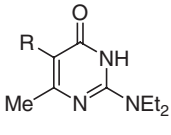
10 kcal/mol (99MI303). The relative stability of the hydroxy tautomer of *S*-alkyl 2-thiouracil was somewhat overestimated by calculations at the SCF/3-21G* level (90JA1504) and by *ab initio* calculations using 6-31G** basis set (90JCS(P2)871).

Tautomerism of 2-hydroxyquinazoline and 4-hydroxyquinazoline was calculated using MNDO, AM1, and PM3 methods. The MNDO method indicates the predominance of hydroxy tautomers in the both cases, whereas AM1 and PM3 methods favor the oxo tautomers in the better agreement with the experimental results (93KG1246).

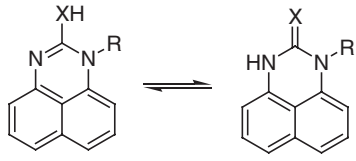
From the tandem mass-spectrometry data, 2-hydroxyperimidine **51** (X = O; R = H) exists in the gas phase in the tautomeric equilibrium of **51a** and **51b** forms (94HCA121). AM1 semiempirical calculations predict the hydroxy form **51a** to be the most stable ($\Delta E = 13.3$ kcal/mol).



50a



50b



51a **51b**

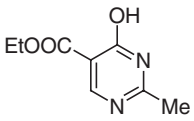
b. Solution and Solid-State Tautomerism. Solvation of 2- and 4-hydroxypyrimidines by the solvent molecules significantly shifts the equilibrium toward the oxo form, the effect being more pronounced for 2-hydroxypyrimidines. The tautomeric equilibrium constants for unsubstituted 2- and 4-hydroxypyrimidine were determined in chloroform, carbon tetrachloride, and water using IR spectroscopy (80TL3359). Whereas the oxo form of 2-hydroxypyrimidine predominated in all the solvents studied, 4-hydroxypyrimidine existed as an equimolar tautomeric mixture in CCl_4, but predominantly in the oxo form in chloroform and water. The magnetic circular dichroism spectra of 2-hydroxypyrimidine indicated that this compound exists in the lactim–lactam tautomeric equilibrium in a heptane–dioxane mixture (80BCJ3069).

5-Substituted 4-hydroxy-2-methylpyrimidines exist in alcoholic solutions (methanol, *n*-butanol) mainly in the 3*H*-oxo form (**49a**) and no effect of the substituent at the 5-position (methyl, methoxy, or ethoxycarbonyl group) on the tautomerism in these solvents was observed. In hexane, the 5-unsubstituted and 5-methyl derivatives also exist mainly in the lactam form, but the 5-ethoxycarbonyl analog **52** exists mainly in the hydroxy form, which is changed into the lactam form upon addition of methanol or *n*-butanol. The conversion to the lactam form may be explained as a result of an association of the pyrimidine molecule with two molecules of alcohol (78CPB1403). The lactim/lactam tautomeric equilibrium of **52** can also be shifted to the 3*H*-oxo form by addition of ethers, such as diethyl ether, *n*-propyl ether, isopropyl ether, *n*-butyl ether or dioxane, to its hexane solution. In pure ethers, hydroxypyrimidine **52** exists as a mixture of hydroxy and 3*H*-oxo tautomers with the latter predominating, except for dioxane, where only the lactam form was detected. The percentage of the hydroxy form decreases with increasing polarity of the solvent and

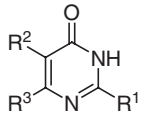
ranges from 9% in isopropyl ether to 15% in butyl ether (78CPB1415, 78CPB1426). In methanol, the lactam form of **52** strongly predominates (81RTC30).

The $^{3}J_{(CH)}$ values for the C–N–CH, C–N = CH, and C = N–CH structural elements were used as a valuable criterion for differentiating aromatic from non-aromatic structures and applied for tautomerism studies in 4-hydroxypyrimidines (83OMR20).

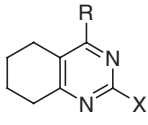
The effect of a 5-substituent on the tautomeric equilibrium of 4-pyrimidinones **53** (R^1 = Me; R^2 = H, Me, MeO, COOEt, $CONH_2$, CN; R^3 = H) was studied using their acidic and basic ionization constants and the results were confirmed by UV spectroscopy (74CPB1239). It was shown that all these compounds exist in aq. solution as an almost equimolar mixture of two oxo forms with the fraction of the hydroxy form not exceeding 4%. 4,6-Dimethyl-2(1*H*)-pyrimidinone and 6-methyl-4-pyrimidinone exist predominantly in the lactam form in solution (80JST(62)47, 84H(22)2591).



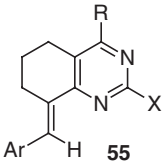
52



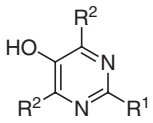
53



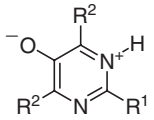
54



55



56a



56b

^{13}C NMR spectroscopy indicated the existence of unsubstituted 4-hydroxypyrimidine and its 2-methylthio- and 5-fluoro-substituted derivatives in polar aprotic and protic solvents as tautomeric mixtures of two oxo forms, 1*H*-oxo and 3*H*-oxo, with the molar fraction of the latter depending on the proton-donating power and dielectric constant of the solvent and the nature of the substituent at the 2-position of the pyrimidine ring (00ZOR1373). In non-aqueous solvents (methanol, isopropanol, acetonitrile), 3*H*-oxo tautomer predominates. Substituents in the 2-position favoring the charge delocalization (2-amino, 2-alkylthio) increase the fraction of the 1*H*-oxo tautomer, which is assigned the zwitterionic structure on the basis of the NMR data. *S*-Methyl 2-thiouracil exists exclusively in the oxo form both in solution and in the solid state (88JST(176)137).

According to IR spectra, unsubstituted 4-hydroxypyrimidine and its 5-halo analogs exist in the solid state exclusively in the oxo form (86JST(140)235, 88JST(175)91). 2-Diethylamino-6-methyl-4(3*H*) pyrimidinones **50** (R = Et) exists as lactam tautomers **50a** and **50b** both in the solid state and in a solution, **50b** being the predominant tautomer (99HC(4)157). The analog **50** (R = *n*-Pr) exists in the solid state exclusively in the **50b** form, the molecules being assembled in planar dimers by strong intermolecular hydrogen bonds (99MI303). Cyclohexane-fused hydroxypyrimidines **54** (X = OH; R = *n*-C_3F_7) and **55** (X = OH; R = CF_3; Ar = Ph, 4-$MeOC_6H_4$) exist both in the solid state and in chloroform solution exclusively as oxo tautomers (00S1738).

Pyrimidinones **53** (R^1 = Ph, $R^2 = R^3$ = H; $R^1 = R^2$ = H, R^3 = Ph) exist in solution as mixtures of hydroxy and 3*H*-oxo tautomers with the latter predominating. The same tautomeric interconversion was observed in solutions of palladium complexes of these compounds (96MI385). The data on tautomerism of perimidinones **51** (X = O; R = H, Me, Et, *n*-Pr) in solution are contradictory suggesting the predominance of either oxo tautomers **51b** (94HCA121) or enol tautomers **51a** (88MRC191). Only oxo tautomer was observed for **51** (X = O; R = Me) in the solid state (94HCA121).

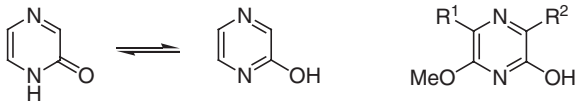
Similarly to 3-hydroxypyridines, 5-hydroxypyrimidines can potentially exist in neutral form **56a** or in zwitterionic form **56b**. The UV-spectroscopic studies of these compounds in aqueous solution showed that the parent compound ($R^1 = R^2$ = H) exists in acidic medium (pH 3.1–4.3) as a mixture of both forms in ratio **56a**:**56b** = 50:1. The introduction of methyl groups (R^1 or R^2 = Me) shifts the equilibrium toward the bipolar form **56b**, although **56a** still predominates. The introduction of a phenyl group into the position 2 induces the opposite effect (89KG1094).

Solvation of both tautomeric forms of 2-hydroxypyrimidine with chloroform (89JST(184)221) and water (85JST(121)247) was investigated by Monte-Carlo method for a cluster consisting of 50 molecules of water at $T = 300$ K. The results indicate that solvation with chloroform shifts the tautomeric equilibrium only slightly toward the lactam form. The proton transfer in the hydrogen-bonded complex of 2-hydroxypyrimidine with water was studied by *ab initio* methods (95JPC14277, 98JPC(A)8157). The theoretical results indicate that the closed N···H–O(H)···HO and C = O···H–O(H)···H–N bonded water complexes are the most stable systems for the hydroxy and the oxo tautomers, respectively. The proton tunneling is suggested as the proton-transfer mechanism. Relative stabilities of complexes of tautomers of 2-hydroxypyrimidine (93MI1) and 4-hydroxypyrimidine (94MI61) with water have been computed using *ab initio* SCF calculations with energetics corrected by the second-order perturbation treatment. Complexes of 2-hydroxypyrimidine and 2-pyrimidone with water were found to coexist at higher temperatures.

8. *Pyrazines and Quinoxalines*

Tautomerism of 2(1*H*)-pyrazinone **57** in low-temperature inert gas matrix has been investigated by means of IR spectroscopy, and the tautomeric equilibrium constant was estimated as $K_T = 8.6$ in the favor of the hydroxy tautomer. The UV-induced phototautomeric reaction has been used to separate the IR spectra of the tautomers (92JPC6250).

For estimation of the 2-(1*H*)-pyrazinone/2-hydroxypyrazine equilibrium in a solution, the $^{13}C,^{1}H$ spin–spin coupling constants were applied, and the results were supported by ^{15}N NMR data. The oxo tautomer **57a** was found to be the dominant species both in DMSO-d_6 and CD_3NO_2 with the molar ratio **57a**:**57b** being *ca.* 9:1 in DMSO-d_6 (82TL4785). UV spectroscopic studies indicate the predominance of the hydroxy form for 2-hydroxy-6-methoxypyrazines **58** (R^1, R^2 = Me, Ph) (97JCS(P1)3167).

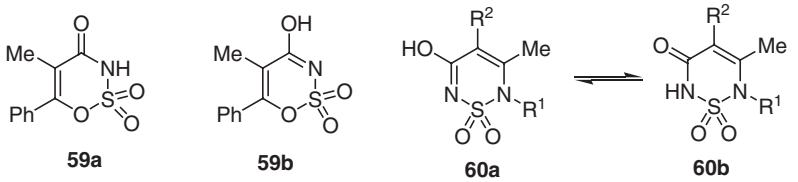


57a 57b 58

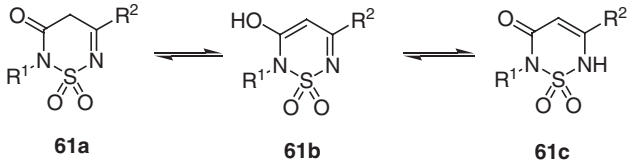
Investigation of the stability of different tautomers of 2-hydroxypyrazine in the gas phase as well as in different media by semiempirical AM1 method (92MI7), density functional theory and *ab initio* calculations (89JST(188)199, 99JST(459)229) revealed that the energy difference between the two tautomers is small and both tautomers should exist in the gas phase at ambient temperature, in agreement with the experimental data. The assignment of the dominating tautomer, however, depends on the calculation method and the basis set used. Generally, the hydroxy tautomer is predicted to be more stable in the gas phase, but, due to the higher dipole moment, the oxo tautomer in expected to be the most stable in solution (99JST(459)229).

9. *Other Heterocyclic Compounds with More Than One Heteroatom*

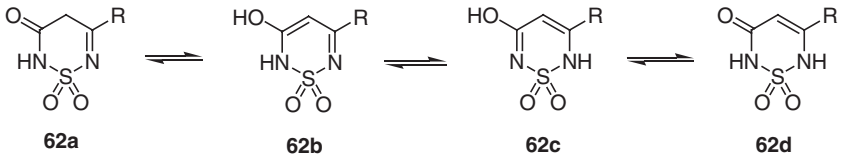
a. Oxathiazines. 5-Methyl-6-phenyl-2,1,3-oxathiazin-4(3*H*)-one 2,2-dioxide **59** exists in chloroform solution and in the crystal as amide **59a** with NH···O = C intermolecular hydrogen bonds. However, this compound can be selectively induced to adopt its enol form or its keto form both in solution and in the solid state by controlling the type of proton acceptors available for intermolecular hydrogen bond formation. For example, in the presence of triphenylphosphine oxide (TPPO), **59a** tautomerizes to an enol form **59b** due to formation of a complex with TPPO through very strong hydrogen bond between the phosphoryl oxygen and the hydrogen of the hydroxy group (86JOC5405).



59a 59b 60a 60b



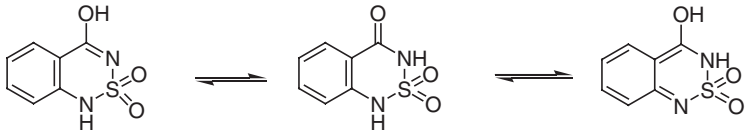
61a 61b 61c



62a 62b 62c 62d

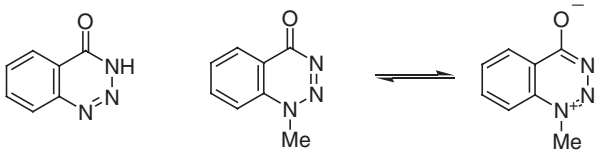
b. Thiadiazines. The effect of solvent, concentration, temperature, and the nature of substituents on the tautomerism of 4,5,6-trisubstituted **60** (R^1 = *n*-Bu, Ph, cyclohexyl; R^2 = H, Br), 2,5-disubstituted **61** (R^1 = Me, *n*-Bu, Ph; R^2 = Me) and 5-substituted 2*H*-1,2,6-thiadiazin-3-one 1,1-dioxides **62** (R = H, Me) has been studied by UV, ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy (88JCS(P2)859). It was shown that whereas **60** (R^1 = *n*-Bu, cyclohexyl; R^2 = H) exist in the hydroxy form **60a** in all the solvents studied, **60** (R^1 = Ph; R^2 = H) exist in the hydroxy form in chloroform, DMSO, and pyridine, but as a mixture of both tautomers in methanol. ^{15}N NMR indicated the predominance (at least 95%) of the amino tautomer **61c** in DMSO-d_6 for all disubstituted thiadiazines **61**; however, in non-polar solvents, such as $CDCl_3$, tautomers **61a** and **61c** coexist in ratios depending on the R^1 substituent. Tautomerism of monosubstituted thiadiazines **62** may include four tautomers. The reports on tautomerism of these compounds are contradictory suggesting either a mixture of tautomers **62c** and **62d** (86MRC444) or the sole amino(hydroxy) tautomer **62c** (88JCS(P2)859) in DMSO-d_6 solution.

Tautomerism of 2,1,3-benzothiadiazinone 2,2,-dioxide **63** and its N-monosubstituted derivatives has been studied experimentally by ^{1}H and ^{13}C NMR and theoretically by *ab initio* calculations. In the gas phase, the oxo form **63b** was found to be more stable (ΔE = 4–6 kcal/mol) than the hydroxy form **63a**; however, due to the higher dipole moment of the latter this energy difference is greatly decreased in solution. Whereas both tautomers **63a** and **63b** were observed in non-polar solvents (THF) and protic solvents (methanol), only hydroxy tautomer **63a** was detected in polar aprotic solvents (DMSO-d_6) and in the solid state. The tautomerism is also present in the N-monosubstituted derivatives of **63**, which exist primarily as oxo tautomers (99T12405).

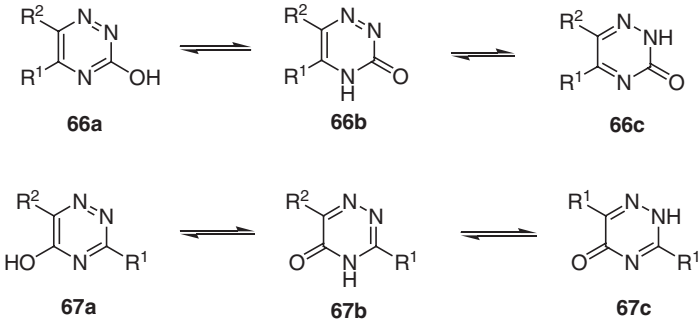


63a **63b** **63c**

c. Triazines. Unsubstituted 1,2,3-benzotriazin-4-one has been known to exist in the 3*H*-form **64** (74JOC2710). Although the prototropic tautomerism in 1-methyl-4(3*H*)-1,2,3-benzotriazinone **65** is not possible, the high melting point and ^{13}C NMR spectra of this compound indicate a large contribution from the dipolar form **65b** (88JCS(CC)631).



64 **65a** **65b**

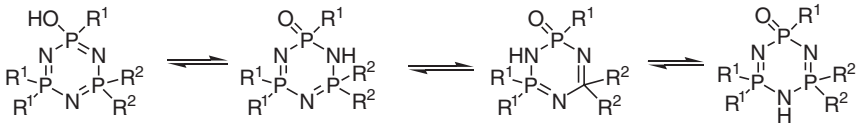


66a **66b** **66c**

67a **67b** **67c**

AM1 semiempirical calculations of the relative stability of tautomers of monosubstituted 1,2,4-triazin-3-ones **66** (R^1 = Ph, R^2 = H; R^1 = H, R^2 = Ph) indicated the (2*H*)-oxo tautomer **66c** to be the most stable in the gas phase in both cases. The tautomer **66b** was found to be less stable by *ca.* 3 kcal/mol and hydroxy tautomer **66a** – by 7–9 kcal/mol. Similar calculations for 1,2,4-triazine-5-ones **67** (R^1 = Ph, R^2 = H; R^1 = H, R^2 = Ph; R^1 = 4-MeC_6H_4, R^2 = H) suggested the predominance of the oxo tautomer **67b** in the gas phase with the other tautomers being almost equal in energy and less stable than **67b** by 3–5 kcal/mol (04ZOR426). The tautomeric equilibrium of **67** in the gas phase has also been studied experimentally by comparing the mass spectra of tautomeric compounds with those of their methylated derivatives (81OMS347). The position of the equilibrium was shown to depend on the nature of the substituents in the 3- and 6-positions of the heterocyclic ring. Thus, triazinones **67** (R^1, R^2 = H, D, Me) exist as mixtures of tautomers **67b** and **67c** with **67c** strongly predominating. In **67** (R^1 = Ph; R^2 = H, Me), tautomers **67c** also predominate, but the small contribution from the hydroxy form **67a** is suggested. The equilibrium is completely shifted toward the hydroxy tautomer **67a** in **67** (R^1 = H, Me; R^2 = Ph), whereas in **67** (R^1 = R^2 = Ph) both **67a** and **67c** forms coexist. IR, UV, and NMR studies indicated the predominance of the *para*-quinoid oxo tautomer **67c** in solution for **67** (R^1 = Ph, R^2 = H; R^1 = H, R^2 = Ph), whereas **67** (R^1 = R^2 = Ph) exists in tautomeric equilibrium of all three forms (74T3171). In the solid state, however, the hydroxy form **67a** predominates. The oxo tautomers **66c** (R^1 = OMe, SMe; R^2 = H) and **67c** (R^1 = OMe, SMe; R^2 = H) were found to be the major forms in a solution (chloroform, DMSO-d_6, water, 96% EtOH) and in the solid state (74CCC2326).

d. Other Heterocycles. The tautomerism of triphosphatriazines **68** was investigated by ^{31}P NMR spectroscopy. No tautomeric interconversion was observed for **68** (R^1 = OMe, OEt; R^2 = NHBu^t), which exist exclusively in the form **68b**. In **68** (R^1 = R^2 = OMe, OPh), the proton exchange occurs between the equivalent sites, and again the form **68b** is the only one present. However, the proton exchange between the non-equivalent sites was observed for **68** (R^1 = OMe, OEt, OPr^n; R^2 = Ph), which exist as mixtures of tautomers **68b** and **68c** in 2:1 to 4:1 ratios (82JCS(D)1549).



68a 68b 68c 68d

B. Thiono-Mercapto Tautomerism

1. *Pyridines, Quinolines, and Acridines*

The systematic IR studies of the functional group and heteroatom effect on the position of the tautomeric equilibrium indicated that the stability of thiols (with respect to the corresponding thione forms) is considerably higher than the stability of the hydroxy forms (with respect to the oxo forms) in the same heterocyclic systems, so the mercapto tautomers of mercaptopyridines should be more favored in the equilibrium than their oxygen analogs (92JPC6250).

In the confirmation of this conclusion, 2- and 4-mercaptopyridine were shown to be the major tautomers in the gas phase by UV and IR spectroscopic measurements ($K_T = <0.1$ (NH/SH) in both cases) (76JA171) and by estimation of their gas phase basicities (77TL1777). Later, the presence of the minor thione tautomer was detected for 2-mercaptopyridine in the vapor (01SA(A)2659) and in argon and nitrogen matrices (thiol:thione = 30:1) (90JPC7406).

Photoelectron spectra of 2-, 3- and 4-mercaptopyridines and fixed structure models have been measured for evaluation of tautomeric populations. Whereas for 3- and 4-mercaptopyridine a great predominance of the mercapto form in vapor phase is demonstrated, 2-mercaptopyridine shows the existence of a prototropic equilibrium between the mercapto and thioxo forms. From the integration of band areas it follows that there is about 10% of the thioxo form in the equilibrium (77JCS(P2)1652, 79TL2585). 3-Formyl-2-mercaptopyridine was found to exist in the gas phase as a tautomeric mixture containing about 16% of the thione form (81T2663).

Nitrogen chemical shifts in ^{14}N NMR spectroscopy have been used to estimate the equilibrium compositions of a series of mercaptopyridines in solution. Thus, *ca.* 95% of the thione form was estimated for 2-mercaptopyridine in acetone and methanol and for 4-mercaptopyridine in methanol and acetone/DMSO (79OMR379). ^{15}N NMR shielding measurements provided the quantitatively reliable estimates of tautomeric equilibria for 3-methoxycarbonyl-2-mercaptopyridine and 3-mercaptopyridine. The equilibrium of 3-methoxycarbonyl-2-mercaptopyridine is shifted predominantly to the thione tautomer (95%), whereas 3-mercaptopyridine exists in the thiol form (at least 94%) (85MRC790). By ^{13}C NMR spectroscopy, 3-nitropyridine-4-thiol exists in the thiol form (86H(24)1301). Another NMR criterion, used for estimation of the tautomeric equilibrium in mercaptopyridines, is based on $^{3}J_{(CH)}$ values for the CN–CH, C–N = CH, and C = N–CH structural elements (83OMR20).

Tautomeric constants of several 2-substituted 5-methoxy-4(1*H*)-pyridinethiones were determined by comparing their pK_a values with those of their 4-methylthio- and *N*-methyl analogs, measured spectrophotometrically in water at 25 °C. The K_T values are affected by the substituent at the position 2 and are decreased by electron-withdrawing groups. The thione forms predominate in aqueous solution by factors of *ca.* 10^5 for 5-methoxy-2-methyl-4(1*H*)-pyridinethione and *ca.* 10^5 for 5-methoxy-2-hydroxymethyl-4(1*H*)-pyridinethione (77BCJ3295).

Values for both self-association and prototropic equilibrium constants of several 2- and 4-mercaptopyridines were determined in different solvents (76JA8284, 78JA3961, 80JOC1347, 80JOC1354, 90CJC1482, 92JPOC191) to estimate the solvent effect on the equilibrium. It was shown that 2-mercaptopyridines are associated as dimers, whereas 4-mercaptopyridines form extended oligomeric systems. In polar or hydrogen-bonding solvents or for sterically hindered pyridines, the self-association is substantially reduced. In dilute solutions of non-polar solvents (e.g., cyclohexane, 1,2-dichloroethane), unsubstituted 2- and 4-mercaptopyridine exist primarily as thiols (76JA8284, 90CJC1482, 92JPOC191, 98JST(441)63), but the thione form predominates in dichloromethane, acetonitrile, dioxane, or water. Addition of solvents, able to participate in hydrogen bonding (ethanol) to dilute solution of 2-mercaptopyridine in 1,2-dichloroethane shifts the equilibrium toward the thione form (90CJC1482), whereas absorption on a silver colloidal surface favors the shift in the opposite direction as only thiol form is absorbed (98JST(441)63). Dilution of the concentrated solutions shifts the equilibrium toward the thiol form.

In the solid state, unsubstituted 4-mercaptopyridine is composed of infinite chains of the thiopyridone molecules associated by NH···S hydrogen bonds (92JPOC191). In contrast, 2-mercaptopyridine is associated into thione dimers, and the tautomeric equilibrium is not affected by pressure or by temperature in the 54–294 K range according to IR and Raman spectroscopic studies (94JST(324)83).

In the complex $Cp^*Rh^{III}(PyS)_2$ (PyS = pyridine-2-thiolato), one PyS ligand is bound to the rhodium ion in an *S*-monodentate mode, while the other ligand chelates to the metal in an *N,S*-bidentate mode. In this complex, the thiol–thione tautomerism occurs in solution at ambient temperature, so its NMR spectra are solvent-dependent (00ICA(299)100).

Tautomerism of 2-mercaptopyridine and 4-mercaptopyridine has been calculated using various semiempirical and *ab initio* methods. The thiol tautomer is predicted to be more stable in the gas phase by the AM1 method ($\Delta E = 3.81$ kcal/mol for 2-mercaptopyridine and $\Delta E = 9.2$ kcal/mol for 4-mercaptopyridine) (89JOC6030, 89JST(184)179) in good agreement with the experimental data ($\Delta E = 2.4$ kcal/mol for 2-mercaptopyridine). The higher stability of the thione forms in the self-associated dimers of 2-mercaptopyridine is also suggested. The similar results were obtained using MNDO method (81JST(86)85).

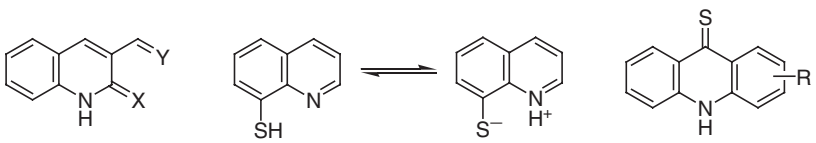
Ab initio (HF, MP2, and MP4) (99JCS(P2)801) and SCF + MBTP(2) methods (90JPC7406) also predict the predominance of the thiol tautomer in the gas phase; however, the relative stability of the thiol tautomer is overestimated by 1 kcal/mol and 6.5 kcal/mol, respectively. Similarly, calculations using large (TZV2P) basis sets and electron correlation at the QCISD(T) level overestimate the thiol stability by 3.6 kcal/mol (93JCS(P2)861). In contrast, the density functional theory (B3LYP)

method systematically overestimates the relative stability of the thione tautomer (96JST(376)325, 99JCS(P2)801). For the selenium analog of 2-mercaptopyridine, the predominance of the selenone tautomer has also been predicted by the B3LYP method, in contrast to the *ab initio* calculation results.

The tautomeric equilibria of 2-, 3-, and 4-mercaptopyridines in water were estimated by the AM1 method suggesting the predominance of the thione tautomers in all three cases (89JOC6030). The equilibrium constants for thiol–thione tautomerism in mercaptopyridines and their benzologues at the isoelectric points in an amphiprotic medium, calculated from exact and asymptotic formulas, predict the predominance of the thione forms in all regioisomeric mercapto-substituted pyridines, quinolines, and acridines in an aqueous solution at 20 °C (80ZOR1499). Enthalpy differences between tautomers and activation energy for tautomeric interconversion in solid, liquid, and vapor states have been calculated (01SA(A)2659).

The IR spectra of 2-mercaptoquinoline in argon and nitrogen matrices were used to study the thiol–thione tautomeric equilibrium (95SA(A)1809). The UV-induced photochemical reaction was applied to separate the spectra of tautomers and allowed to estimate the tautomeric ratio before UV irradiation as thione:thiol = 7:1 and determine the relative energy $\Delta E = -1.41$ kcal/mol (at 360 K). The calculations at the (MP2 + SCF)/6-31G** + ZPE(SCF/6-31G**) level predicted $\Delta E = -1.55$ kcal/mol in good agreement with the experimental data. On the other hand, the AM1 and PM3 methods erroneously suggest the predominance of the thiol form for 2- and 4-mercaptoquinoline in the gas phase; however, the aqueous phase calculations correctly predict the higher stability of the thione form of 2-mercaptoquinoline.

^{1}H, ^{13}C, and ^{15}N NMR, UV, and IR spectroscopic studies showed the thione (selenone) form to be the most stable both in solution and in the solid state for quinolines **69** (X = S, Se; Y = O, $PhCH_2N$, *i*-PrN, 4-MeC_6H_4N) (91MC78). The formation of the mesoionic form **70b** of 8-mercaptoquinoline **70** and its substituted derivatives in a polar medium was examined within the CNDO/2 approximation (80KG1642). The solvation energy plays the principal role in the concentration of the dipolar form, and the pK_T is varied from −0.27 to 3.86 depending on the quinoline ring substituents. The dipolar form predominates for 4-methoxy-substituted derivative, whereas it is practically absent for 3-chloro-8-mercaptoquinoline.



69 **70a** **70b** **71**

Tautomeric equilibria of substituted 9(10*H*)-acridinethiones **71** (R = H, 2-Cl, 3-Cl, 4-Cl, 2-OMe, 2-OEt, 4-OMe, 2-NO_2, 3-NO_2) have been studied by IR, UV, and mass spectroscopy. It has been shown that the thione form predominates both in the solid state and in the gas phase (only for **71** (R = H, 2-Cl) the appreciable amounts of the thiol tautomers were detected in the gas phase); in solution, however, the position of the tautomeric equilibrium depends on the temperature and solvent

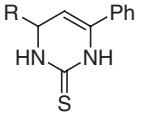
polarity, but not on the electronic effects of the substituents. The content of the thione form ranges from 73% to 77% in toluene to 100% in water. Increasing the ionic strength of the aqueous solution shifts the equilibrium toward the thiol tautomer. The similar shift occurs on increasing the temperature in non-polar solvents; however, no temperature effect was observed in polar solvents (84KG1519).

2. *Pyrimidines and Benzologues*

The stability of the thiol forms of mercaptopyrimidines compared to the thione forms is considerably higher than the relevant stability of hydroxypyrimidines with respect to oxo tautomers, as it was already discussed for mercaptopyridines (92JPC6250).

IR spectra of 4-mercaptopyrimidine isolated in argon and nitrogen matrices showed the presence of two tautomers, thiol and pyrimidine-4(3*H*)-thione, in ratio thiol:thione = 5:1, independently on the matrix used (the UV-induced phototautomerization was used to separate the spectra of the tautomers). In the gas phase, the concentration of the thione tautomer was slightly higher (thiol:thione = 3:1). These ratios allowed to calculate the free energy difference as $\Delta E = 1.12$ kcal/mol in a matrix and $\Delta E = 1.05$ kcal/mol in the gas phase (91JPC2404). In contrast, only thione form of 2-mercaptopyrimidine was detected in diluted argon and nitrogen matrices (91SA(A)339). However, in matrices with high guest-to-host ratio and in annealated matrices, the associations both in thiol and thione forms were observed.

O-Neopentyl 2-thiouracil exists only in the mercapto form in the gas phase (90JCS(P2)871) and in an inert matrix (88JST(176)137), while the thione form is dominant in the solid state and in solution (88JST(176)137). X-ray photoelectron spectroscopy indicated that dihydropyrimidines **72** (R = 3-ClC_6H_4, 4-MeC_6H_4) exist exclusively in the thione form shown, whereas their aromatized analog **73** (R = 3-ClC_6H_4) exists as a mixture of both tautomers containing 65% of the thione form (80JST(60)193).



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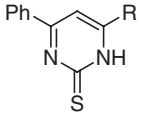

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The $^3J_{(CH)}$ values for the C–N–CH, C–N = CH, and C = N–CH structural elements were found to a valuable criterion for estimation of the tautomeric equilibrium in mercaptopyrimidines in solution (83OMR20).

4,6-Dimethyl-2-mercaptopyrimidine exists as a mixture of thiol and thione tautomers in a solution with the tautomeric ratio depending on the solvent polarity. As expected, the more polar thione form predominates in the polar solvents (dichloromethane, methanol, and DMSO-d_6), whereas the thiol tautomer is favored in non-polar solvents (cyclohexane, 1,2-dichloroethane). Addition of cyclohexane to the dichloromethane solution of 4,6-dimethyl-2-mercaptopyrimidine shifts the equilibrium toward the thiol form. The opposite effect was observed on addition of dichloromethane to the

cyclohexane solution. Dilution of the concentrated solutions shifts the equilibrium toward the thiol form. In the solid state, the thione is the dominant species (84H(22)2591, 90CJC1482, 03JPC(A)7490). Absorption of 2-mercaptopyrimidine on a silver colloidal surface shifts the equilibrium toward the thiol form (98JST(441)63).

Cyclohexane-fused fluoroalkyl pyrimidine **54** (X = SH; R = CF_2CHF_2) exists primarily as thiol in $CDCl_3$ solution, but as thione with hydrogen on N^3 in the solid state. Pyrimidine **54** (X = SH; R = CF_3) was found to exist as a mixture of thione and thiol tautomers in DMSO-d_6 with the tautomeric ratio thione:thiol = 80:20 (00S1738). On complexation of unsubstituted 2-mercaptopyrimidine, which exists in the thione form in DMSO-d_6, with palladium, the thione tautomer is preserved (91P1507). In contrast to their oxygen analog (see Section II.A.7), neither thione nor selenone **51b** (X = S, Se) showed any ^{13}C NMR evidence of tautomeric interconversion in DMSO-d_6 solution (88MRC191).

IR studies of unsubstituted 2-mercaptopyrimidine showed that in the crystalline state, the hydrogen-bonded associations in the thione form dominate, whereas in disordered amorphous layers the associations both in thiol and thione form were observed (91SA(A)339).

The *ab initio* calculations at the SCF/3-21G* level predicted the predominance of the thiol form of unsubstituted 2- and 4-mercaptopyrimidines in the gas phase in accordance with the experimental IR spectra (91JPC2404, 91SA(A)339). *Ab initio* SCRF calculations have been carried out for tautomerism of 2-mercaptopyrimidine in the gas phase and in solution. In the gas phase and non-polar solvents, the thiol tautomer was found to be the most stable ($\Delta E = 8.16$ kcal/mol in the gas phase and 5.91 kcal/mol in cyclohexene), whereas in polar solvents the thione tautomer becomes more stabilized ($\Delta E = -5.51$ kcal/mol in DMSO and -5.83 kcal/mol in water) (95CPL(232)61).

Thermodynamic parameters of a series of substituted 2-mercaptopyrimidines both in the gas phase and in aqueous solution have been calculated by semiempirical methods (AM1, PM3, MNDO). In the gas phase, all the methods predict the significant predominance of the thiol tautomer, the thiol form stability being overestimated. In the aqueous solution, the thione form is favored by the AM1 and PM3 methods, whereas MNDO method erroneously predicts the higher stability of the thiol form (99JST(458)217, 03JST(625)31). The temperature dependence of the tautomeric equilibrium of 2-mercaptopyrimidine was predicted by semiempirical MNDO calculations (91JST(231)257). According to the calculated thermodynamic values, thiol tautomer should be the predominant form at temperatures below 298 K, whereas higher temperatures favor the thione tautomer. Free energies of solvation of both tautomers of 2-mercaptopyrimidine were calculated using the semiempirical AM1-SM2 solvation model. A value of -9.41 kcal/mol for the change in the free energy of solvation indicates that the thione form is the predominant species in aqueous solution (94MI17).

Coexistence of both thiol and thione tautomers of unsubstituted 4-mercaptopyrimidine in the gas phase is predicted by the AM1 method, whereas the MNDO-PM3 method again favors the thiol form (91MI211).

Tautomerism of 4,6-dimethyl-2-mercaptopyrimidine in gas phase and in solution has been studied using density functional theory calculations. While the thiol was

determined to be the most stable structure in the gas phase ($\Delta E = 1.88$ kcal/mol), the energy difference between tautomers becomes negligible once cyclohexane as a solvent is included in calculations. The thione structure was found to be more stable in polar solvents ($\Delta E = 5.7$ kcal/mol) (03JPC(A)7490).

The relative stabilities of *O*-alkyl 2-thiouracil and *O*-alkyl 4-thiouracil were calculated at the SCF/3-21G* level. *O*-Alkyl 2-thiouracil is predicted to exist exclusively as the thiol tautomer ($\Delta E = 5.45$ kcal/mol) in good agreement with the experimental data, whereas the energy difference between the tautomers of *O*-alkyl 4-thiouracil is much smaller ($\Delta E = 0.98$ kcal/mol) and the coexistence of both tautomers in ratio thiol:thione = 3:1 is predicted (90JA1504). Both semiempirical AM1 and MNDO methods predict the predominance of the mercapto tautomer of *O*-methyl 4-thiouracil in agreement with the experimental data (89JCS(P2)1507).

3. *Other Heterocyclic Compounds with More Than One Heteroatom*

Only thione form was observed in the IR spectra of pyridazine-3(2*H*)-thione isolated in argon and nitrogen matrices. *Ab initio* calculations at the SCF/3-21G* level were in a good agreement with the experimental data (91JPC2404).

A comparison of ^{13}C and ^{1}H spin-coupling constants for pyrazine-2(1*H*)-thione establishes the thione tautomer as the dominating structure. A small amount (*ca.* 5%) of the thiol tautomer is also detected in DMSO-d_6. In CD_3NO_2 solution, the tautomeric mixture contains about 3% of the thiol form (82TL4785). The relative energies of tautomers of 2-mercaptopyrazine were calculated by the AM1 method. The predominance of the thiol tautomer is predicted for the gas phase; however, the significant contribution of the thione tautomer in polar solvents is indicated (92MI7).

The tautomerism of 2-mercapto-1,3-thiazines is briefly discussed in a specialized review (90AHC(50)85).

C. Amino–Imino Tautomerism

1. *Pyridines*

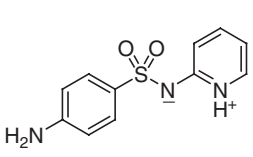
The IR spectra of 4-aminopyridine revealed the large predominance of the amino form in a low-temperature argon matrix with no indication of the presence of the imino form. In the presence of water in the matrix, two 1:1 4-aminopyridine/water complexes with H–N–H$\cdots$OH$_2$ and N$\cdots$HO–H bonding were detected, the former being more stable by only 1.6 kcal/mol (94JST(322)113, 95JPC6387).

The spectroscopic (UV, IR, ^{1}H NMR) studies of 2-aminopyridine, 2-(phenylamino)pyridine and 5-nitro-2-(phenylamino)pyridine indicated the presence of only amino tautomer in a solution. The tautomeric equilibrium constants, calculated from the acidity of the fixed derivatives, were found to be 2×10^5 for 2-(phenylamino)pyridine and 8×10^3 for 5-nitro-2-(phenylamino)pyridine, indicating the shift of the equilibrium toward the imino tautomer on introduction of a nitro group (76BCJ2770, 80BCJ717). The molar fractions of 2-aminopyridine and 4-aminopyridine in acetone were estimated as $92 \pm 6\%$ and $94 \pm 6\%$, respectively, by ^{14}N NMR spectroscopy

(79OMR379). The best fit of theoretically calculated and experimental UV spectra of 2-aminopyridine and 2-(methylamino)pyridine was achieved when the amino–amino dimer was considered instead of monomeric tautomers (93BSCB709). *N*-Acylated 2-aminopyridines (93BSCB709, 94JCS(P2)615, 95JCS(P2)1651) and 2-(2,4,6-trinitrophenylamino)pyridine (92JHC1461) were shown to exist in solution exclusively in the amino form, whereas 2-(*p*-aminobenzenesulfonamido)pyridine favors the zwitterionic imide **74** (75JCS(P2)522).

Interestingly, 4-nitrobenzyl esters of 2-amino, 4-amino-, or 6-aminonicotinates exist in their amino form in DMSO-d_6 solution, whereas their hydrochlorides favor the imino tautomeric form (94CCC2057).

^{15}N NMR spectroscopy studies of a natural toxic pyridine nucleoside, clitidine, in aqueous solution and X-ray crystallographic analysis in the solid state revealed that the imine **75** is predominant in the both states (98H(47)661).



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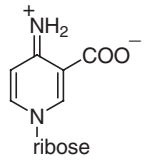

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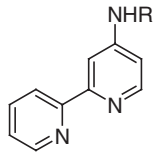

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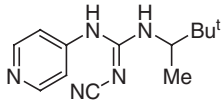

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Unsubstituted and N-substituted bipyridyls **76** (R = H, Me, Ph, MeCO, 4-$MeC_6H_4SO_2$) were investigated for amino–imino tautomerism using basicity measurements and UV spectral data. The bipyridyls **76** (R = H, Me, MeCO) were shown to exist predominantly in the amino form both in aqueous solution and in non-polar media. The tautomeric equilibrium of **76** (R = 4-$MeC_6H_4SO_2$), however, depends on the solvent polarity: whereas the imino tautomer predominates in water and ethanol, significant amounts of the amino tautomer were observed in dioxane and cyclohexane (78JCS(P2)1215).

According to X-ray crystallography and ^{1}H NMR data, pinacidil **77** exists both in the solid state and in solution ($CDCl_3$, DMSO-d_6) predominantly in the amino form shown (93HCA1311).

4-Aminopyridine and its derivatives were studied in various solvents for the effect of concentration on the UV spectra in the concentration range between 10^{-6} and 10^{-3} M/L. It was found that at high concentrations 4-aminopyridines form molecular aggregates as loosely bonded dimers (81H(15)1195).

The formation energies of 2-aminopyridine dimer and 2-aminopyridine – 2-pyridone complex were determined to be 6.0 and 10.6 kcal/mol, respectively, in C_6D_6 solution by ^{1}H NMR spectroscopy (84SA(A)623). The similar values were obtained by CNDO/2 calculations. The dynamics of amino–imino double proton-transfer tautomeric reaction of the 2-aminopyridine-acetic acid system in hexane was studied

by steady-state absorption, steady-state fluorescence, and picosecond time-resolved fluorescence spectroscopy. It has been confirmed that the double proton transfer takes place in the excited state of the double hydrogen-bonded complex of 2-aminopyridine with acetic acid (02JPC(A)2305).

The crystal and molecular stuctures of 2-, 3-, and 4-nitraminopyridines have been solved by X-ray diffraction analysis at ambient temperature. All regioisomers were found to exist in the imino tautomeric form with the strong resonance interactions. Stabilization of the imino form seems to be due to the hydrogen-bonding net in the crystal (96ACSA808).

The relative stabilities of 2-aminopyridine, 3-aminopyridine, and 4-aminopyridine tautomers and tautomeric equilibrium constants in the gas phase were calculated by the AM1 (89JOC6030, 00KG1342), MNDO (81JST(86)85), MINDO (90BCJ971), and MINDO–Forces MO (85ZN(A)1278) methods. In all cases, the amino tautomer was shown to be the most stable, in agreement with the experimental data. The activation energies for the tautomeric interconversion of 2-aminopyridine in vapor, liquid, and solid states have also been calculated (00KG1342, 01SA(A)2659). Combination of the AM1 method with inclusion of the solvent reaction field gave good qualitative estimates of tautomeric equilibria of aminopyridines in aqueous solution (89JOC6030).

The effect of the dimerization, by hydrogen bond complexation, on the tautomerism of a series of N-monosubstituted (R = F, Cl, Me, CN, NO_2, SO_2H) 2-aminopyridines has been carried out using *ab initio* methods. Among the monomers, the amino tautomers were found to be the most stable in the gas phase; however, increasing the electronegativity of the N-substituent leads to decrease in the relative energy of the imino tautomer. The interaction energy of the dimers indicates that for the 2-aminopyridines with electronegative N-substituent the imino–imino cyclic dimers are the most favorable. In several of the compounds studied, the difference was sufficient to overcome the relative stability of the monomers (02JOC1515).

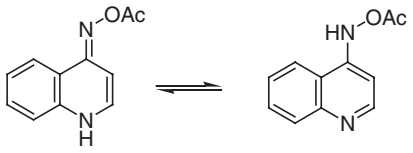
Theoretical calculations on the ground and excited state double proton transfer in the 2-aminopyridine–formic acid (90BCJ971, 92BCJ1002) and 2-aminopyridine–acetic acid (90BCJ971, 03JPC(A)3244) dual hydrogen-bonded systems have been performed. Among the molecular models of three complexes used in the calculations, namely, the 2-aminopyridine- acid complex, (*E*)-2(1*H*)-pyridinimine-acid complex, and 2-aminopyridinium-acetoxide(formate) anion, the former complex was predicted to be the most stable. The energy barriers for the double proton transfer were estimated to be 9.48 and 8.67 kcal/mol (03JPC(A)3244).

AM1 calculations predict the higher stability of the amino tautomer for *N*-nitro-4-aminopyridine in the gas phase ($\Delta E = 7$ kcal/mol), whereas the order of stability of reversed for *N*-nitro-2-aminopyridine (97T17211). This phenomenon is explained by imino group-stabilizing internal hydrogen bonding and dimerization in the latter compound and confirmed by X-ray analysis.

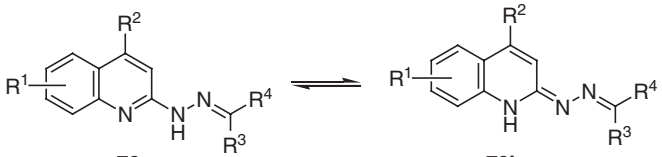
2. *Quinolines and Acridines*

AM1 and PM3 calculations in the gas phase and in aqueous solution indicated that 2-amino-, 3-amino-, and 4-aminoquinolines exist predominantly in the amino

forms in the both phases (02JST(594)185). However, the imino form **78a** of 4-(acetoxyamino)quinoline **78** was found to be predominating in DMSO-d_6 solution by ^{1}H NMR spectroscopy (89JOC399). Pyridine-fused aminoquinoline, 4-phenylamino-1,10-phenanthroline, exists predominantly in the amino form in aqueous solution (78JCS(P2)1215).



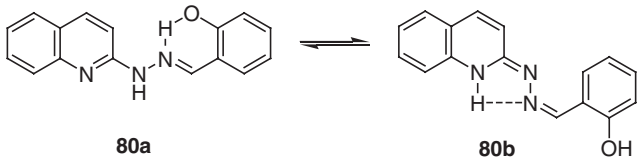
78a **78b**



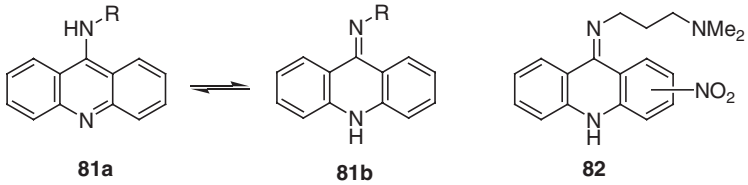
79a **79b**

Analysis of ^{1}H NMR spectra of both amino and imino forms of 2-quinolylhydrazones **79** ($R^1 = R^2 = R^3 = H$; R^4 = aryl) using the chemical shift of the *N*-hydrogen, the coupling constant of H(3) and H(4) of the quinoline ring and the change in chemical shifts of the quinoline H(8) allowed to make a conclusion that these compounds exist in $CDCl_3$ and DMSO-d_6 solution in their amino form **79a** (76JOC2491). Similarly, only amino tautomer was observed in CCl_4 solution of **79** ($R^1 = R^3 = H$; R^2 = Me; R^4 = 4-$MeOC_6H_4$) (01MI238). The methyl pyruvate-derived hydrazones **79** (R^1 = H, 6-Me, 7-Me, 8-Me; R^2 = H, Me; R^3 = Me; R^4 = COOMe) also exist in $CDCl_3$ solution predominantly (>90%) in the amino form, although in this case the imino form was also detected (00JCS(P2)2259). In the solid state, the tautomerism of **79** can be affected by remote substituents. Whereas **79** ($R^1 = R^3 = H$; R^2 = Me; R^4 = 4-$MeOC_6H_4$) (01MI238), **79** (R^1 = H, 6-Me, 7-Me, 8-Me; R^2 = H, Me; R^3 = Me; R^4 = COOMe) (00JCS(P2)2259) and **79** ($R^1 = R^2 = H$; R^3 = H, Me; R^4 = 2-thienyl, 5-chloro-2-thienyl) (97AX(C)973) exist as (*E*)-amino tautomers **79a**, **79** ($R^1 = R^2 = R^3 = H$; R^4 = 5-bromo-2-thienyl) (97AX(C)973) crystallizes in its imino form **79b**, which can be converted into **79a** on photolysis.

Photochromic isomerization of salicylaldehyde 2-quinolylhydrazone **80** involves both amino–imino tautomerism and *E*–*Z* isomerizations. When an ethanolic solution of **80a** is irradiated in the UV region between 250 and 400 nm at room temperature, it is readily converted into the colored isomer **80b**, which is stable in both protic and non-protic solvents at ambient temperature. This conversion presumably occurs *via* an intramolecular hydrogen transfer from the phenolic group, which precedes the double bond isomerization. In the dark, the reverse isomerizations take place (75JOC2512). No substituent effect on this tautomeric equilibrium has been observed (75JCS(P1)2036).



The problem of the true structure of 9-aminoacridine has attracted the attention of chemists since the beginning of the 20th century. This compound has become the subject of intensive investigation since 1950s. (For a discussion of early studies, see (92JOC3720).) Two tautomeric forms, 9-acridinamine **81a** (R = H) and 9(10*H*)-acridinimine **81b** (R = H), have been examined in the gas phase and in solution by the AM1 and PM3 methods (92JOC3720, 97AJC97), the MNDO method (91ZOB186), and the *ab initio* Hartree–Fock and density functional levels of theory with the 6-31G** basis sets (97JPC(A)283). Solvent (hexane, acetonitrile, and water) effects were included in the AM1, PM3, and *ab initio* Hartree–Fock optimizations through the COSMO or SCRF technique. The thermochemical data showed that both tautomers **81a** and **81b** should coexist at ambient temperature for the neutral compound and the doubly protonated form. In confirmation of the theoretical studies, the UV spectra indicated the tautomeric equilibrium of 9-aminoacridine in dioxane and acetonitrile; however, only one tautomer was observed in cyclohexane and aq. KOH. The imino form **81b** (R = H) is suggested to predominate in cyclohexane solution with the equilibrium shifting to the amino form in more polar dioxane (92MI287). Only the amino tautomer of 9-aminoacridine was observed in photoelectron spectra in the gas phase at 151 °C (91ZOB186).

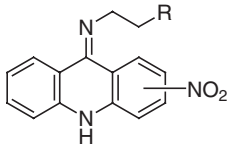


According to its ^{1}H NMR spectrum, 9-cyanoaminoacridine **81** (R = CN) exists in solution as amino tautomer **81a**; although a rapidly exchanging tautomeric equilibrium cannot be strictly ruled out (84H(22)2595).

The tautomeric interconversions in ledakrin, 9-((3-dimethylaminopropyl)imino)-1-nitro-9,10-dihydroacridine **82** (1-nitro), and its nitro regioisomers have been extensively investigated. It was shown that the introduction of the 1-nitro group in the heteroaromatic ring system and basic dimethylamino group into the side chain significantly affect the equilibrium. Thus, ledakrin, both as a base and a salt, exists in the solid state exclusively as imino tautomer **82** (1-nitro), whereas the analogs without the 1-nitro group or with alcohol or carboxy moiety instead of dimethylamino fragment favor the amino tautomer (85JA2067). The structures of amino, imino, and aci tautomers of **82** (1-nitro, 2-nitro, 3-nitro, and 4-nitro) were calculated using the AM1 method (91MI343) and the MNDO method (90JCS(P2)1501). For all the compounds, the predominance of the imino tautomer was predicted. The largest relative energy difference was predicted for 1-nitro and 4-nitro regioisomers

($\Delta E = 5$–8 kcal/mol by AM1 method and 13–14 kcal/mol by MNDO method), whereas it is much smaller for 2- and 3-nitro regioisomers ($\Delta E = 3$–5 kcal/mol). A significant solvent effect has been observed. Thus, UV, fluorescence, and fluorescence excitation spectra indicated the predominance of the imino form of **82** (1-nitro) in polar and protic solvents. However, in non-polar and aprotic solvents the tautomeric equilibrium shifts toward the amino tautomer having the smaller dipole moment, so both tautomeric forms are observed (90JCS(P2)1501, 91MI343, 92SA(A)771). Aminoacridine **82** (2-nitro) crystallizes in the amino form.

According to NMR data, the lower homologs of **82**, regioisomeric 1-, 2-, and 3-nitro aminoacridines **83** (R = NMe_2) and 3-nitro **83** (R = NEt_2), exist in the amino form in dilute $CDCl_3$ solution, whereas the 4-nitro regioisomer appears to exchange slowly between the amino and imino forms. All the protonated compounds (pH 2) favor the amino form. On increasing pH to 7–8 in D_2O, 2- and 3-nitro isomers retain the amino form, whereas 1- and 4-nitro isomers convert into the imino form. The imino form of 1-nitro isomer predominates in concentrated $CDCl_3$ and in acetone solution (90JMC2656, 00ICA(304)274). On complexation with platinum, only exocyclic nitrogen atom of **83** is coordinated, additionally stabilizing the imino form (00ICA(304)274).



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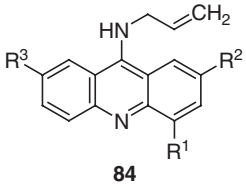

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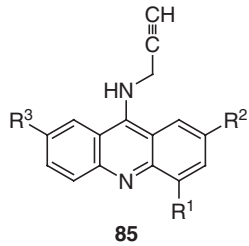


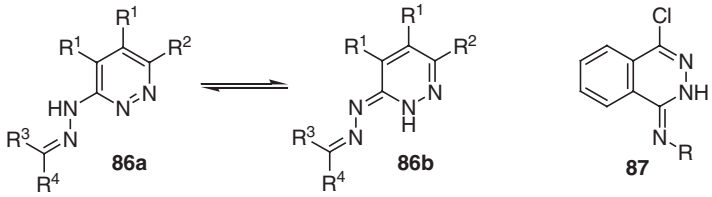
85

Aminoacridines **84** and **85** (R^1 = H, F, Br, Cl; R^2 = Me, CH_2Br, OMe, etc.; R^3 = H, OMe) exist in amino–imino tautomeric equilibrium in DMSO-d_6 solution at ambient temperature; however, increasing the temperature to 370 K results in the complete shift toward the imino tautomers (03MRC549). The tautomeric equilibria in five-membered heterocycle-fused 9-aminoacridines are completely shifted toward the imino tautomers in $CDCl_3$ and DMSO-d_6 solution (01MRC225).

3. *Pyridazines and Benzologues*

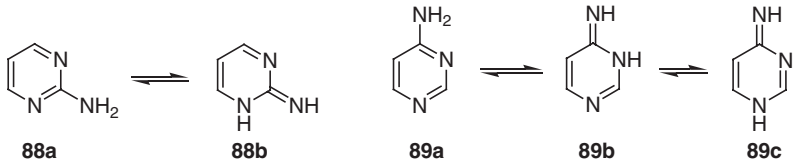
Pyridazinyl hydrazones **86** (R^1 = H; R^2 = Cl; R^3 = H, Me; R^4 = Me, Ph; $R^3R^4 = (CH_2)_4$, $(CH_2)_5$) were shown to exist as amino tautomers **86a** in CCl_4 and $CHCl_3$ solution and as amino–amino dimers in a crystal (01MI238). In contrast, only imino tautomers **86b** were detected for the benzologues **86** (R^1_2 = benzo; R^2 = H, Cl; R^3 = H, Me; R^4 = COOMe, Ph, 4-BrC_6H_4, etc.) both in solution and in the solid state (00JCS(P2)2259, 01MI238). The imino tautomers shown were also predominant forms of 1-aminophthalazines **87** (R = H, Me, Ph) in $CDCl_3$, DMSO-d_6, and dioxane solution and in the solid state. The other tautomer of **87** (R = Ph) is, however, favored in concentrated CCl_4 and isooctane solutions. The tautomeric

equilibrium is virtually temperature-independent in the pure solvents, but shifts somewhat to favor the imino form in isooctane–isopropanol mixture (83KG826).



4. *Pyrimidines and Benzologues*

Two tautomers are possible for 2-aminopyrimidine **88** and three tautomers for 4-aminopyrimidine **89**.



Unsubstituted 2-aminopyrimidine (87JST(158)275) and 4-aminopyrimidine (95JPC6387) were shown by low-temperature IR spectroscopy to exist exclusively in the amino tautomeric form in argon matrices. These findings were confirmed by semiempirical and *ab initio* calculations, which predicted the amino form to be more stable in the gas phase by about 21 kcal/mol and in aqueous solution by about 19 kcal/mol (95MI407, 96JST(376)375, 99JST(458)217).

UV, IR, and ^{1}H NMR spectroscopic studies of 2-(phenylamino)pyrimidine showed that this compound exists as a tautomeric mixture containing only a small amount (*ca.* 0.2%) of the imino tautomer in an aqueous ethanolic solution ($K_T = 5.5 \times 10^2$, amino/imino tautomer), but the K_T value is considerably smaller than that of 2-(phenylamino)pyridine (80BCJ717). The amino tautomer was also found to be highly predominant in solutions of 2-(phenylamino)-4,6-dimethylpyrimidine (84H(22)2591) and 2-[*N*-(2,4,6-trinitrophenyl)amino]pyrimidine in both polar and apolar solvents (92JHC1461). For cyclohexane-fused 2-aminopyrimidines **54** (X = NH_2; R = CF_3) and **55** (X = NH_2; R = CF_3; Ar = 4-$Et_2NC_6H_4$), both amino and imino tautomers are present in the solid state; however, only amino tautomers were observed in $CHCl_3$ solution (00S1738).

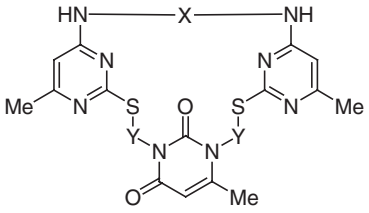
The prototropic tautomerism studies of 4-(*N*-arylamino)-2-(1*H*-pyrazol-1-yl)pyrimidines have shown that these compounds exist in dilute CCl_4, $CHCl_3$ and DMSO-d_6 solution exclusively as amino tautomers; no imino tautomer was detected (80KG1114).

Both semiempirical and *ab initio* calculations of 4-aminopyrimidine predict the highest stability of the amino tautomer (86JST(148)45, 96JST(376)375, 99JST(458)217)). The next stable tautomer is 3*H*-imino tautomer **89b**, which is less stable than **89a** by

17 kcal/mol. The tautomerization constants for 2- and 4-aminopyrimidines in the gas phase and in aqueous solution have been calculated using the AM1 method, the results being in good qualitative agreement with the experimental data (89JOC6030). Complexes of 2-aminopyrimidine (93MI1) and 4-aminopyrimidine (94MI61, 95JPC6387) with water were calculated using *ab initio* SCF method. For 4-aminopyrimidine, the closed N–H···O–H···N_3 structure containing two hydrogen bonds was found to be significantly more stable than singly bonded structures by 2–2.5 kcal/mol.

The spectroscopy and dynamics of the excited state double proton transfer in 2-amino-4,6-dimethylpyrimidine and 2-amino-4-methoxy-6-methylpyrimidine has been studied by steady-state and time-resolved fluorescence spectroscopy (01CP(265)233).

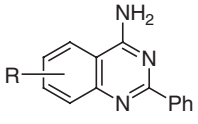
Macrocycles **90** (X = $(CH_2)_6$; Y = $(CH_2)_n$; $n = 4-6$) containing aminopyrimidine and uracil moiety have been studied by IR and UV spectroscopy and calculated by *ab initio* MO (HF/6-31G**, MP2/6-31G**) and density functional theory (B3LYP/6-31G**). The results showed that the aminopyrimidine fragment exists exclusively in the amino form both in the solid state and in solution (04JST(707)1).



90

The substituent effect on tautomerism of benzene ring-substituted 4-amino-2-phenylquinazolines **91** has been studied by ^{1}H NMR spectroscopy in DMSO-d_6 solution. It was shown that, in contrast to compounds with electron-donating substituents (R = 6-Me, 7-Me, 6-MeO, 7-MeO), which mainly occur in the imino form, aminoquinazolines with electron-withdrawing substituents (R = 6-NO_2, 7-NO_2, 6-Br, 6-Cl) exist as amino–imino tautomeric mixtures (00M895).

^{1}H NMR, IR, and mass spectrometry of the potentially tautomeric 4-amidino- and 4-guanidinoquinazolines **92** (R^1 = NH_2, Ph, 4-morpholinyl; R^2 = H, aryl) revealed that these compounds exist entirely in the amino form as shown (76CB2706). On the other hand, 4-tosylimino-3,4-dihydroquinazolines **93** (R^1 = 4-$MeC_6H_4SO_2$; R^2 = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-morpholinyl; R^3 = H, Me) favor the imino tautomer shown (76S534).



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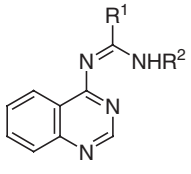

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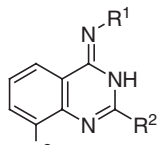
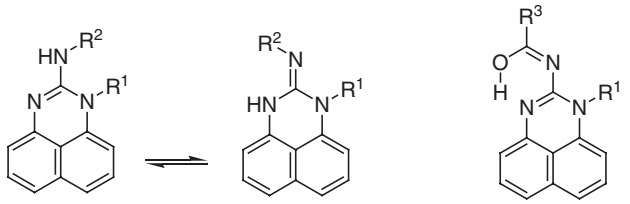


93

Tautomerism of 2-alkylamino- and 2-acylaminoperimidines **94**, which could exist in three tautomeric forms **94a–c** (R^2 = acyl) or in two tautomeric forms **94a** and **94b** (R^2 = alkyl) has been investigated by UV/Vis, IR, and ^{1}H NMR spectroscopy

(78KG113, 78KG843). It was found that whereas unsubstituted 2-aminoperimidine **94** ($R^1 = R^2 = H$) and its *N*-alkyl derivatives, e.g., **94** ($R^1 = H$; $R^2 = n$-Bu), exist almost exclusively in the amino form **94a** with the percentage of the imino tautomer not exceeding 5%, for *N*-acyl derivatives **94** ($R^1 = H$, Me, Et; $R^2 = MeCO$, *n*-PrCO, PhCO) the intramolecularly hydrogen-bonded tautomer **94b** predominates. The complete shift of the tautomeric equilibrium to the imine tautomer **94b** was observed for α-haloacyl-substituted aminoperimidines **94** ($R^1 = H$; $R^2 = ClCH_2CO$, CCl_3CO).

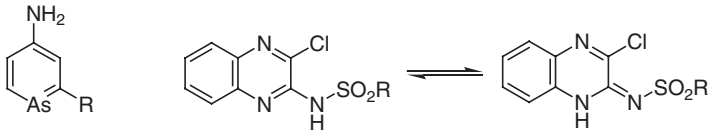


94a **94b** **94c**

5. *Other Heterocyclic Compounds*

a. Arsabenzenes. According to ^1H NMR spectra, arsaniline (4-aminoarsabenzene) and its 2-substituted analogs **95** (R = phenyl, benzyl) exist in chloroform solution exclusively as amines; the imino tautomers were not detected (78TL1175).

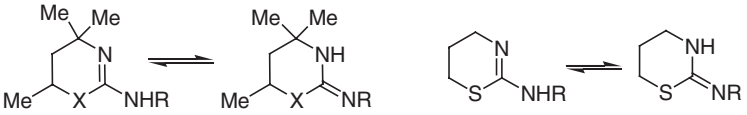
b. Pyrazines and Quinoxalines. ^{13}C and ^1H spin–spin coupling constants clearly establish the amino structure of unsubstituted 2-aminopyrazine, even in the absence of data for the imino tautomer. The results are supported by ^{15}N NMR data (82TL4785). 2-(Arylsulfonylamino)quinoxalines **96** (R = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 4-$MeCOC_6H_4$) were shown to exist as sulfonamides **96a** independent of the nature of the R substituent (94KG387).



95 **96a** **96b**

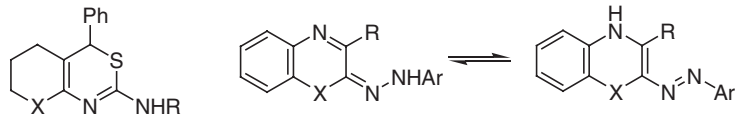
c. Oxazines and Thiazines. The tautomerism of 2-amino-1,3-thiazines was briefly reviewed (90AHC(50)85). N-Monosubstituted dihydrooxazines and dihydrothiazines **97** (X = O, S; R = Ph, 3-ClC_6H_4, 4-MeC_6H_4, etc.) exist in dioxane and acetone-d_6 solution primarily in the amino form **97a** (75KG1614, 77KG346). In hexane solution, both tautomers of oxazines **97** (X = O) were detected by UV and fluorescence spectroscopy (80MI172). Both tautomers of thiazines **97** (X = S) were observed in dilute $CHCl_3$ and CCl_4 solutions, with the tautomeric ratio virtually

independent of the concentration and only slightly dependent on temperature. Interestingly, only one tautomer (presumably, **97b**) was observed in dilute CCl_4 solutions of oxazines **97** (X = O) with the order of stabilities being reversed in $CDCl_3$ (80DOK1144). The basicity method was found unacceptable for tautomeric equilibrium studies of thiazines **97** (X = S) (75KG777). The data on the solid-state tautomerism of **97** (X = O, S) are contradictory. Whereas some reports (77KG346) claim that both oxazines and thiazines **97** exist primarily in the amino form, others (80DOK1144) suggest the presence of both amino and imino tautomers as their cyclic homodimers.



97a **97b** **98a** **98b**

X-ray analysis of thiazines **98** unambiguously established imino structure **98b** for **98** (R = Ph) (77TL4241) and amino structure **98a** for **98** (R = $PhCH_2$) (81CSC979). The data on the solution tautomerism of *N*-phenyl dihydrothiazine **98** (R = Ph) are again contradictory. The earlier report claimed the exclusive presence of the amino tautomer **98a** in $CHCl_3$, dioxane and DMSO solution (76KG1047). Later, however, ^{15}N NMR spectroscopy showed that this compound exists in chloroform in an equilibrium of imino and amino forms in the ratio of 74:26, respectively (82OMR219). The presence of both tautomers was also observed in C_6D_6 and CD_2Cl_2 at ambient temperature with amino tautomer being favored. On raising the temperature up to 80 °C, the equilibrium in the CD_2Cl_2 solution shifts toward the imino tautomer **98b**. No changes in the tautomeric ratio were observed on further temperature increase (91JOC3194). The amino tautomeric structure shown was attributed to cyclohexane-fused thiazines **99** (R = H, Me, MeCO, CD_3CO; X = CH_2, PhCH = C) in the gas phase by electron-impact mass spectrometry (89OMS517).

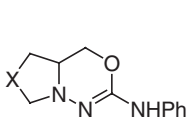


99 **100a** **100b**

Arylazo derivatives of quinoxaline, 1,4-benzothiazine and 1,4-benzoxazine **100** (X = O, S, NH; R = Me, Ph, 4-MeC_6H_4) exist predominantly in the hydrazone tautomeric forms **100a** as shown by spectral data and HMO calculations (84JHC521).

d. Oxadiazines. NOE interaction between NH and *ortho*-hydrogens in 2-arylaminoperhydropyrido[1,2-*d*][1,3,4]oxadiazines and –perhydropyrrolo[1,2-*d*][1,3,4]oxadiazines **101** (X = $(CH_2)_n$; $n = 1, 2$) and X-ray analysis indicated that these compounds exist predominantly in the amino form shown in $CDCl_3$ solution and in the solid state (97H(45)927). The amino form was unambiguously found to be

predominant for cyclohexane-fused 2-arylamino-1,3,4-oxadiazines **102** (R^1 = Me, $PhCH_2$; R^2 = Ph, 4-ClC_6H_4) both in solution and in the solid state (99ACSA103). 5,6-Dihydro-4*H*-1,3,4-oxadiazines **103** (R = Me, Ph, 4-MeC_6H_4, 2-$O_2NC_6H_4$, $PhCH_2$) exist in solution as mixtures of *Z*- and *E-anti* conformers of the imino tautomer shown. The *Z-anti*-imino structure of **103** (R = Ph) in the solid state was established by X-ray analysis (85CB4026).



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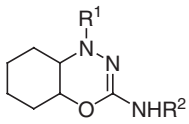

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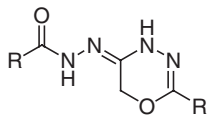
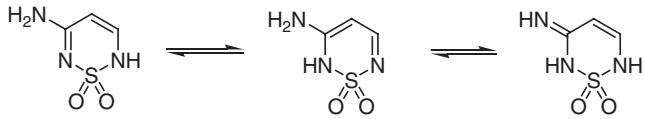


103

e. Thiadiazines. The tautomerism of amino-substituted 2,1,3-thiadiazine 1,1-dioxides **104** has been studied by ^{13}C NMR, where the chemical shifts of two carbon atoms C_4 and C_6 were the most important tools in the determination of the tautomeric preference. It was suggested that tautomers **104a** and **104c** coexist in DMSO-d_6 solution with only a small contribution from the tautomer **104b**. In the solid state, however, only **104a** was observed. The "nonaromaticity" of thiadiazine 1,1-dioxides justifies the relative stability of imino tautomer **104c** (82JOC536).



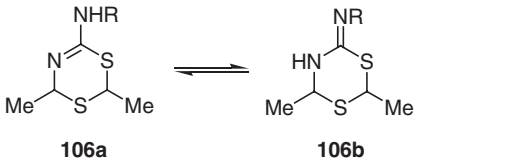
104a **104b** **104c**

105a **105b**

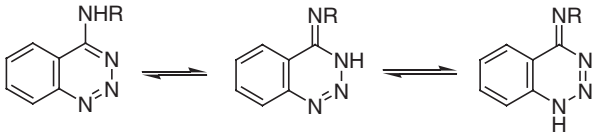
X-ray diffraction studies indicated that the tautomeric preference of 2-acylamino-1,3,4-thiadiazines **105** depends on the substituent in the 5-position. Thus, in the solid-state thiadiazine **105** (R = 4-ClC_6H_4) exists in the imino form **105a**, whereas **105** (R = 4-FC_6H_4, 5-chloro-2-thienyl) favor the amino form **105b** (01AX(C)593).

f. Dithiazines. N-Unsubstituted 4-amino-1,3,5-dithiazine **106** (R = H) exists in CCl_4 and $CDCl_3$ solution exclusively in the amino form **106a** featuring monomers in the dilute solutions and dimers and other polyassociates in concentrated solutions (81KG1050). The tautomeric equilibrium of *N*-acyl derivatives, however, is dependent on the nature of the N-substituent. Electron-donating groups favor the amino form **106a**, whereas the electron-withdrawing groups favor the imino form **106b**.

The polarity of the solvent does not have an appreciable effect on the tautomeric equilibrium. In the solid state, dithiazines with electron-donating N-substituents exist exclusively in the amino form **106a**, whereas those with electron-accepting substituents contain both amino and imino tautomers, although the content of the imino tautomer is lower than that in a solution (82KG622).



106a **106b**



107a **107b** **107c**

g. Triazines. The amino structure **107a** is suggested for N-monosubstituted 4-amino-1,2,3-benzotriazines **107** ($R = MeOCH_2CH_2$, *n*-Bu, 2-pyridylmethyl, 3-pyridylmethyl) in DMSO-d_6 solution on the basis of ^1H and ^{13}C NMR studies (84JCR(S)62).

D. Methylene Tautomerism

Detailed reviews on methylene tautomerism of monocyclic azines and their benzo- and heterocycle-fused derivatives have been published in 1995 (95H(41)2057, 95KG816). The effects of the mesomeric-type substituents (88ZOR1806), the position of the potentially tautomeric group and benzannulation and the solvent effect (94JCS(P2)2461) on the position of the tautomeric equilibrium has been investigated in detail. Studies of the mechanism of methylene tautomeric interconversion in azines have also been undertaken (83IZV1032, 86IZV1166).

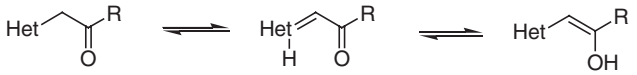
As a result, this review will concentrate on the results published in the last 10 years, except for few older reports omitted in the previous reviews or necessary for a systematic presentation of the methylene tautomerism in monocyclic and benzo-fused azines.

1. *General*

In tautomeric interconversions of azines bearing an acylmethyl group, three potential species **108a–c** could be involved in contrast to the analogs with differently activated methylene group where only two tautomers (of type **108a** and **108b**) are possible. A method for distinguishing enol and enaminone tautomers of acylmethyl heterocycles, based on differences in ^{13}C chemical shifts of the carbonyl carbon atom of the enaminone (C = O) and enolic carbon atom of the enol (= C–OH) was reported; in general, in $CDCl_3$ solution enone or enaminone tautomers were detected

only for 2-substituted heterocycles, which can probably be explained by their stabilization by intramolecular hydrogen bonding (94JCS(P2)2461).

Simple heteroarylpyruvates **108** (R = COOEt), where the heteroaryl part is represented by 2- or 4-pyridyl, 4-pyrimidinyl, 6-methyl-4-pyrimidinyl, 2-pyrazinyl, 2-quinolyl, and 2-pyridyl 1-oxide group, exist in solution ($CDCl_3$ or DMSO-d_6) entirely in the enol form **108c**. The 4-pyridyl derivative, however, is present in solution as a mixture of the enol and keto forms in 2:1 ratio. Significant enolization is ascribed to strong hydrogen bonding (92SC2245).

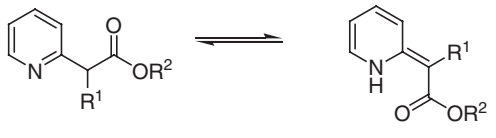


108a **108b** **108c**

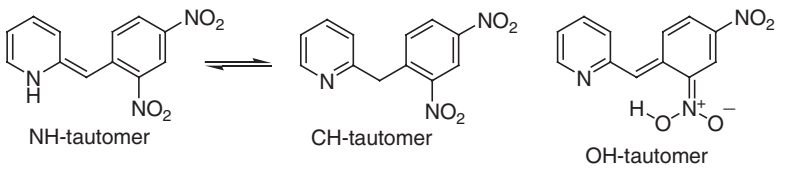
2. *Pyridines*

a. Methylene Group Activated by Electron-Accepting Group Other Than Acyl. According to its ^1H NMR spectra, 2-[(cyano)(ethoxycarbonyl)methyl]pyridine **109** (R^1 = CN; R^2 = Et) exists in the chloroform solution in two forms. The predominant form is **109b** with a *cis*-configuration of the ethoxycarbonyl group with regard to the ring nitrogen, which is stabilized by the intramolecular hydrogen bonding (76JHC1279). The dinitrophenyl-substituted pyridine derivative **109** (R^1 = 2,4-dinitrophenyl; R^2 = Me) also favors the tautomer **109b** (70%) in the $CDCl_3$ solution; however, the removal of one the nitro groups in the side substituent results in a significant shifts of the equilibrium toward the fully aromatic tautomer **109a** (89IZV2323).

The equilibrium constant for imine-enamine tautomerism of 2-(2,4-dinitrobenzyl)pyridine **110** has been determined as 7.5×10^{-9}, indicating a strong predominance of the benzyl tautomer **110b** (89TL4885). Temperature-dependent process of the proton tunneling in different excited states, which dominate in low-temperature regime, can be attributed to tunneling from the excited "CH" state to the excited or ground "NH" state. At higher temperatures, a second thermally activated process, originating from the thermal decay of the "OH" form to the "NH" form may contribute to the overall "NH" tautomer formation (96JPC16175).

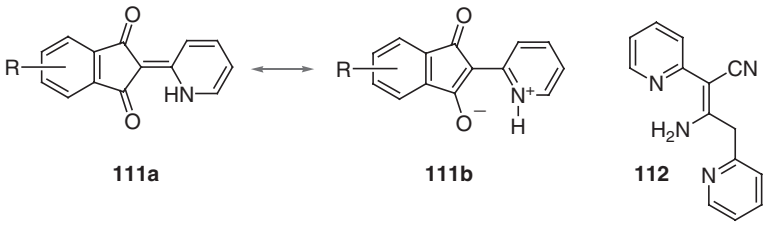


109a **109b**



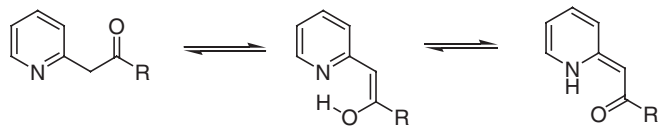
110a **110b** **110c**

UV, IR, and ^{1}H NMR spectroscopic studies indicated that 2-pyridyl- and 4-pyridyl-1,3-indandiones and some of their alkyl analogs exist as β-diketo enamines, e.g., **111a**, which is a resonance form of betaine **111b**. The importance of the latter is suggested on the basis of observation of a negative solvatochromy in the electronic spectra of N-substituted 2-(1,4-dihydro-4-pyridylidene)-1,3-indandiones (80JHC961, 80JHC997). Of the six possible tautomeric structures, the product of dimerization of 2-pyridylacetonitrile favors the tautomer **112** both in the solid state and in DMSO-d_6 solution (87AX(C)1728).



111a **111b** **112**

b. Methylene Group Activated by Acyl Group. The tautomerism of otherwise unsubstituted 2-phenacyl-, 3-phenacyl- and 4-phenacylpyridines, e.g., **113** (R = Ph), has been studied in aqueous solution at 25 °C (65JCS3093, 93JCS(P2)2285). The relative tautomeric stabilities fall in the order ketoimine > enamine > enol for 2- and 4-phenacylpyridines and enol > zwitterion for 3-phenacylpyridine. Whereas ketoimine form **113a** of 2-phenacylpyridine predominates in water (**113a**:**113b** = 2:1), this compound favors the chelated enol **113b** in non-polar media and exists exclusively as **113b** in the solid state. Minor amounts of enamine form **113c** were detected in chloroform solution (86KG802). In contrast, 4-phenacylpyridine exists in non-polar solvents exclusively in the ketoimine form, analogous to **113a** (65JCS3093).



113a **113b** **113c**

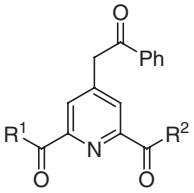
Similar tautomeric equilibrium was observed for 2-phenacylpyridines **113** substituted in the benzene ring in $CDCl_3$ solution. The substituent affects significantly the position of the equilibrium: the compounds with suitably located electron-donating substituents strongly favor the ketoimine form **113a**, whereas the enol form **113b** predominates for derivatives with electron-withdrawing substituents. This dependence is exponential in character: the position of the tautomeric equilibrium is almost independent of the temperature for 2-phenacylpyridines with electron-donating substituents; however, the more electron-withdrawing the substituent is, the more pronounced is the influence of temperature. In the solid state, these compounds exist as the tautomers which predominate in chloroform solution (00JCS(P2)2185).

Studies of the effects of the position of the heteroatom in the pyridine ring and N-substitution upon keto–enol tautomerization of type **113a** ⇌ **113b** showed that polar effects upon bond hybridization and resonance interaction with neutral double bonds significantly affect the enol stability. Unexpectedly, the stabilizing effect of 1-pyridinio group on the enol is smaller than that of phenyl group in acetophenone, while the stabilizing effect of the 4-dimethylamino-1-pyridinio group falls between the two. By contrast, 2-, 3-, and 4-pyridyl and pyridinio substituents are more stabilizing than the phenyl group (88JCS(CC)1097, 93JCS(P2)2297).

The effects of 25 different solvents, including polar, dipolar, aprotic, and amphiprotic examples, on the tautomeric equilibrium of *t*-butyl-2-picolyl ketone **113** (R = *t*-Bu) in semi-dilute solutions have been studied by ^{1}H NMR and UV spectroscopy. An increase in temperature or in the solvent polarity was found to shift the equilibrium toward the keto tautomer **113a** (82JHC785). Whereas diamide **114** ($R^1 = R^2 = NEt_2$) exists exclusively as the keto tautomer shown, the keto:enol ratio in **114** ($R^1 = R^2 = OMe$; $R^1 = OMe$, $R^2 = NEt_2$) depends on the solvent polarity with polar solvents stabilizing the enol form (03OBC737).

The reports on tautomerism of pyridyl-substituted pyruvates are, however, contradictory. Only two of three potential tautomers generally participate in tautomeric equilibrium, one of them always being ascribed to the enol form **113b**. The second tautomer is assigned either ketoimine **113a** or enamine structure **113c** by different authors. Both types of reports are discussed below.

Esters of 3-nitropyridyl-2- and 4-pyruvic acids were examined spectroscopically (UV, IR, ^{1}H NMR) for possible tautomerism. Esters of 3-nitropyridyl-2-pyruvic acids exist in the solid state and in solution almost exclusively in the enol form **115** (R^1 = H, OMe; R^2 = Me, Et). Its 4-substituted analog **116**, however, exists in chloroform, dioxane and carbon tetrachloride as a mixture of **116a** and **116b** and exclusively as enol **116b** in pyridine. The more polar solvents, as expected, favor the enol tautomer (74KG389).



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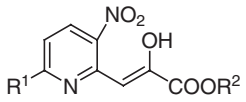

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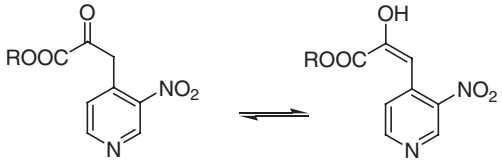
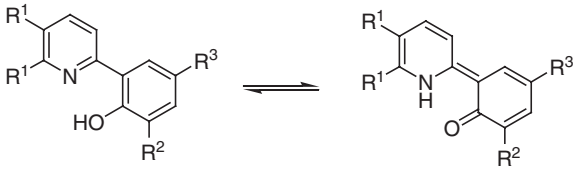


116a **116b**

On the other hand, unsubstituted ethyl (2-pyridyl)pyruvate **113** (R = COOEt) was reported to exist predominantly in the enaminone form **113c** in methanol, but as enol form in cyclohexane (94JCS(P2)2461). The tautomeric equilibrium between **113b**

and **113c** forms is also reported for 2-acylmethyl pyridines with electron-accepting substituents in the side chain (86KG802, 88KG514). The increase in the solvent polarity was found to stabilize the tautomer **113c**. No ketoimine **113a** was detected by ^{1}H NMR with the only exception of **113** (R = CF_3) in methanol.

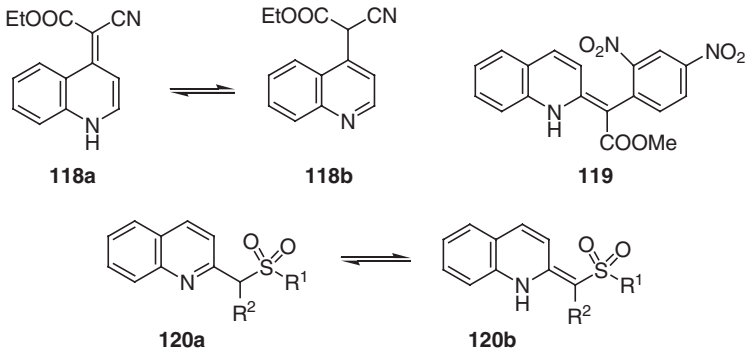
The tautomeric equilibrium in 2-(2-hydroxyphenyl)pyridines **117** (R^1 = H), except for **117** (R^1 = H; R^2 = R^3 = NO_2), is shifted completely toward the aromatic form **117a** in chloroform, ethanol, DMF, and DMSO solution. A significant amount of the quinoid form **117b**, however, was observed for **117** (R^1 = H; R^2 = R^3 = NO_2) in chloroform; the molar fraction of **117b** increases on addition of more polar acetonitrile (90KG75).



117a **117b**

3. *Quinolines*

The tautomeric equilibrium constant for the interconversion 2-benzylquinoline ⇌2-benzylidene-1*H*-quinoline (K_T = 8.7), determined by UV spectroscopy, indicates that the benzyl tautomer is significantly more stable (79JCS(P2)792). 4-Substituted quinoline **118** exists as single tautomer **118a** in DMSO-d_6, but as a mixture of both tautomers in $CDCl_3$ (87JHC1467). 2-Benzyl quinoline **119** favor the enamine form shown (95%) in $CDCl_3$ solution (89IZV2323). Only fully aromatic tautomer **120a** was observed in solutions of 2-(sulfonylmethyl)-substituted quinolines **120** (R^1 = Me, R^2 = H, SO_2Me; R^1 = Ph, R^2 = SO_2Ph), whereas only enamine tautomer **120b** was detected for **120** (R^1 = Me; R^2 = CN). Both tautomers coexist in $CDCl_3$ solution of **120** (R^1 = Ph; R^2 = COOMe) (90JHC1433).

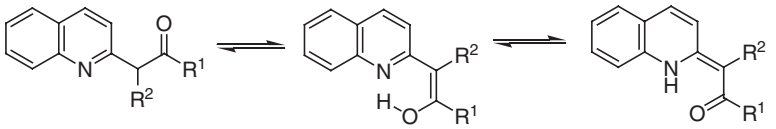


118a **118b** **119**

120a **120b**

Similar discrepancies in determination of the tautomeric structures, as discussed above for acylmethyl-substituted pyridines, exist for their benzo-fused analogs.

However, for the latter only a few early reports claim the detection of enol tautomer **121b** (see discussion in (88T3319)), and in the vast majority of publications only tautomeric interconversion **121a** ⇌ **121c** is discussed. An increase of the molar fraction of the enaminone tautomer (**121c**) on benzannulation of 2-acylmethyl pyridines is suggested (90ZOR1387, 94JCS(P2)2461). UV spectroscopic and deuterium isotope studies indicated that the tautomerism of 2-phenacylquinoline **121** (R^1 = Ph; R^2 = H) is solvent-dependent with the principal tautomer being the enaminone **121c**. In contrast, in 4-phenacylquinoline solutions, only small amount of the enaminone was observed, with the aromatic ketoimine tautomer being the predominant one (79JCS(P2)792, 85JCS(P2)1711, 88KG514, 93JCS(P2)2285, 00JCS(P2)1259).



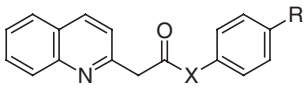
121a **121b** **121c**

Similar to their parent compound, α-unsubstituted 2-aroylmethyl quinolines **121** (R^1 = aryl; R^2 = H) exist in $CDCl_3$ solution predominantly in the enaminone form **121c**. The molar fraction of ketoimine tautomer **121a** ranges from 1% (R^1 = 4-$CF_3C_6H_4$) to 33% (R^1 = 4-$Me_2NC_6H_4$), depending on the aromatic ring substituent. In the crystal, all these compounds exist in enaminone form **121c** (00JCS(P2)1259). Semiempirical AM1 and PM3 calculations predicted the opposite relative stability of tautomers **121a** and **121c** in the gas phase. A similar trend was observed for other quinoline derivatives **121** (R^1 = Me, Et, *i*-Pr, CH_2Br, CF_3, CN, COOEt, etc.). The introduction of a cyano or ethoxycarbonyl group into the α-position does not effect the equilibrium; however, α-methyl, α-bromo-, or α-benzoyl group shift the equilibrium completely toward the tautomer **121a** (88T3319, 90SA(A)803, 91JCS(P1)2831). In the absence of an acid, the quinoline **121** (R^1 = Me; R^2 = $PhCH_2$) exists in a solution exclusively in the enaminone form **121c**; however, when traces of an acid are present, the rapid equilibration occurs with the formation of a mixture **121a**:**121c** = 2:3 (92JHC1361).

The long-range substituent and temperature effects on prototropic tautomerism of 2-(acylmethyl)quinolines **122** (X = $(CH=CH)_n$; n = 0, 1; R = H, 1-pyrrolidinyl) have been studied by ^1H, ^{13}C, and ^{15}N NMR methods (01JPOC201). The ethylene fragment conjugated with the phenyl group and strong electron-donating substituent were found to favor the enolimine structure analogous to **121b**, which undergoes fast exchange (on the NMR time scale) with the enaminone form. The amount of the latter increases with decrease in temperature.

The solvent effects of 25 different solvents, including polar, dipolar, aprotic, and amphiprotic examples, on the tautomeric equilibrium of *t*-butyl quinaldyl ketone **121** (R^1 = *t*-Bu; R^2 = H) in semi-dilute solutions have been studied by ^1H NMR and UV spectroscopy. An increase in temperature or in solvent polarity shifts the **121a** ⇌ **121c** equilibrium toward the ketimine tautomer **121a** (82JHC785).

Although there is a very fast (on the NMR time scale) double proton transfer in quinoline **123**, the enaminone/enolimine tautomers **123a** and **123b** are the only ones present in the chloroform solution. *Ab initio* calculations of the relative stabilities of tautomers using the PCM solvation model produced results contradictory to the experimental data (03CEJ2710).



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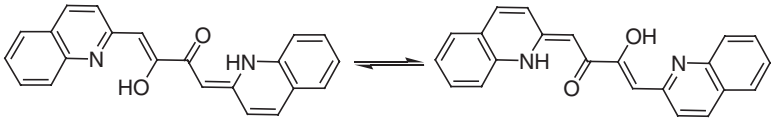
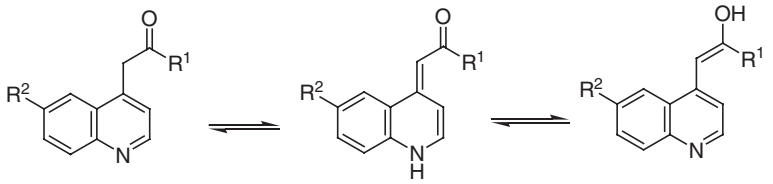


123a **123b**

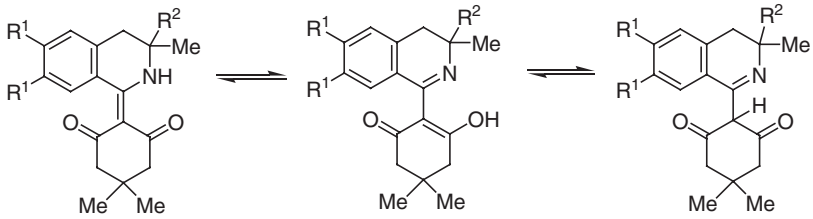
No enaminone tautomer **124b** was observed in $CDCl_3$ solutions of substituted 4-(acylmethyl)quinolines **124**. The position of the tautomeric equilibrium is greatly affected by both R^1 and R^2 substituents. Quinolines **124** (R^1 = alkyl; R^2 = H) exist in solution exclusively as keto tautomers **124a**, whereas only tautomeric form **124c** was observed for diesters **124** (R^1 = COOEt; R^2 = COOMe, COOEt). Both tautomers **124a** and **124c** were observed for **124** (R^1 = COOMe, COOEt, COOBu; R^2 = H, OMe) (91CJC696).



124a **124b** **124c**

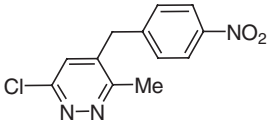
Benzannulation of pyridines **117** (R^1 = H; R^2 = R^3 = H) to quinolines (R^1_2 = benzo) is not sufficient for realization of the tautomer **117b**. However, additional stabilization by introduction of a single nitro group into the phenyl ring results in the appearance of **117b** in tautomeric equilibrium with **117a** (90KG75).

X-ray analysis showed that isoquinolines **125** (R^1 = H, R^2 = H, Me; R^1 = OMe, R^2 = Me) exist in the solid state as NH-tautomers **125a**. The tautomeric equilibrium does not shift noticeably in a solution, and no solvent effects were observed. The MNDO calculations, however, predict the OH-tautomer **125b** to be the most stable, the experimentally observed predominance of **125a** being explained by nonspecific solvation effect (93IZV288, 95KG922).

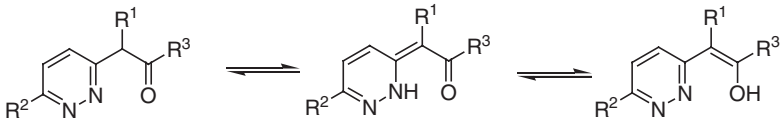


4. *Pyridazines*

NOE studies of 4-(4-nitrobenzyl)pyridazine **126** indicated than this compound exists in $CDCl_3$ and DMSO-d_6 solution as benzyl tautomer shown (95AJC1601). No enol tautomer **127c** has been detected in solutions of acylmethyl pyridazines **127** (R^1 = CN, COOMe; R^2 = H, Cl, Ph, OMe, $MeCOCH_2$, $PhCOCH_2$; R^3 = OMe, OEt, Me, Ph, $PhCH_2$). The position of the tautomeric equilibrium **127a** ⇌ **127b** depends on substituents both in the side chain and heteroaromatic ring. Thus, the ester derivatives **127** (R^3 = OMe, OEt) exist in the equilibrium mixture of both tautomers with tautomer **127a** predominating, except for **127** (R^1 = CN; R^2 = H, Cl; R^3 = OEt), which favor the tautomer **127b** (83IZV1687, 88ZOR1806). For ketones, the tautomeric equilibrium constant (K_T) values decrease in the following order in regard to the substituent at the position 3: phenacyl > phenylacetonyl > acetonyl. A solvent effect on the K_T values was also observed. On the other hand, 4-phenacylpyridazine exists only in the keto form of type **127a** in any examined solvent. Addition of TFA shifts the equilibrium of 3-acylmethylpyridazines nearly quantitatively to the keto form **127a** (78CPB3633).



126

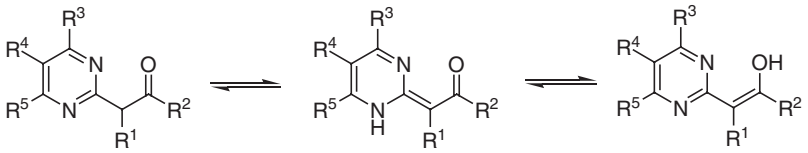


127a **127b** **127c**

5. *Pyrimidines and Benzologues*

The substituent effects on tautomeric equilibrium of α-(2-pyrimidinyl)cyanoacetates **128** (R^1 = CN; R^2 = OEt) have been studied extensively (77IZV2633, 78KG1544, 84KG827, 85T4897, 88ZOR1806). For derivatives with unsubstituted

4(6)-positions ($R^3 = R^5 = H$), only two tautomers, **128a** and **128b**, were observed. The introduction of both electron-donating and electron-accepting substituents into the 5-position of the pyrimidine ring increases the content of the aromatic form **128a** in the following order: ($R^4 = H$, Me) < ($R^4 = Cl$, Br) < ($R^4 = OMe$, NMe_2). The introduction of a substituent into the 4(6) position does not affect significantly the proportion of the tautomer **128a**, but causes the tautomer **128c** to appear. The proportion **128b**/**128c** strongly depends on the type of R^3 substituent, e.g., **128b**:**128c** = 1:1 (R^3 = Me) or 70:28 (R^3 = Ph). Unsymmetrically substituted compounds ($R^3 \neq R^5$) form two types of ylidene tautomers **128b** in the ratio controlled by substituents in 4(6) positions.

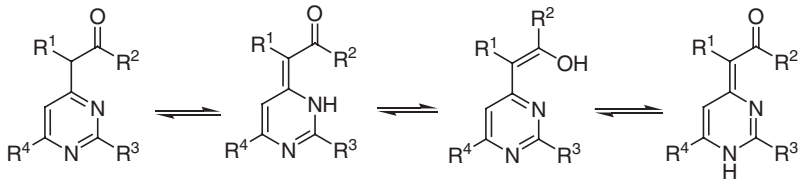


128a **128b** **128c**

The solvent effect on the position of the tautomeric equilibrium in cyanoacetate **128** ($R^1 = CN$; $R^2 = OEt$; $R^3 = R^5 = H$; $R^4 = OMe$) has been studied (87KG1668). An increase in the polarity of the solvent shifts the equilibrium to favor the tautomer **128b**. The tautomeric equilibrium is also highly sensitive to the effects of specific solvation. The tautomer **128b** is stabilized by both proton-donor and proton-acceptor solvents, so the percentage of this form in such solvents is significantly higher than could be expected from the solvent polarities. The equilibrium is also sensitive to temperature changes. Thus, **128** ($R^1 = CN$; $R^2 = OEt$; $R^3 = R^5 = H$; $R^4 = NMe_2$) contains 75% of tautomer **128a** at 370 K and only 5% at 238 K (84KG832).

2-Phenacylpyrimidines **128** ($R^1 = R^3 = R^5 = H$; $R^2 = Ph$; $R^4 = Cl$, Ph) exist in solution as tautomeric mixtures containing 40–50% of **128a** form. The introduction of a halogen into the α-position shifts the equilibrium completely toward **128a** (87KG663). UV, IR, and NMR spectroscopic studies of (α-pyrimidinyl)dicarboxylates **128** ($R^1 = COOMe$, $R^2 = OMe$; $R^1 = COOCH_2Ph$, $R^2 = OCH_2Ph$; $R^3 = R^5 = Cl$; $R^4 = H$) revealed that in a basic solvent **128a** exists in an equilibrium with the resonance-stabilized enolate ions. The existence of a neutral enol **128c** or enamine form **128b** could not be detected (80JHC589). Similarly, only fully aromatic tautomer **128a** was observed in solutions of 2-(nitromethyl)pyrimidines, α-(sulfonyl)pyrimidinylacetates and related compounds (85T4897).

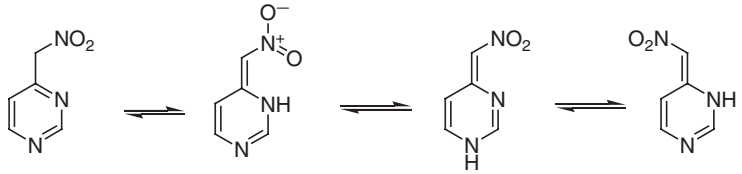
Whereas 4-phenacylpyrimidine contains only 30% of the aromatic form **129a** in $CDCl_3$ solution, the introduction of a bromo substituent into the α-position shifts the equilibrium entirely to the tautomer **129a** (87KG663). 6-Methoxy-4-trichloroacetonylpyrimidine **129** ($R^1 = R^3 = H$; $R^2 = CCl_3$; $R^4 = OMe$) exists in $CDCl_3$ solution as a mixture of tautomers **129a** and **129b** in a 1:3 ratio and its 6-unsubstituted analog exists in CD_2Cl_2 and CCl_4 in an equilibrium of **129b** and **129c** forms with the tautomer **129b** predominating (78KG1256).



129a **129b** **129c** **129d**

The solvent effects on tautomerism of α-(4-pyrimidinyl)cyanoacetates **129** (R^1 = CN; R^2 = OEt; R^3 = Me, CF_3; R^4 = H) were investigated extensively. These compounds exist in chloroform and carbon tetrachloride solution exclusively in the *ortho*-quinoid form **129b**, although some amount of the *para*-quinoid tautomer **129d** is present in dichloromethane, 1,2-dichloroethane and acetonitrile solutions. The addition of solvents, capable of hydrogen bond formation, such as water, DMSO, DMF, shifts the equilibrium toward the *para*-quinoid form **129d** (77KG395, 78KG1544, 78TL3055, 88KG521). CNDO/2 calculations taking into account Germer solvation showed that with the increase in the solvent polarity the tautomer **129d** is stabilized to a greater degree than the tautomer **129b** (88KG521). No tautomer **129a** was detected either in solution or in the solid state. In the solid state, the tautomeric preference depends on the steric demands of the substituents. Thus, both forms **129b** and **129d** were observed for **129** (R^1 = CN; R^2 = OEt; R^3 = Me, CF_3; R^4 = H), whereas **129** (R^1 = CN; R^2 = OEt; R^3 = H, Ph; R^4 = Ph) exist exclusively as tautomers **129b** (77DOK113).

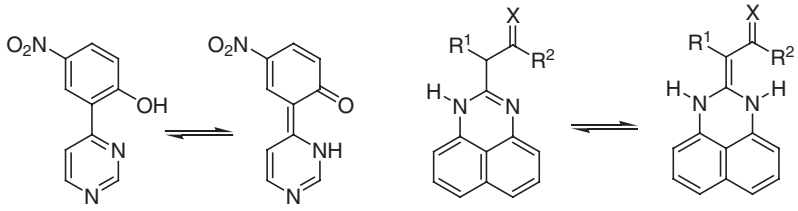
Diesters **129** (R^1 = COOMe, R^2 = OMe; R^1 = COOEt, R^2 = OEt) exist in the tautomeric equilibrium **129a** ⇌ **129b** with the component ratio determined by the substituents at the 2- and 6-positions (77KG395, 88ZOR1806). NMR Fourier spectroscopic studies of 4-pyrimidylnitromethane **130** showed that in $CDCl_3$ this compound exists predominantly as the tautomer **130a** with a small amount of the *ortho*-quinoid form **130b**. In a 3% solution in DMSO, a rapid equilibration of forms **130c** and **130d** with the preference for the former (*ca.* 60% of **130c**) was observed (78KG1544, 78TL3055).



130a **130b** **130c** **130d**

Similar to its pyridine analog, only aromatic form **131a** was observed in solutions of 4-(2-hydroxyphenyl)pyrimidine **131** in various solvents (90KG75). Signals of both tautomers **132a** and **132b** were observed in NMR spectra of ethyl perimidine-2-acetate **132** (R^1 = H; X = O; R^2 = OEt) in $CDCl_3$ (88MRC191). The tautomerism of the amide analogs **132** (R^1 = COOEt; X = O, S; R^2 = NHMe, NHPh, $NHCH_2COOEt$) depends on the acidity of the solvent. Thus, whereas these compounds exist in the

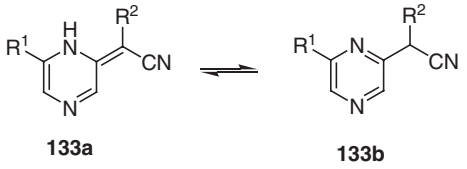
tautomeric form **132a** in the $CDCl_3$ solution, the addition of trifluoroacetic acid shifts the equilibrium toward the tautomer **132b**, although **132a** still predominates (96BSF587).



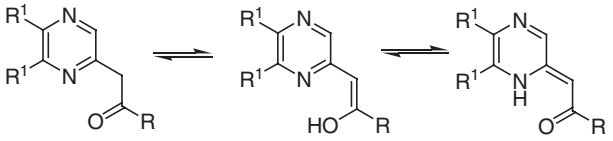
131a **131b** **132a** **132b**

6. *Pyrazines and Quinoxalines*

UV and IR studies showed that (cyanomethyl)pyrazines **133** ($R^1 = H$, Cl, $R^2 = CN$; $R^1 = H$, $R^2 = COOEt$) exist in aqueous solution exclusively in the ylidene form **133a**. In contrast, both tautomers of **133** ($R^1 = Cl$; $R^2 = COOEt$) were found in the liquid state as well as in solution (84M179). The low basicity of the pyrazine nitrogens renders the enaminone form **134c** less stable than enol **134b**, so only two tautomers, **134a** and **134b** are found at the equilibrium, independent of the acyl substituent and the solvent used. The tautomeric equilibrium in pyrazines is more sensitive to the acyl substituents than that in quinoxalines resulting in dramatic decrease in the percentage of the tautomer **134a** with increase in the acceptor character of the substituent R (87KG1663, 94JCS(P2)2471).



133a **133b**

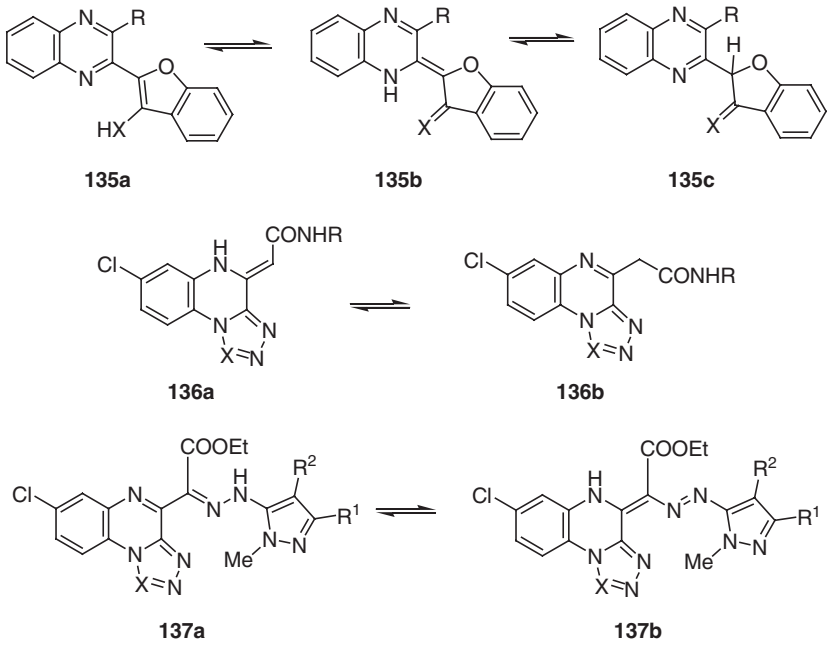


134a **134b** **134c**

The benzannulation leads to appearance of the ylidene tautomer **134c** (R^1_2 = benzo), which becomes the predominant one for **134** (R = CF_3, Ph, 4-$MeOC_6H_4$, 4-pyridyl) (87KG1663, 97JCS(P2)2605). The tautomerism in benzofuryl-substituted quinoxalines **135** (X = O, NH; R = H, Me, Ph), where the potentially tautomeric methylene group is a part of the heterocyclic ring, was studied by both theoretical and experimental methods (00JPOC473). The form **135c** was excluded by ^{1}H NMR

studies, and the relative stabilities of tautomers **135a** and **135b** were estimated at the *ab initio* B3LYP/6-31G** level of theory. The tautomer **135a** is predicted to be the predominant one for all the compounds; however, the difference in the relative stabilities is much smaller for hydroxy derivatives **135** (X = O; R = H, Me) (ΔE = 5–7 kcal/mol) than for their amino analogs (ΔE = 40–70 kcal/mol).

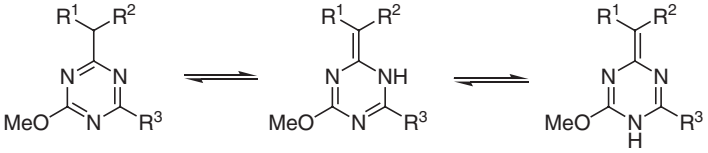
The effects of the basic side chain on the tautomerism of amido-substituted triazole and tetrazole-fused quinoxalines **136** (X = N, CH; R = 4-MeC_6H_4, 4-HOC_6H_4, 4-pyridyl, 2-pyridyl, 3-pyridyl) have been studied by ^{1}H NMR spectroscopy in TFA-d_1 solution (93JHC1463). Whereas only enamine tautomer **136a** is observed for **136** (X = N, CH; R = 4-pyridyl), all other compounds studied exist in equilibrium of the both forms with the percentage of the form **136b** being highest for 2- and 3-pyridyl derivatives. Functionalized ester analogs **137** (X = N, CH; R^1 = H, Me; R^2 = CN, COOEt) also exist in the tautomeric equilibrium of hydrazone imine form **137a** and diazenyl enamine form **137b** in DMSO-d_6 and aqueous TFA solution (94JHC233). The increase in TFA concentration or in temperature shifts the equilibrium toward the tautomer **137b**.



7. *Other Heterocycles*

The position of the tautomeric equilibrium in the trisubstituted triazines **138** depends on the nature of substituents both in the heteroaromatic ring and in the side chain. The enamine structure **138b** was ascribed to the triazines **138** (R^1 = COOMe, COOEt; R^2 = CN; R^3 = OMe) (78RTC107, 88KG241), whereas triazine **138** (R^1 = R^2 = CN; R^3 = OMe) favors the non-aromatic tautomer **138c**. Malonic diester-functionalized

triazine **138** ($R^1 = R^2 = COOEt$; $R^3 = OMe$) exists as the aromatic tautomer **138a** both in solution (independent of the solvent) and in the solid state; however, the tautomeric composition of **138** ($R^1 = R^2 = COOEt$; $R^3 = NH_2$) in solution depends on the solvent polarity shifting toward the tautomer **138b** in more polar solvents. For the latter compound, both **138a** and **138b** tautomers are detected in the solid state (88KG241).



138a **138b** **138c**

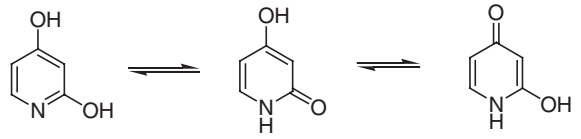
III. Compounds with Two or More Potentially Tautomeric Functional Groups

A. Compounds with Two or More Hydroxy(Oxo) Groups

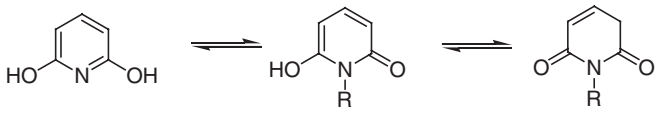
1. *Pyridines and Quinolines*

Determination of the acidity of 2,3-dihydroxypyridine in various solvents indicated that this compound exists mainly as 3-hydroxy-2-pyridone in ethanol, but as the diol tautomer in DMSO and dioxane. This phenomenon is explained by stabilization of the oxo form by hydrogen-bond donating solvents, whereas the hydrogen-bond acceptors stabilize the diol form (95M377). The tautomeric equilibrium of 2,3-dihydroxypyridine *in vacuo* and in ethanol solution has also been studied using density functional theory at the B3LYP/6–31G(d) level. The results indicate that 3-hydroxy-2-pyridone tautomer is more stable in both cases and the energy barrier for the keto–enol transfer is decreased significantly in ethanol (04JCC1833).

The relative stabilities of three tautomers of 2,4-dihydroxypyridine **139** were estimated using the *ab initio* calculations at the HF/3-21G level (82IJQC(22)1041). The *ortho*-quinoid tautomer **139b** was found to be the most stable in agreement with the experimental data. The other tautomers are less stable by 1.9 kcal/mol (**139a**) and by 8.9 kcal/mol (**139c**). The predominance of form **139b** in solution (93CPB1498) and in crystal (94MI371) was confirmed by ^1H NMR studies and pulsed neutron single-crystal diffraction, respectively.



139a **139b** **139c**



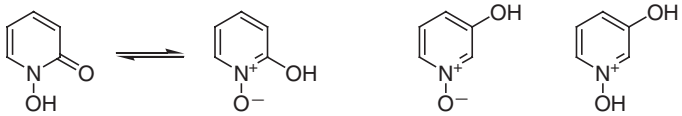
140a **140b** **140c**

UV, IR, and ^{1}H NMR spectra were recorded for 2,6-dihydroxypyridine **140** (R = H) and its *N*–Me derivative (71AJC2557). The hydroxy(oxo) form **140b** is the main or predominant tautomer for 2,6-dihydroxypyridine in water, DMSO, ethanol and ethanol-cyclohexane mixture and for *N*-methyl-2,6-dihydroxypyridine in ethanol. The glutaconamide **140c** is the main or predominant tautomer for 2,6-dihydroxypyridine in dioxane, and for *N*-methyl-2,6-dihydroxypyridine in water, dioxane, and chloroform. In the solid state, both compounds exist as tautomers **140b** linked by short asymmetric hydrogen bonds. Dynamic tautomerism between two hydroxy(oxo) forms was observed for 4-chloro- and 3-cyano-2,6-dihydroxypyridines (77JCS(P1)2536, 93CPB1498).

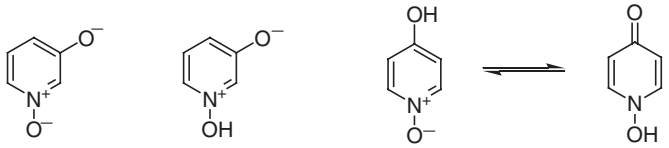
Analysis of the dual phosphorescence indicated that 1-hydroxy-2(1*H*)-pyridone exists in a tautomeric equilibrium between the keto isomer **141a** and the enol isomer **141b** in the excited triplet state in methylcyclohexane at 77 K (81JCS(CC)1004). In the ground state, the enol is thermodynamically unstable and reverts to the more stable keto isomer **141a**. The tautomerization process is also affected by the polarity and hydrogen-bonding ability of solvents. Thus, no dual phosphorescence was observed in ethanol or butyronitrile glasses indicating the presence of sole tautomer **141a** (84JCS(P2)2031). Two conceivable intramolecular tautomerization processes giving the enol form are proposed including either a single dihydropyridine molecule or a dimer. UV–vis spectroscopy has been successfully applied to studies of tautomeric equilibria in 2-hydroxy- and 4-hydroxypyridine *N*-oxides and their mercapto and amino analogs (93KG1662).

Investigations using X-ray photoelectron spectroscopy and the N_{1s} and O_{1s} binding energies revealed that in the ground state the equilibrium of 1-hydroxy-2(1*H*)-pyridone is shifted significantly to the oxo tautomer **141a** (80JA1174). According to their ^{1}H and ^{13}C NMR spectra, 2-hydroxy- and 2,3-dihydroxypyridine *N*-oxides exist in DMSO solution as substituted 1-hydroxy-2(1*H*)-pyridones of type **141a**. X-ray analysis showed that in the solid state 2-hydroxypyridine *N*-oxide also favors the hydroxy(oxo) tautomer (90JCS(P2)1215).

According to UV spectroscopic studies, 3-hydroxypyridine 1-oxide exists in ethanol, and aqueous acidic and alkaline media in forms **142a**, **142b**, and **142c**, respectively. No bipolar form **142d** has been detected (74KG92). The relative stabilities of tautomers of 2-, 3-, and 4-hydroxypyridine *N*-oxides have been calculated at the 6-31G* level (93JST(287)127). Tautomers **141a** and **142a** were found to be the most stable for 2- and 3-hydroxypyridine *N*-oxides, respectively, in agreement with the experimental data. The results for 4-hydroxypyridine *N*-oxide **143**, however, depend on the method used: either predominance of the tautomer **143a** or almost equal stability of both tautomers is predicted.

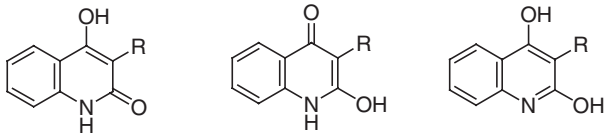


141a **141b** **142a** **142b**

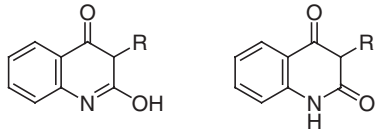


142c **142d** **143a** **143b**

2,4-Dihydroxyquinolines can exist in five possible tautomeric forms **144a–e**. However, in practice, the tautomerism is reduced to forms **144a–c**. The tautomerism of unsubstituted 2,4-dihydroxyquinoline **144** (R = H) in the gas phase is discussed in terms of quantum-chemical calculations by LCAO-MO method in the CNDO/2 approximation (86JST(147)351). The dihydroxy tautomer **144c** is predicted to be slightly more stable. The experimentally found predominance of both quinolone tautomers **144a** and **144b** in solution is explained by self-association in the latter case that stabilizes the oxo forms.



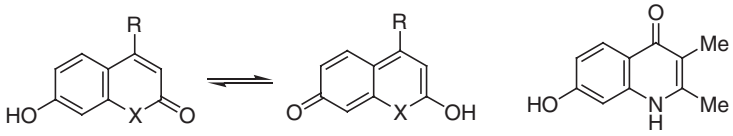
144a **144b** **144c**



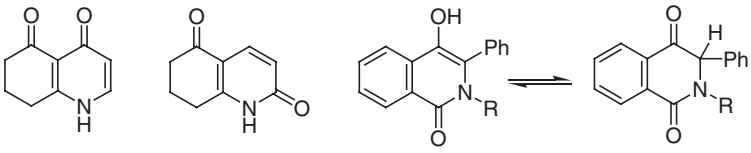
144d **144e**

Tautomerism in solution is significantly affected by the nature of a substituent at the 3-position. Thus, unsubstituted 2,4-dihydroxyquinoline and its thioethers and nitrile derivatives **144** (R = SMe, CN) favor the 2(1*H*)-quinolinone structure **144a**, while the sulfoxide **144** (R = SOMe) and, probably, the sulfone **144** (R = SO_2Me) exist as 4(1*H*)-quinolinone tautomers **144b** (91H(32)2151, 91T2151). Only 4-quinolone tautomer **144b** was observed for 3-substituted *N*-methyl-2,4-dihydroxyquinolines in solution (81OMR242).

Extended Hückel calculations of the (hydroxy)quinolone **145** (X = NH; R = Me) showed that while the tautomer **145a** is more stable in the ground state, the tautomer **145b** becomes the favored one in the excited state (80IJC(B)989). A similar keto–enol tautomerism was observed in fluorescence emission spectra of (hydroxy)quinolone **146** (98TAL1065).



145a **145b** **146**



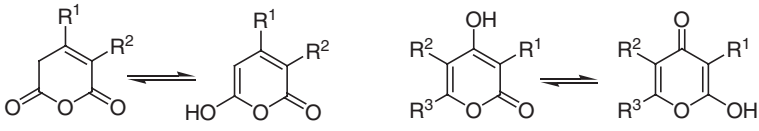
147 148 149a 149b

Dihydroquinolinediones **147** and **148** have been studied by *ab initio* Hartree–Fock calculations (95JST(330)431). For **147**, the 4-hydroxy-5-oxo tautomer, stabilized by intramolecular hydrogen bonding, is predicted to be favored, the 4,5-diketo tautomer being less stable by 15–16 kcal/mol. In contrast, the 2,5-diketo form is preferred for **148** by 1.5–3.5 kcal/mol. The theoretical predictions are confirmed by FT–IR studies in chloroform.

2-Substituted 4-hydroxy-1-isoquinolone **149** (R = 2-($ClCH_2CONH)C_6H_4$) exists in the hydroxy form **149a** in the solid state. In the dioxane solution, **149a** is slowly converted into the oxo tautomer **149b**. Isolated **149b** is claimed not to tautomerize into **149a** in solution (85KG542).

2. *Pyrans and Benzopyrans*

Tautomerism of glutaconic anhydride (6-hydroxy-2-pyrone) **150** ($R^1 = R^2 = H$) was investigated by ^1H NMR spectroscopy providing evidence that this compound exists in $CDCl_3$ exclusively as the dioxo tautomer **150a**. On the addition of CD_3OD to a $CDCl_3$ solution, H–D exchange was observed suggesting that under these conditions the tautomeric equilibrium between the diketo form **150a** and hydroxy(oxo) form **150b** occurs. A small contribution from the hydroxy form **150b** was detected in acetonitrile solution by IR spectroscopy (81JCS(P1)146). The 4-acetoxy derivative **150** (R^1 = OAc; R^2 = H) exists in the dioxo form in $CDCl_3$ and acetone-d_6 solution: no tautomeric equilibrium was detected. The rearranged product, 3-acetylpyran-2,4,6-trione **150** (R^1 = OH; R^2 = COMe), also exists in non-polar solvents ($CDCl_3$) predominantly as the diketo tautomer **150a**; however, in DMSO-d_6 some enolization to **150b** takes place (78JCS(P1)933).



150a 150b 151a 151b

Like unsubstituted 6-hydroxy-2-pyrone, **150** (R^1 = Me; R^2 = H) exists in chloroform solution in the anhydride form **150a**. The tautomerism is solvent-dependent: in non-polar solvents only **150a** is observed, whereas in polar solvents **150b** is also present. Introduction of an acetyl group in the 3-position promotes enolization through the intramolecular hydrogen bonding (see Section III.G.2) (86JCS(P2)973).

^1H and ^{13}C NMR and UV spectroscopic studies established the existence of 4-hydroxy-2*H*-pyran-2-ones **151** (R^1 = H, Me, Et, allyl; R^2 = H, Me; R^3 = H) in

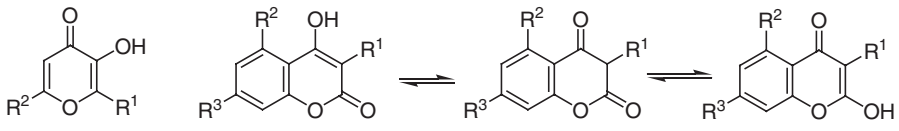
DMSO-d_6 and MeOH solution as 2-oxo-4-hydroxy tautomers **151a** (85CB741). Hydroxypyranone **151** (R^1 = 4-$Et_2NC_6H_4N$ = CMe; R^2 = H; R^3 = Me) also exists exclusively in the 4-hydroxy-2-oxo tautomeric form **151a** with intramolecular hydrogen bonding between the hydroxy group and imine nitrogen. The DFT calculations are in qualitative agreement with the experimental results (04JST(707)69).

The effects of the physical state and the nature and orientation of substituents on the position of the tautomeric equilibrium of pyran-2,4-diones **151** have been studied by ^{1}H and ^{13}C NMR, UV and IR spectroscopy (84JCS(P2)1317). The 2-pyrone form **151a** appears to be predominant for **151** ($R^1 = R^2$ = Me; R^3 = H) and **151** ($R^1 = R^2$ = H; R^3 = Me) in solution; however, the latter exists as a mixture of both tautomers in the solid phase. In contrast to 3-acyl group (see Section III.G.2), 5-acyl group is not capable of forming conjugate chelate rings, so 5-acylpyran-2,4-diones **151** (R^2 = MeCO, PhCO) show varying degrees of tautomeric equilibrium between 2- and 4-pyrone forms in non-polar solvents and in the solid state.

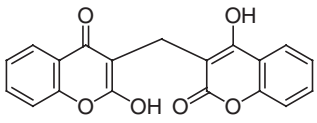
The structures of several 3-hydroxy-4-pyranones, such as pyromeconic acid **152** ($R^1 = R^2$ = H), maltol **152** (R^1 = Me; R^2 = H), ethylmaltol **152** (R^1 = Et; R^2 = H) and kojic acid **152** (R^1 = H; R^2 = CH_2OH) were calculated using 6-311++G(d,p) basis set (03JST(639)87). The 3-hydroxy-4-oxo forms shown were found to be predominant in all cases with the second most stable tautomer being 2*H*-3,4-dioxo form.

4-Hydroxycoumarin/2-hydroxychromone **153a–c** tautomerism was studied by ^{1}H and ^{13}C NMR and IR spectroscopy, by deuterium labeling and by isotope replacement of the carbonyl carbon with ^{13}C (82JHC385, 82JHC475, 97CJC377). An H-D exchange at the C-3 atom of the lactone ring was observed for these compounds in solution. Although only the 4-hydroxy-2-chromenone tautomers **153a** were observed, an equilibrium between the 4-hydroxy-2-chromenone **153a** and 2,4-chromandione **153b** forms is suggested to be the key step in H–D exchange reaction. The stabilities of the different tautomeric forms of five chromones have been evaluated by MNDO calculations (97CJC377). In all the cases, the form **153a** was found to be the most stable. The tautomers **153c** were calculated to be the least stable, except for **153** (R^2 = OH).

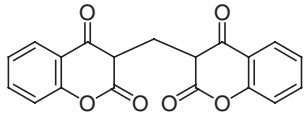
The relative stabilities of the tautomers of dicoumarol, which can potentially exist in six tautomeric forms, and its derivatives were studied by the PM3 method (04JST(678)55). The calculations have been carried out both in the gas phase and in a continuum model of water, on isolated tautomers of 10 systems obtained by single proton transfer. In the most cases, the predominance of the α,γ′-benzopyran tautomeric structure **154a** was predicted in the gas phase. In aqueous solution, the calculations imply significant qualitative differences in the relative stabilities of the tautomers and predict the predominance of the tetra-keto structure **154b**, even though the α,α′-benzopyran structure is the one with the largest dipole moment.



152 **153a** **153b** **153c**



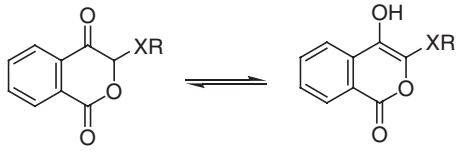
154a



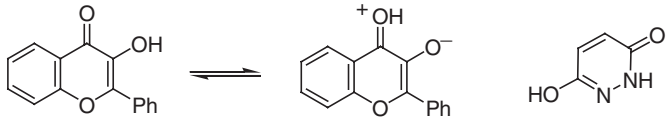
154b

3-(Arylthio)isochromane-1,4-diones **155** (X = S; R = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$, etc.) are completely enolized to **155b**, while their *S*,*S*-dioxides **155** (X = SO_2) show the solvent-dependent keto–enol equilibria in which the oxo species are dominating (78CB2859).

Upon electronic excitation, 3-hydroxyflavone **156**, isolated in solid argon at 15 K, undergoes rapid intramolecular proton transfer. Only fluorescence from the bipolar tautomer **156b** was observed under these conditions (87JPC4261) or in hydrocarbon solvents (cyclohexane, toluene); however, both tautomers fluoresce in hydroxylic solvents (83MI67). The solvent-dependent mechanism of the excited state intramolecular proton transfer in 3-hydroxyflavone has been studied by both steady-state and ultrafast time-resolved fluorescence spectroscopy. In addition, fluorescence spectra of 3-hydroxyflavone **156** in a solid polymethylmethacrylate matrix, where the hydroxy group is additionally stabilized by the intermolecular hydrogen bonding with the ester group of the polymer, were measured (81JA6916).



155a 155b



156a 156b 157

Extended Hückel calculations of the coumarin **145** (X = O; R = Me) showed that while the tautomer **145a** is more stable in the ground state, the tautomer **145b** becomes the favored one in the excited state (80IJC(B)989). The replacement of the methyl group in the 4-position by trifluoromethyl group suppresses the formation of phototautomers even in weakly acidic ethanol solution, as established by fluorescence spectroscopy (84MI1496).

3. *Pyridazines*

The structure of maleic acid hydrazide, 1,2-dihydropyridazine-3,6-dione, has been investigated using ^{1}H NMR, IR, and Raman spectra. In the average, 23% of the four protons of maleic hydrazide are in rapid exchange and 77% of them are position-fixed.

As a consequence of this hydrogen exchange, the tautomeric equilibrium is shifted strongly to the hydroxy(oxo) form **157**. The dioxo structure is energetically unfavorable and is present only to a small extent (75CB478). Similar results were obtained from the investigation of the crystal structure where the pattern of bond lengths and bond angles permits the designation of the molecule as tautomer **157** (76JCS(P2)1386). The 1-α-cumyl-substituted derivative of maleic hydrazide also exists in the hydroxy(oxo) tautomeric form (77JOC296).

The structure and tautomerism of maleic hydrazide were also examined theoretically employing 3-21G and 6-31G* basis sets. The results indicate the hydroxy(oxo) tautomer as the most stable one in the gas phase followed by the diketo form ($\Delta E = 2$ kcal/mol). The dihydroxy tautomer is of minor importance ($\Delta E = 8.9$ kcal/mol). Solvation stabilizes the dioxo tautomer more than the hydroxy(oxo) form, so even though the order of stability is the same, the energy difference between the tautomers becomes negligible ($\Delta E = 0.08$ kcal/mol) (90JST(206)295, 91JST(227)321). In contrast, the semiempirical methods (AM1, MNDO, and MINDO/3) erroneously predicted the greatest stability of the dihydroxy tautomer, both for isolated molecules and homodimers (90JST(206)295).

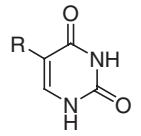
Ab initio calculations (3-21G basis set) of 3,5-dihydroxypyridazine correctly predicted the 4-hydroxy-6-oxo tautomer to be the most stable and the dihydroxy tautomer to be the least stable. Again, semiempirical methods favored the dihydroxy tautomer in contradiction to the experimental results (90JST(206)295).

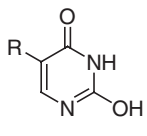
A comprehensive theoretical study of the structure and tautomerism of the four isomeric hydroxypyridazine *N*-oxides and pyridazine 1,2-dioxides in the gas phase and in solution has been carried out using high-level *ab initio* calculations employing large basis sets and quadratic configuration interaction treatment of electron correlation (QCISD(T)). The calculated properties are generally in a good agreement with experimental data, indicating that for 1,3-dihydroxy and 1,6-dihydroxypyridazines, the 3-hydroxy-1-oxo or 6-hydroxy-1-oxo tautomers are preferred over their dioxo forms by 3.3 kcal/mol. The 5-hydroxy-1-oxo tautomer of 1,5-dihydroxypyridazine is preferred by 6.5 kcal/mol. The behavior of 1,4-dihydroxypyridazine is less clear; however, the presence of both 1-hydroxy and 4-hydroxy tautomers in the gas phase and in solution is suggested (97JST(419)97).

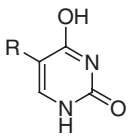
4. *Pyrimidines and Quinazolines*

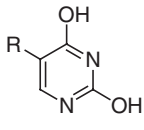
A detailed review on the prototropic tautomerism of 2,4-pyrimidinedione, 2,4,6-pyrimidinetrione and their derivatives including the solvent and substituent effects has been published (98MI309).

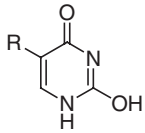
a. Uracil and Its Alkyl-, Aryl-, and Halo-Substituted Derivatives. Prototropic tautomerism of nucleic bases uracil (2,4-dioxopyrimidine) and thymine (5-methyl-2,4-dioxopyrimidine) is extensively studied using both theoretical and experimental approaches as it affects the formation of hydrogen bonds in the nucleic acid pairs and, thus, controls the DNA mutations. These compounds may potentially exist in six tautomeric forms **158a–f**.

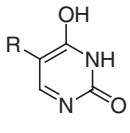

158a


158b


158c


158d


158e


158f

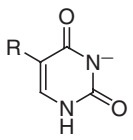
High-resolution IR spectroscopic studies of uracil and thymine in low-temperature argon and nitrogen matrices and IR spectra in the gas phase indicated that these compounds exist exclusively in the dioxo form **158a** (81IJQC(20)573, 84JST(116)49, 90JST(219)311, 97CPL(269)39). The microwave spectra of thymine and of two of its monodeuterated species confirmed that the dioxo tautomer is the predominant form in the gas phase; no other tautomers were detected (89JCS(CC)37). In contrast, two tautomers (dioxo and hydroxy(oxo)) were detected for uracil and thymine in the gas phase by fluorescence excitation and dispersed fluorescence spectroscopy of jet-cooled compounds (86CPL(126)583, 88JPC1760). Successful detection of a very small amount of an oxo–hydroxy tautomer is due to its high-fluorescence yield. The dioxo and oxo–hydroxy tautomer were found to exist in equilibrium in the vapor at 200 °C. The structure of the hydroxy(oxo) tautomer was not determined experimentally, but it is, most likely, the tautomer **158b** according to numerous quantum-chemical calculations (see below).

Calometric measurements of the heat isomerization in liquid were used to determine the relative gas-phase enthalpies of fixed derivatives of uracil and provided estimates of the enthalpy difference between the dioxo form and other tautomers of uracil in vapor (19 ± 6 kcal/mol for **158c** and 22 ± 10 kcal/mol for **158d**) (82JA7073). N^1-Substituted uracils were shown to exist in the dioxo tautomeric form in the vapor (78ZN(C)876).

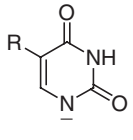
In solution, the tautomeric equilibrium of uracils is not markedly influenced by solvent polarity in contrast to hydroxypyridines and monohydroxypyrimidines. The dioxo tautomer **158a** is the predominant one in all the solvents and the contribution from the other tautomers is very small. Tautomeric equilibrium constants, determined from the protonation constants of uracil in H_2O–H_2SO_4–SO_3 solution, are equal to 3.8×10^3 (for **158a** $\rightleftharpoons$ **158c**) and 1.1×10^5 (**158a** $\rightleftharpoons$ **158b**) (75TL2171). Predominance of the dioxo tautomer for uracil, thymine, and other substituted 2,4-dioxopyrimidines in solution with various polarities (78CJC725, 80BSF410, 84SA(A)675) and in the solid state (74ZOR109, 80BSF410) was established. Fluorescence spectra of 5-chlorouracil (95CPL(237)349) and thymine (99JPC(B)11205), however, indicated the presence of the oxo–hydroxy tautomer **158b** in addition to the major dioxo tautomer in aqueous solution at pH 4–8.

Temperature-jump experiments, performed with aqueous solution of uridine (N^1-ribose-substituted uracil) indicated that the equilibrium between dioxo tautomer and 2-oxo-4-hydroxy form is greatly shifted to the former (77JA4438).

Deprotonation of uracil and thymine occurs predominantly at the N^3 atom resulting in monoanion **159a** (79JOC1627, 80BSF410). The proportion between the tautomeric monoanions (60–70% of **159a** and 30–40% of **159b**) varies slightly with with the base:pyrimidine ratio, i.e., the percentage of **159b** decreases with the total monoanion concentration. In contrast, deprotonation of 6-methoxyuracil gives predominantly monoanion of type **159b** (74ZOR109). Similarly, deprotonated pseudouridine (Ψ-uridine) **159** (R = furanosyl) exists mainly as N^1 anion **159b** (64%) (98JOC1033).



159a



159b

The effects of complexation with metals on tautomerism of neutral and anionic uracils have been reviewed (87CCR97). Interestingly, complexation of 1-methyluracil (89JA7213) or 1-methylthymine (81ICA(55)5) with neutral platinum complexes stabilizes the rare 2-oxo-4-hydroxy tautomeric forms.

Tautomerism of thymine on gold and silver nanoparticle surfaces has been comparatively analyzed by surface-enhanced Raman scattering (05JST(738)9). The results indicate that N^3-deprotonated tautomer should be about 10 times more abundant than N^1-deprotonated tautomer on silver surfaces, whereas no N^1-deprotonated tautomer was observed on gold surfaces. DFT calculations are in good agreement with the experimental findings predicting N^3-deprotonated tautomer to be more stable by 2 kcal/mol on gold surfaces, but only 0.3 kcal/mol on silver surfaces. In the solid state, thymine exists exclusively in the diketo tautomeric form (99ACSA57).

The relative stabilities of uracil tautomers and related derivatives have been investigated by a wide variety of computational methods. Practically all the methods (semiempirical, *ab initio*, and DFT calculations) correctly predict the dioxo tautomer **158a** to be the most stable in the gas phase, in aqueous solution and in some other solvents (dioxane, acetonitrile, CCl_4). The exceptions are semiempirical MINDO/2 method (78IJQC(14)851) and PCILO and MNDO methods (82IJQC(22)89, 83JST(92)255), which erroneously predicted the highest stability of the dihydroxy tautomer. The order of relative stabilities, however, depends on the method and the basis set used. Thus, the following stability order was established for uracil in the gas phase by DFT and *ab initio* calculations (83CPL(98)545, 84JA3737, 88JA2353, 90JCS(P2)329, 93IJQC(47)49, 95IJQC(56)615, 95JST(331)147, 97IJQC(62)489, 99ACSA57, 99CP(242)217, 01MI103, 04CP(303)27): **158a** > **158b** > **158d** > **158c** > **158e** > **158f** (although the reports are somewhat contradictory on the relative stability of tautomers **158c** and **158d**: sometimes, **158c** is predicted to be slightly more stable, e.g., in (84JA3737, 95JST(331)147, 97IJQC(62)489, 01MI103)). The second tautomer **158b** is less stable than **158a** by

11–12 kcal/mol, but more stable than **153c** by 2.1–2.3 kcal/mol. The order of stability, obtained by the semiempirical PM3 method, is similar to the one predicted by the *ab initio* methods, except that the form **158e** is found to be the least stable (01KG1082, 03KG1517). A different order of relative stabilities, however, is provided by the semiempirical MINDO/3 method: **158a** > **158c** > **158f** > **158b** > **158d** > **158e** (79IJQC(16)605). These results are, however, less reliable.

Calculations of four or fewer most important tautomers of uracil in the gas phase and in aqueous solution have also been carried out using AM1 method (87JST(151)259, 91JA1561, 00JST(532)157), β-SCF-CI calculations (73CPB1474), SCF MO method within the π-electron approximation (78KG94), the *ab initio* LCAO-MO method at the MP4 and CISD levels (92JPC1649), both local and gradient-corrected density functional methods (94JPC5653), the coupled-cluster (CCSD, CCSD(T)) method (04CP(303)27) and the second-order many-body perturbation theory (MBPT(2)) with the Gaussian DZP basis sets (89JPC7078). Substitution of uracil at the 5-position does not change the order of stability of tautomers, i.e., essentially the same order was calculated for thymine and 5-fluorouracil (84JA3737, 99JPC(B)11205, 00JST(532)157, 01MI103, 05JPC(A)1981), and only slightly affects the ΔE values (89JPC7078). The order of stability of thymine, calculated at the HF/6-31G* level, differs from that of uracil only by interchanged positions of the third and fifth (by stability) tautomers, the phenomenon being attributed to the steric interactions between the hydroxy and methyl groups (99JPC(B)11205). The effects of substituents at the position 6 are similarly minor (01KG1082, 03KG1517). Calculations of all geometric isomers and tautomeric forms of uracil, bromouracil, and thymine have also been carried out using 3-21G* and 6-31G** basis sets (90JCS(P2)329, 92JST(276)209, 93JA11939, 93JST(300)619, 99JPC(A)6612, 04B6361).

Theoretical estimations at the B3LYP level of the gas-phase acidities of all possible deprotonation sites of the most stable tautomers of uracil and thymine at 298 K showed that N^1 atom is the most acidic (03JPC(A)4893).

The absorption of uracil on the Si(0 0 1) surface has been investigated by density-functional theory calculations using a plane-wave basis in conjunction with ultrasoft pseudopotentials. The absorption of dihydroxy tautomer is energetically not favored. However, the absorption of hydroxy(oxo) tautomers is favorable if two Si dimers are involved in the reaction; thus, the presence of these tautomers is more likely on the Si(0 0 1) surface than in the gas phase (03JPC(B)5031). A systematic theoretical investigation of the effects of intermolecular association on the structure of uracil and its methyl derivatives combined with the solid-state studies indicated that the preferred associations are dimer for 1-methyluracil, trimer for thymine, and hexamer for uracil (99ACSA57).

Tautomeric equilibria of uracil, thymine, and 5-fluorouracil in solution are sensitive to the solvent polarity and, in contrast to the gas-phase equilibria, to the nature of the 5-substituent. In all the cases, however, the dioxo tautomer **158a** is still the most stable. In low polarity solvents, such as dioxane, the order of stability is similar to that in the gas phase and unaffected by the 5-substituent (01MI103). In more polar acetonitrile and water, the tautomer **158c** (for uracil and thymine) or **158e** (for fluorouracil) is better stabilized by solvation than other tautomers, as confirmed by the reaction field

continuum model for solvent effects (81IJQC(19)171, 91CJC1589), Monte-Carlo method (95MI213) and INDO parametrized MO calculations (87JST(158)69). The dihydroxy tautomer **158d** has the smallest base–water interaction energy. Consequently, the order of stability (DFT approach) changes in acetonitrile and water to **158a** > **158c** > **158b** > **158d** ≈ **158f** ≈ **158e** for uracil (95IJQC(56)615, 01MI103) and **158a** > **158b** > **158e** > **158c** > **158d** > **158f** for 5-fluorouracil (01MI103, 05JPC(A)1981). In CCl_4, the four most important tautomers of uracil have the same order of stability as in acetonitrile and water, although the energy differences between the tautomers are smaller (04CP(303)27). The order of stability of thymine is similar to that of uracil (01MI103). In contradiction, the preferential solvation of tautomers **158f** and **158c** was suggested by *ab initio* calculations with 3-21G basis set predicting the rare tautomer **158f** to be the third most stable one for uracil and thymine in aqueous solution. The order of stability for 5-fluorouracil, however, coincides with that predicted by DFT calculations (see above) (84JA3737). The PM3 calculations confirm the order of stability for uracil predicted by the DFT method (01KG1082).

The COSMO solvation model has also been employed for calculations of the tautomer stabilities in aqueous solution (00JST(532)157). The relative stabilizing effects of water on uracil tautomers, calculated using DFT approach, demonstrated that the preferred tautomer stabilization depends on the geometry of the uracil–water complexes (98JCS(F)1277, 04JPC(B)12999). Interestingly, even though the dioxo tautomer **158a** of 5-bromouracil predominates in aqueous solution, water favors somewhat its tautomerization to the hydroxy(oxo) form (04B6361). According to PM3 calculations, the introduction of a methyl substituent at the 6-position of the heterocyclic ring further decreases the tautomer **158d** – water interaction energy making this tautomeric form the least stable. This effect is also observed in 6-phenyl-substituted uracil, though to a lesser degree (01KG1082).

The semiempirical AM1 and PM3 methods (00JST(532)157) and *ab initio* calculations (98JPC(B)5228) of 1-methyluracil, 1-methylthymine, and 1-methyl-5-bromouracil predicted the predominance of the corresponding dioxo forms both in the gas phase and in solution. The order of the tautomer stability is not affected by the N^1-substitution or by solvation in water or in the duplex DNA. The presence of methyl or bromine substituents in the 5-position does not affect greatly the relative hydration of the different tautomers, the largest changes being around 1 kcal/mol. Preferential hydration of tautomers of 1-methyluracil has also been studied using Monte-Carlo method (95MI213).

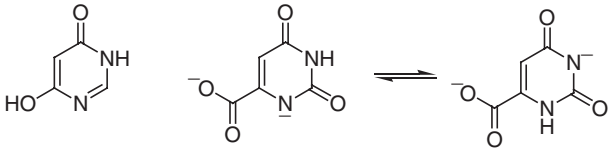
The tautomerism of *N*-methyl and *N*,*N*′-dimethyl derivatives of uracil, 5-fluorouracil, and thymine have been examines both in the gas phase and in water using *ab initio* and DFT calculations at the 6-31G** and 6-31 + G** levels (05JST(713)201). The solvent effects were taken into account using SCRF method. Similar to N-unsubstituted analogs, these compounds exist predominantly in the dioxo form. For N^1-substituted derivatives of uracil and thymine, 2-oxo-4-hydroxy tautomer of type **158c** is the second stable tautomer both in the gas phase and in aqueous solution. In contrast, *para*-quinoid form **158e** is the second stable tautomer of 1-methyl-5-fluorouracil in aqueous solution, whereas in the gas phase these forms are practically isoenergetic. This fluorine effect was not observed for N^3-methyl uracil derivatives, for which the 2-hydroxy-4-oxo form of type **158b** is the second stable tautomer in all

cases. The tautomeric properties of hydroxyl radical thymine derivatives (98JCS(F)1813, 99JST(467)51) and protonated forms of thymine (81TCA283) have been examined by *ab initio* calculations.

b. Other Pyrimidines with Two or More Potentially Tautomeric Hydroxy(oxo) Groups. Six tautomers are possible for 4,6-dihydroxypyrimidine. The hydroxy(oxo) tautomeric structure was suggested for this compound on the basis of its vibrational spectra (84SA(A)675). In DMSO solution, 4,6-dihydroxypyrimidine was reported to exist as a tautomeric mixture of the dihydroxy tautomer (99%) and 6-hydroxy-4-oxo tautomer **160** (1%). The percentage of the latter increases up to 20% in DMSO/acetone (1:1) and DMSO/water (1:1). Trace amounts of other tautomers were also detected. The introduction of 2-methylthio group shifts the equilibrium toward the 4-hydroxy-6-oxo tautomer (89%) (87JHC191).

The tautomeric properties of 5,6-dihydroxyuracil, uracil glycol (99JST(459)1) and thymine glycol (98JCS(F)1813) were characterized using *ab initio* methods. The 2,4-diketo tautomeric form was found to be the most stable for all these compounds in both polar and non-polar solvents. 2-Oxo-4-hydroxy tautomers were found to be more stable than 2-hydroxy-4-oxo tautomers for uracil derivatives, whereas the opposite trend was reported for thymine glycol.

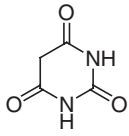
Orotic acid (6-carboxyuracil) exists in DMSO as a dianion (87JHC191). In basic aqueous solution, this dianion exists as an equilibrating mixture of two tautomeric structures, N^3-H form **161a** and N^1-H form **161b**, with **161b** being about twice more abundant. The position of the tautomeric equilibrium is markedly affected by the presence of alkaline earth metal cations owing to the specific complexation of the N^3-H form **161a** (80JA3049). Tautomerism of orotic acid was studied by DFT calculations at the B3LYP/6-311G** level with solvent effects probed using the SCRF model (04JST(685)35). Of the dioxo form, the zwitterion and the four hydroxy(oxo) forms possible, the dioxo form was predicted to be the most stable with the zwitterion form being less stable by 10.8 kcal/mol.

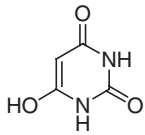


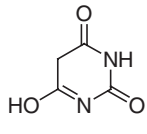
160 **161a** **161b**

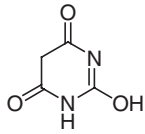
The tautomerism of barbituric acid and its derivatives has been briefly discussed in a review on this class of compounds (85AHC(38)229). Eleven tautomers are possible for unsubstituted barbituric acid **162**. The position of the tautomeric equilibrium **162a** ⇌ **162b** for unsubstituted barbituric acid and its N- and 5-substituted derivatives was investigated in various solvents using ^{13}C NMR and UV spectroscopy (74ZOR113, 75JCS(P2)819, 87JHC191, 00ZOB615). The proportion of the trioxo tautomer **162a** increases on *N*,*N*′-dialkylation; however, introduction of methyl, benzoyl, or halo group into the 5-position has the opposite effect. The tautomer **162a**

predominates in aprotic solvents with various polarities; the proportion of tautomer **162b** increases in amphiprotic solvents (e.g., alcohols) and falls again in solvents with high proton-donating activity. 5-Phenylbarbituric acid exists in hydroxy form in the solid state (86JHC337). Both 5-phenyl- (75JCS(P2)819, 86JHC337) and 5-(4-nitrobenzyl)barbituric acids (86H(24)3129) exist as mixtures of hydroxy and oxo forms in DMSO solution. The substituent effects (including remote substituents) and solvent effects on the tautomerism of type **162a** ⇌ **162b** ⇌ **162g** for barbituric acid **163** (X = O; R^1 = H, Me, cyclohexyl, $PhCH_2$, aryl; R^2 = H, Me; R^3 = H, OMe) were studied in detail (02KG798). A significant shift of the equilibrium toward the hydroxy(oxo) tautomers on introduction of benzyl or aryl group into the N^1-position was demonstrated.


162a


162b


162c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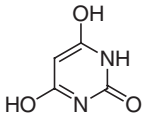
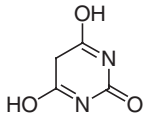

162e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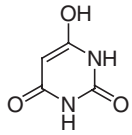
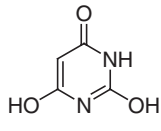

162g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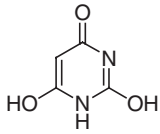
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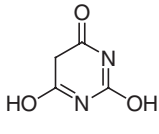
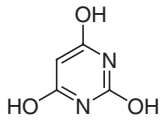

162j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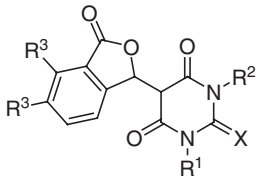
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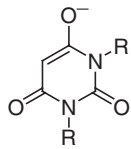
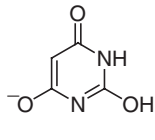

164a


164b

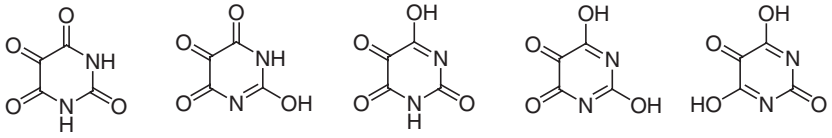
Anions of barbituric acids and related systems exist in one of the two possible forms **164a** or **164b**, depending on whether ring nitrogens are substituted (**164a**) or not (**164b**) (87JHC191).

Tautomerism of unsubstituted barbituric acid has been studied by the AM1 semi-empirical method (89JHC639, 99ZOB986). The trioxo structure **162a** was found to be the most stable followed by **162b**. The tautomeric equilibrium is sensitive to phase change and to substitution at the C-5 position. On passing from vapor to water, the population of the more polar dioxo(hydroxy) form increases, although the order of stability remains unchanged, and only for 5-bromo and 5-iodo derivatives can the coexistence of both forms in solution be suggested. The AM1 method has also been used to study the mechanisms of the proton transfer in barbituric acid (99IJQC(74)327, 99ZOB986). Intermolecular proton transfer was suggested for the neutral molecule. The activation barrier was shown to be dramatically decreased by intervention of a single molecule of water and by bulk dielectric effects, whereas the effects of 5-substituents were minor.

Ab initio and density functional methods were used to estimate the relative stabilities of tautomers of barbituric acid in the gas phase and in solution (02MI263). Hückel Molecular Orbital theory and Pariser–Parr–Pople method predicted the highest stability of the dioxo tautomer **162b** and the possibility of coexistence of **162b** and the dihydroxy tautomer **162e** in the gas phase (99MI223). Tautomeric contributions to the thermodynamic functions of barbituric acid were calculated using statistical thermodynamics (89MI336). The tautomerism of 5-(arylazo)-substituted barbituric acids has been studied using the CNDO method (99MI223).

The tautomeric properties of isodialuric acid (6-hydroxy-2,4,5-trioxopyrimidine) were characterized by the *ab initio* calculations based on 6-311G** full geometry optimization (99JST(459)1). Of 10 possible tautomers, the trioxo form was found to be the most stable. The higher stability of 2-oxo-4-hydroxy tautomers compared to 2-hydroxy-4-oxo tautomers has also been predicted.

The ^{14}N nuclear quadrupole resonance spectra of alloxan **165** monohydrate indicated the predominance of the tetraoxo tautomer in the solid state (80BCJ1443). Lactim–lactam tautomerism of alloxan in liquid and gaseous state has been calculated by INDO MO method (77JMC275). The results indicated that alloxan does display tautomerism in aqueous solution, but not to any extent in the gas phase. The tetraoxo form **165a** is the principal tautomer both in the gas phase and in water; however, in solution a major contribution from the 2-hydroxy form **165b** is also found. In the gas phase, the tetraoxo form is favored by 19 kcal/mol over the next stable tautomer **165c**. The following orders of stability were predicted: **165a** > **165c** > **165b** > **165e** > **165d** (in the gas phase) and **165a** > **165b** > **165c** > **165d** > **165e** (in aqueous solution).



165a **165b** **165c** **165d** **165e**

The significant difference in energy between **165a** and other tautomers excluding the possibility of tautomerism in the gas phase was confirmed by the *ab initio* STO-3G, 3-21G, and 6-31G calculations. The population analysis of the alloxan anion gives evidence that the preferred protonation site is offered by the central oxygen

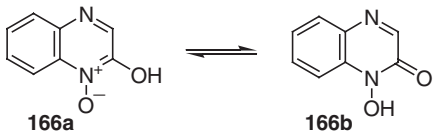
atom of the triketo fragment, and rules out the opposite oxygen atom as a possible protonation site (87JHC525).

Tautomerism of 2,4-dihydroxyquinazoline was investigated using semiempirical MNDO, AM1, and PM3 methods (93KG1246). MNDO method erroneously indicated the predominance of the dihydroxy tautomer in the gas phase, whereas AM1 and PM3 methods predicted the predominance of the dioxo tautomer in agreement with the experimental findings.

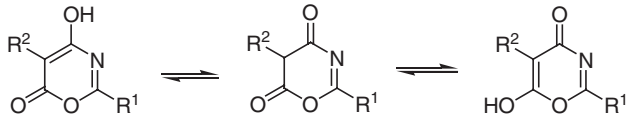
5. *Other Heterocycles*

According to the UV spectra, the dihydroxy form of 2,6-dihydroxypyrazine predominates in ethanol solution (97JCS(P1)3167). A novel 2,5-diketopiperazine metabolite, diatretol, detected in the culture broth of the fungus *Clitocybe diatreta*, exist in the dioxo form both in solution and in the solid state (96LA1875). Semiempirical (AM1 and PM3), *ab initio* and DFT calculations of tautomerism of 2,3-dihydroxypyrazine predicted that α-dioxo and intramolecularly hydrogen-bonded hydroxy(oxo) tautomers are the most stable species in the gas phase (98JCR(S)222, 99JST(459)229). The stability of these tautomers is significantly increased in solution due to their higher dipole moments. The dihydroxy form is less stable than the dioxo form by 5–7 kcal/mol in the gas phase and by 10–13 kcal/mol in solution. The energy barrier for conversion of the hydroxy(oxo) form into the dioxo form is 54 kcal/mol.

The electronic absorption and fluorescence spectra of 2,3-dihydroxyquinoxaline indicate that this compound exists in solution in the dioxo form independent of the solvent polarity (87MI277).



166a **166b**



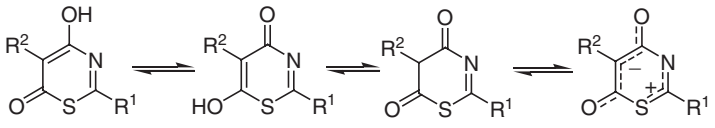
167a **167b** **167c**

2-Hydroxyquinoxaline *N*-oxide **166** exists primarily in the oxo form **166b** both in solution and in the solid state. The similar preference was observed

for 2-hydroxypyrazine *N*,*N*′-dioxide and 2-hydroxyquinoxaline *N*,*N*′-dioxide (76KG278).

The tautomerism of 2-aryl-1,3-oxazine-4,6-diones **167** (R^1 = aryl; R^2 = H, Me) in the gas phase has been studied by mass-spectrometric fragmentation (90KG552). It was shown that in the gas phase these compounds exist as mixtures of 4-hydroxy-6-oxo (**167a**), dipolar-ionic, and dioxo (**167b**) forms; the contributions from the two latter forms increase with increase in electron-acceptor properties of the substituents in the *p*-position of the 2-aryl group. The tautomer **167c** was not observed. In THF or DMSO-d_6 solution, these compounds exist predominantly as tautomers **167a** (87KG386). In contrast to the gas-phase findings, the electronic properties of the 2-aryl substituent do not affect the tautomeric equilibrium significantly. The AM1 semiempirical calculations predicted almost equal stability of tautomers **167a** and **167b** in the gas phase ($\Delta E = 0.05$ kcal/mol; **167b** is slightly more stable) with **167c** being less stable by about 9 kcal/mol (97T225). CNO, CNDO/2, and MINDO/3 calculations, however, strongly favor the tautomer **167a**, with **167c** and **167b** being less stable by 11–36 kcal/mol and 212–248 kcal/mol, respectively, in contradiction to the experimental findings (87KG386).

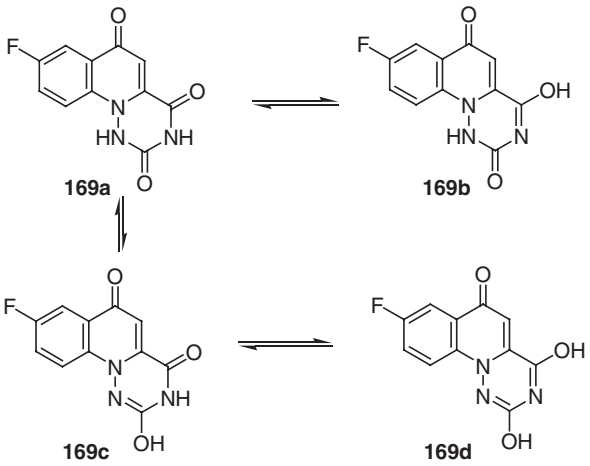
The position of the oxo–hydroxy equilibrium of 2-substituted 1,3-thiazine-4,6-diones **168** in DMSO-d_6 solution is greatly affected by the nature of the 2-substituent (76KG1042, 79KG481, 86KG3). Thus, **168** (R^1 = Ph, PhNMe; R^2 = H) exist exclusively in the oxo(hydroxy) form, whereas **168** (R^1 = $PhCH_2S$; R^2 = H) – only in dioxo form **168c**. In other cases, the tautomerism was observed with hydroxy (R^1 = OEt) or dioxo (R^1 = Me) forms predominating. The addition of water greatly accelerates the tautomerization and increases the percentage of the dioxo form. The calculations of atomization energies of the two hydroxy forms by the Pariser–Parr–Pople method predicted the tautomer **168a** to be more stable for **168** (R^1 = H, Ph, OH, NH_2; R^2 = H) in the gas phase. In the solid state, **168** (R^1 = Me, alkoxy; R^2 = H) exists in a hydroxy form, whereas the zwitterionic structure **168d** was assigned to **168** (R^1 = aryl; R^2 = H) (86KG3).



168a **168b** **168c** **168d**

Disubstituted 1,3-thiazine-4,6-diones **168** (R^1 = Ph; R^2 = Et, Br, NO_2) exist in DMSO and dioxane solution, in crystal and in the gas phase preferentially as enol tautomers **168a**. Other tautomeric forms were detected only in the gas phase (95ZOB926).

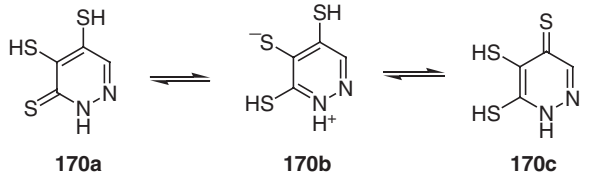
The tautomerism of fused triazinedione **169** was calculated using AM1 method and *ab initio* 3-21G* approach (02JHC1161). Both methods showed without ambiguity that tautomers **169a** and **169c** are the most stable forms and that the nitrogen atom N^3 is more electronegative than N^1 in both forms. The calculations are confirmed by the chemical reactivity of this compound.



B. Compounds with Two or More Mercapto(Thioxo) Groups and Selenium Analogs

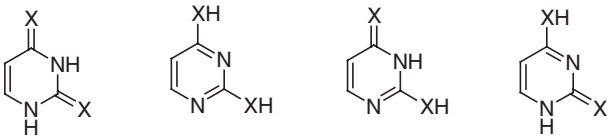
Ab initio calculations at the HF/6-31G** level, performed for 2,6-pyridinedithiol in the gas phase and in solution, predict the predominance of the dithiol tautomer in the gas phase and in solvents of low polarity, whereas the thione tautomer is favored in polar solvents (98MI1813). In contradiction to the theoretical predictions and polarity-based expectations, the predominance of the 6-mercaptopyridine-2-thione in toluene-d_8 solution and the equilibrium shift toward the dithiol tautomer in more polar $CDCl_3$ is reported on the basis of ^1H NMR data. This shift to the dithiol tautomer was also observed on complexation with rhodium diolefin complexes (96IC1782).

Ionization constants and UV spectra of 3,6-dimercaptopyridazine and fixed derivatives indicated that this compound exists in the aqueous solution as 6-mercaptopyridazine-3-thione (74JCS(P2)1199). Of the three possible tautomeric structures of 3,4,5-trimercaptopyridazine **170**, the 4-thioxo structure **170c** was suggested as the predominant tautomer in solution (77JCS(P1)1038).

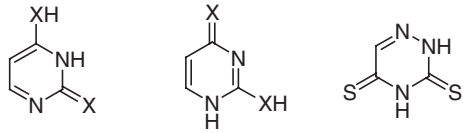


IR-spectroscopic study of 2,4-dithiouracil **171** (X = S) isolated in low-temperature inert matrices demonstrated that this compound exists exclusively in the dithione form **171a** under these conditions (90JA2147). The dithiol form of dithiouracil, 2,4-pyrimidinedithiol, was generated by UV ($\lambda > 335$ nm) irradiation of 2,4-dithiouracil isolated in low-temperature argon or nitrogen matrices (98SA(A)685).

Theoretical studies of 2,4-dithiouracil at the B3LYP/6-31 + G(d,p) computational level were recently reviewed (01MI79). Both semiempirical (AM1, PM3, MNDO) (87JST(149)185, 01JPOC171) and *ab initio* (91JPC3128, 00JPC(A)5122) calculations predict the dithione tautomer to be the most stable in agreement with the experimental data. The order of tautomer stability, predicted by *ab initio* calculations (91JPC3128, 00JPC(A)5122) is as follows: **171a** > **171b** > **171c** > **171d** > **171e** > **171f** with the dithiol tautomer being less stable by 6.7 kcal/mol. The order of stability, predicted by the MNDO method (87JST(149)185), differs only by interchanged positions of tautomers **171c** and **171d**. Similar results were obtained in AM1 and PM3 theoretical studies of 2,4-dithiothymine (01JPOC171). Semiempirical calculations of the tautomeric interconversion **171b** ⇌ **171d** predicted the dithiol tautomer to be more stable in the gas phase. In aqueous solution, however, the predominance of **171b** was predicted only by MNDO method, whereas AM1 and PM3 methods strongly favor (mercapto)thione **171d** (03JST(625)31). Tautomerism of protonated forms of 2,4-dithiouracil has also been studied (00JPC(A)5122).



171a **171b** **171c** **171d**



171e **171f** **172**

The gas-phase tautomeric equilibrium of the selenium analog, 2,4-diselenouracil **171** (X = Se), was studied at the MP2 level of theory with a basis set of DZP quality. The relative energies, estimated at the MP4(SDQ) level, provided the same order of stability, predicted for 2,4-dithiouracil by the *ab initio* methods. The di(hydroselenyl) tautomer **171b** (X = Se) was found to be less stable than diselenone tautomer **171a** by 8.1 kcal/mol (96JST(388)237).

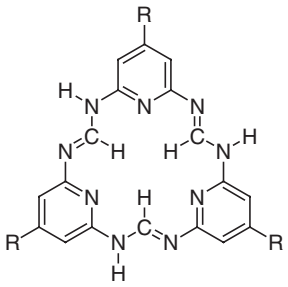
IR spectra of triazinedithione **172**, isolated in low-temperature Ar and N_2 matrices indicated that this compound exists exclusively in the tautomeric form shown (96SA(A)645).

C. Compounds with Two or More Amino(Imino) Groups

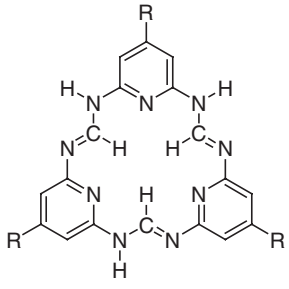
The UV absorption spectrum of 2,6-diaminopyridine in ethanol/isooctane mixed solvent with variable temperature or ethanol concentration is consistent with the formation of the hydrogen-bonded complex of (*E*)-6-amino-2(1*H*)-pyridinimine with two molecules of ethanol. The formation of the imino form may be restricted to the 2,6-diaminopyridine and its methyl derivatives, in which each amino group at the 2- and 6-positions has at least one hydrogen atom. *Ab initio* STO-3G calculations

indicated that 2,6-diamino tautomer is more stable than (*E*)-6-amino-2-imino form by 20.6 kcal/mol in the ground state (90BCJ216). Neutron diffraction method indicated that in the solid state at 20 K 2,6-diaminopyridine exists in the diamino form (87AX(C)2191). 2,6-Bis(dodecylamino)pyridine exists in the DMSO-d_6 solution exclusively in the diamino tautomeric form (93T7627).

Two novel cyclo-tris(4-R-2,6-pyridylformamidine)s **173** (R = H, Me) have been studied by solution and solid-state NMR. In DMSO solution, both symmetric (**173a**) and asymmetric (**173b**) tautomers were observed at 193 K. Two other possible tautomers were not detected. In the solid state, these compounds exist exclusively in the tautomeric form **173b** (02JA11955).

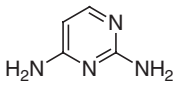


173a

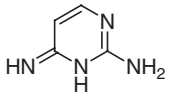


173b

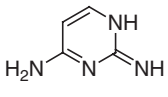
Tautomerism of 2,4-diaminopyrimidine **174** and its protonated forms has been studied by *ab initio* calculations at the 3-21G, 6-31G*, and 6-31G** levels (89JCC35, 90CPL(173)371). The following order of tautomer stability is predicted: **174a** > **174b** ≈ **174c** > **174d** ≈ **174e** ≈ **174f**. The imino(amino) tautomers **174b** and **174c** were found to be less stable than **174a** by 17–19 kcal/mol. The N^1-protonated form was calculated to be more stable than N^3-protonated form.



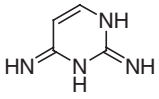
174a



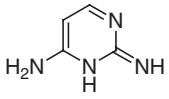
174b



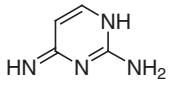
174c



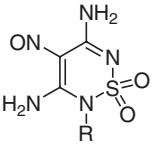
174d



174e



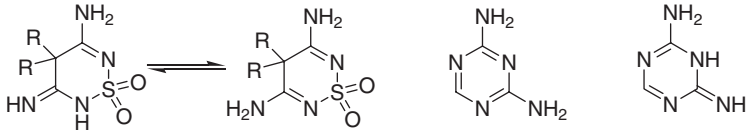
174f



175

Substituted 4,6-diamino-5-nitroso-3*H*-2,1,3-thiadiazine 1,1-dioxides **175** (R = *n*-Bu, Ph, $PhCH_2$, $PhCH_2CH_2$) exist in solution exclusively in the diamino form as two rotational conformers of the nitroso group stabilized by hydrogen bonds with the amino groups (96JCS(P2)293). N-Unsubstituted thiadiazine 1,1-dioxides **176** (R = H, allyl) exist in DMSO solution in the tautomeric equilibrium with diamino form **176b** predominating (86MRC444). Tautomerism in 2,4-diamino-1,3,5-triazines **177** was studied using SCF/STO-3G and SCF/3-21G methods. The diamino tautomer **177a**

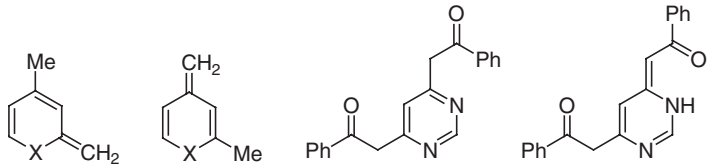
was found to be favored with imino(amino) tautomer **177b** being less stable by 21–23 kcal/mol (89JCC186). Regioisomeric 2-chloro-4,6-bis[(pyrazolylphenyl)amino]-1,3,5-triazines exist as all-amino tautomers both in solution and in the solid state (03OBC4451).



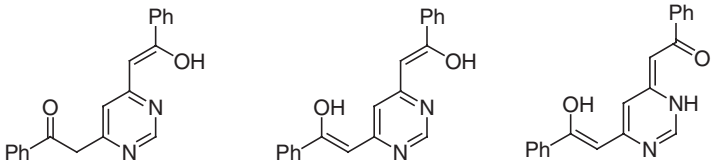
176a **176b** **177a** **177b**

D. Compounds with Two or More Tautomeric Methylene Groups

Semiempirical (MINDO, AM1 and PM3) as well as *ab initio* (MP2/6-31G*, 6-31G*) calculations indicate that γ-methylenepyrans **178b** (X = O) are more stable than their α-methylenepyran isomers **178a** (X = O) ($\Delta E = 0.3$–2.6 kcal/mol). This provides an explanation for the higher rate of hydrogen isotope exchange of γ- over α-methyl substituted pyrylium salts in protic media. For **178** (X = NMe), the calculations predict the opposite α- vs. γ-stability order ($\Delta E = 0.5$–2.1 kcal/mol) and support a similar explanation for the lower rate of hydrogen isotopic exchange at the γ- than at the α-methyl groups (92T6799).



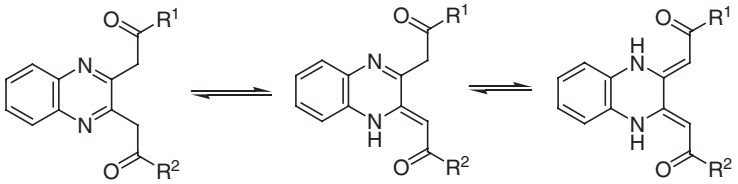
178a **178b** **179a** **179b**



179c **179d** **179e**

^{1}H, ^{14}N, and ^{17}O spectroscopic studies of 4,6-bis(benzoylmethyl)pyrimidine **179** indicated the presence of all five tautomers in $CDCl_3$ solution in ratio **179a**:**179b**:**179c**:**179d**:**179e** = 10:4:44:35:7 (86ZOR2185). According to NMR, UV, and X-ray studies 2,3-bis(benzoylmethyl)quinoxaline **180** ($R^1 = R^2 = Ph$), its hexahydro analog and **180** ($R^1 = R^2 =$ neopentyl) exist both in solution and in the solid state exclusively in the keto–enamine form **180c** (01NJC391). In contrast, all three tautomeric forms were detected for keto esters **180** ($R^1 =$ OMe, OEt, OCH_2Ph; $R^2 =$ aryl) in solution (93ZOR1890). The tautomer **180b** generally predominates

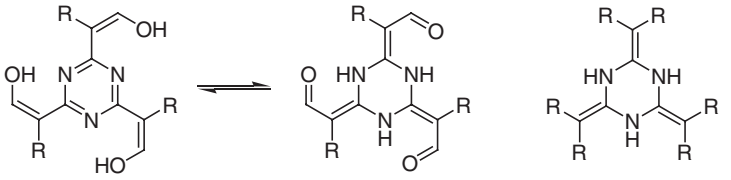
with **180a** being the second most abundant tautomer. Electron-donating substituents in the aromatic ring of the R^2 substituent slightly increase the molar fraction of the tautomer **180b**.



180a **180b** **180c**

2,4,6-Trisubstituted 1,3,5-triazines **181** (R = Me, Et, *n*-Pr, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$) exist in the equilibrium of the enol **181a** and unusual enamine **181b** tautomeric forms with the latter predominating (92JHC1125). Triazine **181** (R = Me) was shown to favor the enamine form **181b** in the solid state.

UV- and ^{1}H NMR-spectroscopic studies of tris-malonic ester derivative of 1,3,5-triazine in various solvents indicated that the enamine structure **182** (R = COOMe) predominates in $CHCl_3$, dioxane, MeOH, and H_2O. A small amount of the enolate is present in acetonitrile and a larger amount in DMSO, DMF, and cyclohexylamine. It is concluded that in a basic solvent this compound exists as a tautomeric mixture of the enamine form and resonance-stabilized enolate ion (75JHC295).



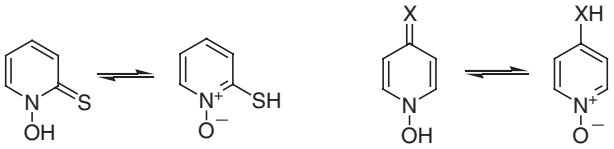
181a **181b** **182**

E. Compounds with Hydroxy(Oxo) and Mercapto(Thione) Groups

1. *Pyridines and Quinolines*

1-Hydroxy-2-pyridinethione **183** exists as OH acid **183a** in the solid state. The same thione structure is retained in $CDCl_3$, DMSO-d_6, and CD_3OD solution for both the neutral compound and its salts with alkali and alkaline earth metals and ammonium salts (86JCS(P1)39, 99EJOC97). In the triplet state in solution, however, the tautomerization **183a** ⇌ **183b**, responsible for the dual phosphorescence emission, takes place. In contrast to 1-hydroxy-2-pyridone, which gives dual phosphorescence emission only in non-polar matrix, this emission of 1-hydroxypyridine-2-thione was observed in polar, non-polar, and hydrogen-bonding solvents. The easier tautomerization is explained by higher polarity and polarizability of the thiocarbonyl group (84JCS(P2)2031).

The strong solvent-dependence of the triplet state tautomeric equilibrium exhibited by *N*-hydroxypyridine-4(1*H*)-thione **184** (X = S) and the distinct absorption properties of the thione and thiol tautomers offer the opportunity to investigate the photochemistry of each form independently. In most organic solvents studied, the thiol and thione tautomers coexist with thiol predominating in ethyl acetate, thione – in methanol, and equimolar mixture of tautomers in acetonitrile. In aprotic non-polar solvents ($CHCl_3$, CH_2Cl_2, C_6H_6), however, only thiol form was observed, whereas in isopropanol only thione tautomer was detected (99JA9977). Tautomerism of 2-mercapto- and 4-mercaptopyridine *N*-oxides and 4-mercaptoquinoline *N*-oxides in various solvents has also been investigated by electron spectroscopy (93KG1662).



183a **183b** **184a** **184b**

185a **185b**

Determination of the acidity of 3-hydroxy-2-mercaptopyridine **185** in different solvents indicated that this compound exists mainly in the thione form **185b** in ethanol, but in hydroxy(mercapto) form **185a** in DMSO and dioxane (95M377). The tautomeric equilibrium of **185** *in vacuo* and in ethanol has also been studied theoretically using the density functional theory at the B3LYP/6-31G(d) level. The thione form **185b** was found to be more stable in the gas phase by 8 kcal/mol (for isolated molecules) and in ethanol by about 10 kcal/mol. The energy barrier for tautomerization is significantly lower in ethanol due to solvent assistance (04JCC1833).

Partially reduced 2-quinolinethiones **186** exist in the solid state in the both tautomeric forms shown. Complete transition from **186a** to **186b** occurs in acetone, DMSO and trifluoroacetic acid (90ZOR1578).

186a **186b**

2. *Thiopyrans*

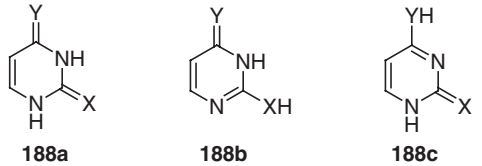
Both tautomers of benzothiopyranethiones **187** (X = H, Cl) are stable in the solid state, although **187b** appears to be less stable thermally than **187a**, and in aprotic

solvents. These forms are difficult to interconvert in contrast to oxygen analogs. In protic solvents, however, **187a** slowly deposits **187b** and the process is accelerated on addition of conc. HCl. The reverse conversion of **187b** into **187a** can be achieved by dissolution in methanolic NaOH followed by acidification (oxygen protonation is a kinetically controlled process) (87AJC1179).

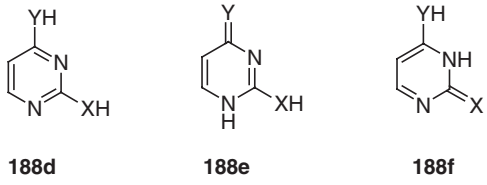
187a **187b**

3. *Pyrimidines and Quinazolines*

a. 2- and 4-Thiouracils. Similarly to uracil discussed above, its thio-analogs, 2-thiouracil **188** (X = S; Y = O) and 4-thiouracil **188** (X = O; Y = S) can potentially exist in six tautomeric forms. Although substitution of the tautomeric oxygen atom with sulfur is suggested to produce a general and small shift in the equilibrium favoring the thiol tautomer (86IJQC(30)225), the oxo–thione tautomer **188a** is still by far the most stable tautomer. IR and UV absorption studies of thiouracils and their fixed derivatives in the vapor phase as well as in the inert low-temperature matrices indicated that both 2- and 4-thiouracils exist under these conditions exclusively in the corresponding oxo–thione forms **188a** (88JST(176)137, 90JA2147). Gas-phase proton affinities of different tautomers of 2-thiouracil, determined using ion cyclotrone resonance mass-spectrometry were used to provide the quantitative estimates of individual tautomer stabilities in the vapor phase. The following order of the tautomer stability is suggested: **188a»188b ≈ 188d»188c ≈ 188e ≈ 188f** (89JCS(P2)1499). The oxo–thione tautomers of 2- and 4-thiouracils and their N-monosubstituted derivatives were also found to be the sole tautomeric forms in solution independent of the polarity of the solvent used and in the solid state. 4-Thiouridine and 5,6-dihydro-4-thiouracil also favor the oxo-thione form in solution (74JA6832, 78CJC725, 81BBA(656)1, 88JST(176)137). However, the thione-thiol tautomerism is suggested for 5-carboxy-2-thiouracil in solution on the basis of UV spectra (03MI430).



188a **188b** **188c**



188d **188e** **188f**

Ionization of 4-thiouracil leads to the formation of an equilibrium mixture of two monoanions in the 1:3 ratio, the N^1-deprotonated species being predominating. The presence of calcium chloride shifts the equilibrium toward the N^3-deprotonated species (74JA6832).

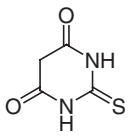
The relative tautomer stabilities of 2-thiouracil and its monomethyl derivatives were calculated by the semiempirical AM1, PM3, and MNDO methods (87JST(149)185, 89JCS(P2)1507, 03JST(625)31, 03KG1517), all-valence CNDO/2 method (86IJC(A)256), and *ab initio* calculations (90JA1504, 00JPC(A)5122, 00MI243). The theoretical tautomeric studies of 2- and 4-thiouracils at the B3LYP/6-31 + G(d,p) level, including interaction with water, were reviewed (01MI79). Both AM1 and *ab initio* methods correctly predict the predominance of the oxo–thione form of 2-thiouracil **188** (X = S; Y = O) with the second tautomer being less stable by about 6.2–6.4 kcal/mol. The relative order of stability is, however, varies. The following order is predicted by the *ab initio* methods: **188a** > **188d** > **188b** > **188c** > **188e** > **188f** (90JA1504, 00JPC(A)5122). The one, suggested by the AM1 calculations, is as follows: **188a** > **188b** > **188d** > **188f** > **188e** > **188c** (89JCS(P2)1507). The MNDO (87JST(149)185, 89JCS(P2)1507) and PM3 (03KG1517) methods, however, overestimate the stability of the (hydroxy)(mercapto) form **188d** predicting it to be of similar or higher stability compared to be oxo–thione form. On the other hand, CNDO/2 method favors the hydroxy-thione tautomer **188c** (86IJC(A)256).

The tautomeric equilibrium of 2-thiouracil in dioxane, water and acetonitrile was studied by *ab initio* calculations using the SCRF theory. The oxo–thione form was predicted to be predominant in all the solvents studied, but the order of tautomer stability was shown to depend on the level of theory and the dielectric constant of the solvent (00MI243). The tautomerism of protonated forms of 2-thiouracil has also been studied (00JPC(A)5122). Semiempirical AM1, PM3 and MNDO calculations of the thiol-thione tautomeric equilibrium **188c** $\rightleftharpoons$ **188d** predicted the mercapto form **188d** to be more stable in the gas phase; in the aqueous solution, however, AM1 and PM3 methods predict the predominance of the thione form **188c**, whereas the MNDO method still favors the thiol tautomer (03JST(625)31).

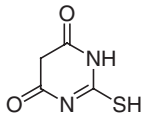
Both AM1 and MNDO methods correctly predict the predominance of the oxo–thione form for *N*-monosubstituted 2-thiouracils in the gas phase (89JCS(P2)1507). The gas phase calculated relative stabilities, proton affinities and aqueous phase calculated acidity constants predicted the higher stability of the oxo–thione form of 6-propyl-2-thiouracil compared to the hydroxy(thiol) tautomer (04JST(679)33).

The tautomerism of 4-thiouracil **188** (X = O; Y = S) was studied theoretically using semiempirical MNDO (87JST(149)185) and *ab initio* calculations (90JA1504, 98JPC(A)2194, 00JPC(A)5122). *Ab initio* methods correctly predict the oxo–thione tautomer **188a** to be the most stable; however, the relative order of the tautomer stability significantly depends on the level of calculations. The following order has been predicted by high-level *ab initio* calculations: **188a** > **188b** > **188d** > **188c** > **188f** > **188e**. Aqueous solution destabilizes the minor tautomers and changes their order of stability as follows: **188a** > **188b** > **188c** > **188d** > **188e** > **188f**. In contrast, the possibility of coexistence of two tautomers in ethanol was suggested due to stabilization of the minor tautomers with ethanol molecules (98JPC(A)2194, 00JPC(A)5122). MNDO method favors the tautomer **188b** in the gas phase.

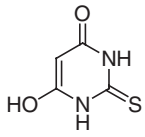
b. Other Pyrimidines and Quinazolines. Unsubstituted thiobarbituric acid **189** can potentially exist in six tautomeric forms. ^{13}C NMR spectroscopic studies indicated the presence of two equilibrating tautomers, **189a** (46%) and **189c** (54%), in methanol solution. In DMSO-d_6 solution, the percentage of the tautomer **189a** is decreased to 35%. Only tautomer **189a** was observed for *N*,*N*′-diethyl thiobarbituric acid in chloroform and acetone; however, both tautomers **189a** and **189c** were observed in methanol and DMSO/D_2O (1:1) in 67:33 and 55:45 ratios, respectively (87JHC191). *N*,*N*′-Diaryl-substituted thiobarbituric acids (aryl = Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$) exist in chloroform solution as mixture of **189a** and **189c** tautomers with the latter predominating, whereas only tautomers **189a** were detected in CCl_4 solution. Both tautomeric forms were observed in the solid state (89SA(A)917). The substituent effects (including remote substituents) and solvent effects on the tautomerism of thiobarbituric acids **163** (X = S; R^1, R^2 = H, Me, Et; R^3 = H, OMe) were studied in detail. These compounds were found to exist exclusively as hydroxy(oxo) tautomers of type **189c** in DMSO-d_6 solution independent of the substitution pattern, whereas in $CDCl_3$ only oxo–thione tautomers were detected (02KG798).



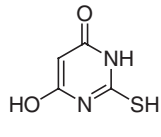
189a



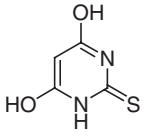
189b



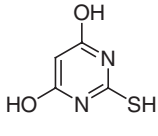
189c



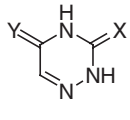
189d



189e



189f



190

The relative stabilities of tautomers of unsubstituted thiobarbituric acid were calculated using the AM1 method. The oxo–thione structure **189a** was found to be the most stable in the gas phase. On transition from vapor to water, the population of the most polar tautomer, the oxo(hydroxy) form, increases. However, the order of stability remains unchanged, and only for 5-halo derivatives the possibility of coexistence of two tautomeric forms in solution has been suggested (89JHC639).

2-Thioxo-4-quinazolone was shown to exist in oxo–thione tautomeric form in ethanol or DMSO solution and in the solid state (86KG1236, 93MRC832). This tautomeric form is preserved in the complexes with Cd^{2+} and Hg^{2+} (93MRC832); however, spectroscopic data for complexes with organomercury and organothallium compounds are in better agreement with the aromatic (hydroxy)(mercapto) form of the ligands (92ICA(201)35).

4. *Other Heterocycles*

IR spectra of (oxo)triazinethiones **190** (X = O, Y = S; X = S, Y = O), isolated in low-temperature argon and nitrogen matrices, indicated that these compounds exist in the tautomeric form shown (96SA(A)645).

F. Compounds with Hydroxy(Oxo) and Amino(Imino) Groups

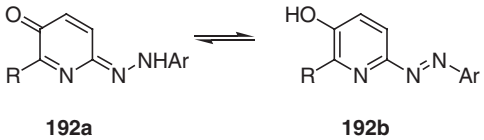
1. *Pyridines and Benzologues*

2-Hydrazinopyridine 1-oxides **191** (R = CN, $CONH_2$, CONHCOOEt, 2-benzimidazolyl) exist as mixtures of both tautomers in dichloromethane solution (88CCC626). Theoretical studies of the tautomerism of 4-(hydroxyamino)pyridine 1-oxides **184** (X = NOH) using the MINDO/2 method predict almost equal stability of pyridines **184a** and **184b** ($\Delta E = 0.3$ kcal/mol in favor of **184b**) (75CPB1256). Tautomerism of substituted 2-aminopyridine *N*-oxides has been studied by UV spectroscopy (93KG1662).

191a **191b**

6-Amino-2-hydroxy-3,5-dinitropyridine was shown to exist in the amino(oxo) tautomeric form in the solid state; however, the amino(hydroxy) form predominates in solution in chloroform, methanol, or acetonitrile (95JHC585). Oxo-hydroxy tautomerism of 3-amino-, 4-amino-, 5-amino-, and 6-amino-2-hydroxypyridines (the participation of amino group in the equilibrium is not considered) was studied both experimentally by UV and fluorescence spectroscopy and theoretically by MINDO/3 calculations. The dimer formation energies were evaluated by CNDO/2 method. Among the compounds studied, 6-amino-2-pyridone has the largest dimer formation energy, and the 3-amino analog – the smallest. 3-Amino-2-hydroxypyridine exists as pyridone monomer in THF and THF/MeCN, whereas the tautomeric equilibrium was observed for 5-amino- and 6-amino-2-hydroxypyridines. The oxo form becomes predominant with the increase in the solvent polarity, and increase in substrate concentration facilitates the dimer formation (90BCJ2292).

Azo- and quinonehydrazone tautomerism of 2-methoxy-3-oxo-6-phenylazopyridine **192** (R = OMe; Ar = Ph) was investigated by UV and IR spectroscopy. In the gas phase at 140 °C in the absence of intermolecular interactions, this compound exists in the azo form **192b**. With the increase in concentration and reduction in temperature, it starts to display the tautomeric equilibrium forming the homodimers of quinonehydrazone tautomer **192a**. In solution, the concentration of the tautomer **192a** depends on the nature of the solvent increasing in the following order: hexane < CCl_4 < benzene < chlorobenzene < chloroform (74KG1364).

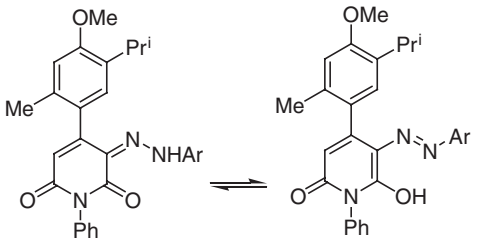


192a **192b**

193a **193b**

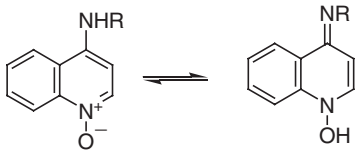
The thermal transformation of low **192b** to the high-temperature **192a** form of 2-amino-3-hydroxy-6-phenylazopyridine **192** (R = NH_2, Ar = Ph) in the solid state and in solution has been studied by differential scanning calorimetry, variable temperature IR spectroscopy, and X-ray structure analysis. It has been shown that the thermal rearrangement of **192b** to **192a** in the solid state involves intermolecular proton shifts from the phenolic oxygen in the azo-form to the hydrazone nitrogen in the quinoid form (83JCS(P2)1025). 2-Unsubstituted 3-hydroxy-6-arylazopyridines **192** (R = H; Ar = Ph, 4-MeC_6H_4, 3-BrC_6H_4, etc.) and 3-hydroxy-2-arylazopyridines **193** exist in nitromethane and acetonitrile solution in the hydroxy(azo) forms **192b** and **193b**, respectively (84KG1656).

UV, IR, and ^{1}H NMR spectroscopic studies of tautomeric lactams **194** (Ar = Ph, 2-ClC_6H_4, 3-$O_2NC_6H_4$, etc.) indicated that these compounds exist exclusively in the hydrazone form **194a** (76IJC(B)486).



194a **194b**

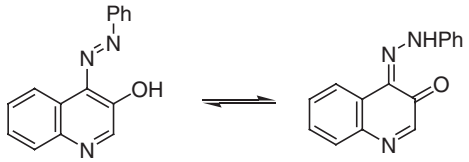
According to MINDO/2 calculations, in constrast to the pyridine analog **184** (X = NOH) discussed above, 4-(hydroxyamino)quinoline 1-oxide **195** (R = OH) strongly favors the *N*-hydroxy tautomer of type **195b** ($\Delta E = 8.7$ kcal/mol) (75CPB1256). The corresponding acetate **195** (R = OAc) was shown to exist in DMSO-d_6 in the tautomeric equilibrium with *N*-hydroxy tautomer **195b** predominating. The protic solvents shift the equilibrium toward the *N*-oxide **195a** (89JOC399). Tautomerism of 2-aminoquinoline *N*-oxides has also been studied by UV spectroscopy (93KG1662).



195a **195b**

In contradiction to earlier findings claiming that 4-amino-3-methoxycarbonylquinolin-2-one exists in solution as a mixture of amino-oxo and imino-hydroxy forms, the latest studies indicated the presence of a single amino-oxo form, both in DMSO-d_6 solution and in the solid state (04MI39).

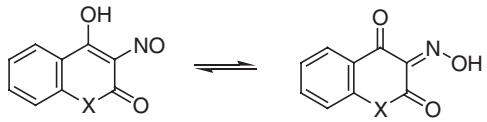
UV and IR spectroscopic studies have shown that derivatives of 3-hydroxy-4-arylazoquinoline **196** exist in organic solvents primarily in the azo form **196a**, whereas the isoquinoline analogs **197** favor the quinonehydrazone form **197b**. The introduction of a strong electron-accepting group (such as NO_2) into the *p*-position of the phenyl ring of **196** shifts the equilibrium toward the quinonoid form **196b**. The introduction of such substituents as Me, Br, OMe, or SO_3H does not have any significant effect on the equilibrium (74KG1522). The structures **196** and **197** were calculated using the MO LCAO method within the PPP approximation (74KG952). The azo form **196a** was found to be energetically more preferable than **196b**, whereas the opposite trend was observed for isoquinoline analog **197** in agreement with the experimental data.



196a **196b**

197a **197b**

The preference of the form **198b** for 3-nitroso-2,4-quinolinediones **198** (X = NMe, NPh), existing as mixtures of both tautomers in the gas phase, was established by mass spectroscopy. The molar fraction of the minor nitroso tautomer **198a** decreases on transition from **198** (X = NMe) to **198** (X = NPh) (89KG1243).



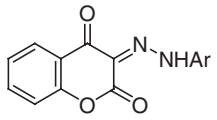
198a **198b**

The tautomeric equilibrium in 1-Btz-9-acridone (Btz = substituted benzothiazol-2-ylamino) is completely shifted toward the oxo–amino tautomer stabilized by

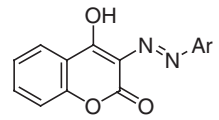
intramolecular hydrogen bonding. No tautomerism was observed for 2-amino-, 2-Btz-, and 3-Btz-substituted 9-acridones. In contrast, 4-amino- and 4-Btz-9-acridones display the slow-exchange tautomerism in solution with oxo–amino tautomers always predominating (02MRC545).

2. *Pyrans and Benzologs*

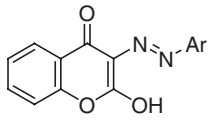
In contrast to the aza analogs, 3-nitroso-4-hydroxycoumarin **198** (X = O) exists in the gas phase exclusively in the dioxo tautomeric form **198b** (89KG1243). Four tautomeric structures are possible for 3-arylazo-4-hydroxycoumarins **199**. IR, UV, and ^{1}H NMR spectroscopic studies indicated that these compounds exist in the keto hydrazone form **199a** both in the solid state and in solution. The HMO calculations confirmed the experimental findings providing the following order of the tautomer stability: **199a** > **199b** > **199c** > **199d** (78IJC(B)295, 85JHC1397).



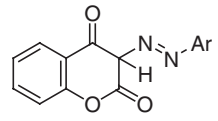
199a



199b

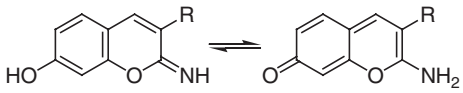


199c

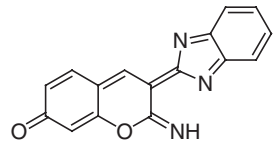


199d

The tautomeric equilibrium between forms **200a** and **200b** was observed in solutions of iminocoumarin **200** (R = 2-benzimidazolyl) in protic solvents. The tautomerization constant does not depend on the pH and was estimated to be $K_T = 2.6$ (aq. MeOH) and 2.26 (aq. acetonitrile) in favor of the amino tautomer **200b**. No bis(imino) tautomer **200c** was detected (95ZOB1416).



200a **200b**

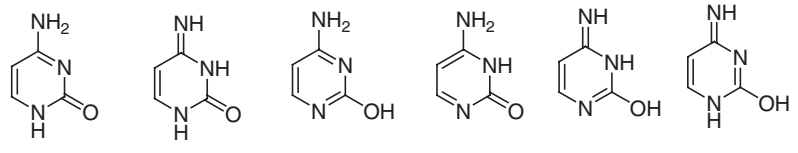


200c

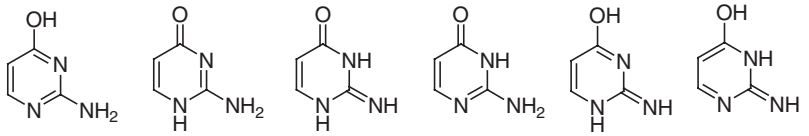
3. *Pyrimidines and Quinazolines*

a. Cytosine and Isocytosine. Six tautomeric forms are possible for each of nucleic acid bases cytosine **201** and isocytosine **202**. High-resolution IR spectra of cytosine and its deuterated derivatives isolated in inert Ar and N_2 matrices indicated that

isolated cytosine exists as a mixture of amino–oxo **201a** and amino–hydroxy tautomer **201c**. The latter form predominates in both matrices with an equilibrium constant $K_T = 0.5$. The irradiation of cytosine isolated in an Ar matrix with UV light changes the relative concentrations of the two tautomers in the matrix in favor of the hydroxy form. The molar fraction of the oxo form in the matrix can be increased by increasing the substrate concentration (dimer stabilization energy is highest for the oxo–oxo dimer) or by hydration (84JST(116)387, 88JA8319, 89SA(A)229, 90JST(219)311). Three tautomers of cytosine, namely, **201a–c**, were detected in the gas phase by microwave spectroscopy (89JA2308). This contrasts with observation of only two tautomers by matrix isolation technique.



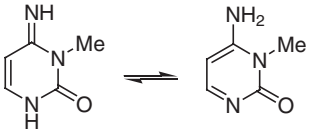
201a **201b** **201c** **201d** **201e** **201f**



202a **202b** **202c** **202d** **202e** **202f**

IR studies of 5-methylcytosine in Ar matrix indicated the simultaneous presence of three tautomers, methyl-substituted analogs of **201a–c**. A UV-induced transformation of the amino–oxo into amino–hydroxy form was observed and used to separate the spectra of tautomers. The amino-hydroxy form dominates strongly, and the other two tautomers are present in nearly equal concentrations. *Ab initio* calculations confirm the experimental findings predicting the amino-hydroxy form to be the most stable, and amino–oxo and imino–oxo forms to be higher in energy by about 3.5 kcal/mol (90JPC6555).

Two isomers of 1-methylcytosine, amino–oxo and (*E*)-imino–oxo, were observed in IR spectra in Ar and N_2 matrices. The tautomerization constant was experimentally estimated to be $K_T = 0.15$ in favor of the amino–oxo form. *Ab initio* calculations predicted (*E*)-imino–oxo form to be less stable by 1.0 kcal/mol and amount up to 10% of the substrate molecules in a matrix (84JST(115)221, 92JA2731, 96JPC6434). Cytosine and its several *C*-methyl and ring nitrogen *N*-methyl derivatives were investigated using UV photoelectron spectroscopy and CNDO/S MO calculations. Except for 3-methylcytosine **203**, these compounds exist in the most stable amino–oxo forms of type **201a**. For 3-methylcytosine, however, the imino tautomer **203a** was found to be the most stable (78JA2303). The predominance of the imino–oxo form of 3-methylcytosine in the gas phase was confirmed by IR spectra (84JST(115)221).



203a **203b**

With an exception of one report, which claims the predominance of the amino–oxo form of isocytosine in the Ar matrix (87JST(158)275), high-resolution IR-spectroscopic studies of matrix-isolated isocytosine indicate that, of two tautomers present, the amino-hydroxy form strongly predominates (about 85%) (89MI1650, 90JST(216)77, 94JST(322)113, 94SA(A)875). On transition from a matrix to the gas phase, the oxo–hydroxy equilibrium of isocytosine shifts toward the amino-hydroxy form (90JST(216)77). 1-Methyl- and 6-methylisocytosine were shown to exist predominantly in the imino–oxo form in the nitrogen matrix (84JST(115)221).

The tautomeric compositions of cytosine, isocytosine, and their derivatives dramatically change on transition from the gas phase to solution and to the solid state. Magnetic circular dichroism (MCD) and absorption spectra of cytosine indicated that the tautomer **201a** is the most stable both in neutral aqueous solution and in acetonitrile (80BCJ3073). The stability of abnormal rare forms of cytosine, 3-methylcytosine, and cytidine in aqueous solution was investigated using the temperature-jump relaxation technique (76JA6338, 77JA4438). In water cytosine, which exists mainly in the amino–oxo form **201a**, tautomerizes slightly to the N(3)–H form **201d** and the equilibrium constant is estimated to be 2.5×10^{-3} at 25 °C. The interconversion process is catalyzed by water, H^+, OH^-, and the cytosinium cation. The tautomeric equilibrium of 3-methylcytosine **203** depends on the solvent used: thus, while the tautomer **203a** is the major form in the nonpolar solvents, the amino form **203b** largely predominates in water, the equilibrium constant being estimated as *ca.* 3×10^{-2} at 25 °C. In dioxane and chloroform, the tautomer **203b** no longer predominates. In aqueous solution of cytidine, the rare imino–oxo form is present in minute quantities.

UV and NMR studies showed that 1-methyl-N^4-hydroxycytosine and its methyl derivatives exist predominantly in the oxo–imino form (up to 90%) (98BPC87). A review of the structure and properties of isolated nucleic acid bases with the special attention given to metal-cation-assisted tautomerization and the solvent effects has been published (99CR3247). Tautomerism of protonated cytosine has been studied experimentally by IR and Raman spectra and theoretically by *ab initio* and DFT calculations (96JPC5578). Neutral and protonated forms of cytidine monophosphate have been studied by ultraviolet resonance Raman spectroscopy. The amino–oxo tautomer was found to be the most stable, followed by the imino–oxo form. The imino-hydroxy tautomer was determined to be the least stable one. Upon protonation, the amino–oxo structure is retained (93JA760).

According to MCD, absorption, and ^{13}C NMR spectra, isocytosine exists in solution in equilibrium of two amino–oxo forms **202b** and **202d** (80BCJ3073, 00ZOR1373). The similar tautomeric interconversion with predominating form **202d** was observed in solution of its 6-substituted derivative, 6-(9-heptadecyl)isocytosine.

The complexation of the latter with creatinine analog shifts the equilibrium further in favor of **202d** (93T7627). IR spectra and X-ray diffraction studies showed only the normal amino–oxo tautomer of cytosine (88JA8319) and 3-methylcytosine hemihydrate (78AX(B)1730) in the solid state.

Owing to importance of cytosine in biochemistry and significant effects of tautomeric interconversions on DNA mutations, the tautomerism in cytosine was extensively studied by quantum-mechanical calculations on various levels. In contrast to uracil, the dioxo tautomer of which is significantly more stable than the other tautomers, three tautomers of cytosine (**201a–c**) are reasonably close in energy, so the order of stability is essentially determined by the level of calculations.

In the gas phase, the amino–oxo tautomer **201a** is predicted to be the most stable by the semiempirical AM1 (87JST(151)259, 91JA1561), MINDO/3 (79IJQC(16)605, 82ZN(C)937, 83JST(92)283), *ab initio* post-Hartree–Fock (HF) (97JST(413/414)271) and density functional calculations (94CPL(220)129, 95IJQC(56)615, 95JST(331)147). Coupled-cluster calculations at the single, double, and perturbative triple excitation level (89JPC4001, 98JPC(A)10813), SCRF calculations (92JOC4434), and calculations at the 6-31G** level (89CPL(161)185) predicted the highest stability of the amino-hydroxy tautomer **201c** closely followed by amino–oxo form **201a**. The same order of tautomers is provided by semiempirical MNDO method, which, however, suggest a significant difference in energy between **201c** and **201a** (83JST(92)2551). CCSD//MBPT(2) calculations also favor the amino-hydroxy tautomer **201c**, but suggest imino–oxo tautomer **201b** to be the second most stable ($\Delta E = 0.2$ kcal/mol) (97JST(413/414)271). *Ab initio* SCF MO calculations predict almost equal stability of amino–oxo **201a** and imino–oxo **201b** tautomers ($\Delta E = 0.13$ kcal/mol in favor of **201b**) (83JST(92)283). On the other hand, calculations using 3-21G basis set slightly favor the tautomer **201a** predicting **201b** to be the second stable form ($\Delta E = 0.4$ kcal/mol) (84JA3737, 84JCS(CC)102). Almost equal stability of all three tautomers **201a–c** with **201c** slightly favored and **201a** as second stable tautomer is provided by *ab initio* calculations at the HF and MP2 levels (95JST(331)147, 99JST(487)47) and at the Møller–Plesset level (96JA6811). Relative stabilities of cytosine tautomers have also been calculated at the HF/6-31G** level (92JST(276)209, 93JA11939, 93JST(300)619, 99JPC(A)6612).

Amino-imino tautomeric interconversion **201a** $\rightleftharpoons$ **201b** for cytosine (78IJQC(14)851, 87JA6283, 88JA2353) and N^4-hydroxycytosine (82ZN(C)937) was studied using semiempirical MINDO/2 and MINDO/3 methods and *ab initio* SCF and MBPT(2) methods. All calculations predicted the higher stability of the amino tautomer **201a**. The transition from cytosine to N^4-hydroxycytosine shifts the equilibrium toward the imino form (83JST(92)283). The structures of cytosine dimers formed between the same or different tautomeric forms were studied using a combined quantum-mechanical approach. The homodimerization stabilizes the amino–oxo tautomer **201a** the most, confirming the experimental observation of increase of the molar fraction of **201a** in concentrated matrices. The order of dimer stabilization energy is similar to the stability order, thus, lowering the probability of occurrence of rare tautomers in complexes compared to individual molecules (89JST(198)297).

Theoretical estimations at the B3LYP level for the 298 K gas-phase acidities of all possible deprotonation sites of the most stable tautomers of cytosine predicted the almost equal acidity of the oxo and hydroxy forms (03JPC(A)4893). Relative stabilities

of the protonated forms of cytosine were calculated using the *ab initio* Hartree–Fock–Roothaan SCF method (81TCA283). The metal-assisted tautomerization was studied by the MP2/6-31G** method (99JPC(A)11406). Whereas the neutral tautomers of cytosine almost isoenergetic in the gas phase, mercuration of exocyclic amino group destabilizes the imino tautomer and shifts the equilibrium toward the amino–oxo form **201a**. On platination, the imino tautomer is even more destabilized. The activation energies of intramolecular proton-transfer reactions of cytosine in the gas phase were computed using *ab initio* HF and MP2 calculations (97CPL(280)233).

The tautomeric equilibrium of cytosine is sensitive to phase change. The solvent effects were studied using Onsager's reaction field model in the framework of DFT (95IJQC(56)615), a simple model of solvation using 3-21G basis set (84JA3737), *ab initio* post-Hartree–Fock method (99JST(487)47), SCRF (78KG94, 91CJC1589), Monte-Carlo free energy perturbation simulations (96JA6811), and electrostatic model of solvation within CNDO/2 method (78TCA223). The solvation energy in water is the largest for the tautomer **201d** and smallest for **201e**. This phenomenon drastically changes the order of the tautomer stability making **201d** the second most stable tautomeric form in aqueous solution. The identical order of stability was calculated for a solution in polar solvents, such as acetonitrile.

The calculations of hydration energies of tautomers **201a** and **201b** using semiempirical AM1 and MNDO methods with incorporated continuum model (91JA1561, 92JA10563), LCAO-MO method with 6-31G(d) basis set (03MI410), *ab initio* HF/6-31G(d) method (96JA6811), Monte-Carlo simulations (00CPL(328)75), and coupled reference interaction site model (RISM)/molecular dynamics approach (04JPC(B)19043) predicted the better solvation of the amino–oxo form **201a** with the difference in the solvation energies being in range 5–7 kcal/mol. As the result, the calculations at all levels predict the amino–oxo tautomer **201a** to be the most stable in aqueous solution (by more than 5 kcal/mol relative to any other tautomer) and the significant decrease in concentration of the tautomer **201b** in water (6–31% depending on the level of calculations) compared to the gas phase. Assistance by water also accelerates proton transfer. In general, the oxo tautomers of cytosine were found to be slightly better hydrated than hydroxy tautomers (97JPC(A)3589). The *ab initio* calculations of all hydrated tautomers of cytosine using 3-21G basis set (84JCS(CC)102) or SCRF model (92JOC4434) gave the following order of stability in the aqueous solution: **201a** > **201d** > **201b** > **201c**, which agrees well with the experimental findings. The polarization continuum method, however, found the form **201d** to be less stable than **201b** and **201c** providing the incorrect order of tautomer stability (92JOC4434). Interestingly, cytosine photohydrate is more stable in the imino than in amino form (00CPL(328)75).

The oxo–hydroxy tautomeric equilibrium of cytosine in aqueous solution (the participation of the amino group in not considered) was studied using both combined discrete/SCRF and SCRF calculations (00CP(253)13). Complexes containing a cluster of seven water molecules filling up the first solvation shell of cytosine were used. The results indicated that the SCRF methods overestimate the stability of hydroxy tautomers by about 10 kcal/mol. The proton-transfer reactions in the hydrogen-bonded complex of cytosine with water were investigated using the CASSCF method and the second-order perturbation theory (95JCP5708).

N^1-Methylation of cytosine stabilizes the amino–oxo tautomer, which is predicted to be the most stable form of 1-methylcytosine in the gas phase independent of the level of calculations. The stabilization of the amino–oxo tautomer of 1-methylcytosine on hydration is even more pronounced than that of the parent cytosine, so the population of the imino tautomer in aqueous solution is insignificant (86JST(148)45, 00JST(532)157, 01JPC(A)6575). For 3-methylcytosine, the imino-keto form **203a** was predicted to be predominant in the gas phase (86JST(148)45).

The tautomeric equilibrium of 5-methylcytosine in the gas phase was studied by high-level *ab initio* calculations (90JST(221)209), DFT calculations (02IJQC(89)106), and all-valence CNDO/2 method (86IJC(A)107). The amino-hydroxy tautomer was predicted to be the most stable by *ab initio* and CNDO/2 methods, whereas DFT calculations slightly favor amino–oxo tautomer ($\Delta E = 0.47$ kcal/mol). The hydration of 5-methylcytosine is similar to that of the parent cytosine, so the equilibrium shift toward the amino–oxo tautomer in a polar solvent is predicted (90JST(221)209, 01JPC(A)6575). The slight predominance of the amino–oxo tautomer of type **201a** was predicted for 5-fluorocytosine in the gas phase by the MNDO method (86JST(148)45).

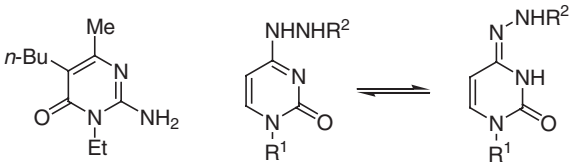
SCF *ab initio* calculations of 5-hydroxycytosine predicted that in the vapor phase the oxo–imino isomer is the most stable. However, due to the large difference in the stabilization energy the amino–oxo tautomer is preferred in solution. Increase in the solvent polarity further stabilizes the amino–oxo tautomer (99JST(466)49). The amino–oxo tautomer was also found to be the most stable for 5,6-dihydroxycytosine in solution independent of the solvent polarity (99JST(459)1).

Tautomerism of isocytosine **202** in the gas phase has been extensively studied by the semiempirical MNDO (86JST(148)45, 90JST(216)77), MINDO/3 (79IJQC(16)605), and PM3 (03KG1517) and *ab initio* methods (90JST(208)35, 94JST(322)113, 94SA(A)875, 96JST(376)375). The *ab initio* methods predict the amino-hydroxy form **202a** to be the most stable followed by the amino–oxo form **202d** ($\Delta E = 2.7$ kcal/mol). A similar order of the tautomer stability is predicted by the PM3 and MNDO/3-21G methods. In contrast, MNDO/4-21 method favors the amino–oxo form **202d** by 2 kcal/mol, whereas the MINDO/3 method predicts the highest stability for the oxo–amino form **202b**.

The amino–oxo form of type **202d** is predicted to be the most stable for 3-methylisocytosine. For 1-methylisocytosine, the imino–oxo form was found to be more stable than amino–oxo form in the gas phase by at least 3.7 kcal/mol, but the relative stability is reversed in water (86JST(148)45). The amino–oxo form of type **202d** was predicted to the most stable for isocytosines acylated at the amino group independent of the substituent at the 5-position (03KG1517). Coordinates of the proton-transfer reaction of isocytosine from the oxo to the hydroxy form in dimers and in hydrated complexes with one or two molecules of water were calculated using the MNDO method (91MI1124). The dimerization and hydration of the isocytosine molecules were shown to lead to the preferential stabilization of the oxo form.

b. Other Pyrimidines and Quinazolines. X-ray structure analysis established that 2-aminopyrimidin-6-one **204** exists in the solid state exclusively in the amino–oxo form shown. *Ab initio* calculations at the HF/6-21G* level favor the same tautomer in the

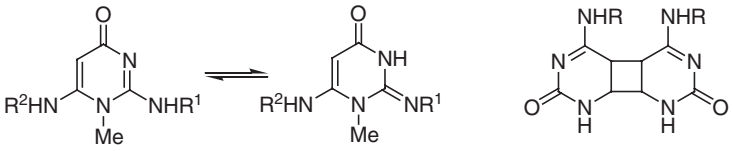
gas phase by 7.5 kcal/mol (98M735). According to the semiempirical AM1 calculations, the amino–oxo tautomer predominates for both 2-methylthio- and 2-methoxy-6-aminopyrimidin-4-ones in the gas phase and also in aqueous solution (96MI355).



204 **205a** **205b**

4-Phenylhydrazino-2-pyrimidones **205** (R^1 = H, Me; R^2 = Ph) have been shown by ^{1}H NMR spectroscopy to exist in slowly interconverting hydrazine and hydrazone forms into DMSO. Variable temperature studies showed relatively high-energy barriers to tautomerization resulting from both solvation and intramolecular hydrogen bonding. Increasing solvent polarity favors the hydrazine form **205a**. The tautomerization constant K_T is 1.3 for **205** (R^1 = H; R^2 = Ph) and 3.5 for **205** (R^1 = Me; R^2 = Ph) in DMSO-d_6 and independent on the temperature and concentration. In methanol, both these compounds exist primarily in the hydrazine form **205a**. In contrast, the 3-methyl analog exists only in the hydrazone form. 1-Methyl-4-hydrazino-2(1*H*)-pyrimidinone **205** (R^1 = R^2 = H) exists predominantly as hydrazone **205b** in DMSO-d_6 and methanol, although the tautomerization barrier is similar to that of the phenylhydrazine analogs (83JHC1037).

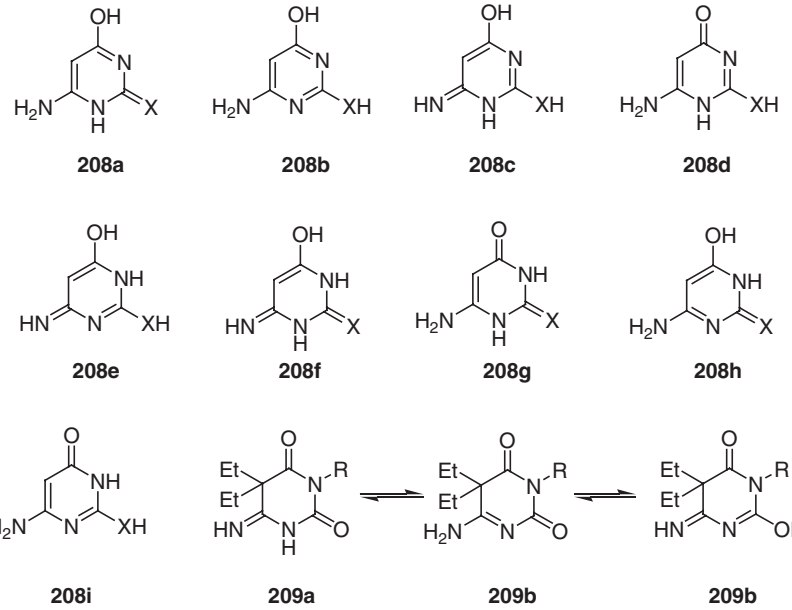
In contrast to 5-unsubstituted analogs, N^4-benzoylated *N*-glycosidyl-substituted 5-methylcytosines exist in tautomeric equilibrium between amino and imino tautomers. The imino form in preferred both in solution and in the solid state (99MI1079). 2,6-Diaminopyrimidin-4-one **206** (R^1 = R^2 = H) exists exclusively in the diamino–oxo form **206a** both in neutral and basic solutions. In contrast, **206** (R^1 = Me; R^2 = H) displays solvent-dependent tautomerism with the form **206a** being predominant in DMSO-d_6 and protic neutral and basic solvents and form **206b** being predominant in DMSO-d_6/$CDCl_3$ mixture. The equilibrium shifts toward **206b** on the temperature increase. Monoacetamide **206** (R^1 = Me; R^2 = COMe) also exists in the tautomeric equilibrium with the similar solvent dependency (87JOC5655).



206a **206b** **207**

According to IR spectra, the diamino form **207** predominates for N-unsubstituted cytosine dimers, whereas N^4-disubstituted analogs favor the bis(imino–oxo) form. Both

forms are present at equilibrium for N^4-monosubstituted derivatives with the amino form **207** preferred in polar solvents (77JOC4127). The relative stabilities of tautomers of 6-aminouracil **208** (X = O) were investigated using the all-valence CNDO/2 method. The amino–oxo–hydroxy form **208a** was found to be the most stable and the order of the tautomer stability is as follows: **208a** > **208b** > **208c** > **208d** > **208e** > **208f** > **208g** > **208h** > **208i** (86IJC(A)256).

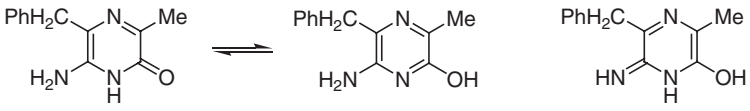


Tautomerism of 6-iminobarbiturates **209** depends upon the substituent on the N(3) atom. ^{1}H NMR spectra in dipolar aprotic solvents, UV spectra in water and ethanol, IR spectra and studies at different temperatures indicate the conjugated structure **209b** for **209** (R = H) and non-conjugated structure **209a** for **209** (R = Me, Ph) (88CPB563).

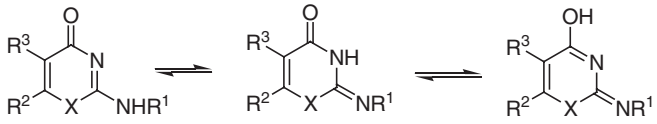
Molecular orbital CNDO/2 studies of 2,6-diamino-4-hydroxypyrimidine and 2-amino-4-hydroxyquinazoline predicted that in both cases the aromatic amino-hydroxy tautomer is the most stable. Of the other tautomers, N(1H)–oxo form is more stable than N(3H)–oxo form for 2,6-diamino-4-hydroxypyrimidine, whereas the opposite trend is calculated for 2-amino-4-hydroxyquinazoline (85IJQC(28)315).

4. *Other Heterocycles*

6-Amino-5-benzyl-3-methyl-2(1*H*)-pyrazinone **210** exists predominantly in the oxo form **210a** in aqueous buffered solution ($K_T \approx 2000$), but as the tautomer **210b** in dioxane. The equimolar mixture of tautomers was observed in dioxane/aq. buffer = 90:10. The linear dependence of the tautomerization constant on the solvent polarity was established. No imino tautomer **210c** was observed (93JOC7542).



210a **210b** **210c**

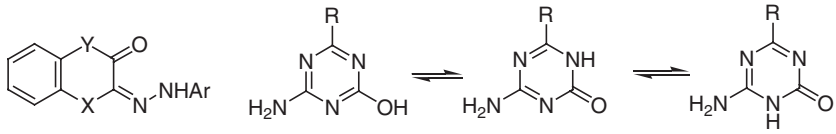


211a **211b** **211c**

IR spectra of benzoxazines **211** (X = O; R^1 = aryl; R^2R^3 = benzo) suggest the oxo–imino structure **211b** both in solution and in the solid state (91JHC133). 2-Amino-4-oxo-1,3-thiazines **211** (X = S; R^1 = alkyl; R^2 = Ph; R^3 = H) exist in chloroform solution as mixtures of tautomers **211a** and **211b** with **211a** predominating. In contrast, the imino form **211b** is favored for **211** (X = S; R^1 = aryl; R^2 = Ph; R^3 = H) in solution. In the solid state, the shift of the tautomeric equilibrium toward the amino tautomer is observed independent of the amino group substitution (82CCC3268). Arylazo derivatives of quinoxaline, 1,4-benzothiazine, and 1,4-benzoxazine **212** (X = S, Y = NH; X = NH, Y = O, S, NH) exist predominantly in the hydrazone tautomeric forms shown as indicated by the spectral data and HMO calculations (84JHC521, 03JHC207).

In contrast to the 6-alkyl analogs, which display the solvent-dependent equilibrium in solution (see Section II.A.9), the tautomeric equilibrium of 6-amino-2,1,3-thiadiazin-4-one **61** (R^1 = *n*-Bu; R^2 = NH_2) is completely shifted toward the oxo tautomer **61a**, independent of the solvent polarity (88JCS(P2)859).

2-Hydroxy-4-amino-1,3,5-triazines **213** (R = *n*-dodecyl, *n*-heptadecyl) exist in the solid state as oxo tautomers **213b** or **213c** with strong intermolecular hydrogen bonding (85KG1557). The tautomerism of ammeline **213** (R = NH_2) has been studied by *ab initio* calculations at the SCF-level using several different basis sets. The hydroxy tautomer **213a** is predicted to be more stable than the *o*-quinoid oxo tautomer by 4.8 kcal/mol and than the *p*-quinoid oxo tautomer by 23.8 kcal/mol (93JOC3085). Molecular orbital CNDO/2 calculations predict the hydroxy tautomer of 2-amino-4-hydroxy-5,6-dihydro-6,6-dimethyl-1,3,5-triazine to be more stable than the oxo tautomer by 9.75 kcal/mol (85IJQC(28)315).

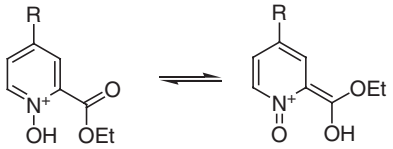


212 **213a** **213b** **213c**

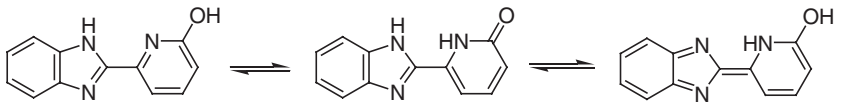
G. Compounds with Hydroxy(Oxo) and Methylene Groups

1. *Pyridines and Quinolines*

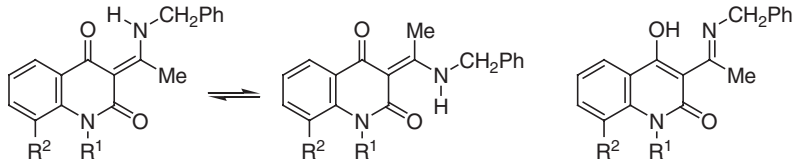
The tautomerism of protonated 2-(ethoxycarbonyl)pyridine *N*-oxides **214** (R = H, NO_2, OEt) has been studied by comparison of their FTIR spectra with those of their salts with $HAuCl_4$ in acetonitrile. The findings clearly indicate that both tautomeric forms exist in solution with the relative ratio depending on the substituents. The electron-withdrawing substituents shift the equilibrium toward form **214b**, whereas the electron-releasing substituents favor the tautomeric forms **214a** (89JCS(P2)2109).



214a **214b**



215a **215b** **215c**



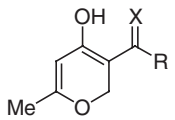
216a **216b** **216c**

The tautomerism of 2-(3′-hydroxy-2′-pyridyl)benzimidazole **215** in the ground and first excited singlet states in various solvents has been investigated by UV–vis absorption spectroscopy, by steady-state and time-resolved fluorescence spectroscopy, and by semiempirical AM1 and *ab initio* RHF calculations. In the ground state, the tautomeric equilibrium **215a** ⇌ **215b** was observed, the equilibrium shifting toward **215b** with increase in the solvent polarity or at higher temperatures. The form **215a** was predicted to be more stable than **215b** by 2–3 kcal/mol in the gas state, which implies about 2% of **215b** at equilibrium. Upon excitation, the proton transfer from benzimidazole occurs to give **215c** in acetonitrile. This phototautomerization is assisted by solvent and was not observed in water (94JPC8666, 04JPC(A)6117).

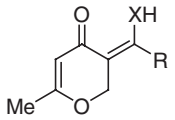
2,4-Quinolinediones **216** (R^1 = Me, $PhCH_2$, R^2 = H; $R^1R^2 = (CH_2)_3$) exist in equilibrium **216a** ⇌ **216b** in non-polar solvents with **216a** predominating. No tautomer **216c** was detected (95JCS(P2)1901).

2. *Pyrans and Benzopyrans*

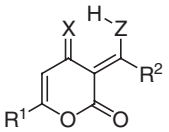
For pyranones **217** (X = O; R = Me), the prototropic exchange between two oxygen atoms is fast on the NMR time scale. Owing to the extensive electron-delocalization in the conjugated chelate ring, the tautomeric pair **217a** and **217b** may be described as resonance hybrid. Pyranones **217** (X = O; R = CH:CR^{1}NHR^2; R^1 = Me, COOEt; R^2 = 1-naphthyl) exist in $CDCl_3$ solution as tautomers **217a** and in the solid state in **217a** or electron-delocalized chelate form (01CCA441).



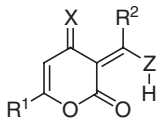
217a



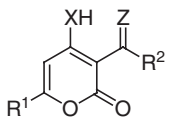
217b



218a



218b



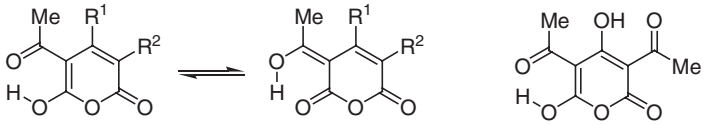
218c

Pyran-2,4-dione **218** (X = Z = O; R^1 = R^2 = Me) was shown to exist as the enol tautomer **218c** both in solution in various solvents and in the solid state. The AM1 calculations confirmed the highest stability of this tautomer predicting the relevant tautomers **218a** and **218b** to be less stable by 1.6 and 2.2 kcal/mol, respectively (00JST(554)225). The relative energies of tautomers of the Schiff base **218** (X = O; Z = NMe; R^1 = R^2 = H) were estimated by *ab initio* calculations at the HF and MP2 levels. The tautomers **218a** and **218b** were found to be almost isoenergetic (ΔE = 0.2–0.7 kcal/mol in favor of **218a**) and more stable than **218c** by 5.7–10.2 kcal/mol (depending on the level of calculations) (93JCS(P2)2423). The Schiff bases **218** (X = O; Z = NMe, NCH_2Ph; R^1 = R^2 = Me), however, were found to exist exclusively in the form **218a**; the rotamers **218b** were not observed even at low temperatures (82JCS(P2)513). The introduction of an additional acyl group into the 5-position of **218** (X = Z = O) does not have any noticeable effect on the tautomeric equilibrium as 4-hydroxy group still preferentially chelates with the 3-acyl group (84JCS(P2)1317).

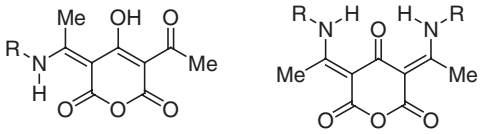
The UV spectra of 3-acetylpyran-2,6-diones **219** (R^1 = H, Me, R^2 = H; R^1 = Me, R^2 = COMe) are comparable to that of the isomeric pyran-2,4-diones **218**, except for significant red shift on addition of water to the solution, which indicates the presence of extensively delocalized anions in polar solvents. Schiff bases of **219** (R^1 = Me; R^2 = H) with aniline and *p*-toluidine exist predominantly in the amino–oxo form in chloroform solution (86JCS(P2)973).

Diacetyl-substituted pyran-2,4,6-trione **220** exists in the 2-pyrone tautomeric form shown in the solid state. This tautomer is also the predominant form in solution; however, the symmetrical 2,6-dioxo-4-hydroxy tautomer was also detected. Mono-Schiff

bases of **220** show predominance of the amino–oxo form **221** in solution, whereas bis-Schiff bases favor the trioxo–diamino form **222**. Unsymmetrical minor rotamers of **222** were also observed in ratios depending on the R substituent and the temperature (82JCS(P2)513, 95JCS(P2)1901).



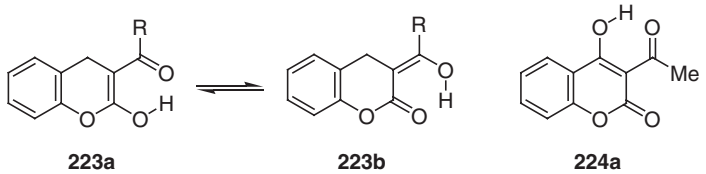
219a **219b** **220**



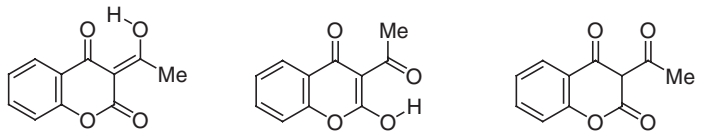
221 **222**

The steric and electronic effects of acyl substituents upon tautomeric equilibria of 3-acyl-3,4-dihydrocoumarins **223** (R = Me, *i*-Pr, *t*-Bu, Ph) have been studied by ^{1}H and ^{13}C NMR spectroscopy. The preference for the oxo form **223b** was shown to increase significantly with the increase in the effective size of the R substituent. Thus, the ratio **223a**:**223b** in $CDCl_3$ varies from 56:44 (R = Me) to 0:100 (R = *t*-Bu). Transition from $CDCl_3$ to acetone-d_6 shifts the equilibrium toward the tautomer **223b** for all the compounds studied (85JST(127)127).

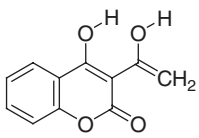
Tautomerism in 3-acetyl-4-hydroxycoumarin **224** has been investigated experimentally by UV spectroscopy and theoretically by the semiempirical MNDO, AM1 and PM3 and *ab initio* calculations (97CJC365, 00ZOB793). The tautomer **224a** was found to be predominant in non-polar solvents (hexane, CCl_4), whereas in polar solvents (methanol, ethanol) the dioxo tautomer **224b** was favored. Calculations at all levels predict **224a** and **224b** to be more stable than the other possible tautomers and almost isoenergetic, the energy difference being only about 1 kcal/mol. Tautomers **224d** and **224e** were found to be the least stable forms.



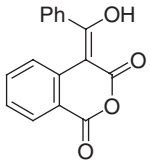
223a **223b** **224a**



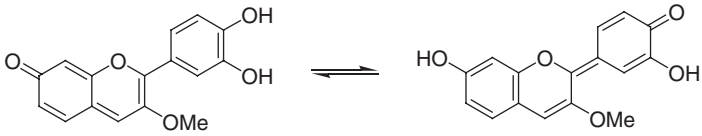
224b **224c** **224d**



224e



225



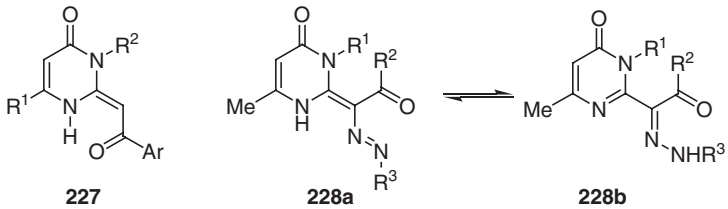
226a 226b

Benzoyl-substituted isobenzopyrandione **225** was shown to exist as exocyclic enol tautomer shown in the crystal by X-ray analysis (99AX(C)1591).

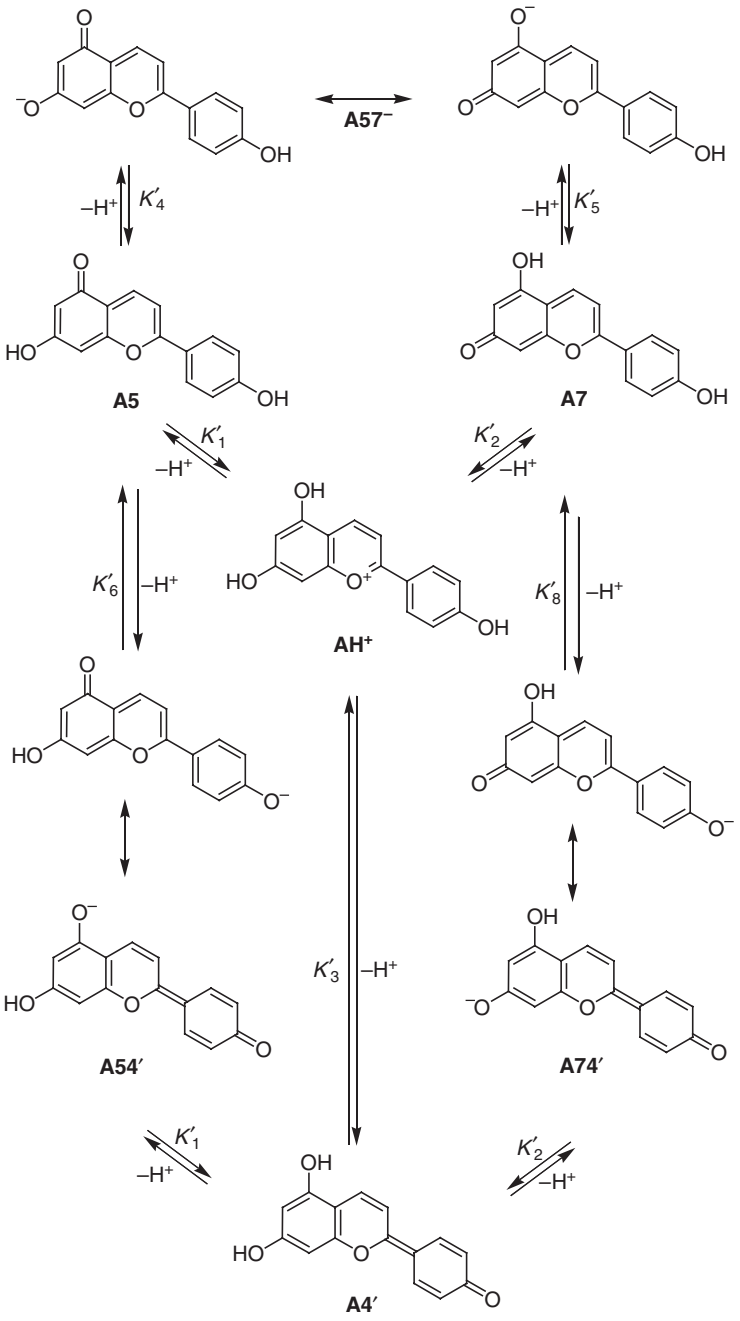
HyperChem calculations of the tautomerism of benzopyranone **226** indicated that the tautomer **226a** is more stable than **226b** by 1.4 kcal/mol (94JCS(P2)2587). The anthocyanidin apigeninidin, 5,7-dihydroxy-2-(4′-hydroxyphenyl)benzopyrylium chloride, may deprotonate, leading to the formation of three tautomeric neutral and anionic forms. Using the protonation constants, the tautomeric constants for both neutral and anionic forms of apigeninidin were determined. The abundance percentage of neutral tautomers was calculated from the tautomeric constants to be 81.8% **A7**, 17.5% **A5**, and 0.7% **A4′**. Analogous calculations for the anionic forms provided 83.9% $\mathbf{A57}^-$, 11.9% $\mathbf{A74'}^-$, and 4.2% $\mathbf{A54'}^-$. These experimental data on the neutral forms agree qualitatively with the results of AM1 calculations, which predicted the form **A4′** to be less stable than **A5** and **A7** by 4.1 and 2.9 kcal/mol, respectively (95JCS(P2)227) (Scheme 1).

3. *Pyrimidines and Quinazolines*

2-Phenacyl-4-pyrimidinones **227** ($R^1 = H$, $R^2 = Me$; $R^1 = Me$, $R^2 = H$, Me; Ar = Ph, 4-BrC_6H_4, 4-MeC_6H_4) were shown to exist exclusively in the benzoylmethylene tautomeric form shown both in solution ($CDCl_3$, DMSO-d_6) and in the solid state. AM1 calculations of the parent system are in agreement with the experimental observations (89CB919, 04T3051). In contrast, their α-azo-substituted analogs **228** ($R^1 = H$, Me; $R^2 = Ph$, 4-MeC_6H_4; $R^3 = 4$-$MeOC_6H_4$, 3-ClC_6H_4, etc.) exist predominantly in the hydrazone tautomeric form **228b** (04T3051).



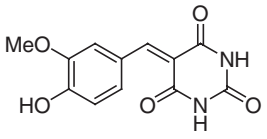
227 228a 228b



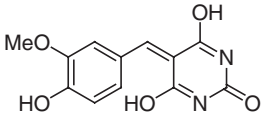
Scheme 1

IR and UV spectroscopy as well as AM1 semiempirical calculations were employed to investigate the stucture of arylidenebarbiturate **229** (97IZV739). Of nine tautomers possible, only trioxo form **229a** was observed in polar aprotic solvents. The AM1 calculations confirmed the highest stability of **229a**. In proton-donating media, however, the tautomer **229b** was also detected along with **229a**. In alkaline water–dioxane solutions with a high content of alkali, the tautomer **229b** becomes predominating.

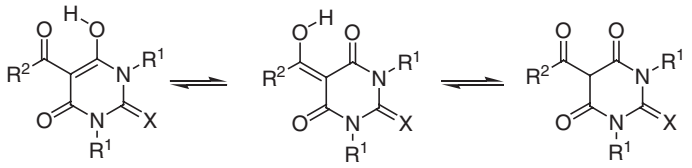
The tautomerism of acyl derivatives of barbituric acid **230** (X = O; R^1 = H, Me; R^2 = H, Me, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$) was studied by NMR, UV, and IR spectroscopy and quantum-chemical calculations. For 5-formyl- and 5-acetyl derivatives, a tautomeric equilibrium between two enol forms **230a** and **230b** was observed in aqueous solution as well as in alcohols and dioxane. The tautomer **230b** predominates in solutions of **230** (R^2 = H), whereas the acetyl analog favors the tautomer **230a**. A similar tautomeric equilibrium was observed for 4,6-dihydroxy-2-methylthiopyrimidine with enol of type **230a** being the major tautomer (02ZOB949). Deuterium isotope effects studies showed that the position of the tautomeric equilibrium is unaffected by the steric demands of the acyl group (98MRC315). Aroyl-substituted barbiturates exist primarily as exocyclic enols **230b** in DMSO and water. The trioxo form **230c** is suggested to be the dominant or only present tautomer in solvents incapable of forming strong hydrogen bonds with deprotonated barbiturates (04JHC233). Hydrazones **231** of aroyl barbiturates exist in acidic polar media and in the solid state in the enaminone form **231a**, while in neutral polar media the tautomer **231b** is also present (04JHC233).



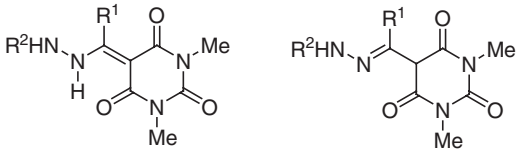
229a



229b



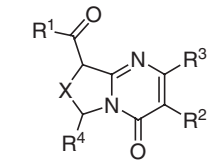
230a **230b** **230c**



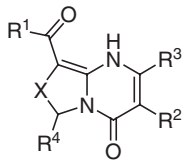
231a **231b**

^{1}H and ^{13}C NMR spectroscopic studies indicated that for 9-formyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **232** (X = $(CH_2)_2$; R^1 = R^3 = H; R^2 = H, CN, Ph,

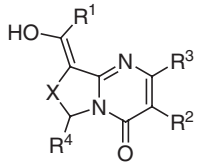
COOEt; R^4 = H, Me) the tautomeric equilibrium is dominated by tautomer **232b**, which is stabilized by internal hydrogen bonds. The presence of about 15% of **232c** in the equilibrium was shown by ^{15}N NMR spectroscopy, while no **232a** could be detected (83JCS(P2)1153). The position of the tautomeric equilibrium in oxalates **232** (X = $(CH_2)_n$; n = 1, 2; R^1 = COOEt; R^2 = H, COOEt, R^3 = H; R^2R^3 = $(CH_2)_4$; R^4 = H, Me) depends on the size on the ring fused to pyrimidine. Thus, oxalates **232** (X = CH_2) exist in solution as enols **232c**, whereas **232** (X = $(CH_2)_2$) favor the tautomeric form **232b** (89JCS(P2)1613). 9-Aminomethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and the corresponding pyrrolo and azepino homologs **233** (X = $(CH_2)_n$; n = 1–3; R_2N = NMe_2, NHPh) exist in the aminomethylene form shown either as *E*- or as mixtures of *E*- and *Z*-isomers (83JCS(P2)1409).



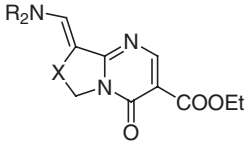
232a



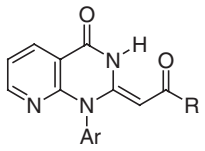
232b



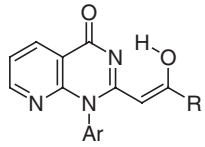
232c



233



234a

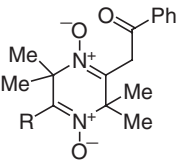


234b

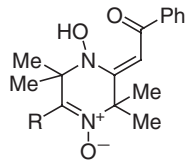
Pyridopyrimidinones **234** (Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, etc.; R = Me, Ph, 4-BrC_6H_4, PhNH) exist in solution as mixtures of two chelate tautomers **234a** and **234b**. No non-chelated tautomers were detected. The tautomer **234a** predominates for **234** (Ar = Ph; R = Me, Ph) in DMSO-d_6 solution (91KG1397).

4. *Pyrazines and Quinoxalines*

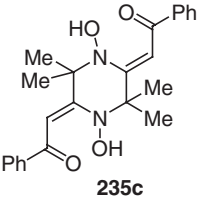
Benzoylmethyl-substituted pyrazine *N*,*N*′-dioxide **235** (R = Me) exists as a mixture of both tautomers (15% of **235a**) in $CDCl_3$ solution. All three tautomers **235a–c** were observed for bis(benzoylmethyl) derivative **235** (R = $PhCOCH_2$) in solution. In the latter case, the tautomer **235a** is the predominant form, whereas the molar fraction of **235c** is the smallest (93IZV885).



235a

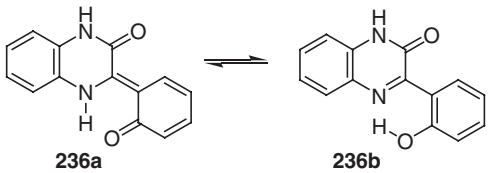


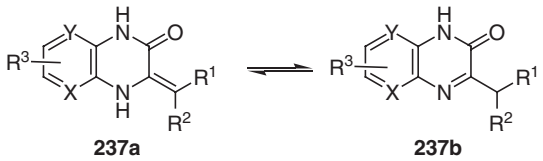
235b



235c

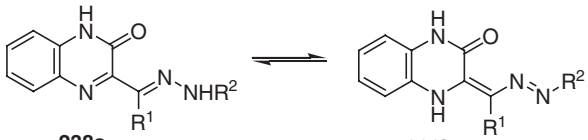
3-(2-Hydroxyphenyl)quinoxalin-2-one **236** exists exclusively in the *o*-quinoid form **236a** neat or in alcohol solution (77KG1126). The tautomeric equilibrium **237a** ⇌ **237b** was observed in series of 1,3,4-oxadiazol-2-ylmethyl-substituted quinoxalines in neutral and protonated states (83H(20)1917) and electron-deficient group-activated methyl quinoxalines **237** (X = Y = CH; R^1 = CN, COMe, COOEt, COPh; R^2 = H, Me; R^3 = H, Me, Cl) (76JHC681, 78CCC1634, 97JHC773). The position of the tautomeric equilibrium in the latter significantly depends on the substitution pattern including remote substituents in the aromatic ring. Thus, transition from R^1 = CN, COOEt to R^1 = COMe increases the molar fraction of the enamine **237a** from 63% to 96%. The increase in molar fraction of **237a** can also be achieved by introduction of an electron-accepting group into the benzo ring, whereas replacement of R^2 = H by R^2 = Me has the opposite effect (78CCC1634). Quinoxalines **237** (R^1 = benzoyl, isonicotinoyl, 2-furoyl; R^2 = H) exist exclusively in the enamine form **237a** both in solution and in the solid state (76JHC681, 78CCC1634). Similarly, **237** (R^1 = 2,5-$(MeO)_2C_6H_3CO$; R^2 = R^3 = H) exists in the enamine form **237a** in the solid state, while **237** (R^1 = PhCO; R^2 = Me; R^3 = H) favors the imine form **237b** (97JHC773).





Aza analogs **237** (X = N; Y = CH; R^1 = COOEt, COPh; R^2 = Me; R^3 = H) exist as tautomers **237b** in solution, whereas the enamine form **237a** was observed for **237** (X = N, Y = CH; X = CH, Y = N; R^1 = COMe; R^2 = R^3 = H). The tautomeric interconversion of the latter is temperature-dependent: the content of the imino form **237b** increases at higher temperatures (97JHC773).

3-(Arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **238** (R^1 = H, COOMe, PhCHOH, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazol-2-yl) exist in tautomeric equilibrium between the hydrazone imine **238a** and diazenylenamine **238b** forms (86H(24)2321, 86JHC637, 86JHC957, 86JHC1245, 90JCS(P1)2513, 94JHC527, 96JHC421, 97JHC305). The presence of an electron-withdrawing group in the α-position of the side chain (R^1) increases the molar fraction of **238a** regardless of the character of the aryl substituent. However, when R^1 = H, the presence of an electron-withdrawing group in the aromatic ring of R^2 substituent tends to elevate the molar fraction of **238b**. In acidic media, the tautomeric equilibrium is claimed to be shifted toward the tautomer **238b**. The similar tautomeric equilibrium was observed in solutions of pyrazolylhydrazono analogs **238** (R^1 = H, COOMe; R^2 = 4-ethoxycarbonylpyrazol-2-yl, 3-cyano-4-methylpyrazol-2-yl) (89JHC857).

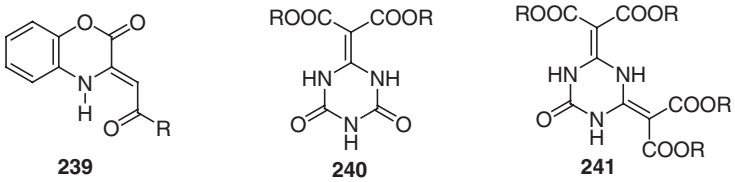


238a 238b

5. *Other Heterocycles*

2*H*-1,4-Benzoxazin-2-ones **239** (R = Ph, 4-pyridyl, 2-furyl) exist both in the crystalline state and in solution in the enamine form shown stabilized by internal hydrogen bond (76JHC681).

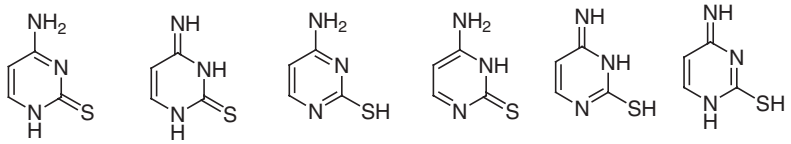
Mono- and bis-malonic ester derivatives of 1,3,5-triazine **240** and **241** were studied in various solvents by UV and ^{1}H NMR spectroscopy. The enamine structures as shown predominate in $CHCl_3$, dioxane, MeOH, and H_2O; however, a small amount of the enolate was observed for **241** in acetonitrile and a larger amount in DMSO, DMF and cyclohexylamine. Approximately 33% of **241** exists in the enol form in $CDCl_3$/DMSO-d_6 (1:1) at 0 °C. In a basic solvent, **241** exists as a tautomeric mixture of the enamine form and resonance-stabilized enolate ions (75JHC295).



239 240 241

H. Compounds with Mercapto(Thioxo) and Amino(Imino) Groups

Six tautomeric forms **242a–f** are possible for 2-thiocytosine. IR absorption spectra of 2-thiocytosine and 5-fluoro-2-thiocytosine, isolated in low-temperature gas matrices and in thin polycrystalline films showed that both compounds exist in amino-thiol form **242c** in the gas phase, whereas in films only amino-thione tautomer **242a** was detected (93SA(A)551). The absorption, circular dichroism, and magnetic circular dichroism spectra indicated that 2-thiocytosine exists in tautomeric equilibrium of thione (**242a** or **242b**) and thiol **242c** forms in solution in water, methanol, and acetonitrile (81BBA(656)1).



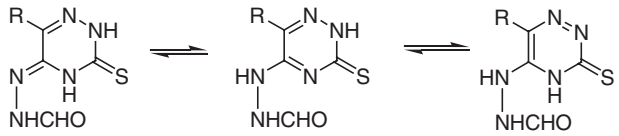
242a 242b 242c 242d 242e 242f

MNDO semiempirical calculations of 2-thiocytosine showed that tautomers **242a** and **242c** should be predominant species at ambient and low temperature, whereas at

high temperatures the tautomer **242f** should become important. The aromatic form **242c** is predicted to be the most stable at ambient temperature (91JST(251)195). The thiol–thione tautomeric equilibrium **242a** ⇌ **242c** of 2-thiocytosine has been studied by semiempirical AM1, PM3, and MNDO methods both in the gas phase and in aqueous solution. AM1 and PM3 methods predict the predominance of the thiol form in the gas phase, but favor the thione form in aqueous solution. MNDO method indicates the thiol form to be the major one in both phases (03JST(625)31). Free energies of solvation were calculated for the four stable gas-phase tautomeric forms of 2-thiocytosine using SCF procedure with the SM2 solvation model. The calculated changes in free energies favor the amino-thione species **242a** and **242d** (95JPOC395).

The relative stabilities of tautomers of 5-methyl-2-thiocytosine in the gas phase have been investigated by all-valence CNDO/2 method. The following order of stability is predicted: **242a** > **242d** > **242b** > **242e** > **242f** > **242c**, with the amino-thiol tautomer **242c** being the least stable form in contradiction to the experimental findings (86IJC(A)1072).

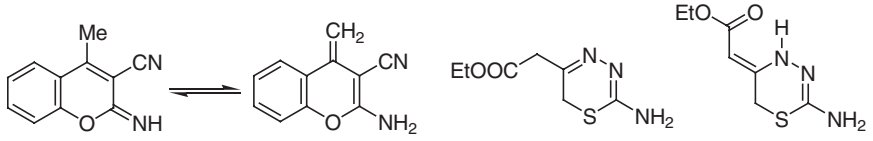
NMR studies and PCILO calculations of the tautomerism of triazinethiones **243** (R = H, Me) favor the imino-thione form **243a** both in the gas phase and in solution (79RTC503).



243a **243b** **243c**

I. Compounds with Amino(Imino) and Methylene Groups

On dissolution in DMSO-d_6, 2-imino-4-methyl-2*H*-benzopyran-3-carbonitrile **244a** undergoes [1,5] tautomeric shift to 2-amino-4-methylidene-4*H*-benzopyran-3-carbonitrile **244b**, providing the equimolar mixture of tautomers after 48 h at ambient temperature (96JCS(P1)1067).

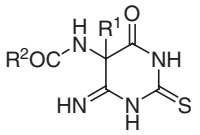


244a **244b** **245a** **245b**

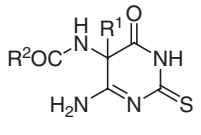
According to the UV, IR, and ^{1}H NMR spectra, the tautomeric form **245b** of ethyl 2-amino-6*H*-1,3,4-thiadiazine-5-acetate usually prevails in solution. The tautomer **245a** was observed only in trifluoroacetic acid (78JHC401).

J. Compounds with Three Different Potentially Tautomeric Groups

5,5-Disubstituted 6-amino-2-thiouracil analogs **246** (R^1 = Me, allyl, *i*-Pr, $PhCH_2$; R^2 = H, Me, Ph) exist in DMSO-d_6 solution in the tautomeric form **246a**. Such tautomeric preference is different from that of 6-amino-2-thiouracil, which is known to exist in the amino form (90JCS(P2)1001). The tautomeric equilibrium of 6-amino-2-thiouracil **208** (X = S) was studied using the all-valence CNDO method. The hydroxy-thione form was found to be the most stable in the gas phase, and the following order of the relative stability of the tautomers was predicted: **208a** > **208b** > **208d** > **208e** > **208c** > **208h** > **208f** > **208g** > **208i** (86IJC(A)256). The thiol–thione tautomeric equilibrium **208a** ⇌ **208b** of 6-amino-2-thiouracil in the gas phase and in aqueous solution was studied by semiempirical AM1, PM3, and MNDO methods. Both AM1 and MNDO methods predict the predominance of the mercapto form in the gas phase. In aqueous solution, however, AM1 and PM3 methods predict the highest stability of the thione form, whereas MNDO method still favors the thiol (03JST(625)31).



246a



246b

The relative energies of tautomeric and rotameric forms **218** (X = S, Se; Z = NMe; R^1 = R^2 = H) as well as barriers to N→X hydrogen transfer were estimated by *ab initio* calculations with the 6-31G* basis at the HF and MP2 levels. The form **218a** was found to be the most stable for **218** (X = Se) by all methods used; however, the HF method predicted the form **218b** to be the most stable for **218** (X = S). The calculated energy gap between the tautomers **218a** and **218b** was found to be rather significant for **218** (X = Se) (ΔE = 3.8–5.5 kcal/mol) but negligible for the sulfur analog (<0.7 kcal/mol). The tautomer **218c** was found to be less stable than **218a** by 11–14 kcal/mol (93JCS(P2)2423).

Tautomerism of 5-formyl- and 5-acetyl derivatives of 2-thioxopyrimidine-2,4-dione **230** (X = S; R^1 = H; R^2 = H, Me) has been studied by NMR, IR, and UV spectroscopy as well as semiempirical AM1 and PM3 methods. The equilibrium between the two enol forms **230a** and **230b** was observed in solution with the tautomer **230a** slightly preferred for **230a** (R^2 = Me) (02ZOB949).

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Homologation of Heterocycles by a Sequential Reductive Opening Lithiation–Electrophilic Substitution–Cyclization

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I. Introduction

The development of new methodologies for the conversion of simple reactants into more complex compounds is the main goal of synthetic organic chemistry (99MI1). For instance, transforming readily available small heterocycles into much less

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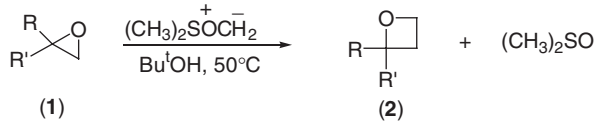
common medium-sized rings would be of great interest, because many biological active compounds possess medium-sized heterocyclic units in their structure (91MI2). Thus, synthetic approaches for heterocyclic compounds require the development of methodologies for easily repeatable heterocycle homologation and multicarbon ring expansion.

A. Methods for Homologation of Heterocycles

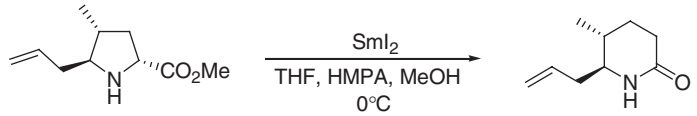
Many methodologies have been developed for the ring expansion of heterocycles involving different reaction intermediates, such as carbenes, nitrenes, radicals and a large number of anionic species; these processes being promoted thermically, photochemically or by means of transition metals.

The reaction of epoxides (**1**) with trimethylsulfoxonium ylide leads to oxetanes (**2**) in high yields through a nucleophilic ring opening followed by intramolecular dimethylsulfoxide elimination (Eq. (1)) (83JOC5133). This is probably the simplest homologation reaction of a three-membered heterocycle.



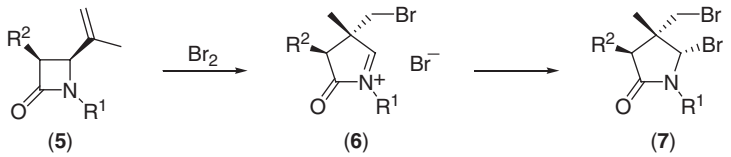
(**1**) (**2**) (1)

Reductive deamination of pyrrolidine (**3**) with samarium diiodide in THF-HMPA in the presence of methanol as the proton source yielded the desired piperidone (**4**) stereoselectively in 90% yield (Eq. (2)), where a carbon–nitrogen bond cleavage reaction and subsequent recyclization took place simultaneously (05TL5161).



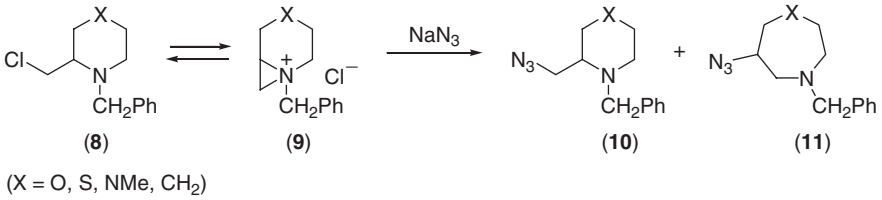
(**3**) (**4**) (2)

Diastereoselective ring expansion of β- toward γ-lactams *via* *N*-acyliminium intermediates have also been described (05JOC3369, 00T3871, 85T4367). Thus, when 4-isopropenylazetidin-2-ones (**5**) were treated with bromine in dichloromethane, a diastereoselective electrophile-induced ring expansion toward 5-bromopyrrolidin-2-ones (**7**) took place, acyliminiums (**6**) acting probably as the reaction intermediates (Scheme 1) (05JOC8717).



(**5**) (**6**) (**7**)

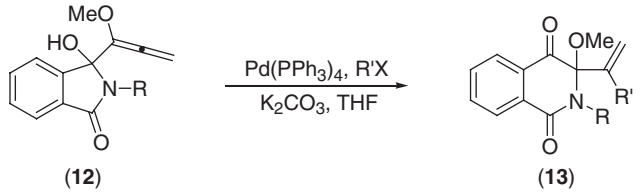
Scheme 1



Scheme 2

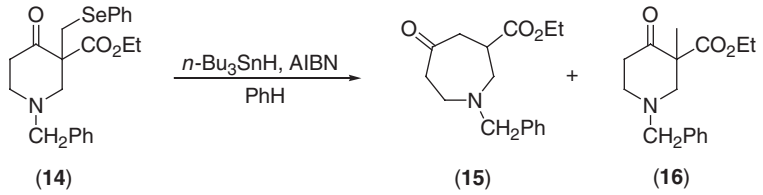
The reaction of sodium azide with chloromethyl heterocycles (**8**) derived from morpholine, thiazine, piperazine and piperidine gave the corresponding ring-expanded compounds (**11**) along with the normally substituted compounds (**10**) *via* the postulated aziridinium intermediate (**9**) (Scheme 2) (94JCS(P1)2565).

Palladium(0)-catalyzed one-atom ring expansion of various hydroxylic methoxyallenylisoindolinones (**12**) proceeded in the presence of aryl and vinyl halides to give the corresponding isoquinolinediones (**13**) in various yields (Eq. (3)). Tandem intramolecular carbo-palladation-heterocyclic ring expansion reaction of compound (**12**) was also achieved to give a tetracyclic compound (02SL480, 98TL8677).



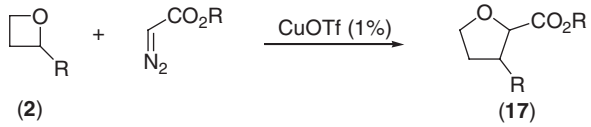
(3)

The treatment of phenylselenomethyl nitrogen-, oxygen- and sulfur-containing heterocyclic β-ketoesters with tri-*n*-butyltin hydride leads to smooth one-carbon ring expansion through the corresponding radical intermediate. Thus, in the case of the piperidine β-ketoester derivative (**14**), the expected azetidine (**15**) was obtained in 15% yield along with the undesired direct reduction product (**16**) in 26% yield (91T4847).



(4)

Copper catalysts promote the ring expansion of oxetanes (**2**) to tetrahydrofurans (**17**) by reacting with diazocompounds. The stereochemistry of these processes can be controlled by performing the reactions in the presence of chiral ligands. For this purpose, C_2-symmetric bipyridine (96T3905) as well as bisazaferrocene ligands (01T2621) have been used.

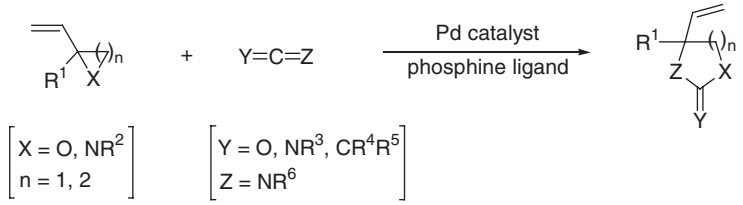


(2) (17) (5)

Carbenes, generated by thermolysis of α-oxacyclo- and α-azacyclo-*N*-aziridinylimines in refluxing toluene, underwent ring expansion *via* insertion into carbon–carbon bonds and intramolecular ammonium ylide formation, respectively. Ring expansion reaction of α-oxetanyl-*N*-aziridinylimines occurred *via* alkylidenecarbene intermediates, whereas thermal reaction of α-azetidinyl-*N*-aziridinylimined afforded α-aminoacetylene compounds *via* 1,2-H migration of the same intermediates (00S1622). Fischer carbene complexes react with some 1,2-dithiole-3-thiones to give cyclohexadithiine derivatives by insertion of the carbene ligand into the C3–C4 bond of the heterocycle (02TL8037).

The introduction of a carbonyl moiety into an organic molecule using carbon monoxide requires the presence of a transition metal complex either as a catalyst or as a stoichiometric reactant. The insertion of carbon monoxide into a carbon–heteroatom bond of the heterocyclic compound comprises a simultaneous ring expansion and functionalization of a heterocyclic substrate. The carbonylation reaction provides a very convenient and effective one-step procedure for ring homologation (95ACR414).

The ring expansion of heterocycles can be performed to produce new heterocycles with two (bishomologation), three or even more carbon atoms or heteroatoms in the ring unit. Thus, the palladium-catalyzed ring-opening cycloaddition reactions of vinyloxiranes (97JA3709, 98JOC6229), vinyloxetanes (99JOC4152), vinylaziridines (00JOC5887) and 2-vinylthiiranes (01JOC3502) with heterocumulenes lead to the regio- and stereoselective formation of five- and six-membered heterocycles (Eq. (6)).

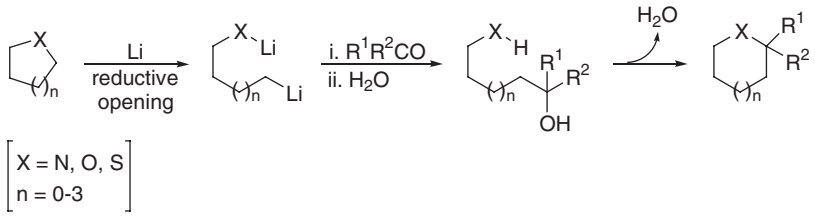


(6)

A three carbon ring expansion of α-vinyltetrahydrothiophene and 2-vinyl-*N*-benzylpyrrolidine was accomplished by the conversion of these heterocycles into the corresponding ylides (by alkylation followed by deprotonation), which underwent a [2,3]sigmatropic shift, giving the corresponding eight-membered heterocycles (78JOC1185).

B. Reductive Opening of Heterocycles as a Source of Functionalized Organolithium Compounds

Functionalized organolithium compounds (91MI3, 95OPP383, 97MI4, 03T9255, 04CRV2667) are of great interest in organic synthesis because polyfunctionalized molecules are obtained by reaction with electrophilic reagents in a single synthetic



Scheme 3

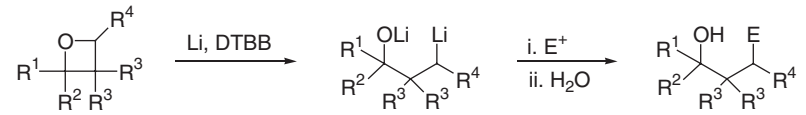
operation (95MI5, 02MI6). Functionalized organolithium compounds can be prepared by halogen–lithium exchange, metal–lithium exchange, direct deprotonation, addition of organolithium compounds to unsaturated systems, and also by reductive opening of different appropriate oxygen-, nitrogen- and sulfur-containing heterocycles (97RHA73, 02MI7). The last methodology is probably the most elegant and direct strategy considering atom economy. Since most functionalized organolithium compounds are very unstable molecules, they have to be prepared at low temperature in order to avoid their decomposition. For that purpose, in the last few years a methodology consisting of the use of an excess of lithium in the presence of a catalytic amount of an arene has been developed as a lithiating agent, naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the most commonly used electron carriers (96CSR155, 00EJO225, 01SL1197). Some requirements should be accomplished in order to get the reductive opening of a heterocycle: (a) small heterocycles (three- and four-membered rings) can easily be opened due to a release of the strain energy and (b) heterocycles with activated bonds can be reductively broken by means of the above-mentioned lithiating reagent, as in the case of compounds with allylic (98JA2534, 98TL3303, 00T1745, 00TL1661) and benzylic (95TL5641, 97MI8, 97T16205) carbon–heteroatom bonds, as well as cyclic aryl ethers (87AGE972, 89JA8640, 00JOC322, 90JOC5386, 92JOC1444) and thioethers (78JOC1064, 79JOC713, 89ACR152).

Specically interesting is the reaction of functionalized organolithium compounds, resulting from the reductive opening of heterocycles, with a carbonyl compound because after hydrolysis functionalized alcohols are obtained. These polyfunctionalized molecules can undergo intramolecular dehydration to afford a new regioselectively substituted heterocycle, which is homologous to the starting material (Scheme 3). A compilation of most of the heterocycle homologation processes by the tandem reductive opening lithiation-electrophilic substitution by reaction with a carbonyl compound dehydration, which have been reported in the literature, follows.

II. Homologation of Four-Membered Heterocycles

A. Oxetanes

Cohen and Mudryk reported in 1989 for the first time the reductive opening of oxetanes (89JOC5657). Thus, treatment of oxetanes **2** with lithium and a stoichiometric



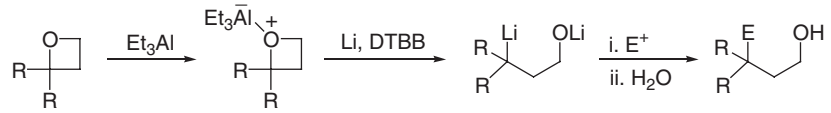
(**2**) (**18**) (**19**)

(45-87%)

a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = R^2 = R^4 = H$, $R^3 = Me$
c: R^1-$R^2 = (CH_2)_5$, $R^3 = R^4 = H$
d: $R^1 = R^2 = R^3 = H$, $R^4 = Ph$

[$E^+ = CO_2$, CH_2=CHCHO, (*E*)-PhSCH=CHCHO, *p*-$MeOC_6H_4CHO$, $(CH_2)_5CO$]

Scheme 4



(**2**) (**18**) (**19**)

(38-68%)

c: R-R = $(CH_2)_5$
e: R = Me

[$E^+ = Pr^iCHO$, Bu^tCHO, (*E*)-MeCH=CHCHO, PhCHO, $(CH_2)_5CO$]

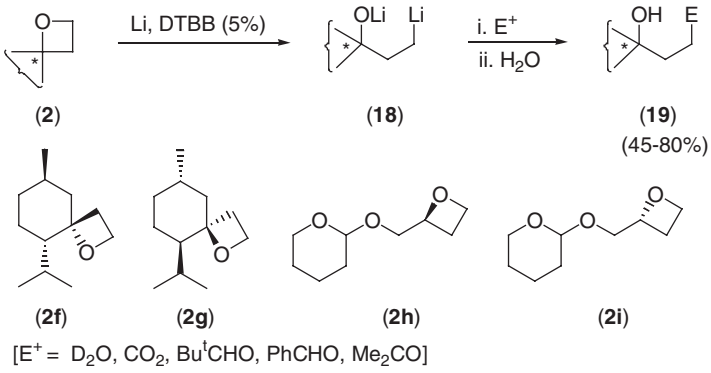
Scheme 5

amount of DTBB in THF at 0 °C gave dianionic species **18**, which by reaction with electrophiles and final hydrolysis yielded functionalized alcohols **19** (Scheme 4). Regarding the regiochemistry of the process for unsymmetrical substituted oxetanes, the reductive opening takes place always to give the most stable organolithium compound **18**, which are the less substituted ones except in the case of the benzyl derivative (**18d**) (Scheme 4).

When reductive opening of unsymmetrical oxetanes takes place in the presence of a Lewis acid, such as $AlEt_3$, the regiochemistry of the ring cleavage is the opposite to that commented above, this strategy being complementary to the former one (Scheme 5) (91JOC5760).

Enantiomerically pure functionalized alcohols **19** are obtained from chiral oxetanes (**2f**)–(**2i**), derived from menthone and glycidol, when the reductive opening is performed with lithium and a substoichiometric amount of DTBB in THF at 0 °C, followed by the reaction with electrophiles and final hydrolysis with water (Scheme 6) (97TA2633).

The above shown methodology has found wide application in organic synthesis. For instance, the reaction of intermediates (**18**) with carbonyl compounds gives 1,4-diols that undergo cyclization leading to tetrahydrofurans (**20**) under acidic conditions (Table 1).

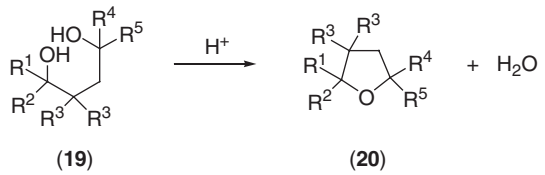


Scheme 6

Table 1. Preparation of tetrahydrofurans (**20**) from oxetanes (**2**)

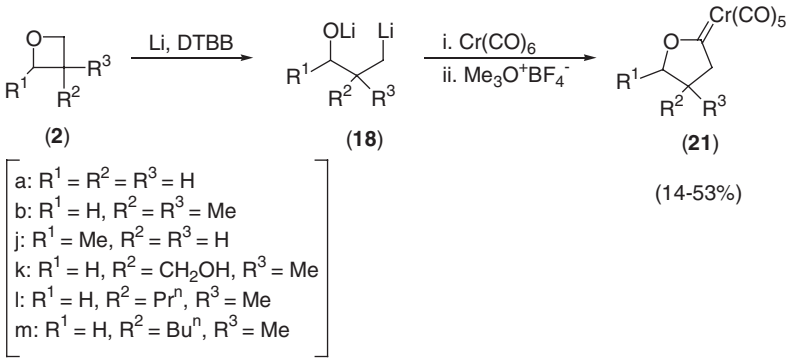
	Starting	Product						
Entry	Oxetane	No.	R^1	R^2	R^3	R^4	R^5	Yield (%)
1	(**2a**)	(**20a**)	H	H	H	H	p-$MeOC_6H_4$	93[a]
2	(**2a**)	(**20b**)	H	H	H	H	PhSCH = CH	76[a]
3	(**2a**)	(**20c**)	H	H	H		$(CH_2)_5$	85[a]
4	(**2a**)	(**20d**)	H	H	H		$CH = CH(CH_2)_3$	76[a]
5	(**2h**)	(**20e**)	Me	Me	H	H	$CH_3C = CHCH_3$	57[b]
6	(**2h**)	(**20f**)	H	$THPOCH_2$	H		$(CH_2)_5$	95[a]
7	(**2i**)	(**20g**)	H	$THPOCH_2$	H		$(CH_2)_5$	95[a]

[a]Based on the diol (**19**).
[b]Based on the starting oxetane (**2**).

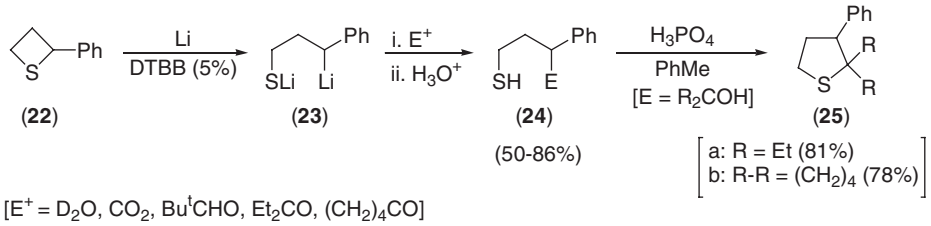


(7)

In the case of using lactones as electrophiles in the presence of cerium trichloride, spiroketals are obtained after acidic work-up (90JA6389). Cyclic Fischer-type chromium carbene complexes (**21**) have also been prepared when hexacarbonyl chromium was added to intermediates (**18**), followed by treatment with trimethyloxonium tetrafluoroborate (Scheme 7) (92JCS(CC)1623).



Scheme 7



Scheme 8

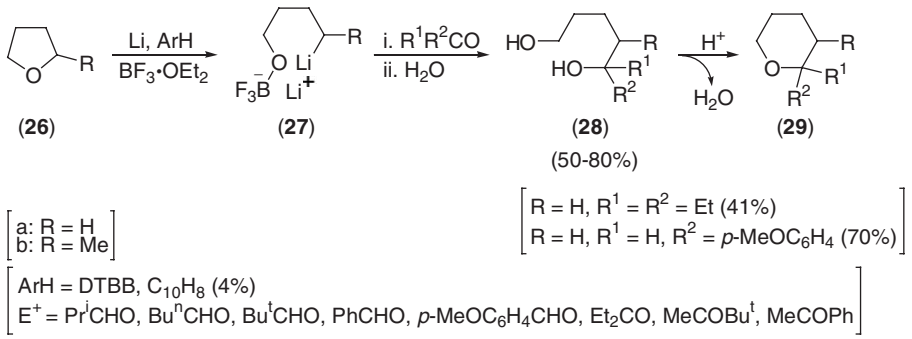
B. Thietanes

Oxetanes (**2**) undergo reductive opening by means of alkali metals in the presence of an arene, but thietane itself or alkyl-substituted thietanes are stable compounds toward the same reductive reagents because they are less-strained heterocycles due to the longer carbon–heteroatom bond distances. However, 2-phenylthietane (**22**) can be reductively opened with lithium in the presence of a catalytic amount of DTBB at low temperature. In this case, a phenyl group at 2-position is necessary for the reductive opening to take place in order to stabilize the γ-thiofunctionalized organolithium compound (**23**). The reaction of (**23**) with electrophiles gave, after acidic hydrolysis, functionalized thiols (**24**). When 3-pentanone and cyclopentanone were used as electrophiles, the resulting thiols (**24**) underwent acidic cyclization to give a good yield of tetrahydrothiophenes (**25**) (Scheme 8) (97T5563).

III. Homologation of Five-Membered Heterocycles

A. Tetrahydrofurans

In sharp contrast to the behavior of epoxides and oxetanes, tetrahydrofuran itself (**26a**) does not undergo reductive opening by means of lithium metal alone or even in



Scheme 9

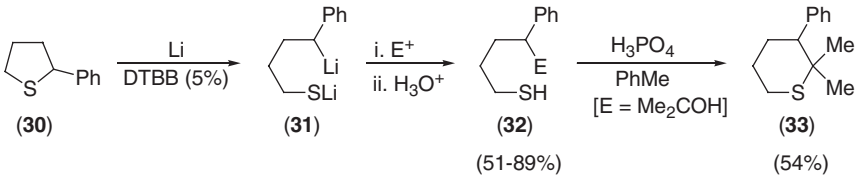
the presence of arenes as electron carriers at low temperatures. However, it is also possible to carry out this process at low temperature but necessarily in the presence of boron trifluoride etherate. Thus, treatment of the complex resulting from (**26a**) and the Lewis acid with lithium and DTBB in a stoichiometric ratio at –78 °C leads to δ-oxygenated functionalized organolithium compound (**27a**), which after reaction with electrophiles and final hydrolysis with water gives functionalized alcohols (**28a**) (Scheme 9) (91JA1866). The same process can be performed using an excess of lithium and a catalytic amount of naphthalene as lithiating mixture (92T3585). In the case of 2-methyltetrahydrofuran (**26b**), the reductive ring opening leads to the formation of the more substituted organolithium derivative (**27b**), in a similar way as for oxetanes (see above) (Scheme 9) (91JA1866). Acidic cyclization of compounds (**28**) gives the corresponding tetrahydropyrane derivatives (**29**) (Scheme 9).

B. Tetrahydrothiophenes

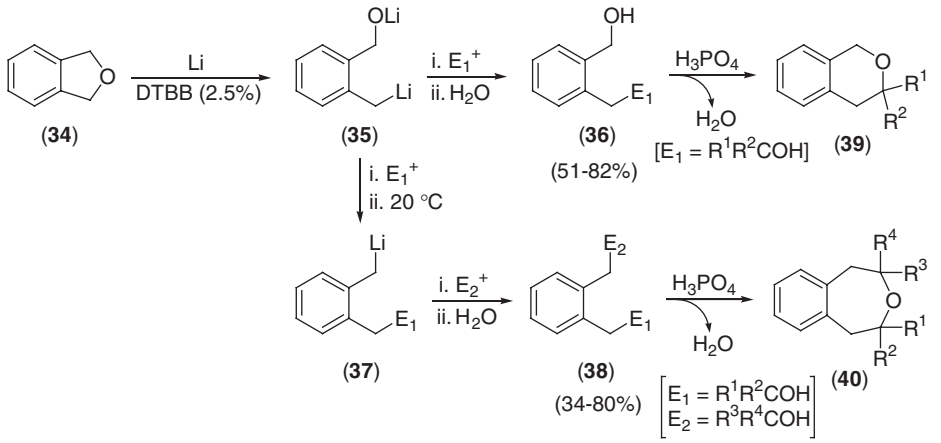
Reductive opening of 2-phenyltetrahydrothiophene (**30**) takes place by treatment with lithium in the presence of a catalytic amount of DTBB at low temperature to give the benzylic dianion (**31**) in a similar way as for thietane (**22**) (e.g., see Section II.B). The reaction with electrophiles followed by hydrolysis gives functionalized thiols (**32**). The treatment of the sulfanyl alcohol obtained by addition of acetone as electrophile with 85% phosphoric acid leads to the expected tetrahydrothiopyran (**33**) (Scheme 10) (97T5563).

C. Phthalan: A Versatile Starting Material

Phthalan (**34**) is opened reductively with lithium and a catalytic amount of DTBB at 0 °C to afford the dianion (**35**), which has shown a wide use in organic synthesis, reacts with electrophiles at –78 °C, and final hydrolysis, functionalized alcohols (**36**) (Scheme 11) (95T3351). The lithiation of compound (**34**) can be directed to the introduction of two different electrophiles at both benzylic positions in a sequential manner. Thus, after the addition of the first electrophile E_I^+, the resulting alcoholate



Scheme 10



Scheme 11

is stirred in the presence of the excess of lithiating mixture at room temperature for four additional hours to give a new organolithium intermediate (**37**), which finally reacts with a second electrophile E_2^+ to yield difunctionalized products (**38**) (Scheme 11). Diols (**36**) derived from the reaction of the intermediate (**35**) with carbonyl compounds ($E_1^+ = R^1R^2CO$), are easily cyclized under acidic conditions to give the corresponding six-membered benzocondensed cyclic ethers (**39**) (Scheme 11) (Table 2), whereas, diols (**38**) derived from the reaction with two carbonyl compounds ($E_1^+ = R^1R^2CO$, $E_2^+ = R^3R^4CO$) under acidic conditions leads to tetrahydrobenzoxepines (**40**) (Scheme 11) (Table 2).

Using *N*-silylaldimines as electrophiles, aminoalcohols (**41**) are obtained as reaction products, which after chlorination followed by cyclization under basic conditions lead to the formation of tetrahydroisoquinolines (**42**) (Figure 1) (00JHC1061). When ketones derived from D-fructose, and D-glucose, as well as *O*-ethoxymethyl-substituted estrone and (–)-menthone are used as electrophiles, diols (**36f**)–(**36i**)

Table 2. Preparation of isochromans (**39**) and tetrahydrobenzoxepines (**40**)

	Product					
Entry	No.	R^1	R^2	R^3	R^4	Yield (%)
1	(**39a**)	H	Bu^t	–	–	82
2	(**39b**)	H	Ph	–	–	90
3	(**39c**)	Et	Et	–	–	83
4	(**39d**)	$(CH_2)_5$		–	–	96
5	(**39e**)	Ph	Me	–	–	94
6	(**40a**)	H	Bu^t	$(CH_2)_5$		68
7	(**40b**)	Me	Me	H	Et	71
8	(**40c**)	Et	Et	H	Et	52
9	(**40d**)	$(CH_2)_4$		H	Et	61

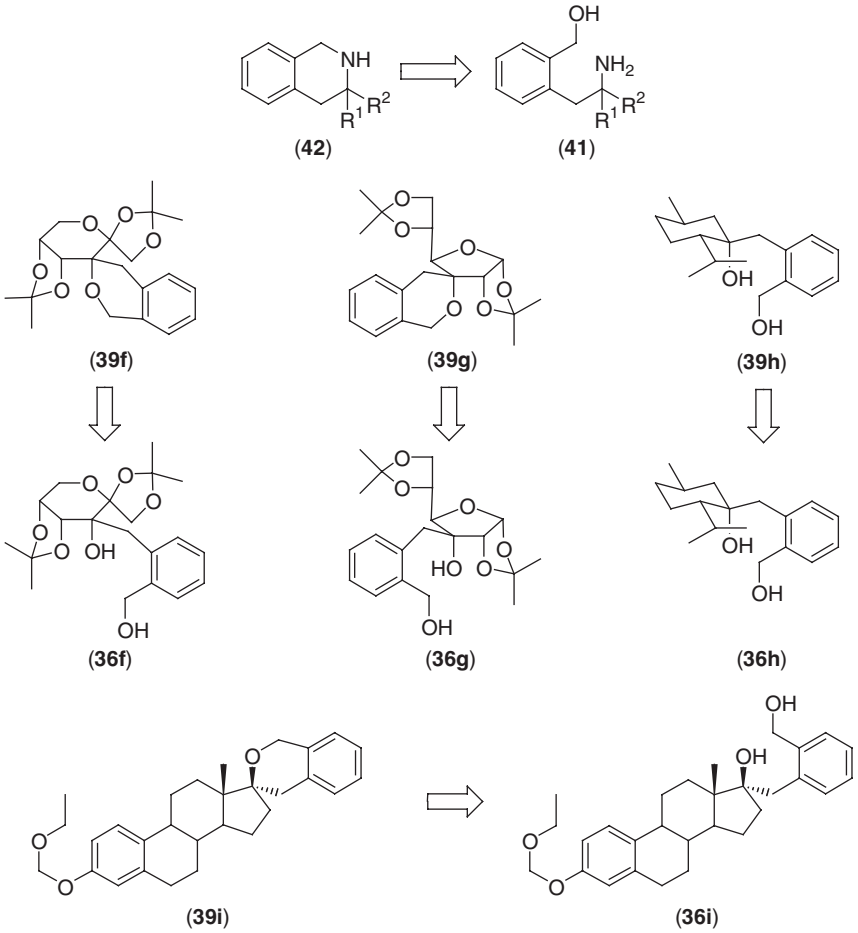


Figure 1. Homologation of phthalan (**34**)

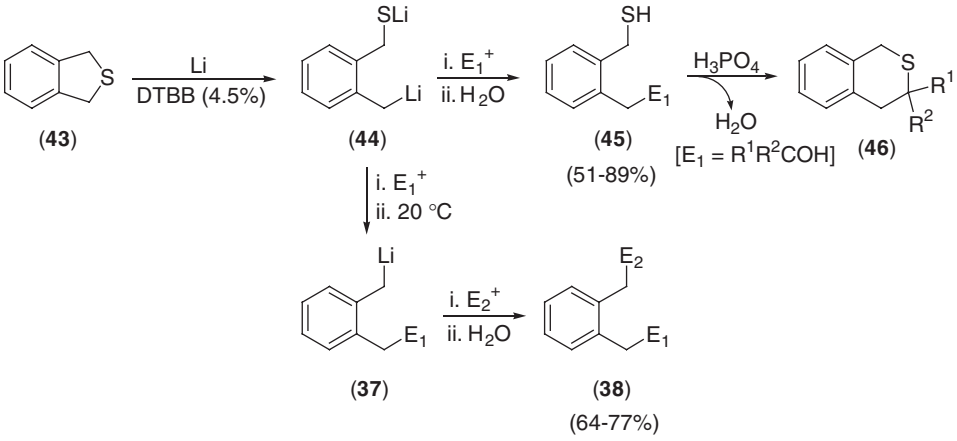
(00TA493, 01TA801, 04S1115) are obtained as reaction products (Figure 1). The transformation of these compounds into the expected isochroman derivatives (**39f**)–(**39i**) (98TA3939, 00TA2063, 04S1115) is easily achieved under typical Mitsunobu reaction conditions (Figure 1).

D. Thiophthalan

As it could be expected considering the reactivity of phthalan (**34**), thiophthalan (**43**) is reductively opened with lithium and a catalytic amount of DTBB at –78 °C (instead of 0 °C for (**34**)) in order to avoid undesired side reactions. The reaction of the resulting dianionic intermediates (**44**) with different electrophiles leads to compounds (**45**), after hydrolysis (Scheme 12) (96JOC1859). In a similar manner to phthalan (**34**) (see Scheme 11), in the case of thiophthalan (**43**), two electrophilic fragments can be introduced at both benzylic positions by a double sequential lithiation reaction with electrophiles through the intermediate (**37**) to give difunctionalized compounds (**38**). Thiols (**45**) derived from the reaction of intermediate (**44**) with carbonyl compounds ($E_1^+ = R^1R^2CO$), cyclize under acidic conditions to give thioisochromans (**46**) (Scheme 12) (Table 3).

E. 2,3-Dihydrobenzofuran

Cyclic alkyl aryl ethers lead also to functionalized organolithium compounds by reductive carbon–oxygen bond cleavage in arene-catalyzed lithiation process. Thus, the treatment of 2,3-dihydrobenzofuran (**47**) with an excess of lithium in the presence of a catalytic amount of DTBB in THF at 0 °C gives the dianion (**48**) which after reaction with different carbonyl compounds and final hydrolysis with water leads to

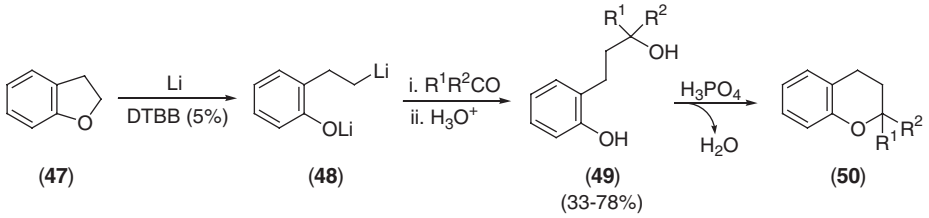


$E_1^+ = H_2O, D_2O, CO_2, EtCHO, Pr^iCHO, Bu^tCHO, PhCHO, (CH_2)_4CO, MeCOPh$
$E_2^+ = H_2O, D_2O$

Scheme 12

Table 3. Preparation of thioisochromans (**46**)

Entry	Product			
	No.	R^1	R^2	Yield (%)
1	(**46a**)	H	Pr^i	51
2	(**46b**)	H	Bu^t	35
3	(**46c**)	H	Ph	97
4	(**46d**)	Me	Me	89
5	(**46e**)	$(CH_2)_4$		85
6	(**46f**)	Me	Ph	94



Scheme 13

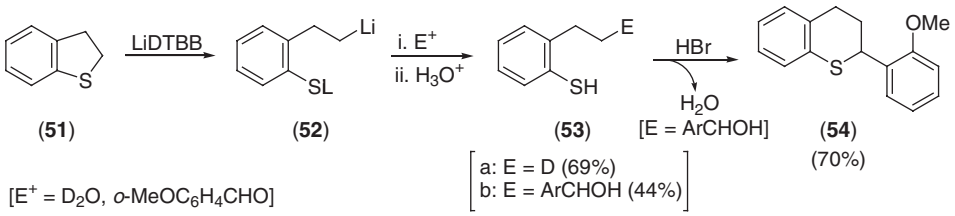
diols (**49**) (Scheme 13) (98TL7759, 02T4907). Dehydration of compounds (**49**) under acidic conditions leads to chromans (**50**) (Scheme 13) (Table 4).

F. 2,3-Dihydrobenzothiophene

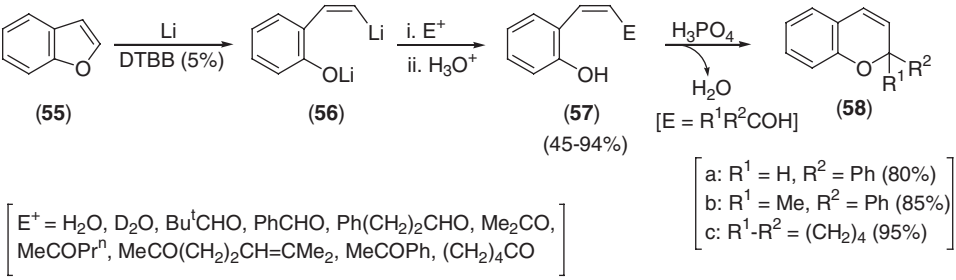
Screttas and Micha-Screttas (78JOC1064, 79JOC713) developed a methodology for the preparation of organolithium compounds starting from phenylthioethers, this procedure being an alternative to the use of chlorinated materials as precursors of this intermediates. Since then, the cleavage of the carbon–sulfur bond in phenylthioethers using either the stoichiometric or the catalytic version of the arene-mediated lithiation has been extensively used to generate organolithium compounds by sulfur–lithium exchange. The reductive cleavage of benzodihydrothiophene (**51**) with lithium di-*tert*-butylbiphenylide takes place at 0 °C to give the dilithium intermediate (**52**) which reacted with electrophiles to give compound (**53**). When *o*-methoxybenzaldehyde was used as an electrophile, the resulting sulfanyl alcohol underwent acidic cyclization to yield the thiochroman (**54**) in good yield (Scheme 14) (95TL4459).

Table 4. Preparation of chromans (**50**)

Entry	Product			
	No.	R^1	R^2	Yield (%)
1	(**50a**)	H	Ph	>95
2	(**50b**)	Et	Et	92
3	(**50c**)	$(CH_2)_5$		>95
4	(**50d**)	$(CH_2)_7$		68



Scheme 14



Scheme 15

G. 2,3-Benzofuran

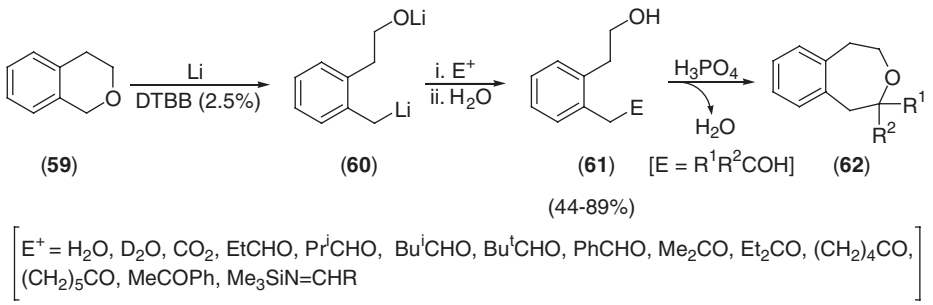
In the case of 2,3-benzofuran (**55**), a stereoselective ring opening lithiation takes place under the same reaction conditions as for 2,3-dihydrobenzofuran (**47**) shown in Scheme 13, yielding the (*Z*)-organolithium intermediate (**56**) which, by reaction with different electrophiles and final acidic hydrolysis, gives the expected (*Z*)-products (**57**). The cyclization of the products obtained by reaction of intermediate (**56**) with carbonyl compounds under acidic conditions, affords the expected substituted 2H-chromenes (**58**) (Scheme 15) (01EJO2809).

IV. Homologation of Six-Membered Heterocycles

A. Isochroman

Isochroman (**59**) undergoes a reductive opening with lithium and a catalytic amount of DTBB at 20 °C to afford the dianion (**60**), which after reaction with electrophiles and final hydrolysis leads to alcohols (**61**). Dehydration of these alcohols with H_3PO_4 allows the preparation of tetrahydrobenzoxepines (**62**). The whole process represents the homologation of the oxygen-containing starting six-membered heterocycle (**59**) (Scheme 16) (Table 5) (95T3365).

Similar to phthalan (**34**) (see Figure 1), when ketones derived from D-fructose, and D-glucose, *O*-ethoxymethylsubstituted estrone and (–)-menthone are used as electrophiles, the resulting diols (00TA493, 01TA801, 04S1115) were transformed by dehydration to benzoxepines (**62g**)–(**62j**) (98TA3939, 00TA2063, 04S1115) (Figure 2). On the other hand, when *N*-silylaldimines are used as electrophiles, the resulting aminoalcohols can easily be transformed into benzoazepines (**63**) (Figure 2) (00JHC1061).



Scheme 16

Table 5. Preparation of benzooxepines (**62**)

Entry	Product			
	No.	R^1	R^2	Yield (%)
1	(**62a**)	H	Ph	67
2	(**62b**)	Me	Me	72
3	(**62c**)	Et	Et	79
4	(**62d**)	$(CH_2)_4$		69
5	(**62e**)	$(CH_2)_7$		68
6	(**62f**)	Me	Ph	72

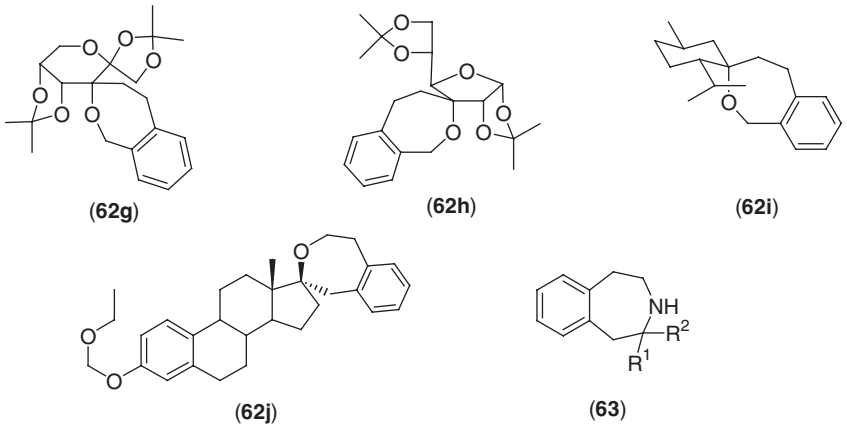
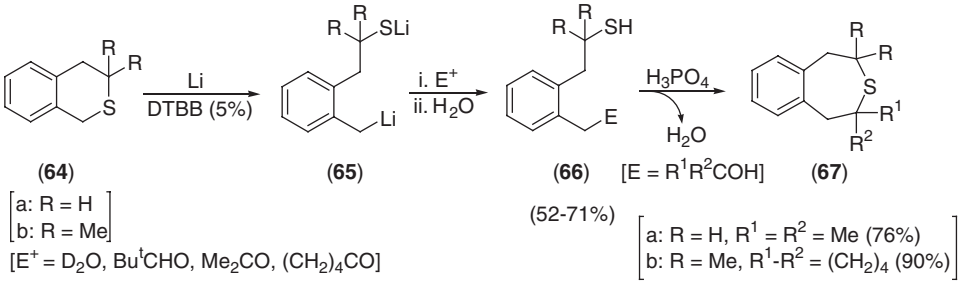


Figure 2. Homologation of isochroman (**59**)



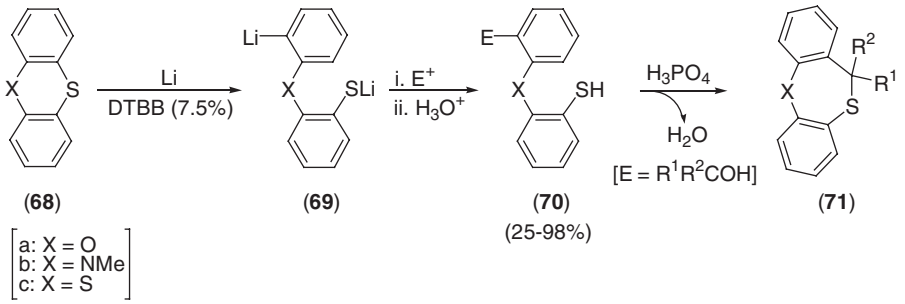
Scheme 17

B. Thioisochroman

By applying to thioisochromans (**64**) the same methodology than to isochroman (**59**) (see above), it was possible to transform them into tetrahydrobenzothiepins (**67**) (Scheme 17) (96JOC1859), which are their homologous heterocycles. The only difference is that in this case, the reductive opening lithiation should be performed at −78 °C instead of 20 °C.

C. 4-Heterosubstituted Dibenzothiins: Phenoxathiin, Phenothiazine, and Thianthrene

The DTBB-catalyzed lithiation of 4-hetero-substituted dibenzothiins (**68**), such as phenoxathiin (**68a**), phenothiazine (**68b**) and thianthrene (**68c**), at low temperature gives the corresponding functionalized organolithium intermediates (**69**), which by reaction with different electrophiles afford, after hydrolysis, the expected functionalized



Scheme 18

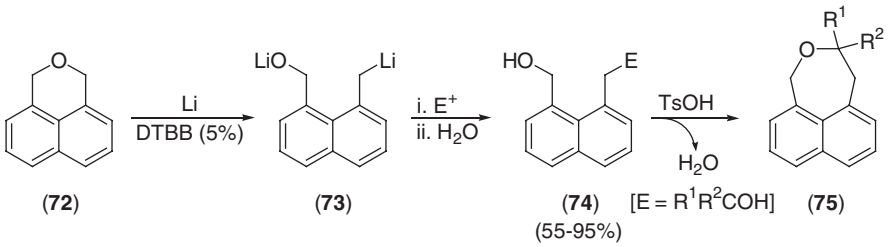
Table 6. Preparation of seven-membered heterocycles (**71**)

	Product				
Entry	No.	X	R^1	R^2	Yield (%)
1	(**71a**)	O	H	Ph	78
2	(**71b**)	O	Et	Et	85
3	(**71c**)	S	H	Bu^t	74
4	(**71d**)	S	H	Ph	97

thiols (**70**). The cyclization of some carbonyl compound derivatives under acidic conditions gives the corresponding homologous seven-membered dibenzo heterocycles (**71**) (Scheme 18) (Table 6) (02CL726). Again, from a synthetic point of view, the whole process (**68**)→(**71**) represents a homologation of the starting materials (**68**). In the case of thianthrene (**68c**), all the reactions should be performed at –90 °C in order to avoid undesired side processes.

D. 1H,3H-Benzo[de]Isochromene

The reductive opening lithiation of benzoisocromene (**72**) to give the intermediate (**73**) should be performed at −50 °C for 6 h with an excess of lithium in the presence of a catalytic amount of DTBB. At higher temperatures, a double carbon–oxygen bond reductive cleavage takes place leading to 1,8-*bis*(lithiomethyl)naphthalene. The reaction of the intermediate (**73**) with electrophiles yields, after hydrolysis, functionalized alcohols (**74**). Dehydration of diols (**74**) resulting from the reaction with a carbonyl compound as electrophile under acidic conditions leads to dihydronaphthooxepines (**75**) (Scheme 19) (Table 7) (04T4655).



Scheme 19

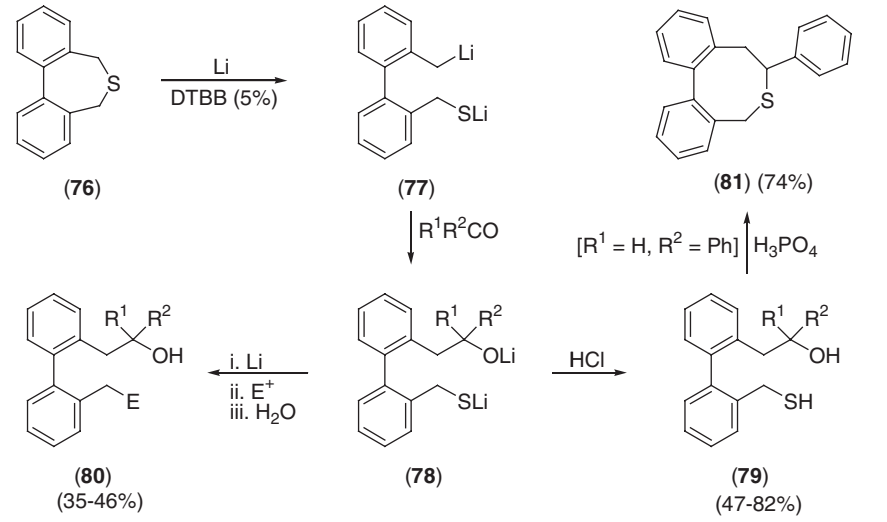
Table 7. Preparation of dihydronaphthooxepines (**75**)

	Product			
Entry	No.	R^1	R^2	Yield (%)
1	(**75a**)	Me	Me	95
2	(**75b**)	Et	Et	95
3	(**75c**)	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$	89
4	(**75d**)	$(CH_2)_5$		95
5	(**75e**)	$(CH_2)_7$		56

V. Homologation of Seven-Membered Heterocycles

A. 2,7-Dihydrodibenzothiepine

Applying the same strategy as for phthalan (**34**) and thiophthalan (**43**), the lithiation of 2,7-dihydrodibenzothiepin (**76**) can be directed either to the formation of sulfanyl alcohols (**79**) or to the introduction of two different electrophiles at both benzylic positions in a sequential manner, to yield difunctionalized biphenyls (**80**). Thus, the treatment of compound (**76**) with an excess of lithium and a catalytic amount of DTBB at –78 °C leads to the intermediate (**77**), which reacts with carbonyl compounds to give alkoxides (**78**), and after acidic hydrolysis to the afore mentioned sulfanyl alcohols (**79**). However, when alkoxides (**78**) are stirred at room temperature in the presence of the excess of the mentioned lithiating mixture, the remaining benzylic carbon–sulfur bond is cleaved and after reaction with a second electrophile, and final hydrolysis with water, polyfunctionalized compounds (**80**) are obtained (Scheme 20) (01TL2469). Compounds (**79**) can be cyclized under acidic conditions as is exemplified for the benzaldehyde derivative ((**79**), $R^1 = H$, $R^2 = Ph$). Treatment of this compound with 85% phosphoric acid under toluene reflux yields the dihydrodibenzothiocine (**81**) (Scheme 20) (05T9082).

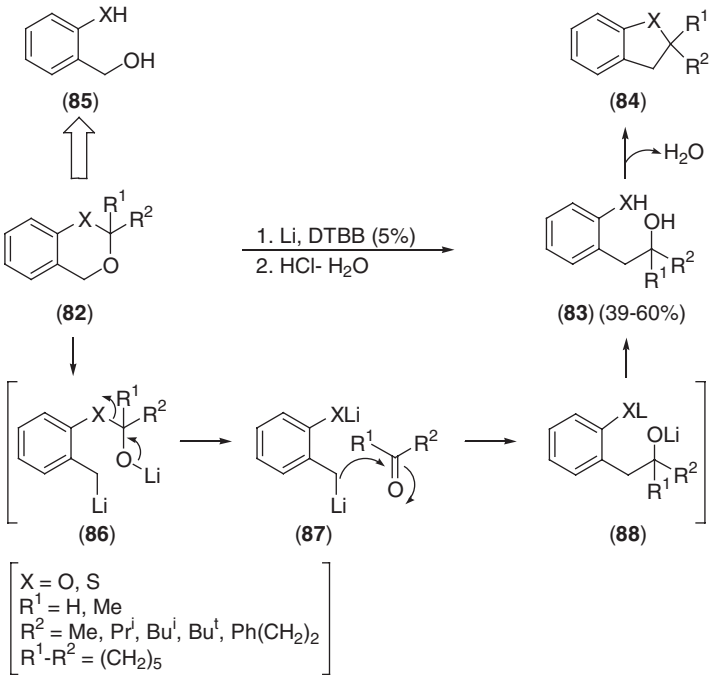


Scheme 20

VI. Related Processes

A. Benzodioxane and Benzooxathiane

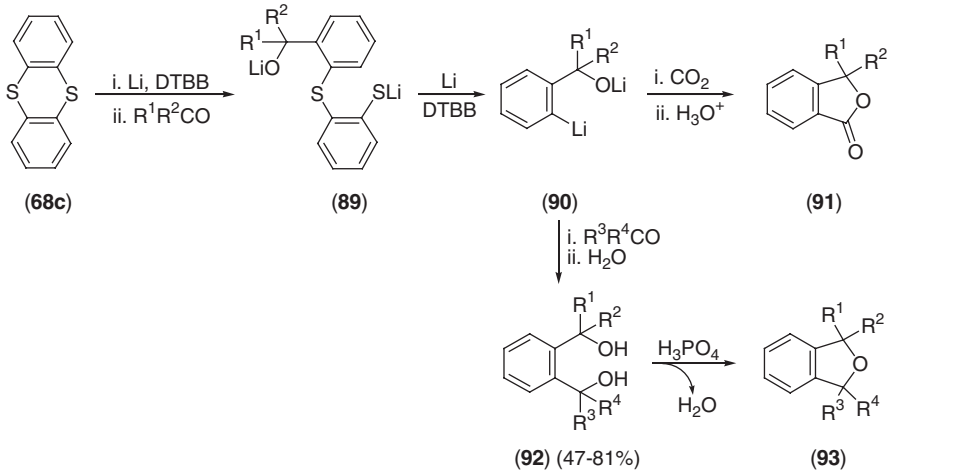
Reductive opening of heterocycles by a lithiation has also been employed in processes which allow the synthesis of new heterocycles but different for those previously mentioned homologation methodologies. For instance, starting from six-membered heterocycles benzo[c]-1,3-dioxane and 1,3-oxathiane derivatives (**82**), it is possible to prepare five-membered heterocycles such as 2,3-dihydro-2-substituted benzofurans or thiophenes (**84**). The whole process (**82**)→(**84**) represents a ring contraction instead of a ring expansion. Thus, the treatment of heterocycles (**82**) with excess of lithium and a catalytic amount of DTBB at 20 °C for dioxanes ((**82**), X = O) or at –78 °C for oxathianes ((**82**), X = S) followed by hydrolysis, leads to the formation of 2-substituted homobenzylic alcohols (**83**). Cyclization of these alcohols either under acidic conditions in refluxing toluene or under Mitsunobu-type reaction conditions gives 2,3-dihydro-2-substituted benzofurans or thiophenes (**84**) (Scheme 21) (Table 8) (97T17373). Starting heterocycles (**82**) are easily prepared by ketalyzation of carbonyl compounds with *o*-(hydroxymethyl)phenol or *o*-(hydroxymethyl)thiophenol (**85**) (Scheme 21). In the lithiation process, a benzylic carbon–oxygen bond cleavage takes place first leading to dianionic alcoholates (**86**), which undergo β-elimination giving benzylic dianions (**87**) together with the carbonyl compound used for the preparation of the starting heterocycles. These



Scheme 21

Table 8. Preparation of 2,3-dihydrobenzo-furans or -thiophenes (**84**)

	Product				
Entry	No.	X	R^1	R^2	Yield (%)
1	(**84a**)	O	H	Me	57
2	(**84b**)	S	H	Me	66
3	(**84c**)	O	Me	Me	65
4	(**84d**)	S	Me	Me	62
5	(**84e**)	O	H	Pr^i	66
6	(**84f**)	S	H	Pr^i	74
7	(**84g**)	O	H	Bu^i	69
8	(**84h**)	S	H	Bu^i	70
9	(**84i**)	O	H	Bu^t	52
10	(**84j**)	S	H	Bu^t	19
11	(**84k**)	O		$(CH_2)_5$	79
12	(**84l**)	S		$(CH_2)_5$	83
13	(**84m**)	O	H	$Ph(CH_2)_2$	68
14	(**84n**)	S	H	$Ph(CH_2)_2$	61



Scheme 22

Table 9. Preparation of phthalides (**91**) and phthalans (**93**) from thianthrene (**68c**)

Entry	No.	Product R^1	R^2	R^3	R^4	Yield (%)
1	(**91a**)	H	Me	–	–	58
2	(**91b**)	H	Bu^n	–	–	78
3	(**91c**)	H	$Me(CH_2)_7$	–	–	38
4	(**91d**)	H	Ph	–	–	58
5	(**91e**)	Me	Me	–	–	59
6	(**91f**)	Me	Et	–	–	78
7	(**91g**)		$(CH_2)_5$	–	–	39
8	(**93a**)	Me	Me	H	$Ph(CH_2)_2$	>95
9	(**93b**)	Me	Me	Me	Me	>95
10	(**93c**)	Me	Me		$(CH_2)_5$	>95
11	(**93d**)	Et	Et	Et	Et	>95
12	(**93e**)		$(CH_2)_5$		$(CH_2)_5$	>95

species react immediately to give (**88**), which after hydrolysis with hydrochloric acid, lead to compounds (**83**) (Scheme 21) (97T17373).

B. Double Lithiation of Thianthrene

The reductive opening of thianthrene (**68c**) has been reported in Section IV.C for homologation purposes. However, the lithiation of (**68c**) and reaction with appropriate electrophiles led to other interesting organic compounds. Thus, after the reductive opening lithiation of (**68c**) and reaction with a carbonyl compound as the

first electrophile, the resulting intermediate (**89**) is allowed to react with the excess of the litihiation mixture present in the reaction medium, so a new intermediate (**90**) is formed. The addition of carbon dioxide as the second electrophile gives directly phthalides (**91**) after acidic work-up (Scheme 22) (Table 9) (02TL7205, 03T2083). Meanwhile, the addition of a second carbonyl compound as electrophile leads to diols (**92**) after hydrolysis. These diols undergo acidic cyclization to give phthalans (**93**) (Scheme 22) (Table 9) (02TL7205, 03T2083).

VII. Conclusions

The tandem reductive opening lithiation-electrophilic substitution by reaction with a carbonyl compound-dehydration is a useful strategy for the homologation of heterocycles. This methodology allows the regioselective preparation of substituted heterocycles, the key step of the method being the reductive opening of the starting heterocycle.

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Coenzyme 5,10-Methylene and Methenyltetrahydrofolate Models in Organic Synthesis

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I. Introduction

Simulation of the synthesizing power of nature's chemical reagents and catalysts (enzymes/coenzymes) with smaller molecular models, mostly heterocycles of synthetic origin designed by rational considerations of three-dimensional structures and physicochemical characters of participating structural constituents of enzymes and coenzymes, is a challenging area of contemporary research (98CRV721, 84MI). Such investigations serve the dual objectives of achieving better understanding of the molecular mechanisms for biological reactions and of evolving reagents and catalysts of synthetic consequence. Indeed, such models designed on the basis of reactivity patterns of enzymes/coenzymes could overcome the limitation of their high specificity and express synthetic utility in a more versatile manner. Thus, synthetic organic chemistry, with its rich history of borrowing its targets from nature, could equally well make use of the wisdom of nature in developing strategies for chemical synthesis. Among various coenzymes, one such source is folate cofactors, the one-carbon derivatives of tetrahydrofolate (THF, $H_4 \cdot$ folate) system which through their carbon transfer reactions at various oxidation levels invoke bond formation reactions that are of preeminent synthetic relevance. 5,10-Methylene-/methenyl-tetrahydrofolates (**1** and **2**), respectively, perform carbon transfers at formaldehyde and formate group oxidation levels to nucleophilic centers (85MI). The electrophilic

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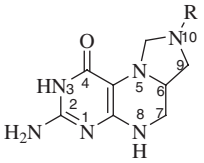
carbon flanked by nitrogens in the heterocyclic imidazolidine and Δ^2-imidazolinium units in **1** and **2** constitute the reactive species at the oxidation levels of carbonyl and carboxylic groups. Most coenzymes are capable of performing reactions although weakly even in the absence of apoenzymes. Apparently, the essence of carbon unit transfer chemistry of these tetrahydrofolate derivatives could be mimicked into the practice of organic synthesis for performing synthetically useful bond formation reactions by devising models based on imidazolidines and Δ^2-imidazolinium cations and their other 1,3-heterocyclic analogs, and this article aims at presenting salient aspects of such investigations. The results of studies on imidazolidine and Δ^2-imidazolinium cation-based models have been briefly reviewed earlier (88RTC111).



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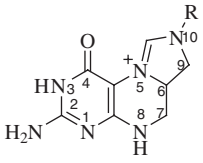

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R = -$C_6H_4CONHCH(COOH)(CH_2)_2COOH$

II. Designs of Models

A. General

One salient physico-chemical feature of the chemically active imidazolidine unit of cofactor **1** is the difference in basicity of N^5 (pK_a, 4.8–5.0) and N^{10} (pK_a, −1.3) (66JBC5845). In his pioneering investigations, Pandit designed imidazolidines and Δ^2-imidazolinium salts as models, possessing an electron-releasing methyl group at one nitrogen and an electron-withdrawing acetyl/tosyl group at the second nitrogen to invoke difference in their basicity and evolved synthetic strategies so that any imaginable functionalized appendage could be attached at their transferable C-2 carbon (88RTC111, 94PAC759). However, Jones has employed 1-benzyl-Δ^2-imidazoline and its 2-methyl derivative as models of **2** (86JCS(P1)1995, 90TL1767).

Tetrahydrofuran, *N*-methylpyrrolidine, and tetrahydrothiophene with three different heteroatoms placed in identical environments show pK_a values of −2.1, 10.4, and −4.5, respectively (79MI). If two of these heteroatoms are placed at 1,3- positions with a linking sp^3 hybridized carbon, in a five- or six-membered heterocyclic ring, they would retain a difference in basicity for invoking carbon transfer character on C-2, which would be similar to that of the above imidazolidine designs. Thus, heterocyclic systems having NMe, NAc/Ts, or O, N as well as S, N at 1,3- positions, which have enormous possibilities of derivatization, homologation, and functionalization of C-2 appendages, have been developed as carbon transfer models of **1**. The synthetic utility and synthesis of these models are elaborated.

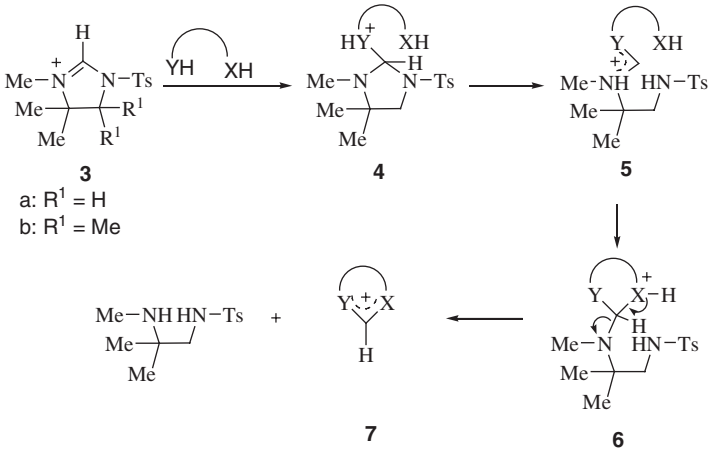
B. Models of 5,10-Methenyltetrahydrofolate and their Reactions

1. *Imidazolinium Cations*

Coenzyme 5,10-methenyltetrahydrofolate **2** in its biological reactions, transfers the carbon flanked by N^5 and N^{10} at the carboxylic acid group oxidation level to carbon and nitrogen nucleophiles (85MI). For mimicking the biological reactions of this coenzyme, in a simplistic approach, symmetric as well as asymmetric 1,3-disubstituted-Δ^2-imidazolinium salts were subjected to reactions with oxygen nucleophiles and BH_4^- and carboxylic acids (75JCS(P1)894). Jones has extensively exploited (86JCS(P1)1995, 82JCS(CC)282) the reactivity at C-2 H and C-2 alkyl/alkenyl units of imidazoline derivatives to generate carboxylic acids by hydrolysis of the derived Δ^2-imidazolines and a variety of condensation products of synthetic consequence.

For procuring rationally designed Δ^2-imidazolinium models **3**, the Δ^2-imidazolines formed from appropriate diamines and carboxylic acid derivatives were sequentially acetylated/tosylated and methylated. The incorporation of a gem-dimethyl group at C-4/C-5 of **3** stabilizes the highly reactive parent Δ^2-imidazoline system, and the optimum reactivity was found in system **3a** as a high order of deactivation was reflected in lower yields and multitude of products in the reactions of nucleophiles with Δ^2-imidazolinium cation **3b** having two gem-dimethyl groups at positions 4- and 5- (79JCS(CC)117, 83T3971). The reactions of **3a** with binucleophiles, such as *o*-phenylenediamine, *o*-aminothiophenol, and *o*-aminophenol, provide benzimidazole, benzothiazole, and benzoxazole representing carbon (C-2) transfer reactions of models of **2** at the carboxylic acid group oxidation level (83T3971).

The essence of the results of these reactions with mechanistic overtones was schematically depicted by Pandit (Scheme 1) (83T3971) who suggests that the nucleophile adds on **3** to give adduct imidazolidines **4**, which having an additional H on the



Scheme 1

attacking nucleophilic center opens to **5** that cyclizes to **6** when a second nucleophile is available. Following elimination of diamine **6** forms the cyclic carbon transferred product **7**. The reactions of **3a** with borohydride and Grignard reagents provide a highly practical approach for procuring imidazolidine adducts, which on hydrolysis form aldehydes representing a formyl group transfer to carbon nucleophiles as is desired of coenzyme **1** models. 1-Benzyl-2-alkyl-3-methyl-Δ^2-imidazolinium salts react with Grignard reagents to give addition products that are hydrolyzed to ketones (86JCS(P1)1995, 90TL1767). Mononucleophiles, which have two acidic hydrogens on the nucleophilic site, cause the initially formed imidazolidine ring to open to form acyclic isomeric products **5** (Section II.C.1).

2. *Oxazolinium and Thiazolinium Cations*

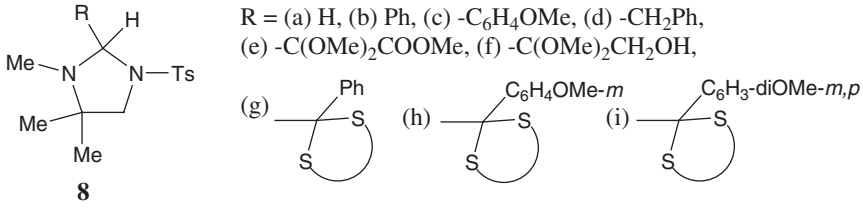
The alkyl and aryl C-2 substituents of Δ^2-oxazolines, so readily available from β-aminoalcohols and carboxylic acids, nitriles, etc., have been extensively elaborated at C-2 while its ring nitrogen atom undergoes facile quaternization. All Δ^2-oxazolinium and thiazolinium cations having H, Me, or Ph substituents at C-2 including even those lacking an N–Me substituent react equally well with binucleophiles, such as *o*-phenylenediamine, *o*-aminothiophenol, *o*-aminobenzamide, 1,2- or 1,3-diaminoalkanes, 2-aminoalkylthiols, and thiosemicarbazide, to furnish aromatic as well as nonaromatic heterocycles, by transfer of C–H, C–Me, and C–Ph units between nucleophilic centers (84H1101, 86T1449). These reactions of Δ^2-oxazolinium and thiazolinium cation models represent a case of their synthetically useful one-pot heterocyclic transformation. Even analogous benzoxazolium and benzothiazolium cations give similar carbon transfer reactions (88IJC(B)132).

C. Models of Coenzyme 5,10-Methylenetetrahydrofolate

1. *Imidazolidine and Perhydropyrimidine Derivatives*

a. Syntheses and Structures. In the straightforward condensation of 1,2-diamines with aldehydes, the substitution profiles of C-2 appendages of imidazolidines thus formed are limited to their availability in the aldehydes used, and their formation is attended by side reactions in the case of aliphatic aldehydes. However, the facility of elaboration of the C-2 substituents in Δ^2-imidazolines followed by their quaternization and BH_4^- reduction provides a broad range of C-2 substituted imidazolidines. The direct addition of hydride, aryl, and benzyl Grignard reagents, and relevant carbanions on C-2 of cation **3a** provides imidazolidines **8**, which would serve as models of 5,10-methylenetetrahydrofolate coenzyme for the transfer of their C-2 fragments to nucleophiles at the carbonyl group oxidation level. But these fragments lack functionalities, so critically required for projected intramolecular condensation reactions desired of the initial carbon transfer products for attaining the target molecules. The synthesis and structures of some imidazolidines subsequently used for devising synthetic methodologies are elaborated.

Imidazolidine derivative **9** was obtained by the borohydride reduction of the corresponding Δ^2-imidazolinium cation precursor formed by the condensation of the acetonide of the ethyl ester of D,L-glyceric acid and 1,1-dimethyl-1,2-diamine followed by acetylation and methylation (80H947, 83T3987).



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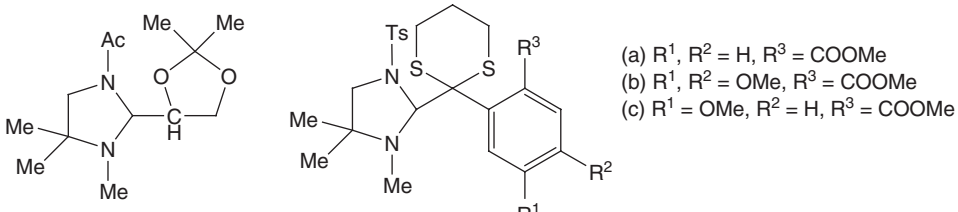
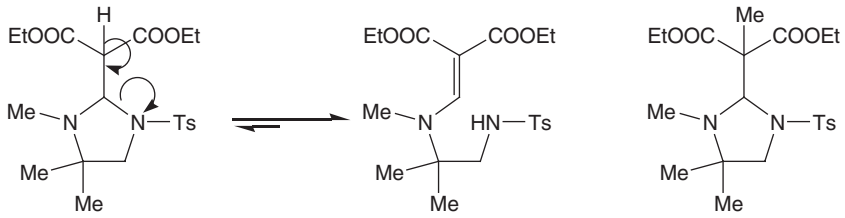
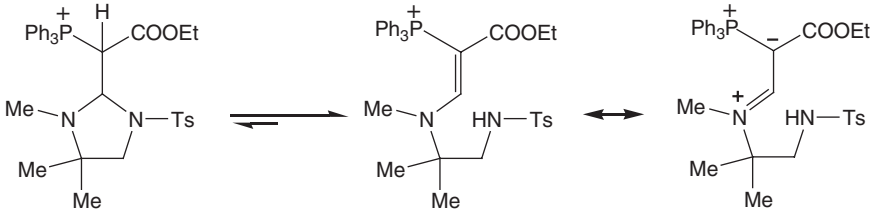


9 **10**

The addition reactions of appropriately functionalized mono- and *bis*-carbanions on **3a** constitute a versatile approach for such imidazolidines embroidered at C-2 with a variety of functionalized appendages. 2-Benzylimidazolidines (**10**), having functionalization at the benzylic carbon and also in the aryl ring, were obtained by the addition of carbanions derived from dithiane derivatives of aromatic aldehydes having appropriate substituents in the aryl ring, at C-2 of **3a** (81H239, 83T3981). The carbanions derived from an ethyl malonate, $Ph_3P^+CH_2COOEt$, and ethyl 2-methyl propionate add to **3a** to form **11**, **13**, and **12**, respectively (79JCS(CC)117, 83T3971). Evidently, in the cases where the incoming carbanion carbon has an additional H, the initially formed imidazolidine transforms to an acyclic structure (Scheme 1) to exhibit a case of imidazolidine–enamine, ring-chain tautomerism.



11 **12**



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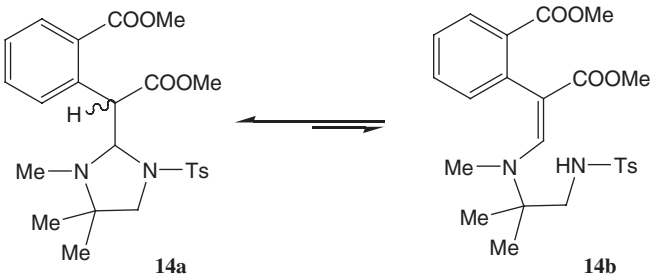
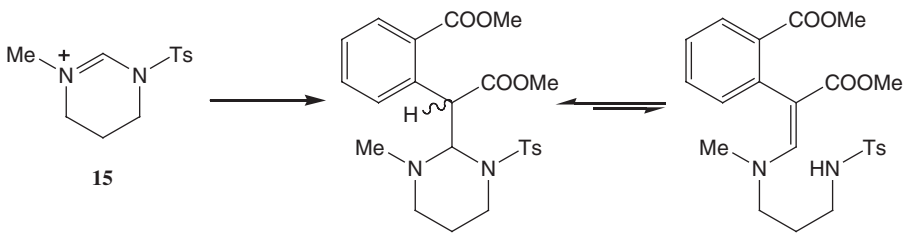
The carbanion derived from methyl homophthalate adds to **3a** to provide a mixture of imidazolidine derivative **14a** and its enaminic (aminostyrene) acyclic tautomer **14b**. Likewise, a mixture of homologous perhydropyrimidine **16a** and enamine (aminostyrene) **16b** was formed by addition of the same carbanion to 1-methyl-3-tosyl-tetrahydropyrimidinium cation (**15**). The stereochemistry of the products has been adequately established (85T3355).

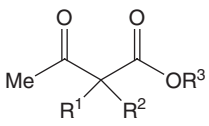


14a 14b



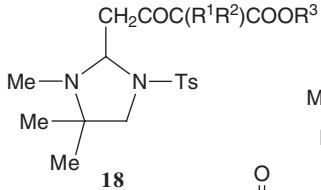
15 16a 16b

The *bis*-carbanions derived from alkyl acetoacetates **17a–e** add on the Δ^2-imidazolinium cation **3a** to form adduct imidazolidines **18a–e**, which could not be obtained in a pure state and were isolated as tautomeric enaminoketoesters **19a–e** (82TL3301, 83H2129, 85T3345). The formation of homologous enaminoketoester **20** from **15** and the *bis*-carbanion of ethyl acetoacetate **17a** is also reported (91T4155).



17

(a) R^1, R^2 = H, R^3 = Et
(b) R^1 = H, R^2 = R^3 = Et
(c) R^1, R^2 = Me, R^3 = Et
(d) R^1 = Et, R^2 = COOMe, R^3 = Me
(e) R^1 = Et, R^2 = SPh, R^3 = Me



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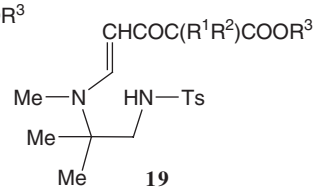

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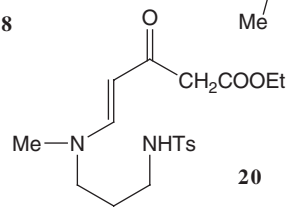

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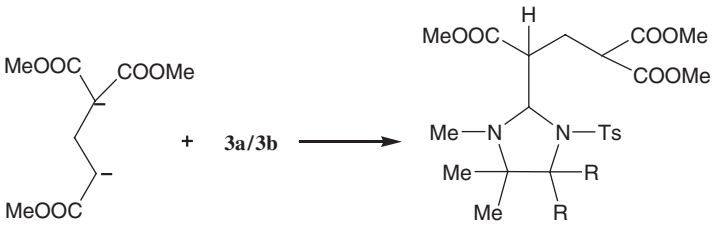
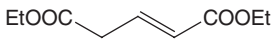
When the *bis*-carbanion **21** of the precursor triester is added to **3a** and **3b**, only the corresponding imidazolidines **22a** and **22b** are formed, and despite the availability of an acidic H at the α-carbon of the C-2 appendage, their enamine tautomers are not even detected (89T849).



21 22 (a) R = H (b) R = Me

The additions of the anion of ethyl glutaconate ester (**23**) on cations **3a** and **15** were found to form entirely the extended enamine ester tautomers **24** and **25** of the initially formed imidazolidine and perhydropyrimidine derivatives (88T6187).



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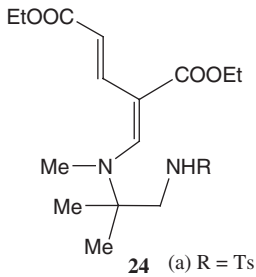
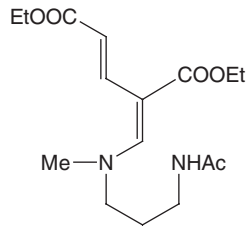


24 (a) R = Ts (b) R = Ac



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b. Ring–Chain Tautomerism. Imidazolidines and perhydropyrimidines formed by the addition of carbanions on Δ^2-imidazolinium and tetrahydro-Δ^2-pyrimidinium

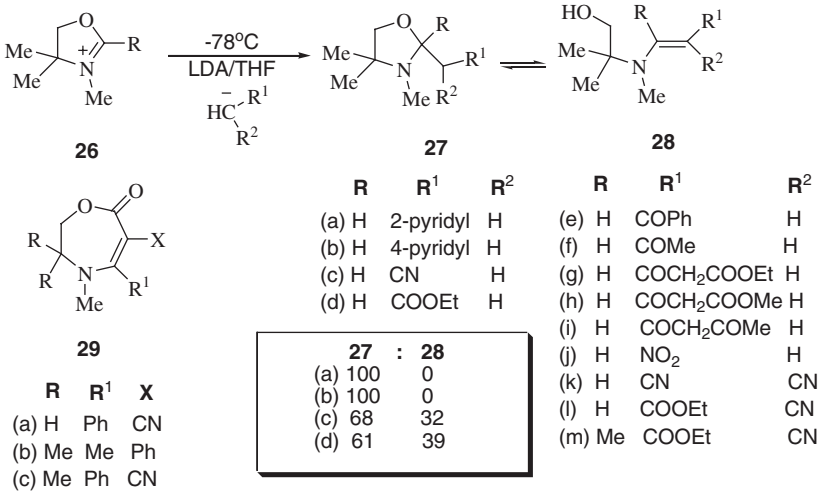
cations, structurally exist either as cyclic systems or their acyclic enamine tautomers or a mixture of both the tautomers. Evidently, in solution, ring opening of these perhydroheterocycles is initiated by the removal of an acidic H from the α-carbon of the C-2 appendage and is promoted by both the acidity of the α-CH and stereoelectronic stabilization of the acyclic tautomers. Thus, when the α-substituent on the C-2 appendage is an alkyl, aryl, vinyl, or ester group, only the cyclic products are isolated. In the case of $-COC(R^1,R^2)COOR^3$ substituents at the α-carbon, acyclic tautomers predominate. The products, having at the α-carbon two ester groups **11** or a combination of an ester with α,β-unsaturated ester **24**/**25** or with P^+Ph_3 **13**, are entirely acyclic in nature. In the case of a combination of carboalkoxy and *o*-carbomethoxyphenyl groups as substituents at the α-carbon, a mixture of cyclic and acyclic products **16a**/**16b**, with a preference for the latter, is formed.

2. *Oxazolidines*

The direct condensation of aldehydes with appropriate amino alcohols including chiral ones and hydride/Grignard addition to *N*-quaternized Δ^2-oxazolines constitute general syntheses of oxazolidines (85T837, 94T2297). Some C-2 elaborated oxazolidines have been procured by addition of Δ^2-oxazoline anions formed by electrochemical reduction (87TL4411) of Δ^2-oxazolinium cations, on Michael acceptors, and by formylation of silyl enol ethers (92T6011)/enamines (90T4223) with 2-methoxy-1,3-oxazolidines in the presence of Lewis acids.

Addition of carbanions at C-2 of Δ^2-imidazolinium cations to provide imidazolidines and/or their enamine tautomers is a facile mode of converting a protected carboxylic acid into its protected homologated and/or further functionalized carbonyl equivalent (Section II.C.1). But a similar reaction of ethyl cyanoacetate with 2-phenyl-Δ^2-oxazolinium cation was reported (84T349) to proceed by indiscriminate attack of its carbanion at C-5 and/or C-2 to form ring-opened products, which in the latter case through subsequent cyclization formed oxazepine derivative **29a**. However, reactions of 3,4,4-trimethyl-Δ^2-oxazolinium cations (**26**), performed by addition to pregenerated carbanions at $-78\,^{\circ}C$ in an inert atmosphere (Scheme 2), have been found to proceed smoothly (96IJC(B)881, 98T3567). In the reactions of the cation **26** with anions of β- and γ-picolines, only oxazolidines **27a** and **27b** were formed, whereas the anions of acetophenone, acetone, ethyl/methyl acetoacetate, acetylacetone, nitromethane, malononitrile, and ethyl cyanoacetate, formed the corresponding functionalized aldehyde enamine chain tautomers **28e**–**m** of the initially formed oxazolidines. The reactions of the anions of acetonitrile as well as ethyl acetate form inseparable equilibrating mixture of **27c**/**28c** and **27d**/**28d**, respectively. However, mono-/*bis*-carbanions derived from very weak acids, such as toluene, 2-methyl oxazolidine, 2,4,4,6-tetramethyl-5,6-dihydro-(4*H*)-1,3-oxazine, and *o*-toluic acid/methyl ester, induce reactions other than nucleophilic addition at C-2 of **26**.

In oxazolidines, the extent of ring–chain tautomerism is also governed both by the acidity of its α-CH and by stereoelectronic stabilization of acyclic tautomers. Deprotonation at the α-carbon of the C-2 appendage induces ring opening of the oxazolidine to its chain tautomer. In **27a** and **27b**, steric hindrance to deprotonation and possible nonplanarity of the carbanion system due to the orthogonal disposition



Scheme 2

of the pyridine ring, might not allow enamine formation resulting in isolation of only ring tautomers. The reactions of carbanions of ethyl phenylacetate and ethyl cyanoacetate with **26** (R = Me) and **26** (R = Ph), respectively, form oxazepine derivatives **29b** and **29c** by lactonization of the initially formed enamine tautomers. These cyclizations are probably facilitated by the presence of a bulky phenyl group at α- or β-enamine carbon of **28** as in the case of the reaction of **26** (R = Me) with ethyl cyanoacetate, only corresponding **28** was formed (98T3567).

3. *Oxazinanes*

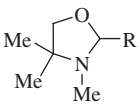
Tetrahydro-(2*H*)-1,3-oxazines (**31**, THOs, oxazinanes) are mostly formed by borohydride reduction of 5,6-dihydro-(4*H*)-1,3-oxazines (DHOs) (73JOC36), but direct condensation of γ-hydroxypropylamines and aldehydes has also been used for their synthesis (71JCS1300). The sulfuric acid-induced reactions of nitriles with 2-methyl-2,4-pentanediol is the most convenient method for procuring DHOs (57JOC839, 71S92); the corresponding nitriles give 2-hydroxymethyl-, 2-acetoxymethyl-, 2-(2-phenylthio)ethyl-, 2-(2-ethylthio)ethyl-, and 2-(chloromethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazines. 2-(β-Cyano)ethyl-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine was prepared through an halide displacement reaction of a 2-chloromethyl analog with the carbanion of acetonitrile generated at −78 °C (2000TL4977, 2001T7939). The optically pure 2-(*p*-tolylsulfinylmethyl)-4,4,6-trimethyl-5,6-dihydro-(4*H*)-1,3-oxazine has been synthesized in high yields by the reaction of the carbanion of 2,4,4,6-tetramethyl DHO with (−)-(*S*)-menthyl-*p*-toluene sulfinate at −78 °C (2004T9171). All these DHOs have been reduced to the corresponding THOs using BH_4^- reduction at −40 °C. The facility of generation of carbanions at an α-carbon of a C-2 substituent of DHOs followed by reactions with

electrophiles invokes a variety of C-2 elaborations (73JOC36, 2001T7939). Some cycloaddition reactions also find limited use in the synthesis of DHOs (70S49).

III. Models of 5,10-Methylenetetrahydrofolate in Organic Synthesis

A. General

The strategy of synthesis here would involve both the construction of appropriate 5,10-methylene THF analogs and a judicious choice of the substrates. For performing reactions of imidazolidines **8**, oxazolidines **30**, oxazinanes **31**, or their ring–chain enamine tautomers with nucleophiles, the presence of added acid would be obligatory for their conversion to iminium cations which could be visualized as prototypes of the activated form [$CH_2 = N^+(5)H_4 \cdot$ folate] of the coenzyme **1**. The orientation of acid-induced ring opening of imidazolidine **8a** has been found to be such that it generates the iminium cation **32** whose structure is supported by its cyanoborohydride reduction to diaminoethane derivative **33** (83T3981). A similar acid-induced ring-opening mode could be visualized for oxazolidine- and oxazinane-based models to form iminium cations, which are also generated by treatment of enamine tautomers of these models with acid. Obviously, these models constitute reagents possessing an appropriately functionalized electrophilic carbon fragment to be transferred to the nucleophile(s).



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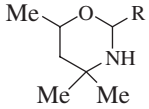

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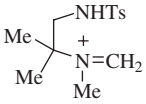

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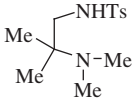


33

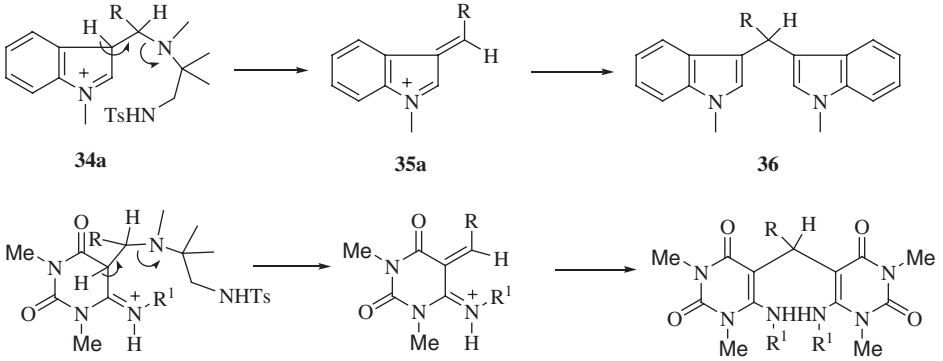
Based on the possibility of the transfer of C(2) and the associated functionalized carbon fragment of the appropriately tuned models, at the carbonyl group oxidation level to various bi- and mononucleophiles, a whole set of their synthetic applications have emerged. Thus, mononucleophilic substrates, such as indole, alkyl-*β*-amino/anilino crotonates, and pyrroles, or their combinations react with such models to provide efficacious synthetic methods for 3,3′-diindolylmethane derivatives, dihydropyridine derivatives, di/tripyrromethanes, *bis*(heterocyclyl)methanes, substituted pyridines, as well as their ring-annulated systems. The reactions of binucleophilic (Ar*C*∼*N*H_2) substrates including tryptamine, *β*-phenethylamine, homoveratrylamine, tryptophan ester derivatives with these models have abundantly been used in evolving a synthesis of various heterocycles and indole/isoquinoline alkaloids. In our presentation, the results of these investigations are classified primarily according to the use of the mono- and binucleophilic substrates and subclassified with respect to the synthetic targets.

B. Syntheses using Mononucleophiles

The reactions of 5,10-methylene THF models with mononucleophiles mainly take place in 1:2 stoichiometry but in some highly functionalized systems an alternate 1:1 condensation mode of reaction prevails. The syntheses of various targets obtained through these reactions are elaborated.

1. *Di(3-indolyl)methanes and 2,2′-Dipyrromethanes*

The di(3-indolyl)methane moiety constitutes the core structural unit of 1,1-di(1H-3-indolyl)-propane-2′,3′-diol (**36**, R = $CH(OH)CH_2OH$) isolated from *Balansia epichloe* (77MI) and streptindole (**36**, R = CH_2OAc), a genotoxic metabolite isolated from intestinal bacteria (83TL4719). Except for a recent highly efficacious approach, using silica chloride under microwave irradiation (2005IJC(B)327), earlier efforts at procuring diindolylmethane derivatives by acid-induced condensations of indoles and carbonyl compounds were attended by drawbacks of formation of mixtures of di-, tri-, or tetraindolylmethanes, lack of practicability, nonavailability of desired additional functional groups in carbonyl compounds, and formation of polymeric products. The reaction of imidazolidine **8a** with indole as well as 6-aminouracil derivatives, performed with the aim of evolving mechanistic support to 5,10-methylenetetrahydrofolate-induced 2′-deoxyuridylate to 2′-deoxythymidylate conversion (Section IV), was found to give di(3-indolyl)methane (**36**, R = H) and biuracilylmethane derivative (**37**, R^1 = Me, $PhCH_2$), presumably by reaction of the second molecule of the substrate at the exocyclic methylene group of the initially formed indolenium **35a** (R = H) and iminium **35b** (R = H) intermediates, respectively (83T3971). These intermediates are formed by elimination of the diamine from the adducts **34a** and **34b** of the nucleophilic indole and uracil derivatives with acyclic iminium cation **32** generated by acid-catalyzed ring opening of imidazolidine **8a**. These reactions constitute a potentially versatile process for synthetically useful transfer of methylene and substituted methylene fragments to mononucleophiles in 1:2 stoichiometry using THF models.



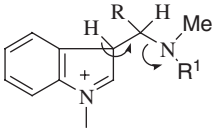
34a **35a** **36**

34b **35b** **37**

The oxazolidine **30** and oxazinane **31** derivatives, in the presence of an acid, react with indole to provide exclusively diindolylmethane derivatives **36**, variously substituted at the methylene bridge (88T5897). In a straightforward reaction of **31** ($R = CH_2OAc$) with indole, streptindole was formed in good yields as against its formation in trace amounts from acetoxyacetaldehyde and indole (77MI). Alternately, **36** ($R = CH_2OH$) formed from **31** ($R = CH_2OH$) and indole has been acetylated to streptindole. The reactions of oxazinane **31** ($R = CH_2CH_2OH$) and indole give **36** ($R = CH_2CH_2OH$) in low yield along with **36** ($R = CH_2C_6H_4NH_2$-*o*) formed by acid-catalyzed reactions between three indole molecules. However, LAH reduction of **36** ($R = CH_2COOEt$) formed from **31** ($R = CH_2COOEt$) and indole gave **36** ($R = CH_2CH_2OH$) in high yield. Evidently, the iminium cations **38a–c** formed by acid-induced ring opening of oxazolidine **30**, oxazinane **31**, and 2-substituted 1,3-oxazinanes, respectively, react with indole to form adducts **39a–c**, which by loss of aminoalcohol could generate alkylidene indolenium cation **35a**, subsequently undergoing nucleophilic attack of indole to form mainly diindolylmethane derivatives. Here, the nature of intermediate adduct **39**, as well as the incipient cation **38** having a hydroxyalkyl chain might be responsible for regulating the overall reaction to avoid formation of tri-/tetraindolylmethane derivatives (88T5897).

Acid-catalyzed reactions of pyrroles with oxazinanes in near stoichiometric amounts provide mainly 5-substituted dipyrromethanes **40** ($R = H$, alkyl, aryl, CH_2CN, CH_2COOEt, etc.) and in very few cases the correspondingly substituted 5,10-disubstituted tripyrranes **41** are also formed. These linear oligomers constitute precursors for bridge substituted *meso*-porphyrins, calix[4]phyrins, calix[4]pyrroles, and other heterocalixarenes. This approach for the synthesis of dipyrromethanes offers synthetic advantages of high order of pliability in bridge substitution and practicability in respect to the use of equivalents of otherwise inaccessible carbonyl components and simplicity of single-pot operation in relation to the known methodologies (2005SC929, 2005T6614). However, reactions of oxazinanes with two different pyrroles or a mixture of a pyrrole and another electron-rich heterocycle provide mixtures of products including the hybrid linear oligomers. The mode of reaction would obviously be similar to that of reactions of indoles. The reactions of pyrrole and oxazinanes in refluxing acetic/propionic acid furnish *meso*-tetraarylporphyrins in high yields (30–35%, scalable upto 5.0 g quantity) in a single-pot reaction (2005UP1) in analogy with an Adler synthesis (67JOC476). This modified route obviates the use of DDQ for oxidation of the intermediate porphyrinogen.

38



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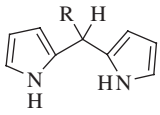

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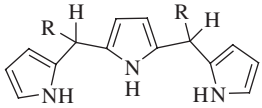


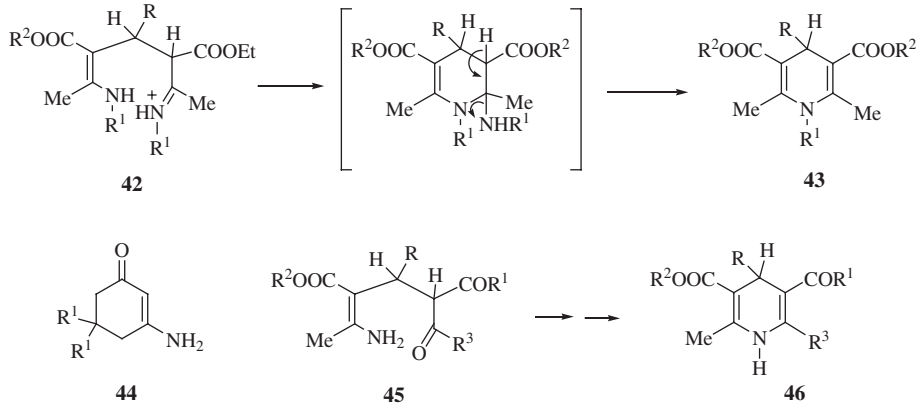
41

(a) $R^1 = -C(Me)_2CH_2OH$
(b) $R^1 = -C(Me)_2CH_2CH(Me)OH$
(c) $R^1 = -(CH_2)_3OH$

2. *1,4-Dihydropyridines, Acridine-1,8-diones, 3,4-Dihydropyrimidine-2(1H)-ones, and Related Systems*

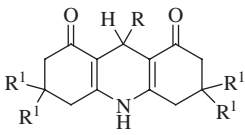
The synthetic activity in 1,4-dihydropyridines and their analogs has been stimulated by their medicinal potential (89MI, 91AGE1559) as well as the synthetic significance of their hydride/enolate ion transfer reactions (78T2377, 79JOC4953, 83JA7792). We envisaged that alkyl-β-aminocrotonate having an enamine nucleophilic β-carbon, such as indole and pyrrole, would undergo acid-catalyzed reactions with oxazolidines **30** and oxazinanes **31** in 2:1 stoichiometry to form **42**, which should promptly undergo cycloelimination to form the 1,4-dihydropyridine **43**. Thus, in one-pot reactions of ethyl-β-aminocrotonate and various oxazolidines or oxazinanes, **43** (R = H, Me, Ph, CH_2Ph, CH_2COOEt, CH_2OH, $-C_6H_4NO_2$-*o,m,p*, etc.; R^1 = H, Me, Ph; R^2 = Et), including cardiovascular drug nifedipine **43** (R = $-C_6H_4-NO_2$-*o*, R^1 = H, R^2 = Me) were formed in a practicable manner (89T3967). Here, the high order of synthetic pliability at C-4 of **43** was possible because of the availability of a broad range of substitution profiles at C-2 of oxazolidines and oxazinanes, which constitute equivalents of some of the otherwise inaccessible aldehydes to be deployed for a synthesis of **43** through reactions with alkyl-β-aminocrotonates. In contrast to the cumbersome reactions of benzaldehyde and acetaldehyde (45JA1382, 49JA4003) with ethyl-β-anilinocrotonate, its reactions with oxazolidines and oxazinanes having Ph/Me substituents at C-2 form products **43** (R = Ph/Me, R^1 = Ph, R^2 = Et), in much shorter time, better yields, and without the formation of by-products (89T3967).

1,4-Dihydropyridines **46** (R = H, Me, Ph; R^1, R^3 = Me and $-CH_2C(Me)_2CH_2-$; R^2 = Et) having unsymmetrical substitution patterns at C-2, C-6 and C-3, C-5 positions have been formed by reactions of equivalent amounts of ethyl-β-aminocrotonate and methyl acetoacetate or dimedone, with respective oxazinanes **31** in acetic acid/acetonitrile (1:10 v/v). Since methyl acetoacetate and dimedone fail to react with oxazinanes under these reaction conditions, it may be visualized that the preference of the reactivity of oxazinanes with enamines over the enols facilitates the generation of intermediate **45**, the precursor of **46** (93JCR(S)120).



Like alkyl-β-aminocrotonates, enaminoketones **44** (R^1 = H, Me) derived from cyclic 1,3-diketones, react with oxazinanes **31** to provide the corresponding acridine-1,8-diones **47** (R = H, Me, Ph, CH_2COOEt) with an embedded dihydropyridine moiety, in a synthetically useful manner. But in the reactions of oxazinane **31** (R = CH_2COOEt) with **44** (R^1 = H and Me), in addition to **48** (R = CH_2COOEt), a minor product **49** (R^1 = H, Me) was also isolated. Evidently, the major course of the reaction is a 2:1 stoichiometric condensation of the enaminoketone and oxazinane in a mode illustrated for alkyl-β-aminocrotonate and only in the case of an oxazinane having CH_2COOEt as a C-2 substituent, the initial 1:1 stoichiometric iminium intermediate through the loss of acidic H from CH_2COOEt formed dienamine esters **48** (R^1 = Me, H), which in case of **48** (R^1 = H) cyclized to quinolinone derivatives **49** (98T935).

A heterocyclic enamide, 1,3-dimethyl-6-aminouracil, likewise, condensed with oxazinanes **31** (R = Me, Ph), under nitrogen to form **50** (R = Me, Ph) having an inbuilt dihydropyridine, in a synthetically advantageous manner over conventional methodologies (79T4415, 90TL5631). On performing the reactions in the presence of air, dihydropyridine units oxidized to form corresponding **51**, indicating the sensitivity of **50** toward air oxidation as compared to acridine 1,8-diones **47** that are quite stable under these conditions (98T935).



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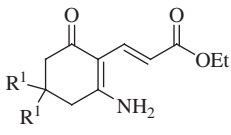

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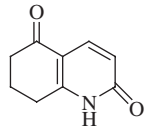

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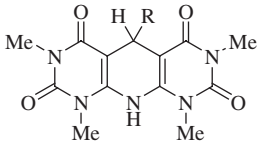

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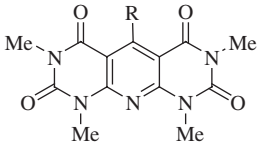

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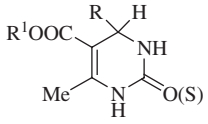

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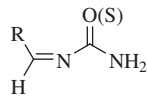


53

The considerable interest in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones(thiones) **52** (DHPMs) stems from their structural similarity to 1,4-dihydropyridines **43** and their medicinal potential (2003MI). Biginelli synthesis (1893G360) involving condensation of a carbonyl compound, urea or thiourea, and an alkyl acetoacetate and its several operational modifications, gives moderate to good yields of DHPMs especially in the case of substituted aromatic and aliphatic aldehydes. One-pot acid-catalyzed condensations of oxazolidines and oxazinanes with ethyl acetoacetate and ureas provide convenient syntheses of the corresponding DHPMs in high yields without the need of chromatographic purifications (99T12873). This protocol is quite flexible to a variety of substitutional variations at C-4 of **52** (R = H, Me, Et, Ar, CH_2COOEt, CH_2CN, etc.). The peripheral elaboration at C-6 methyl has been conveniently performed through LDA metalation followed by reactions with a

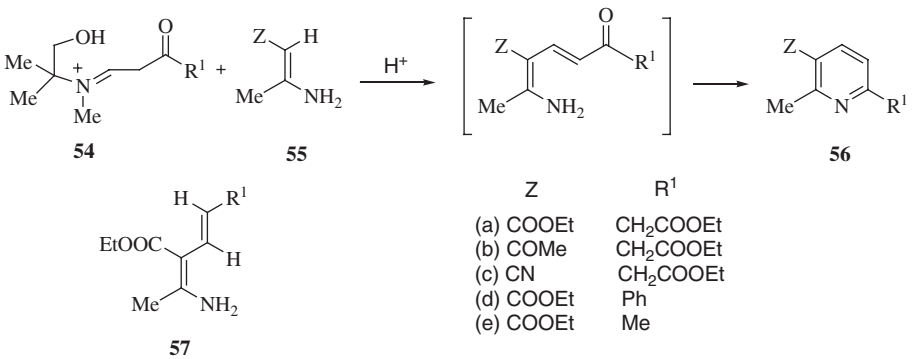
variety of electrophiles (2005JOC6114). In the above formation of **52**, the intermediacy of **53** generated by reaction of **38** with urea or thiourea and elimination of aminoalcohol is amply rationalized. Evidently, **52** are formed by cycloelimination of adducts formed by nucleophilic addition of enols of alkyl acetoacetates on **53** (99T12873).

3. *Pyridine and Its Condensed Systems*

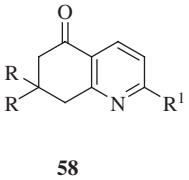
In the above reactions of enamine derivatives with oxazolidines and oxazinanes, pyridine systems did not constitute direct targets but were formed, in a few cases, by air oxidation of initially formed dihydropyridine derivatives. Oxazolidines **30**, possessing electron-withdrawing groups in C-2 substituents, exist mainly as tautomeric acyclic enamines **28** (Section II.C.2), which in the presence of an acid would also generate iminium cations such as **54** that should react with nucleophiles. Thus, it has been found that such oxazolidines in presence of an acid, react with acyclic, cyclic, and heterocyclic enamine derivatives in 1:1 stoichiometry to provide a unique synthesis of pyridine, quinolinone, and pyridopyrimidine derivatives (98T935).

The results depicted in Scheme 3 reveal that β-ethoxycarbonyl/acetyl/cyano enamines **55** react with **54** having a β-carbonyl group in its C-2 substituent to form pyridine derivatives **56a–e**, obviously by cyclodehydration of the initial C-2 unit transfer product. But in the reactions of **55** (Z = COOEt) with oxazolidines **27d, c, b** only open-chain products **57** (R^1 = COOEt, CN, 4-pyridyl) are isolated. This approach offers a convincing advantage of bringing about a myriad of substitutional variations in pyridine **56** and piperylene **57** based targets (Scheme 3).

The enaminones **44** (R^1 = Me, H) react with oxazolidines **27/28g, f** to form partially reduced quinolinones **58a–c**. 6-Amino-1,3-dimethyluracil reacts with oxazolidines **27/28f, e** to form pyridopyrimidine derivatives **59a**, **b** respectively in over 80% yields as against reported low-yield methodologies. Similarly, **27/28g, i, c** react with 6-amino-1,3-dimethyluracil to give **59c**, **d**, **e**, but in the case of **27/28d, b** the uncyclized products **60a**,**b** are isolated exclusively (98T935).

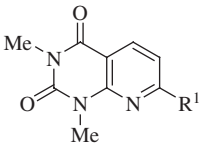


Scheme 3



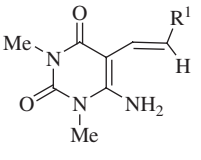
58

R	R^1
(a) Me	CH_2COOEt
(b) Me	Me
(c) H	CH_2COOEt



59

(a) R^1 = Me, (b) R^1 = Ph
(c) R^1 = CH_2COOEt,
(d) R^1 = CH_2COMe, (e) R^1 = NH_2



60

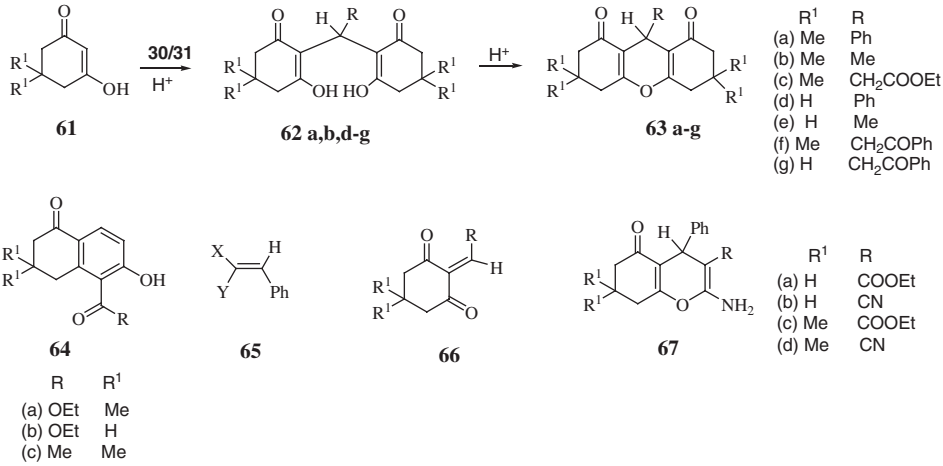
(a) R = COOEt
(b) R = 4-pyridyl

4. *Fused Pyran Derivatives*

Oxazolidines **30** and oxazinanes **31**, depending upon the nature of their C-2 substituents, could react with 1,3-dicarbonyl systems which have considerable enolic tautomer components in 1:2 or 1:1 stoichiometry in a manner analogous to their reactions with enamines to form oxygen isosteres of pyridine derivatives (96T14273).

As depicted in Scheme 4, oxazinanes **31** (R = Ph, Me, CH_2COOEt) and oxazolidine **30** (R = CH_2COPh) react with 1,3-cyclohexanediones **61** (R^1 = Me, H) to form the corresponding 1:2 stoichiometric products **62** and xanthene derivatives **63**. However, **30** (R = CH_2COCH_2COMe/OEt, in similar reactions form functionalized α-tetralones **64a–c**. Acyclic carbon nucleophiles, such as ethyl acetoacetate, malononitrile, nitromethane, dibenzoylmethane, and diethyl malonate, react with **31** (R = Ph) in the presence of an acid to form the corresponding styrene derivatives **65** (X = MeCO, CN, NO_2, COPh, COOEt; Y = COOEt, CN, H, COPh, COOEt) only.

Thus, in the case of 1,3-cyclohexanediones, the 1:1 stoichiometric alkylidene 1,3-diketone intermediate **66** (R = CH_2COCH_2COMe/OEt) undergoes intramolecular cyclodehydration to **64** but in all other cases, it reacts with another molecule of the



61 **62 a,b,d-g** **63 a-g**

R^1	R
(a) Me	Ph
(b) Me	Me
(c) Me	CH_2COOEt
(d) H	Ph
(e) H	Me
(f) Me	CH_2COPh
(g) H	CH_2COPh

64 **65** **66** **67**

R	R^1
(a) OEt	Me
(b) OEt	H
(c) Me	Me

R^1	R
(a) H	COOEt
(b) H	CN
(c) Me	COOEt
(d) Me	CN

Scheme 4

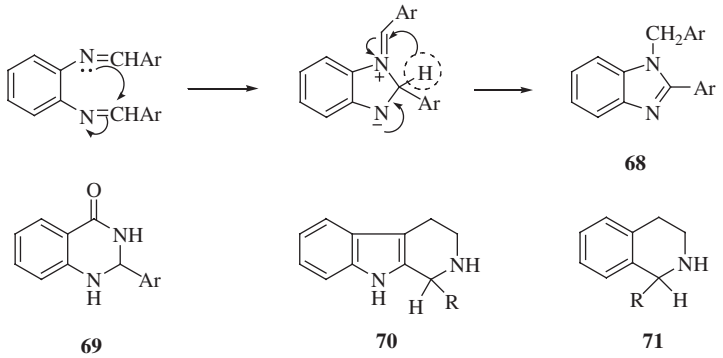
nucleophile to form **62** and **63**. In the case of acyclic nucleophiles, 1:1 stoichiometric product styrenes probably are stable and do not react further with acyclic nucleophiles that may also not be sufficiently enolic. Apparently, cyclic 1,3-diketone nucleophiles are more reactive, and acid-catalyzed reactions of 1,3-cyclohexanedione with β-cyano-β-carbethoxy styrene **65** (X = CN, Y = COOEt) or with a mixture of ethyl cyanoacetate and **31** (R = Ph) furnish 4*H*-benzopyran derivative **67a**. Likewise, the mixtures of 1,3-cyclohexanedione/malononitrile, dimedone/ethyl cyanoacetate, and dimedone/malononitrile undergo reactions with **31** (R = Ph) to give **67b, c, d**, respectively (96T14273). For these syntheses of **67**, the presence of at least one nitrile group on the acyclic nucleophile is necessary for the final cyclization, which provides a driving force for the reaction. In view of the facile C-2 derivatization of **30** and **31**, the present approach could be implemented to obtain other derivatives of **63**, **65**, and **67**.

C. Syntheses using Binucleophiles

In general, binucleophilic substrates react with THF models in 1:1 stoichiometric cyclization mode and have been beneficially used in the synthesis of some simple heterocycles and a variety of alkaloids that are described in respect of the targets.

1. *Heterocycles*

THF models transfer their C-2 fragment in between 1,4- or 1,5-binucleophilic sites to generate five- or six-membered rings. The acid-catalyzed reactions of 2-aryloxazolidines and oxazinanes with *o*-aminobenzamide, *o*-aminothiophenol, and *o*-phenylenediamine give 2-aryl-4(1*H*)-quinazolinones **69**, 2-arylthiazoles, and a mixture of 2-arylbenzimidazole and 1-benzyl-2-arylbenzimidazole **68**, respectively. Whereas benzothiazole and benzimidazole could be formed by air oxidation of their initially formed dihydro derivatives, 1-benzyl-2-phenylbenzimidazole, as formulated below, could arise from initially formed diimine, its cyclization, and subsequent 1,3-hydride shift (88JCR(S)322, 89IJC(B)802). It is the sole product when *o*-phenylenediamine and the model are used in 1:2 stoichiometry.



1-Acetyl-3,4,4-trimethylimidazolidine and its many C-2 derivatives **8** react with tryptamine in the presence of an acid to form corresponding tetrahydro-β-carboline

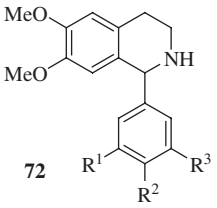
derivatives **70** in a facile manner. Using β-phenethylamine substrates, some tetrahydroisoquinoline derivatives **71** have also been obtained (79H221). In corresponding oxazolidine **30** and oxazinane **31** models to perform similar C-2 fragment transfers, the presence of substituent(s) on the heteroatom or in the ring were not absolutely necessary but the presence of a methyl and acetyl or phenyl group at N, respectively, increase and decrease the reactivity of the models (88JCR(S)322, 89IJC(B)802).

2. *Alkaloids and Related Systems*

a. General. The synthesis of tetrahydroisoquinoline and tetrahydro-β-carboline systems using a Pictet–Spengler reaction of β-phenethylamine/tryptamine/tryptophan ester binucleophiles and carbonyl compounds constitutes the basis of synthetic strategies for many categories of alkaloids. The use of acid-catalyzed transfer of appropriately functionalized C-2 fragments of THF models, the equivalents of carbonyl components, to these substrates would add tremendous versatility to this methodology because these C-2 fragments can be suitably embroidered with functionalities (Sections II.C.1, II.C.2, and II.C.3) for performing subsequently desired transformations to procure the targets. This strategy encompassed in the Pictet–Spengler cyclization through THF models rather than carbonyl compounds would be highly useful because the models, which are readily available, constitute protected carbonyl systems of which free aldehydes are either inaccessible or difficult to prepare or undergo side reactions. The following examples of synthesis of some categories of alkaloids and related systems illustrate this concept.

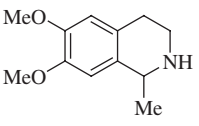
b. Tetrahydroisoquinoline Alkaloids. Homoveratrylamine reacts with 4,4-dimethyl-2-(3,4-methylenedioxyphenyl)oxazolidine, 4,4-dimethyl-2-(3,4-dimethoxyphenyl)oxazolidine, and 4,4-dimethyl-2-(3,4,5-trimethoxyphenyl)oxazolidine in refluxing TFA to furnish the alkaloids, *nor*-cryptostylline I **72a**, *nor*-cryptostylline II **72b**, and *nor*-cryptostylline III **72c**, respectively (88JCR(S)322).

Acid-catalyzed reactions of **31** (R = Me) and **31** (R = –CH_2OH) with homoveratrylamine provide salsolidine **73** and calycotomine **74**, respectively. It may be noticed that calycotomine could not be obtained by Pictet–Spengler reaction using hydroxyacetaldehyde (89IJC(B)802).



72

	R^1	R^2	R^3
(a)	-OCH_2O-		H
(b)	OMe	OMe	H
(c)	OMe	OMe	OMe



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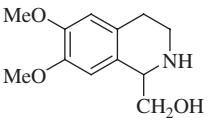

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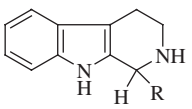
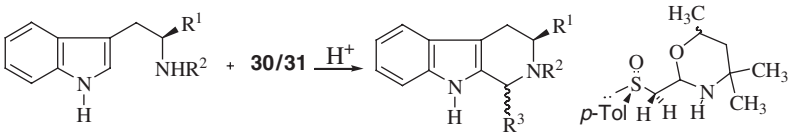


75 (a) R = Me
(b) R = CH_2OH

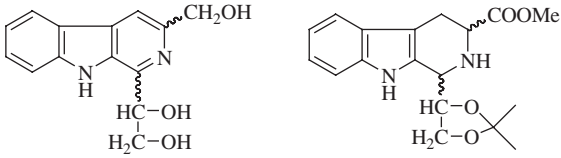
c. β-Carboline Alkaloids. The herman alkaloid, (±)-eleagnine **75a**, which had earlier been synthesized by a strict pH controlled reaction of acetaldehyde and tryptamine, has been smoothly formed by acid-catalyzed transfer of –C(H)Me of 2, 3-dimethyloxazolidine as well as **31** (R = Me) to tryptamine (88JCR(S)322). 1-Hydroxymethyl-1,2,3,4-tetrahydro-β-carboline **75b**, a precursor of alkaloid 1-hydroxymethyl-β-carboline, was formed smoothly by acid-catalyzed reaction of **31** (R = -CH_2OH) and tryptamine (89IJC(B)802). Some similar transfers of C-2 fragments could also be performed with thiazolidines and benzothiazolines (88IJC(B)132).

L-Tryptophan esters **76** (R^1 = COOMe/*i*-Pr; R^2 = H) react with derivatives of **30** and **31** to furnish mixtures of *cis*/*trans* 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines **77** (R^2 = H). Similar reactions of **76** (R^1 = COOMe/*i*-Pr; R^2 = CH_2Ph, *p*-MeOPh) furnish 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines **77** with high *trans*-diastereoselectivity (94–98% de). This protocol has provided a number of tailor-made 1-alkyl-substituted tetrahydro-β-carbolines including pivotal intermediates for corynantheidol and dihydrocorynantheol and related seco-alkaloids (2000TL4977, 2001T7939). In a similar reaction of tryptamine **76** (R^1, R^2 = H) with **28g**, the corresponding 1-substituted-1,2,3,4-tetrahydro-β-carboline **77** (R^1 = R^2 = H, R^3 = CH_2COCH_2COOEt), a useful intermediate for the synthesis of indoloquinolizine and vindoline alkaloids, has been synthesized by acid-catalyzed cyclization of the initially formed enaminoketoester intermediate. Acid-catalyzed reactions of chiral oxazinane **78** with tryptamine and tryptophan derivatives furnish 1,2-disubstituted and 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines convertible into herman and yohimbane alkaloids through simple chemical modifications such as desulfurization using Raney Ni, Pd/C catalyzed debenzylation and removal of the ester function from C-3 (2001H1937, 2004T9171).



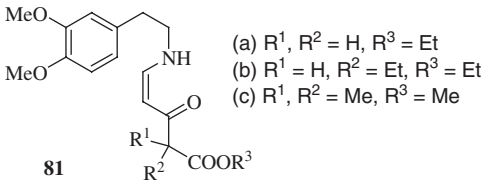
76 **77** **78**

For the synthesis of alkaloid D,L-pyridindolol **79**, a diastereomeric mixture of the precursor ester **80** (79JOC535) has been conveniently obtained by the acid-catalyzed reaction of the 5,10-methylenetetrahydrofolate model imidazolidine **9** with methyl tryptophanate (83T3987).



79 **80**

d. Benzoquinolizine Systems. A convenient synthesis of a benzo[*a*]quinolizine scaffold has potential for elaboration to a number of alkaloids. The imidazolidine–enamine tautomers **18a**/**19a**, **18b**/**19b**, and **18c**/**19c** (Section II.C.1) condensed with homoveratrylamine in the presence of an acid to form enaminoketoester intermediates **81a**, **b**, **c**, respectively. Whereas, **81a** and **81b** having an enolizable proton in a β-ketoester moiety failed to undergo base-catalyzed cyclization, **81c** lacking such a proton gave pyridone **82** that underwent smooth acid-catalyzed cyclization to benzoquinolizine **83** (83H2129, 85T3345).



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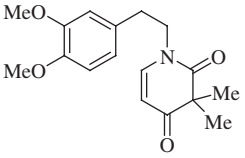

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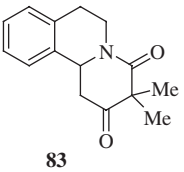
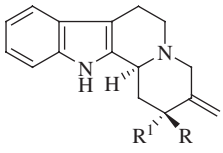


83

e. Indoloquinolizine Alkaloids and Related Systems. A methylenetetrahydrofolate model approach has been conveniently used in the synthesis of indoloquinolizine alkaloids, 18-*nor*-deplancheine **84a**, 18-*nor*-epigeissoschizoate **84b**, 18-*nor*-geissoschizoate **84c**, a precursor of deethyl epi-eburnamonine and a variety of related indoloquinolizine tetracyclic systems, which could be precursors of eburna or related vinca alkaloids (89T849, 88T6187). These synthetic strategies basically focused on the design of appropriate imidazolidine models having functionalized five to seven carbon C-2 fragments, which could be smoothly transferred to tryptamine.

The open-chain tautomers **24b** and **25** of precursor incipient imidazolidine and perhydropyrimidine derivatives, which bear a six carbon transferable fragment, on acid-catalyzed reactions with tryptamine formed the diester **85**. A similar reaction of **24a** leads to quantitative formation of **86** and the reaction of **25** with tryptamine is appreciably faster than that of **24b**. Sodium cyanoborohydride/acetic acid reduction of **85** was accompanied by intramolecular aminolysis to form piperidone **87**. Its Bischler–Napieralski cyclization followed by borohydride reduction gave *cis*- and *trans*-isomers of indoloquinolizine ester **88**, which on hydrolysis to acid and subsequent methylene lactam rearrangement gave methylene lactam **89**. Its DIBAL reduction gave 18-*nor*-deplancheine **84a** (88T6187).

Sodium hydride in benzene-induced cyclization of **85** to pyridone **90**, which on Bischler–Napieralski cyclization followed by borohydride/MeOH reduction formed the unsaturated ester **91a**. DIBAL reduction of **91a** gave alcohol **91b**, which on acid-catalyzed reaction with 1,1,1-trimethoxyethane through [3,3] sigmatropic rearrangement of the intermediate allyl vinyl ether gave 18-*nor*-epigeissoschizoate **84b** and 18-*nor*-geissoschizoate **84c**. The pure **84b** on heating with propionic acid converts into **84c** (88T6187).



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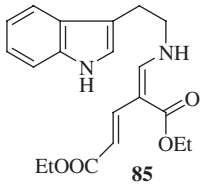
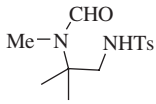
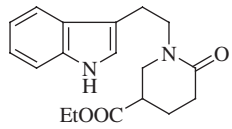


85

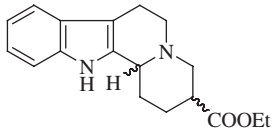


86



87

(a) $R^1 = R = H$
(b) $R^1 = CH_2COOMe$, $R = H$
(c) $R^1 = H$, $R = CH_2COOMe$



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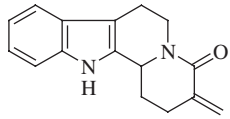

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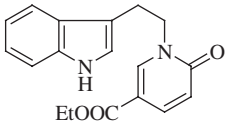

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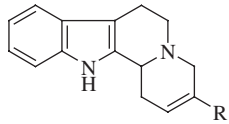
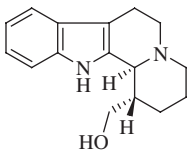


91

(a) R = COOEt
(b) R = CH_2OH

Acid-catalyzed reaction of tryptamine and imidazolidine model **22a** having a suitably functionalized seven carbon transferable C-2 fragment formed isomeric **93** and **94** in 3:2 proportion but **22b** failed to react because being highly stable, it was unable to undergo initial acid-induced ring opening. The cyclization of mixture of **93** and **94** with HCl to **95** followed by Et_3N/AcOH treatment provided lactams **96a** and **97a**, which on LiCl-catalyzed decarbomethoxylation formed tetracyclic ring systems **96b** and **97b**. The reduction of **96b** with DIBAL gave appropriately functionalized indoloquinolizidine system **92**, which in view of the known methodology for its conversion into an eburnamonine skeleton constitutes a practical precursor of deethyl epi-eburnamonine **98**. Similarly, **97b** could be envisaged as a precursor for deethyleburnamonine (89T849).



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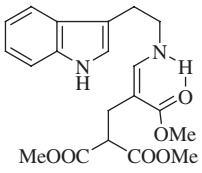

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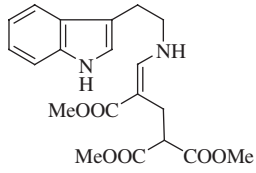

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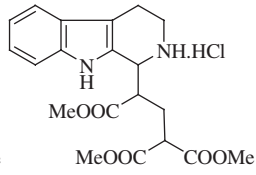

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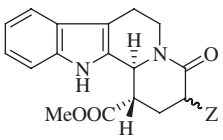
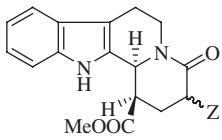
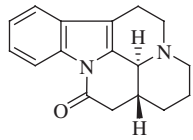


96 (a) Z = COOMe
(b) Z = H



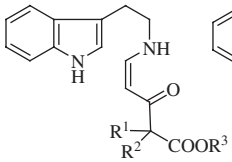
97 (a) Z = COOMe
(b) Z = H



98

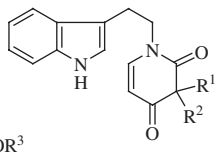
The four carbon C-2 fragment of imidazolidine–enamine tautomers, **18a**/**19a** and **18b**/**19b**, was transferred to tryptamine to form enaminoketoester intermediates **99a**, **b** that could not be efficiently cyclized to indoloquinolizine derivatives. It was argued that the enolizable proton of the β-ketoester moiety interfered with the base-catalyzed cyclization step and hence models **18c**/**19c** and **18d**, **e**/**19d**, **e**, having at the α-carbon of the keto group of the C-2 fragment, a dialkyl group and a combination of an alkyl group and a subsequently removable blocking group were employed. Thus pyridone **100a** formed by base-catalyzed cyclization of **99c**, underwent acid-catalyzed cyclization to tetracyclic indoloquinolizine system **101a**, which on air oxidation formed **102**.

In the second blocking–deblocking approach, the model **18d**/**19d** transferred its C-2 fragment to tryptamine to form **99d**. The NaH-induced cyclization of **99d** to **100b** was attended by decarbomethoxylation to form pyridone **100c**, which again owing to the presence of an acidic H did not cyclize smoothly to **101c**. However, **100b**, available only in restricted amount, cyclized smoothly to **101b**. The model **18e**/**19e** having a thiophenyl blocking group, on reaction with tryptamine formed the enaminoketo ester **99e** which cyclized under the influence of base to give pyridones **100c** and **103**. To allow their formation, the –SPh group has migrated from its original position to the indole nitrogen; a mechanism has been advanced (82TL3301, 83H2129, 85T3345).



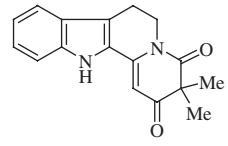
99

	R^1	R^2	R^3
(a)	H	H	Et
(b)	H	Et	Et
(c)	Me	Me	Me
(d)	Et	COOMe	Me
(e)	Et	SPh	Me



100 **101**

	R^1	R^2
(a)	Me	Me
(b)	Et	COOMe
(c)	Et	H



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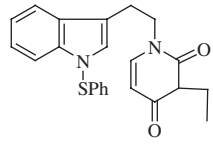
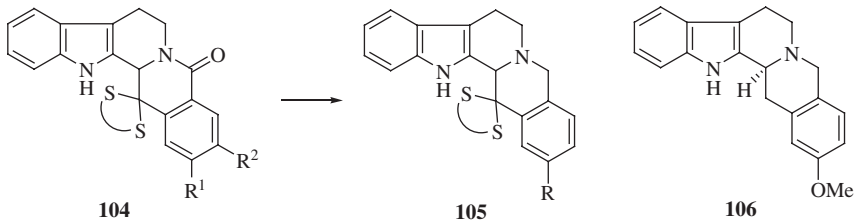
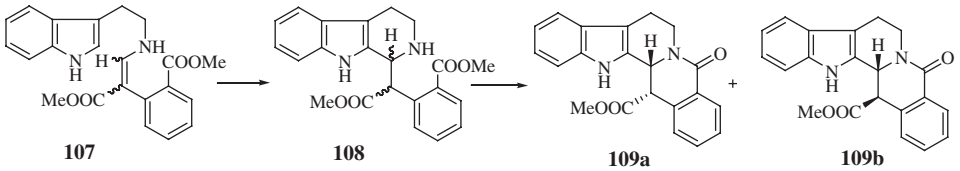


103

f. Yohimbane Alkaloidal Systems. The pentacyclic systems **104** corresponding to the yohimbane skeleton could be formed in a one-pot operation by acid-catalyzed reactions of imidazolidines **10a–c** with tryptamine. LAH reduction of the amide group in **104a**, **b** provided *trans*-quinolizidines **105a**, **b**. Raney Ni/H_2-induced reductive removal of the dithiane group in **105b** gave **106** (81H239, 83T3981), a precursor of epi- and allo-yohimbanes. The pentacyclic intermediate **106** has also been obtained from tetrahydro-β-carboline **77** ($R^1 = H$, $R^2 = p$-$MeOPhCH_2$, $R^3 = p$-tolylsulfinylmethyl) (97TL3001).

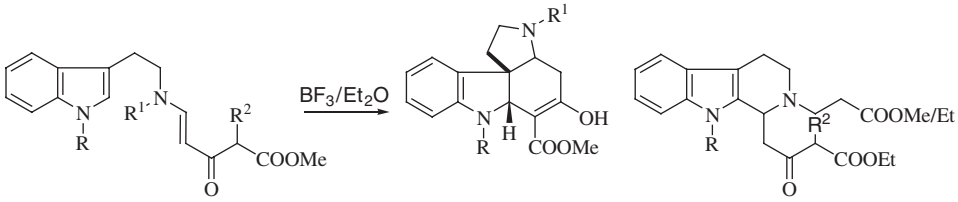


In another approach, the transfer of homophthalate derived C-2 fragment of **14a**/**14b** and **16a**/**16b** in their acetic acid-catalyzed reactions with tryptamine gave mixtures of *Z*/*E* isomers of **107**, which on HCl treatment formed diastereomeric mixture of β-carboline derivatives **108**. Triethylamine/acetic acid treatment of **108** provided pentacyclic products **109a** and **109b** that have been subjected to some chemical modifications (85T3355).



g. Pyrrolocarbazole and Aspidosperma Alkaloidal Systems. The tetracyclic pyrrolocarbazole systems, which constitute templates for pentacyclic vinca alkaloids, have been procured from 5,10-methylenetetrahydrofolate models and tryptamine-based substrates. The enaminoketoester **99a**, which could not be efficiently cyclized to indoloquinolizine system, when acetylated to **110c** gave on treatment with $BF_3 \cdot Et_2O$ the tetracyclic pyrrolocarbazole system **111c**, a potential vindoline intermediate (82TL3301). It was further found that enaminoketoesters **110a** and **110b**, formed by

the reactions of **20** with **113a** and **113b** obtained by Michael reaction of tryptamine or its *N*-methyl derivative with ethyl/methyl acrylate, on $BF_3 \cdot Et_2O$-catalyzed cyclization gave predominantly *β*-carbolines **112a**, **112b**, but $TiCl_4$-induced cyclizations exclusively formed pyrrolocarbazole products **111a**, **111b**. The selectivity of the cyclization mode as well as of the stereochemistry of **111** has been rationalized with respect to stereoelectronic factors. The role of steric interaction in the cyclization step is revealed by a $TiCl_4$-induced cyclization reaction of enaminone **110d** having steric interactions from both Me and Et substituents where only *β*-carboline system **112c** and not corresponding **111** is formed. The enaminoketoester **114** obtained by the above sequence of reactions with methyl tryptophanate, on $TiCl_4$-induced cyclization formed **115** with absolute stereochemistry identical with the natural vindoline template (91T4155).



110

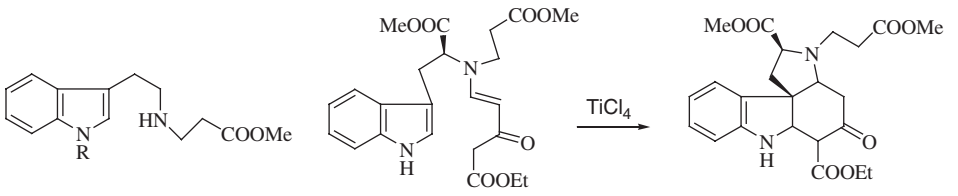
	R	R^1	R^2
(a)	H	CH_2CH_2COOEt	H
(b)	Me	CH_2CH_2COOEt	H
(c)	H	COMe	H
(d)	Me	CH_2CH_2COOMe	Et

111

(a) R = H, $R^1 = CH_2CH_2COOEt$
(b) R = Me, $R^1 = CH_2CH_2COOEt$
(c) R = H, R^1 = COMe

112

(a) $R = R^2 = H$
(b) R = Me, R^2 = H
(c) R = Me, R^2 = Et

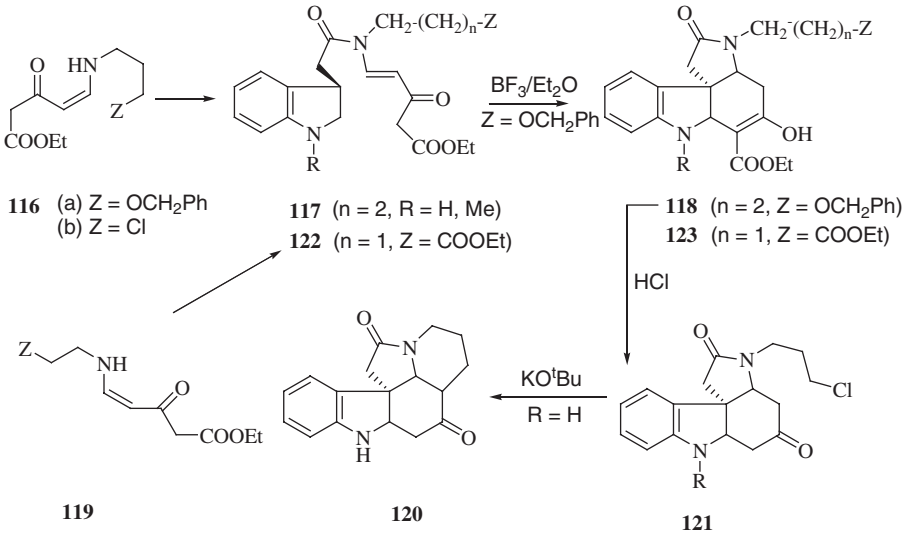


113 (a) R = H (b) R = Me

114

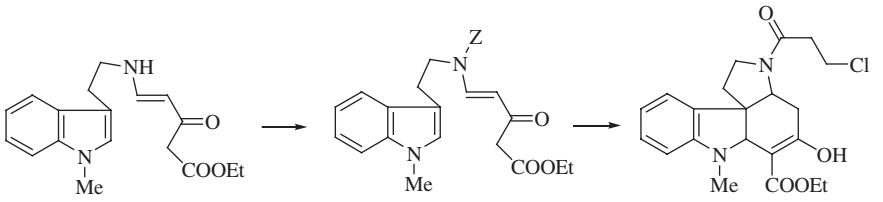
115

The THF model **18a**/**19a** transfers the functionalized carbon fragment to 3-benzyloxypropylamine and 3-chloropropylamine to form **116a** and **116b**, which acylate with indolyl-3-acetyl chloride and its *N*-methyl derivative to form **117a** ($Z = OCH_2Ph$) and **117b** ($Z = Cl$) that undergo BF_3-induced cyclization to **118** and **121**, respectively. On HCl treatment, **118** also gave **121**, which undergoes potassium *tert*-butoxide-induced cyclization to pentacyclic product **120** (84TL1513, 91T4165).

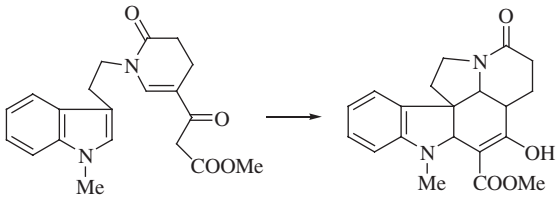


The enaminone **119** (Z = COOEt) obtained from **18a**/**19a** or **20** and ethyl *β*-alanate on reaction with 3-indolylacetyl chloride and its *N*-methyl derivative gave enamides **122** (R = H, Me), which on $TiCl_4$-induced cyclization gave corresponding pyrrolocarbazoles **123** (R = H, Me). The base-induced transformations of these tetracycles to corresponding pentacyclic systems could not be achieved (91T4165).

The enaminone **124** obtained from model **18a**/**19a** and *N*-methyltryptamine, on acylation with 3-chloropropionyl chloride gave enamide **125** ($Z = COCH_2CH_2Cl$), which on treatment with $BF_3 \cdot Et_2O$ formed the tetracyclic system **126**.



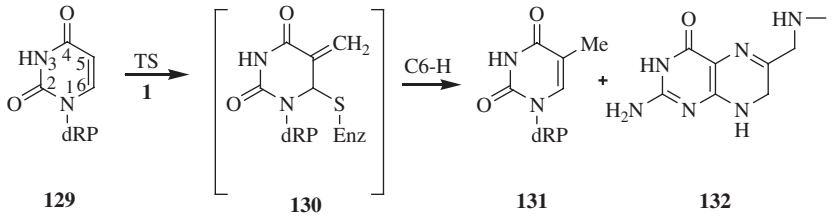
The enaminone **124** on acylation with acryloyl chloride furnished mainly **127** by the intramolecular addition of enamine to the acrylamide moiety in initial intermediate **125** ($Z = COCH = CH_2$). The cyclization of **127** is affected by $TiCl_4$ to form aspidosperma alkaloid pentacyclic skeleton **128** (91T4165).



127 **128**

IV. Molecular Mechanism of Carbon Transfer Reactions

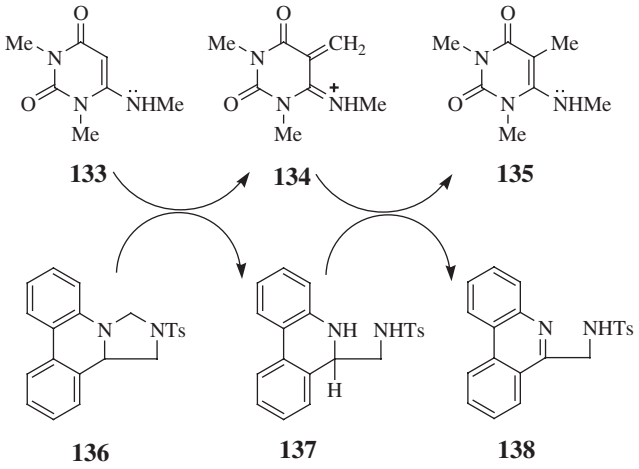
Of the two objectives (Section I) of investigations on the models of this cofactor, the one translating its functional capability of carbon transfers in the evolution of chemical synthesis has been amply illustrated. With respect to the second objective of providing support to the molecular mechanism of the enzymatic process in which this cofactor plays an essential role, Pandit chose to mimic in totality the thymidylate synthase (TS) catalyzed conversion of deoxyuridine monophosphate (dUMP, **129**) to deoxythymine monophosphate (dTMP, **131**) that is reported to proceed by transfer of a methylene group of an imidazolidine component of **1** to C-5 of dUMP **129**, the nucleophilicity of which is enhanced by the addition of a thiol of apoenzyme at C-6, generating the methylene intermediate **130**. The subsequent delivery of the C-6H of **1** as an hydride equivalent to the methylene carbon is followed by elimination of a thiol and formation of dTMP **131** along with 7,8-dihydrofolate **132**.



129 **130** **131** **132**

For mimicking the above overall reaction of cofactor **1** in a nonenzymatic mode involving overall transfer of a methyl group to nucleophilic substrates, the model, 2-tosyl-1,2,3,12*b*-tetrahydroimidazo[1,5-*f*]-phenanthridine (**136**), which could act both as a carbon transfer agent and a reductant, was designed and synthesized. 1,3-Dimethyl-6-methylaminouracil **133** having inbuilt enhanced nucleophilicity at C-6 was used as substrate. In the acid-catalyzed reaction of **136** and **133**, the initial formation of methylene intermediate **134**, which bears resemblance to intermediate **130** except its higher oxidation level, could be visualized. The hydride transfer from **137** here induces an addition reaction as against elimination in **130** and **138** and **135**

are formed (87T4015). The intermediacy of corresponding **134** in the reactions of 1,3-dimethyl-6-aminouracil and its derivatives with **136** was amply demonstrated by trapping experiments, reduction to corresponding 5-methyluracil derivatives and UV/NMR monitoring experiments (86T3921).



V. Conclusions

The potential growth of the chemistry of heterocycles (70CEN80) prophesied in 1970 was exploited so vigorously that in almost a decade it needed a multivolume treatise (84CHEC) to comprehend their phenomenal advances. For synthetic organic chemists, an aspect of immense relevance was the synthetic utility of heterocycles as precursors, reagents, vehicles, and transient intermediates (74MI). A unique mode of designing heterocyclic reagents and catalysts for achieving targeted synthetic aims was the development of structurally simpler synthetic models of coenzymes, which could imitate the highly efficient biological reactions of these cofactors in a synthetically useful manner. The structural designs of these coenzyme models were rationally based on the physicochemical character of the active participating heterocyclic components of the coenzymes (84MI). Thus thiazolium cations and their analogs, as models of thiamine, catalyze many acyloin and related reactions that could not be achieved by the traditional catalysts. The synthetic spectrum revealed here by imidazolidines, Δ^2-imidazolinium cations, and their other 1,3-heterocyclic analogs as THF models, point to the scope and promise that the exploitation of coenzyme model strategy holds for use of heterocycles in organic synthesis.

Acknowledgment

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Advances in the Chemistry of Naphthyridines

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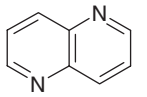
I. Introduction

In the present review, an analysis is made of the synthesis and properties of six isomeric heterocyclic systems containing two fused pyridine rings with different mutual arrangements of nitrogen atoms – naphthyridines (pyridopyridines, diazanaphthalenes). They include two groups of compounds – $N(1)$,$N(i)$-naphthyridines ($i = 5, 6, 7, 8$) **1–4** and $N(2)$,$N(j)$-naphthyridines ($j = 6, 7$) **5**, **6**.



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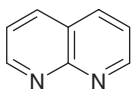

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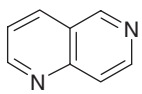

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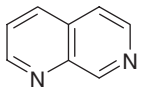

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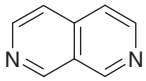
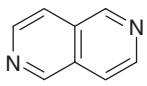
1,7-naphthyridine



5
2,7-naphthyridine



6
2,6-naphthyridine

The first derivative of the cyclic naphthyridine system was obtained in 1893 by Reissert (1893B2137), who proposed this name for the new class of heterocyclic

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compounds. The first representatives of unsubstituted naphthyridines – 1,5-naphthyridine **1** (1927B1081) and 1,8-naphthyridine **2** (1927B1918) – were described only in 1927. Naphthyridines containing nitrogen atoms at positions 1,6 (**3**) (1958CPB263), 1,7 (**4**) (1958CPB401) and 2,7 (**5**) (1958CPB269) were prepared in 1958, and 2,6-naphthyridine (1965TL1117, 1965TL2737) was synthesized only in 1965.

Since then, researchers from different countries have shown an ever-increasing interest in the chemistry of naphthyridines. Indeed, the bibliography of a review (1950CR275) published in 1950 included 75 references, while that of an initial review in this series (1970AHC123) comprised 242 references. The reviews (1983AHC95, 1983AHC147) published in 1983 present 223 studies. Several reviews dealing with more specific aspects were also published before 1983 (1961MI1, 1970WCH773, 1973MI1, 1974MI1, 1978WCH91, 1979KGS3, 1979WCH235, 1980WCH263, 1980WCH593, 1981WCH441). In recent years, the number of publications devoted to various aspects of naphthyridine chemistry has sharply increased. More than 1000 publications have appeared during the last 15 years, 40% of them being patents.

This interest in naphthyridine derivatives is due to its practical importance. They have an exceptionally broad spectrum of biological activities and are used for the diagnosis 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.

This review is based on the papers published by the author in a recent *Russian Chemical Reviews* (2000RCR201, 2001RCR299, 2004RCR637) and mainly on surveys of the data over the last 15 years; however, earlier fundamental studies also are invoked in the discussion of structure, chemical and physicochemical properties, biological activities and others practical aspects.

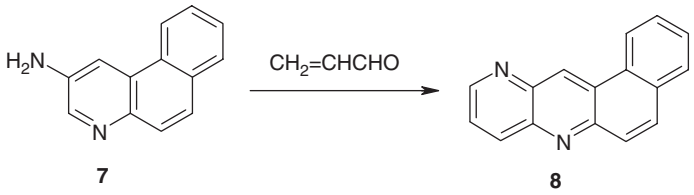
II. Synthesis of Naphthyridines

General synthetic methods used to prepare various types of naphthyridines include the Skraup, Friedlander and some other name reactions. They include cyclization, cyclocondensation, dimerization reactions, etc.

A. 1,5-Naphthyridines

The major synthetic approach to the 1,5-naphthyridine system **1** involves 3-aminopyridine derivatives condensing with dicarbonyl compounds followed by an intramolecular reaction of the pyridine ring with a 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, Friedlander, Knorr, etc. Amino derivatives of pyridine (1993S1227), indole (1985FRP2548667, 1985EUP130878, 1987BCJ3797, 1991EUP327426) and quinuclidine (1994TL5939), oximes of the isoquinoline series (1986USP4742171, 1987USP4652567, 1988USP4742061) and substituted anilines (1998PIAWO9818795) were successfully used as substrates.

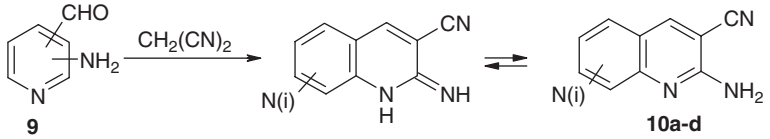
In recent years, a modified Skraup reaction (20% oleum, nitrobenzene, $FeSO_4 \cdot 7H_2O$, H_3BO_4) has been used to synthesize fused naphthyridines. Thus, 3-aminobenzo[*h*]quinoline 7 was converted in this way into naphtho[2,1-*b*]-1,5-naphthyridine **8**(1989H2109).



7 **8**

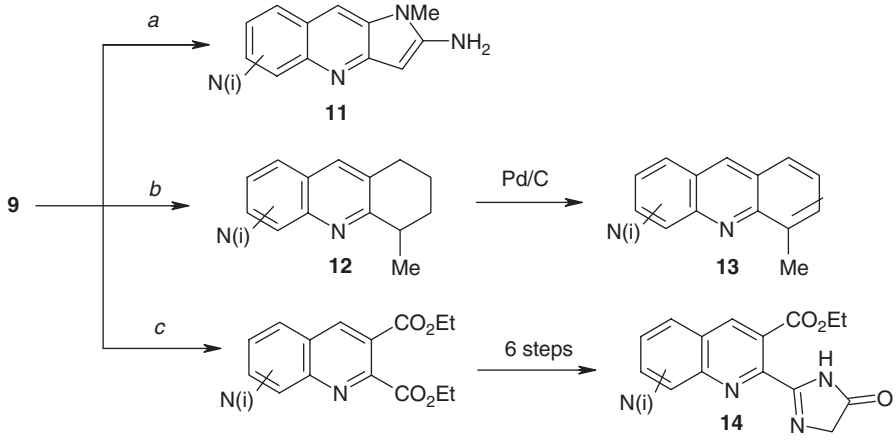
A modified Skraup method, namely, the reaction of 4-aminoisoquinoline with methyl vinyl ketone in the presence of As_2O_5 and concentrated sulfuric acid, was used to prepare 4-methylbenzo[*c*]-1,5-naphthyridine (1994AJC2129).

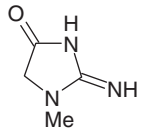
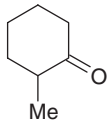
Another general procedure for the preparation of naphthyridines **1–4** based on the condensation of vicinal aminopyridinecarbaldehydes **9** with malononitrile in ethanol in the presence of base (according to the Knoevenagel reaction pattern) furnished 2-amino-3-cyano-*N*(1),*N*(*i*)-naphthyridines **10a–d**; some were found to be effective diuretics (1987MI1, 1991MI1). The condensation of aldehydes **9** with creatinine in ethylene glycol affords imidazo[4,5-*b*]-*N*(1),*N*(*i*)-naphthyridines **11a–d** (1994JCR(S)268). The reaction of **9** with 2-methylcyclohexanone in ^{t}BuOH in the presence of ^{t}BuOK followed by dehydrogenation of the products **12a,c,d** thus formed (refluxing with Pd/C in Ph_2O) gives rise to benzo[*b*]-*N*(1),*N*(*i*)-naphthyridines **13a,c,d**. Using the Friedlander reaction, naphthyridines **14** have been synthesized; they are active components of herbicide formulations (1986SAP85/04792, 1987GEP3601688).



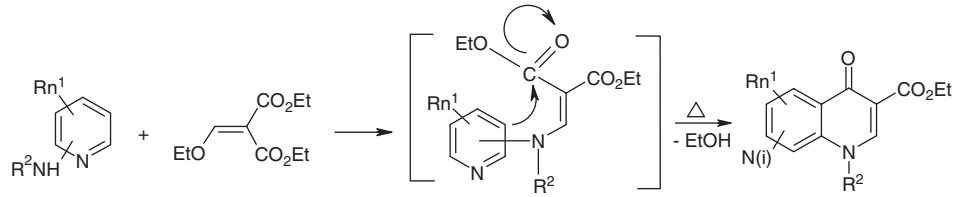
9 **10a-d**

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



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

As in the previous cases, the condensation of aminopyridines with diethyl ethoxymethylidenemalonate for the synthesis of naphthyridines **1–4** attracts attention, because it provides the possibility of synthesizing diverse naphthyridines exhibiting a broad range of biological activities. Thus, the condensation of substituted aminopyridines **15** with diethyl ethoxymethylidenemalonate **16** and subsequent cyclization on refluxing the resulting diesters of *N*-(pyridyl)aminomethylidenemalonic acids **17** gives derivatives of naphthyridinecarboxylic acids **18** possessing antibacterial activity or serving as intermediates in the synthesis of compounds with this type of activity (1983EUP58614, 1984AJC1065, 1984CPB4914, 1984JHC673, 1984FRP2531084, 1985AJC459, 1985EUP146243, 1986EUP172651, 1990IJC98, 1991CCC2240, 1991EUP387802, 1995JMC973, 1996PLP165956, 1999JAP1112279).

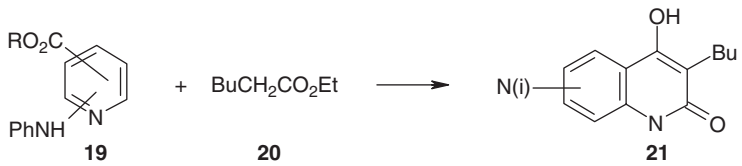


15 **16** **17** **18**

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

Naphthyridines **18** (R^2=H) without substituents at nitrogen have served as the starting compounds to pyrazolo[3,4-*c*]naphthyridines, which act as modulators of benzodiazepine receptors and possess sedative and antispasmodic activities (1984EUP115469, 1986EUP168350, 1986USP4560691).

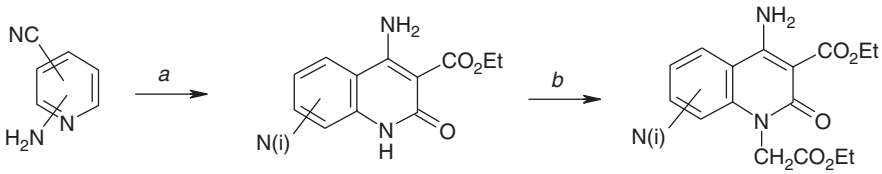
The condensation of vicinal aminopyridinecarboxylic acids or esters **19** with ethyl hexanoate **20** in the presence of ^{t}BuOK under a nitrogen atmosphere gave *N*(1),*N*(*i*)-naphthyridin-2(1*H*)-ones **21a–c**, exhibiting antiallergic activities (1988JMC2108).



19 **20** **21**

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

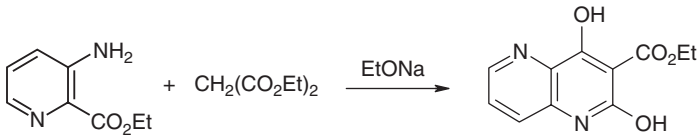
Naphthyridones **22**, which are of interest as pharmacological preparations, have been synthesized by the reaction of vicinal aminopyridinecarbonitriles **23** with diethyl malonate. Alkylation of these products with ethyl monobromoacetate results in N-substituted compounds **24** (1990ZC20)



23 **22** **24**

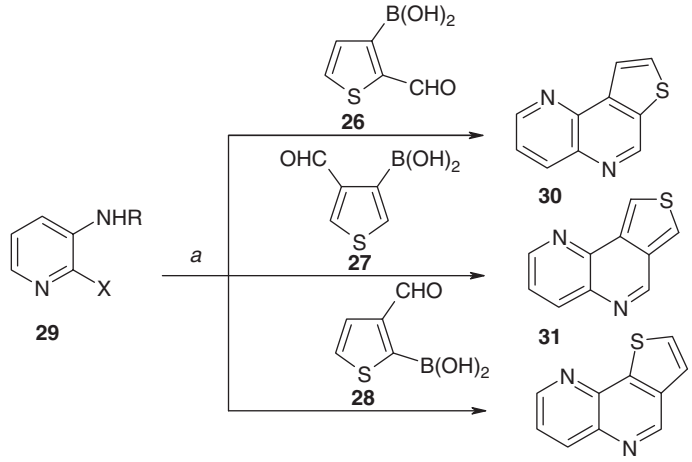
(a) $CH_2(CO_2Et)_2$, EtONa;
(b)$BrCH_2CO_2Et$, BuOH, K_2CO_3; i = 5-8

When diethyl malonate reacts with ethyl 3-aminopicolinate, substituted 1,5-naphthyridine **25** is formed; it is used in the synthesis of potential antimalarial remedies (1984AJC2469).



25

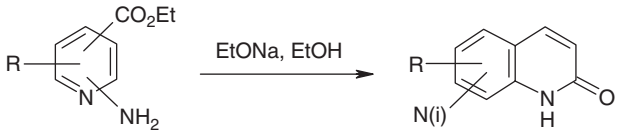
A one-stage procedure has been proposed (1986CS311, 1987CS535, 1991CCC2340, 1993H245) for the preparation of isomeric *N*(1),*N*(*i*)-naphthyridines; the procedure used $Pd(PPh_3)_4$-catalyzed cross-coupling of thiopheneboronic acids **26–28** containing an *ortho*-formyl group with *o*-aminohetaryl halides **29**. The cross-coupling products cyclized spontaneously during the reaction to give thienonaphthyridines **30–32** with all possible types of ring fusion. The effects of the amount of the catalyst, the nature of the base and the reaction time on the yield of the naphthyridine **31** have been studied (1991CCC2340).



R = H: X = Cl (a), Br (b); R = Ac, X = Br (c);

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

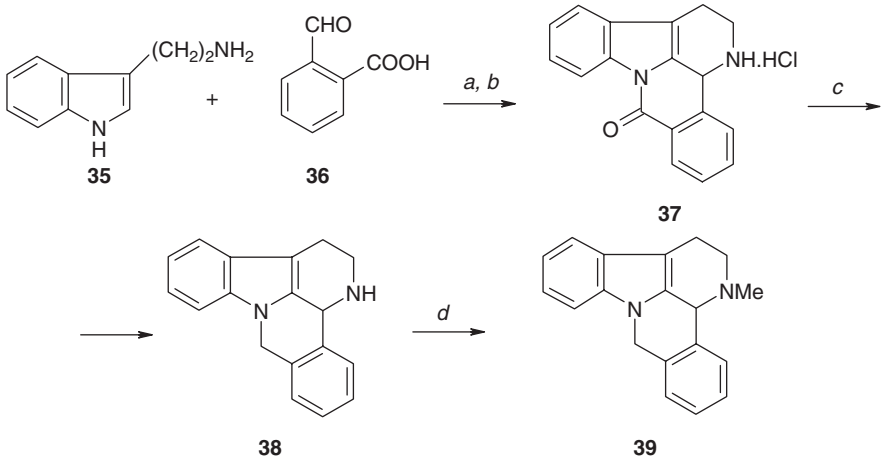
Other general methods for the synthesis of naphthyridines **1–4** start from pyridine derivatives containing an amino (or protected amino) group and a carbonyl group or its synthetic equivalent in vicinal positions. Cyclization of ethyl aminopyridineacrylates **33** in ethanol with sodium ethoxide has served as a rout to *N*(1),*N*(*i*)-naphthyridin-2(1*H*)-ones **34** (1985CPB4764).



33 **34**

R = H, Me; i = 5-8.

Tryptamine, tryptophan and their derivatives are widely used in the synthesis of indolo[3,2,1-*de*][1,5]naphthyridine derivatives. Thus, refluxing tryptamine **35** with 2-formylbenzoic acid **36** in alcohol followed by the addition of concentrated hydrochloric acid afforded hexahydrobenzo[*h*]indolo[3,2,1-*de*][1,5]naphthyridine hydrochloride **37** used as the starting compound in the synthesis of **38** and **39**. The latter have an application in the treatment of oxygen deficiency (1985FRP2548667).



35 **36** **37** **38** **39**

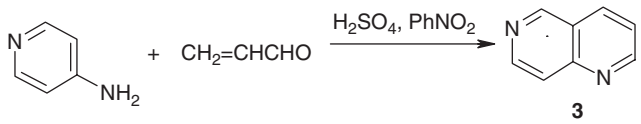
(a) EtOH, △, 2.5 h; (b) HCl; (c) $LiAlH_4$, $AlCl_3$; (d) 37%CH_2O, $NaBH_3CN$, AcOH, MeCN

Some other methods for the synthesis of 1,5-naphthyridines (1985EUP130878, 1986FRP2567887, 1986USP4742171, 1987JHC1009, 1989KGS557, 1990EUP346207, 1990EUP346208, 1991JHC1997, 1992LA1159, 1993H245, 1993S1227) were described.

Recently, the synthesis and purification of 6-ethoxy-4-oxo-1,4-dihydro[1,5]naphthyridine-3-carboxylic acid benzylamide have been published (2003MI1).

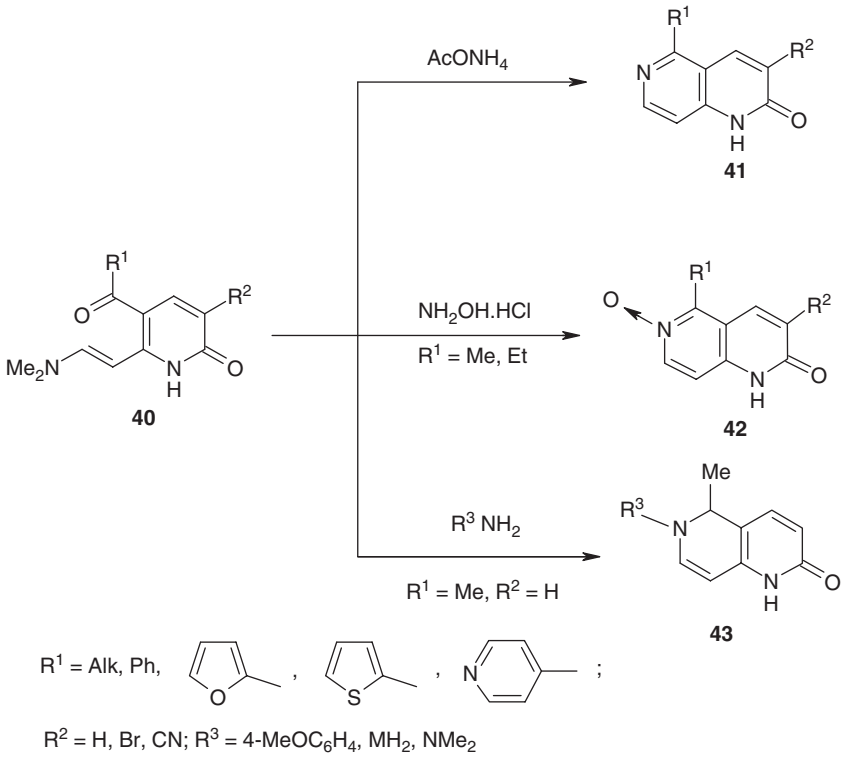
B. 1,6-Naphthyridines

1,6-Naphthyridine **3** has been prepared by the Skraup method by heating 4-aminopyridine with glycerol, fuming sulfuric acid and nitrobenzene (1990EUP321191).



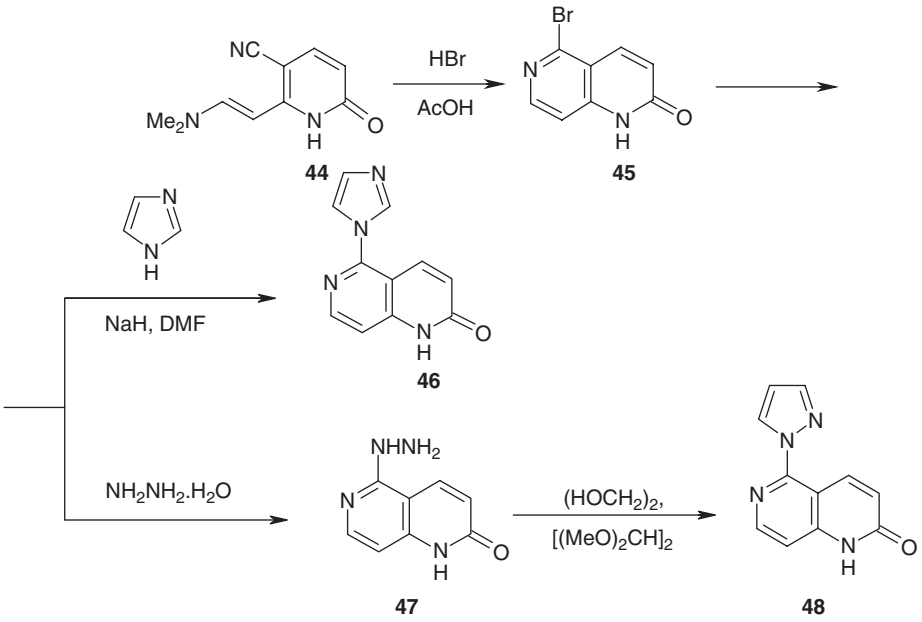
3

One of the promising procedures for the synthesis of 1,6-naphthyridine derivatives involves functionally substituted pyridones as the starting compounds. Thus, enamines **40** prepared from 6-formylpyrid-2-ones underwent cyclization upon refluxing with ammonium acetate in DMF to give 1,6-naphthyridin-2-ones **41** in good yields (1983USP4517190, 1983USP4532247, 1984USP4604399, 1985USP4567186, 1985USP4650806, 1990JHC2085). *N*-oxides **42** were prepared by cyclization of the enamines **40** under the action of hydroxylamine hydrochloride (1983USP4532247, 1984USP4604399). The reactions of compounds **40** with amines in methanol or DMF afforded 6-substituted 1,2,5,6-tetrahydro-1,6-naphthyridin-2-ones **43** (1992S279).

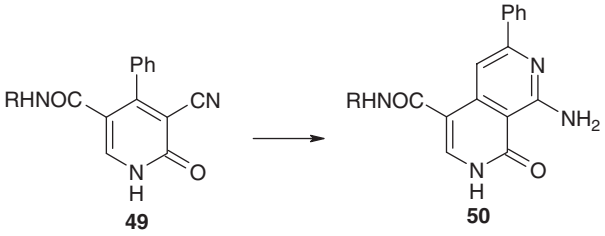


40

Treatment of enamine 44 derived from 5-cyano-6-formyl-2-pyridone with gaseous HBr in AcOH gave rise to 5-bromo-1,6-naphthyridin-2-one **45**. The bromine atom in **45** is readily replaced by nitrogen nucleophiles. This fact was used in the synthesis of naphthyridine derivatives **46–48** (1986USP4634772, 1986USP4657915, 1986USP4697021, 1986USP4716170). The compounds **41**, **42** and **45–48** exhibit cardiotonic activity (1983USP4532247, 1984USP4559347, 1984USP4604399, 1985USP4567186, 1985USP4650806, 1986USP4634772, 1986USP4657915, 1986USP4697021, 1986USP4716170, 1990JHC2085, 1992S279).



Condensation of cyanopyridinone **49** with benzaldehyde followed by NH_4OH gave naphthyridinone **50** (2003MI2).



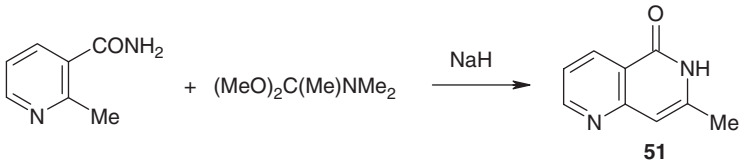
R = 4-ClC_6H_4.

Many other substituted pyridones and piperidones are widely used as the starting compounds in the synthesis of substituted 1,6-naphthyridines, which possess various types of biological activities (1984CPB2522, 1985AP175, 1986KFZ830, 1986KGS1118, 1987GEP3502831, 1987USP4751305, 1988GEP3609785, 1988USP4748246, 1989USP4808612, 1989JHC577, 1994T1877, 1995IJC17, 1995JAP477488, 1995JMC25461997LA1777).

Pyridinecarboxylamides are widely used in the synthesis of 1,6-naphthyridines (1984JGU2083, 1986H1247, 1986MI1, 1987USP4791108, 1988USP4956365, 1989EUP288196, 1989KGS238, 1989JMC2034, 1989USP4960891, 1991JMC705, 1991USP5229387, 1991USP5231181, 1992KGS92, 1992MI1, 1992USP5391554, 1993JOC1935, 1996MI1, 1997JHC397).

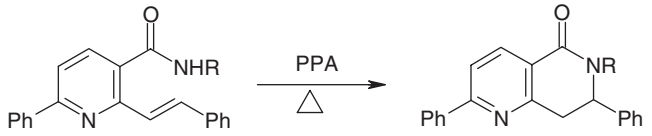
For example, heating a mixture of 2-methylnicotinamide with *N*,*N*-dimethylacetamide dimethyl acetal in the presence of NaH gave rise to 7-methyl-1,6-naphthyridin-5(6*H*)-one **51**, which is used for eliminating harmful effects caused by ionizing

radiation or chemotherapeutic agents during tumor treatment (1984JGU2083, 1992USP5391554).



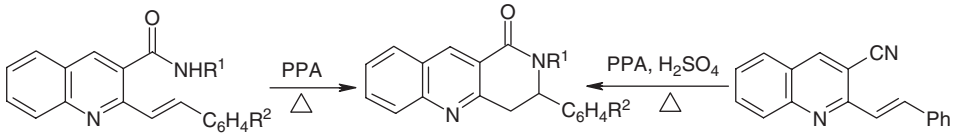
51

When heated in polyphosphoric acid (PPA), 6-phenyl-2styrylnicotinamides **52** underwent cyclization to form substituted 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridines **53** (1984JGU2083). Analogously, benzo[*h*][1,6]naphthyridines **54** were prepared from amides of the quinoline series **55** (1984JGU2083, 1989KGS238, 1992KGS92). Naphthyridine **54** (R^1=R^2=H) was also synthesized by cyclization of 3-cyano-2styrylquinoline **56** under the action of a mixture of polyphosphoric and sulfuric acids (1992KGS92).



52 53

R = CH_2=$CHCH_2$, iso-C_5H_{11}, Ph, 4-MeC_6H_4.



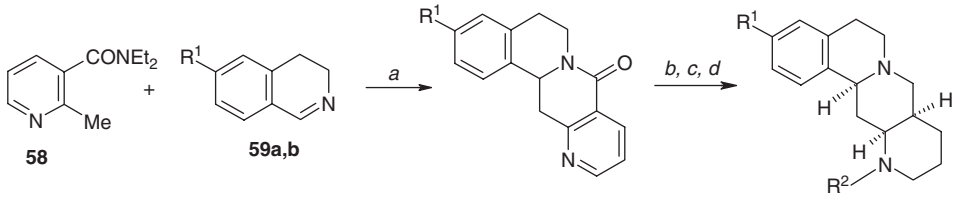
55 54 56

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 an 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 (1996MI1, 1997JHC397).

A procedure was developed for the synthesis of dodecahydroisoquinolino[2,1-*g*][1,6]naphthyridines **57** based on diethyl-2-methylnicotinamide **58** and 3,4-dihydroisoquinolines **59a,b**. The compounds **57** are highly efficient α_2-adrenoreceptor antagonists (1989JMC2034, 1991JMC705) and were covered by patents as drugs for the treatment of hypertonia, depression and diabetes, for inhibition of thrombocyte aggregation and for weight reduction (1987USP4791108, 1988USP4956365, 1989EUP288196, 1989USP4960891, 1991USP5229387, 1991USP5231181). It should be noted that the structural analog of α-yohimbine, viz., 6-methoxy-*N*-methylsulfonyl-6*H*-isoquinolino[2,1-*g*][1,6]naphthyridine (**57**, R^1=MeO, R^2=$MeSO_2$, the preparation

RS-15385) (1993JOC1935), proved to be a very efficient drug for the treatment of impotence. A laboratory procedure for its preparation on a kilogram scale was developed (1986MI1, 1992MI1).



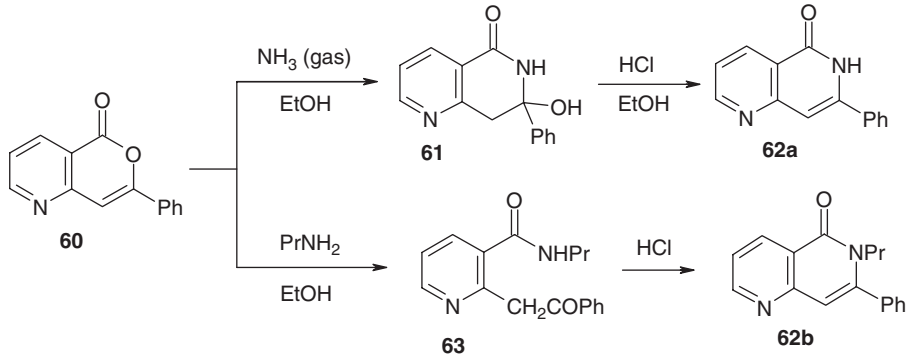
R^1 = H (**59a**), MeO (**59b**);

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_2^i NLi, THF,2-40°C; (b) H_2, Rh/Al_2O_3, AcOH; (c) $LiAlH_4$, THF, Δ;

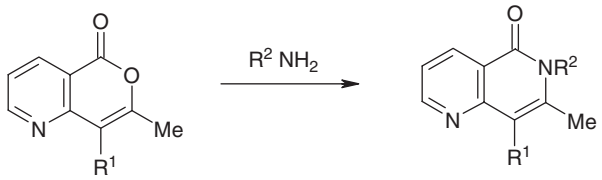
(d) R^2X (X = Cl, Br), CH_2Cl_2, Et_3N.

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 **60** 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 **61**. The latter was dehydrated with an alcoholic solution of HCl to give 7-phenyl-1,6-naphthyridin-5(6*H*)-one **62a**. Treatment of pyranopyridine with propylamine led to pyran ring opening to form 2-phenacyl-*N*-propylpyridine-3-carboxamide **63**, which underwent cyclization under the action of a 5% HCl solution giving rise to *N*-propyl-substituted naphthyridinone **62b** (1991S41).



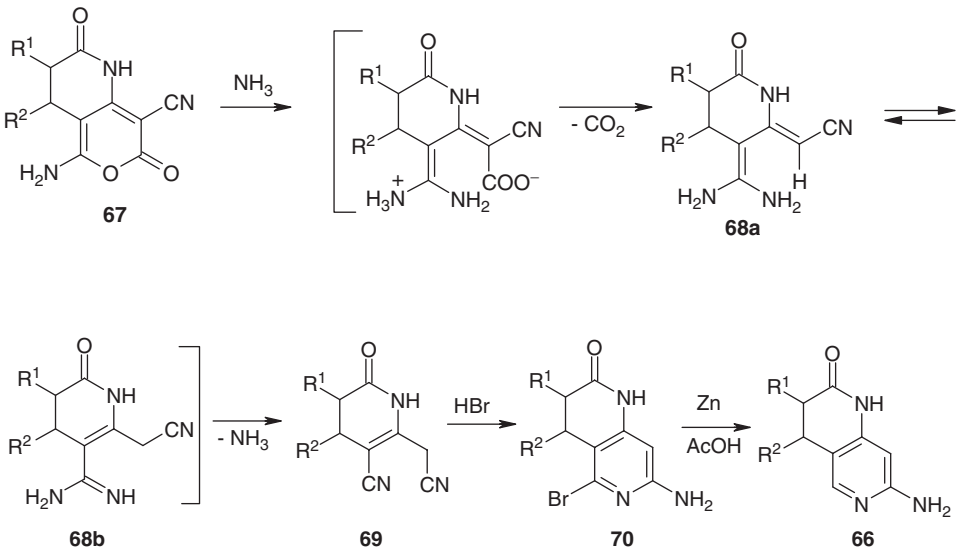
N-Hydroxyethyl-substituted 1,6-naphthyridione **62a** was prepared by refluxing pyranopyridine **60** with ethanolamine (1992SC1239).

An analogous reaction of 7-methylpyrano[4,3-*b*]pyridines **64** with ammonia or aliphatic primary amines afforded 1,6-naphthyridinones **65** (1989IJC173).



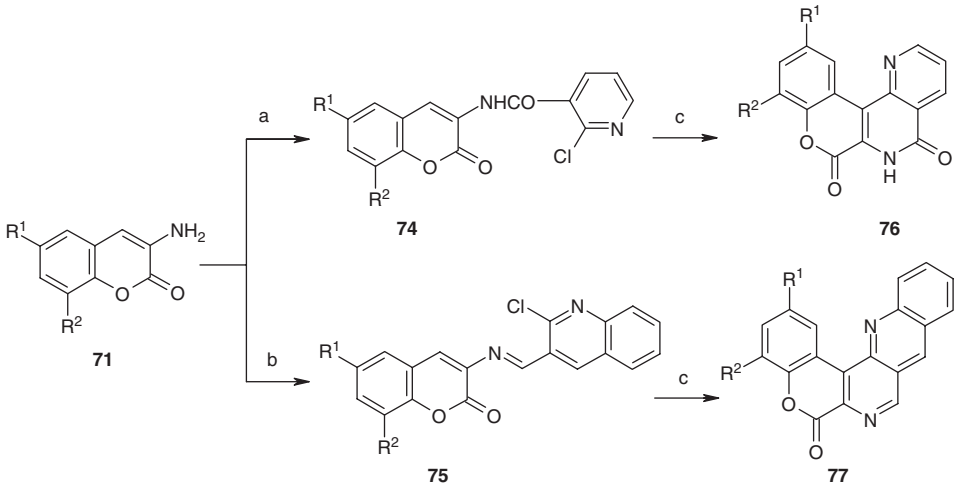
R^1= Ac, CO_2Et R^2= H, Me, Bu, $(CH_2)_2NH_2$, $(CH_2)_2OH$, CH_2=$CHCH_2$.

1,6-Naphthyridin-2(1*H*)-ones **66** were prepared from pyrano[4,3-*b*]pyridine-2,7-diones **67** by successive treatment with NH_3, HBr and Zn in acetic acid (1993H1). It was believed that the attack of the ammonia molecule on the C(5) atom led to pyran ring opening. Subsequent decarboxylation afforded a tautomeric mixture of substituted tetrahydropyridines **68a,b**. Dinitrile **69** generated by elimination of ammonia underwent cyclization under the action of HBr to form 1,6-naphthyridine derivative **70**. Dehydrobromination with Zn in acetic acid gave the final products **66**.



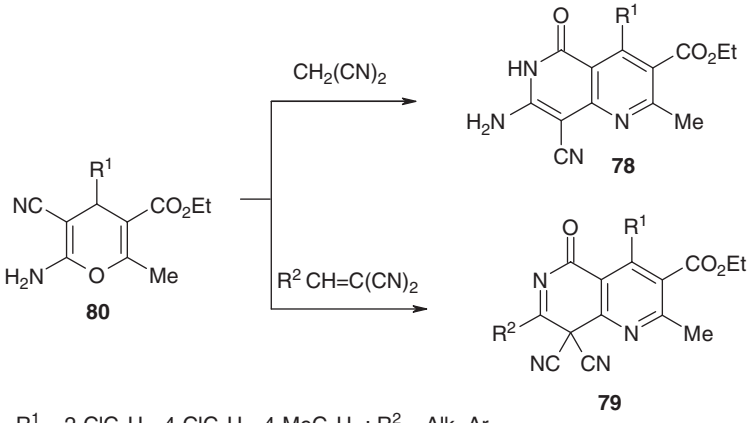
R^1, R^2 = H, Me, Ph.

The reaction of 3-aminocoumarins **71** with 2-chloronicotinoyl chloride **72** or 2-chloro-3-formylquinone **73** afforded *N*-acyl derivatives **74** or Schiff bases **75**, which were dehydrochlorinated by bases with simultaneous cyclization to give benzopyrano[3,4-*h*][1,6]naphthyridines **76** or **77**, respectively (1992SC2479, 1995MI1, 1995OPP547).



R^1 = H, Br, Cl; R^2 = H, OMe, Br; (a)**72**, Et_3N, PhH, Δ, 8 h; (b) **73**, AcOH; (c) Py or Et_3N-$PdCl_2$.

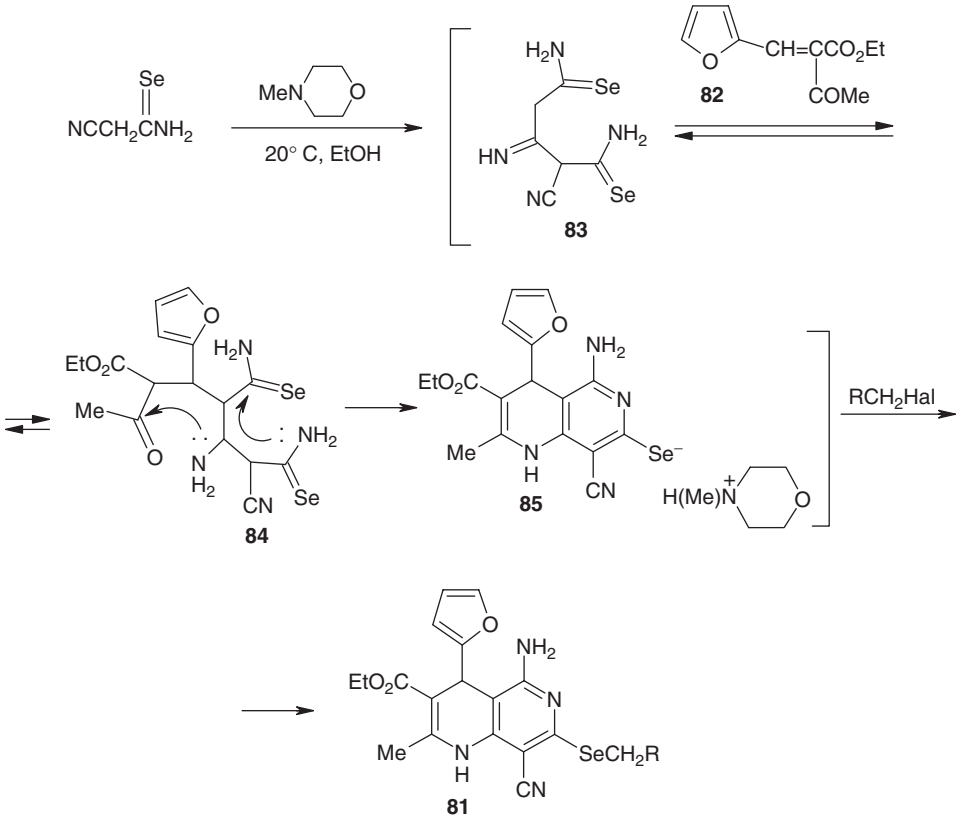
The synthetic routes to 1,6-naphthyridones **78** and **79** make use of the reactions of pyrans **80** with malononitrile or its derivatives. The reactions are carried out in ethanol in the presence of piperidine (1989LA585, 1995JCR(S)490, 1996JCS(P1)1067).



R^1 = 2-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4 ; R^2 = Alk, Ar.

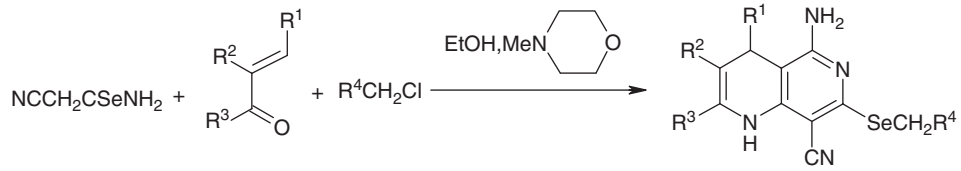
A convenient procedure was developed (1996IZV437, 2000IZV121) for the synthesis of 1,6-naphthyridine derivatives **81** containing the alkylselanyl substituent at position 7. Thus, multicomponent condensation of cyanoselenoacetamide, 2-furfurylideneacetoacetic ester **82** and alkyl halides was carried out under the action of a two-fold excess of *N*-methylmorpholine. The reaction involves the Thorpe dimerization of the cyanoselenoamide yielding compound **83**, its reaction with a molecule of ester **82** to form adduct **84**, regioselective cyclocondensation of the adduct **84**

producing substituted 1,4-dihydro-1,6-naphthyridine-7-selenolate **85** and alkylation of selenolate **85** with alkyl halides giving rise to naphthyridines **81**.



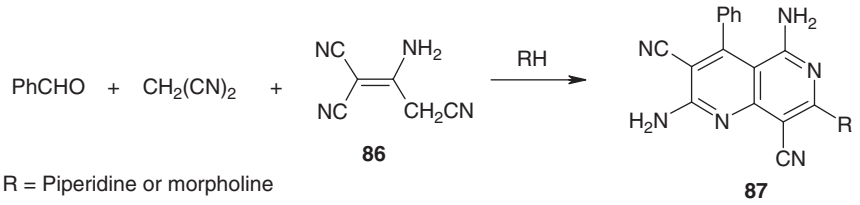
R = Alk, CH_2Br, $(CH_2)_3Br$, $C(Me)=CH_2$, $CH=CH_2$, CO_2Et; Hal = I, Br, Cl.

This procedure also allows one to construct the naphthyridine system from other α,β-unsaturated carbonyl compounds under mild conditions (1999MI1).

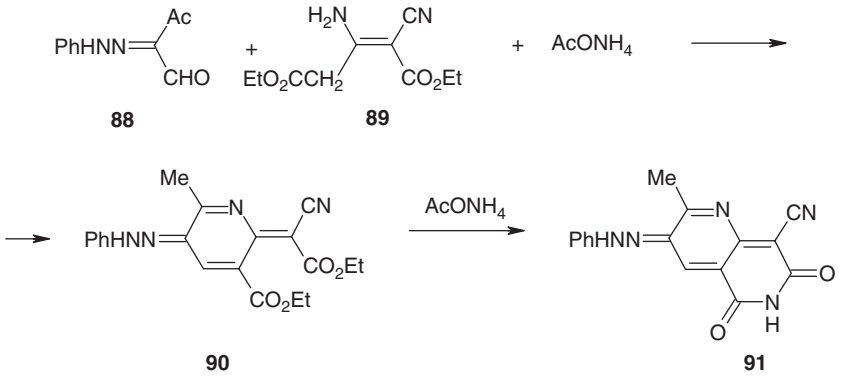


R^1 - R^3 = H, Alk, Ar, Het, CN, CO_2H, CO_2Alk, COAr, COHet, $CONH_2$, CONHAr ; R^4= Alk.

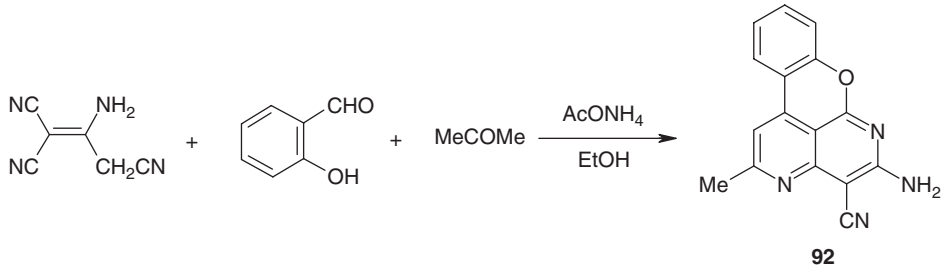
Multicomponent heterocyclization of benzaldehyde with malononitrile and its dimer **86** in the presence of piperidine or morpholine was used for the construction of the 1,6-naphthyridine **87**. Heterocyclization was accompanied by the insertion of the cyclic amine fragment into the molecule to form **87** (1999KGS1435).



Of the other procedures for the synthesis of 1,6-naphthyridines, noteworthy is the three-component cyclization of 2,3-dioxobutanal phenylhydrazone **88** with diethyl 3-amino-2-cyanopent-2-enedioate **89** and ammonium acetate to form substituted 1,6-naphthyridine-5,7-(3*H*, 6*H*)-dione **90**. Polyfunctionalized pyridine derivative **91** was obtained as the intermediate (1996JCR(S)434).



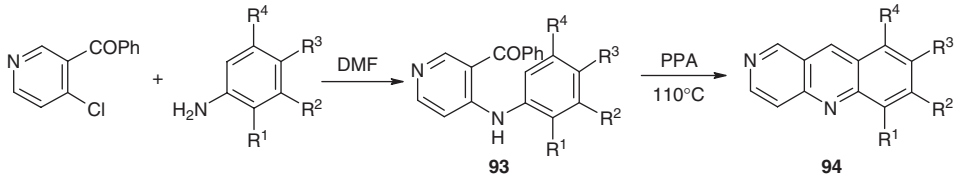
A noteworthy procedure for the synthesis of annulated 1,6-naphthyridines also uses a three-component condensation of the malononitrile dimer, salicylaldehyde and acetone giving rise to 1,6-naphthyridines **92** (1988JCS(P1)2053).



A simple procedure is described for the preparation of substituted 1,6-naphthyridinones in good yields from the dianions of 2-methylnicotinic acids (2002A80), 2-chloronicotinoyl chloride or 2,6-dichloro-5-fluoronicotinoyl chloride (2002T8543) and α-oxoketene *O*,*N*-acetals (2003MI2).

Consider a special procedure for the preparation of the annulated analogs of 1,6-naphthyridines. Thus, a general procedure involves cyclization of carbonyl derivatives of 4-chloropyridine with aromatic and heterocyclic amines under the action of acids.

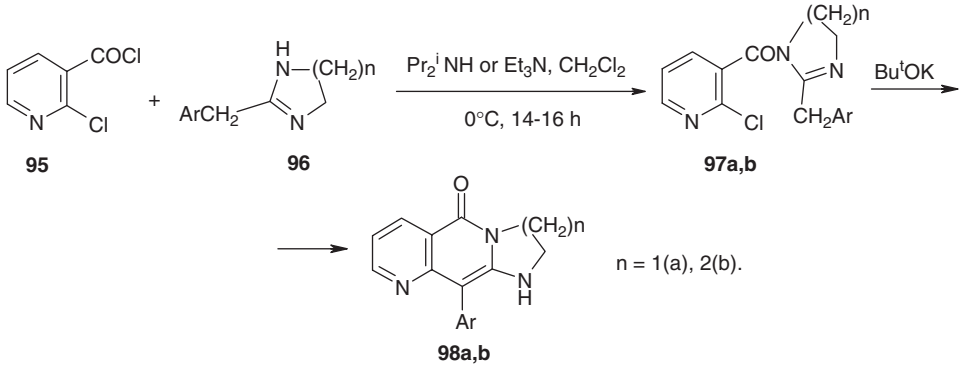
The reaction of 3-benzoyl-4-chloropyridine with substituted anilines afforded amine **93**, which underwent cyclization under the action of PPA to form 1,6-naphthyridine derivatives **94** (1989MI1).



93 **94**

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.

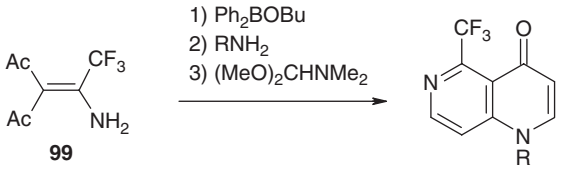
2-Chloronicotinoyl chloride **95** was used as the starting compound in the synthesis of hetaryl annulated 1,6-naphthyridines. Its reactions with 4,5-dihydro-1*H*-imidazolines **96a** or tetrahydropyrimidines **96b** gave the corresponding *N*-acyl derivatives **97a,b**, which underwent cyclization with potassium *tert*-butoxide to yield imidazo- **98a** or pyrimido[1,2-*g*[[1,6]naphthyridinones **98b**, respectively. Compounds **98a,b** exhibit antiallergic and anti-inflammatory activitives (1990JHC189, 1990USP5070086).



95 **96** **97a,b** **98a,b**

The reaction of enaminones with 2-chloronicotinoyl chloride **95** or 2,6-dichloro-5-fluoronicotinoyl chloride mainly leads to N-acylation products that cyclize directly or on reacting with sodium hydride to form 8-acyl-7-alkyl-1,6-naphrhyridin-5(6*H*)-ones. Owing to their easy availability, these compounds are attractive precursors for the synthesis of polycondensed heterocycles like naphtha[3,4-*h*][1,6]naphthyridin-5-ones and pyrido[3,2-*c*][1,6]naphthyridine (2002T8543).

An ingenious method for the construction of the 1,6-naphthyridine system with the use of "chelate" methodology was developed (1994IZV1510). Thus, the reaction of 3-acetyl-4-amino-5,5,5-trifluoro-3-penten-2-one **99** with Ph_2BOBu afforded a chelate complex, which reacted with primary amines and then with two equivalents of dimethylformamide dimethyl acetal to give 5-trifluoromethyl-1,6-naphthyridin-4(1*H*)-ones **100**.

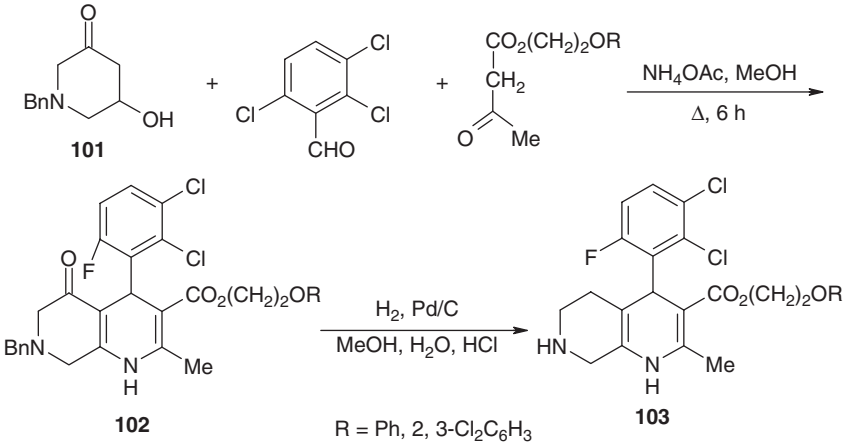


A reinvestigation of the recently described efficient synthesis of substituted 1,6-naphthyridines was carried out. It was found that the reaction of chalcones with malononitrile catalyzed by pyrrolidine afforded a mixture of four products; thermal or microwave heating was used. The previously claimed 1,6-naphthyridine formation was an exception (2002SC2903).

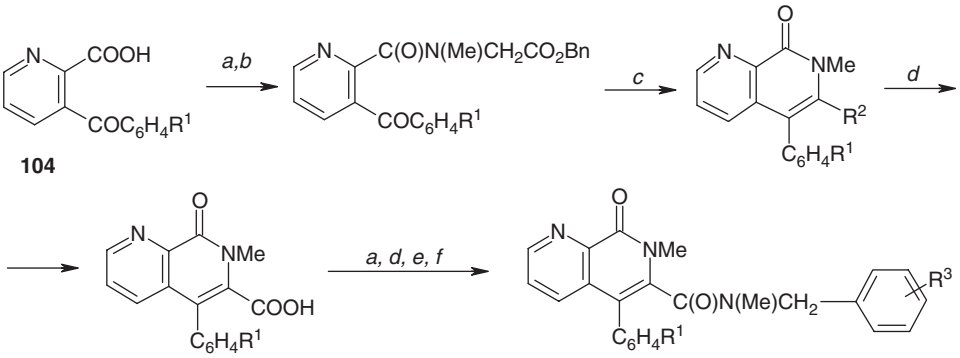
Other approaches to the synthesis of 1,6-naphthyridines and their fused analogs include (1984CC1304, 1985EUP130878, 1985GEP3327650, 1985JOC1005, 1985ZN(B)1537, 1986BSB49, 1986CPB3588, 1986GEP3431303, 1986JAP59-48482, 1986JCS(P1)753, 1986USP4742171, 1987GEP3502790, 1987S301, 1988AKZ687, 1988AP477, 1988G623, 1988GEP3602655, 1988GEP3605743, 1988TL5725, 1989JHC1755, 1989JOU1980, 1989KGS557, 1989T2693, 1989TL2355, 1990JCS(P1)3193, 1991JHC203, 1991JHC497, 1992AX(C)104, 1992H1905, 1992JHC1197, 1992JOC7352, 1993AJC987, 1993AJC1909, 1993H1, 1993H245, 1993SC2931, 1995JAP491090, 1995JHC751, 1995SL622, 1996PLP165956, 1998MI1, 1998TL7767, 2002CP309, 2003AJC500, 2003PIAWO2003051289).

C. 1,7-Napthyridines

Among procedures for the synthesis of 1,7-naphthyridines, four-component condensation of 1-benzyl-3-hydroxy-5-piperidone **101** with 2,3-dichloro-6-fluorobenzaldehyde, acetoacetic esters and ammonium acetate giving rise to 1,4,5,6,7-hexahydro-1,7-naphtyridin-5-one-3-carboxylic esters **102** attracts attention due to its simplicity. The compounds **102** and their N-debenzylation products **103** exhibit hypotensive activity (1985USP4596873, 1985USP4618678).



3-Aroylpyridine-2-carboxylic acids **104** were used as the starting compounds for the preparation of 7-methyl-1,7-naphthyridin-8(7*H*)-one derivatives **105**, which are new strong neurokinin NK_1-receptor antagonists (1995JMC3106).



104

105

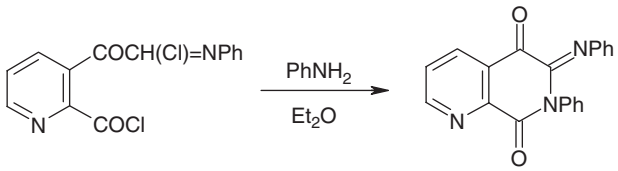
R^1 = H, 4-Me, 4-F; R^2 = CO_2CH_2Ph, CN, CHO, $CONH_2$; R^3 = 3,5-$(CF_3)_2$,2-MeO, 2,5-Cl_2;

(a) $SOCl_2$,DMF, THF; (b) $BnCO_2CH_2NHMe.HCl$, Et_3N, CH_2Cl_2;

(c) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhMe; (d) H_2, Pd/c, MeOH;

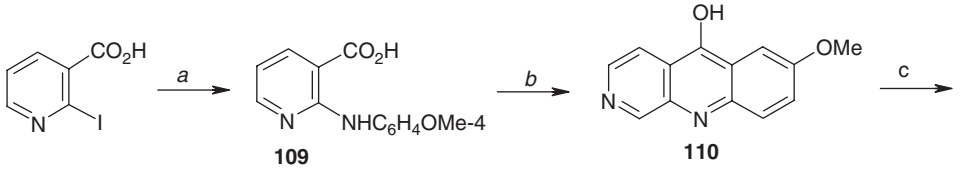
(d) R $C_6H_4NH_2$, Et_3N, CH_2Cl_2; MeI, NaH, DMF

The imino derivative of tetrahydro-1,7-naphthyridinedione **106** was synthesized from acid chloride **107** with aniline in ether (1986LA132).

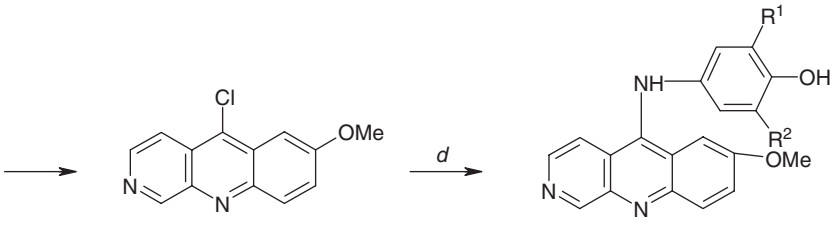


106 **107**

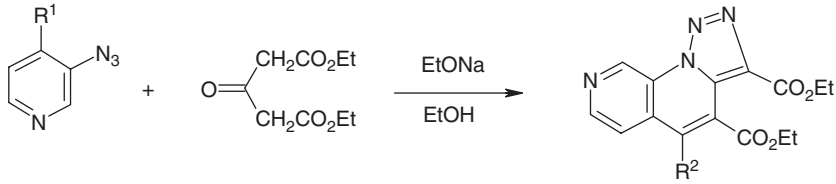
With the aim of searching for new antimalarial drugs among annulated 1,7-naphthyridines, compounds **108** were synthesized. Cyclization of amino acid **109**, prepared from 2-iodonicotinic acid, under the action of $POCl_3$ in PPA afforded 10-hydroxy-2-methoxybenzo[*b*][1,7]naphthyridine **110**. The subsequent reactions with $POCl_3$ and then with aminophenols complete the synthesis. The preliminary assay of the biological activities of compounds **108** demonstrated that these compounds are inferior to the well-known antimalarial agent pyronaridine (1989MI2).



109 **110**



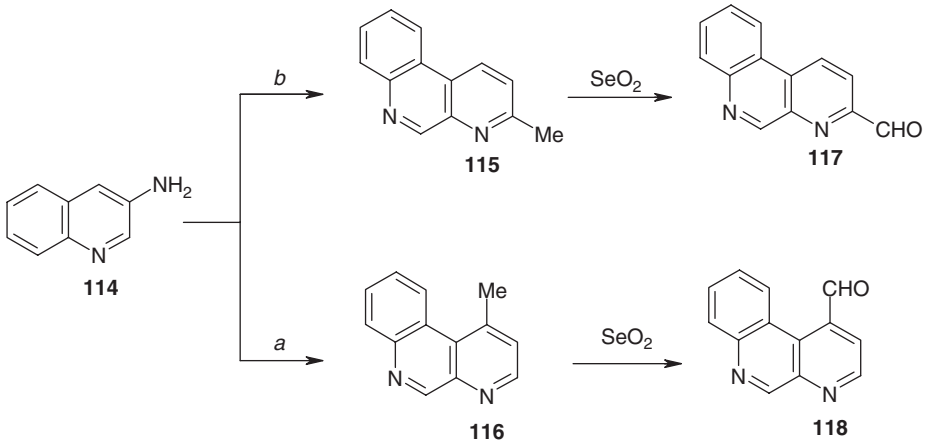
1,2,3-Triazolo[1,5-*a*][1,7]naphthyridines **111a,b** were synthesized from diethyl acetone-1,3-dicarboxylate **112** with *ortho*-substituted azides of the pyridine series **113** (1990S654).



113a,b **112** **111a,b**

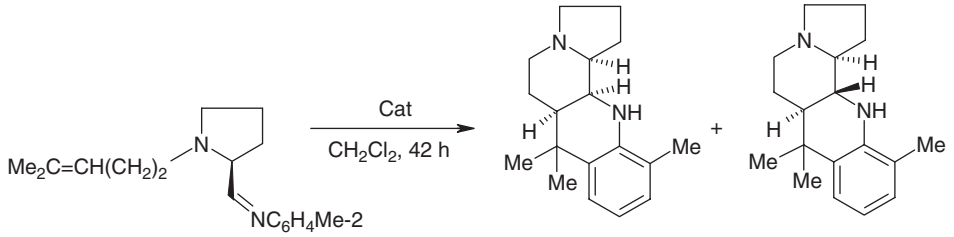
R^1 = CN (**113a**), CO_2Et(**113b**); R^2 =NH_2(**111a**), OH (**111b**).

A modified Skraup method involving 3-aminoquinoline **114** with crotonaldehyde or methyl vinyl ketone results in 2-methyl- (**115**) or 4-methyl-benzo[*f*]-1,7-naphthyridine **116**. Oxidation of **115** and **116** on treatment with SeO_2 in dioxane yields aldehydes **117, 118** (1994AJC2129).



(a) CH_2=CHCOMe; (b) MeCH=CHCHO

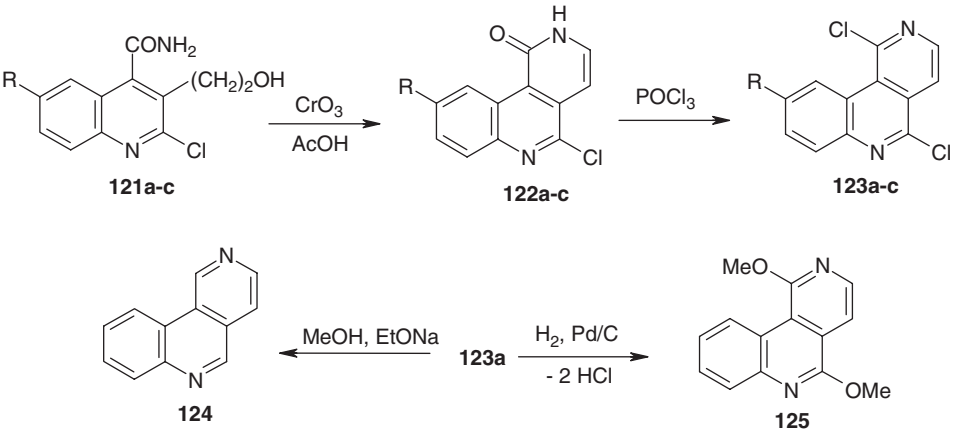
Some other approaches to the synthesis of 1,7-naphthyridines and their fused analogs were described (1989MI2, 1991MI1, 1995JCS(P1)2643, 1996JHC361). For example, treatment of (*S*)-*N*-[*N*-(4-methylpent-3-enyl)pyrrolin-2-ylmethylidene]-*o*-toluidine **119** with Lewis acids ($FeCl_3$, $SnCl_4$, $AlCl_3$, $MeAlCl_2$, $EtAlCl_2$, Et_2AlCl or BF_3OEt_2) or Bronsted acids (CF_3COOH or TsOH) led to formal Diels–Alder heterocyclization giving 1,7-naphthyridines **120a,b** in yields of >80%. The isomer ratio depends substantially on the nature of the catalyst. In the case of monodentate Lewis acids of the $MeAlCl_2$ or $EtAlCl_2$ type, the *cis*-isomer **120a** was obtained as the major product (99%), whereas the reactions involving bidentate Lewis acids of the $SnCl_4$ type or Bronsted acids afforded predominantly the *trans*-isomer **120b** (87–99%) (1995LA985).



119 **120a** **120b**

D. 2,6-Naphthyridine

Judging from the number of papers published over the last 20 years, the chemistry of 2,6-naphthyridines attracted much less attention than the 1,5-, 1,6- or 1,7-naphthyridines. Of the synthetic procedures developed over this period, noteworthy is oxidative cyclization of 4-carbamoyl-3-(2-hydroxyethyl)quinolines **121a–c** under the action of CrO_3 in glacial AcOH giving rise to benzo[*c*][2,6]naphthyridines **122a–c**. The latter were used in the synthesis of 2,6-naphthyridines **123–125** (1985S541).

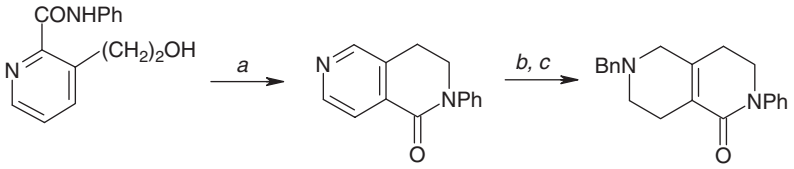


121a-c **122a-c** **123a-c**

124 **125**

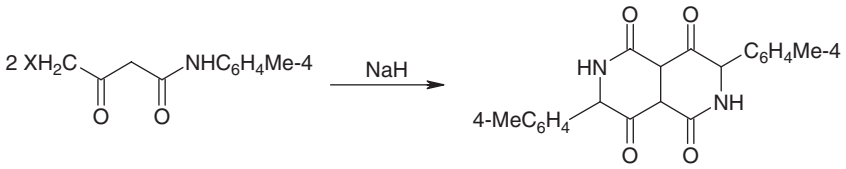
R = H (a), Cl (b), Me (c).

Cyclization of the 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 **126** with phenacyl bromide and then with sodium borohydride afforded octahydro-2,6-naphtyridine **127** covered by a patent as a medicine for prophylaxis and treatment of schizophrenia and depressions (1997BRP2299582).



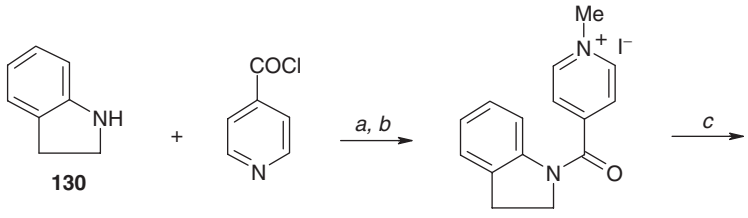
(a) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF; (b) BnBr, PhMe; (c) $NaBH_4$, MeOH.

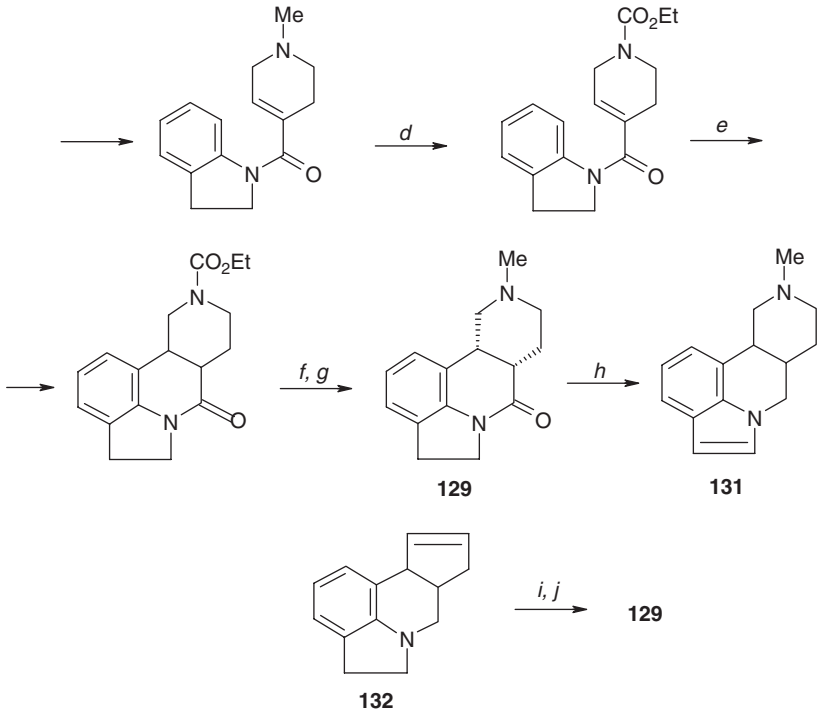
Treatment of toluidides of halogen-substituted acetoacetic acids with sodium hydride in dioxane led to intermolecular cyclization to form completely hydrogenated 2,6-naphthyridinetetrone **128** (1985ZN129).



X = Br, I.

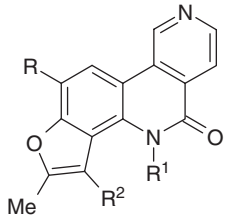
Indolo[1,7-*b*,*c*][2,6]naphthyridine **129** is a strong and selective antagonist of serotonin receptors of the 5-$HT_{2C/2B}$ subtypes possessing relatively weak affinity for 5-HT_{2A} subtype receptors (1992GEP473550, 1995JMC28, 1996C209). The compound **129** was synthesized starting from indoline **130** and isonicotinoyl chloride (1995JMC28). Oxidation of **129** with MnO_2 afforded indolonaphthyridine **131**. Yet another approach to **129** involves oxidation of the double bond in **132** with ozone or osmium tetroxide followed by treatment with methylamine (1993GEP4027018). The indolonaphthyridines **129** and **131** were covered by patents as drugs for the treatment of appetite disturbance, obsessive states (phobia and depressions) and other diseases (1992GEP473550, 1993GEP4027018).



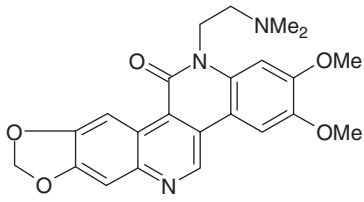


(a) Et_3N; (b) MeI; (c) $NaBH_4$; (d) $ClCO_2Et$; (e) hv; (f) AlH_3, THF; (g) (-)-di-p-tolyltartaric acid; (h) MnO2; (i) O_3 (OsO_4); (j) $MeNH_2$.

Methylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones (*R*, R^1, R^2=H, Me) were synthesized, first building the pyridine nucleus on the appropriate quinolin-2-ones, and then condensing the furan ring on the preconstituted benzonaphthyridinones. The benzo[*c*][2,6]naphthyridine nucleus is interesting for its known pharmacological properties and is an intermediate for the synthesis of natural product analogs (2002T9959).



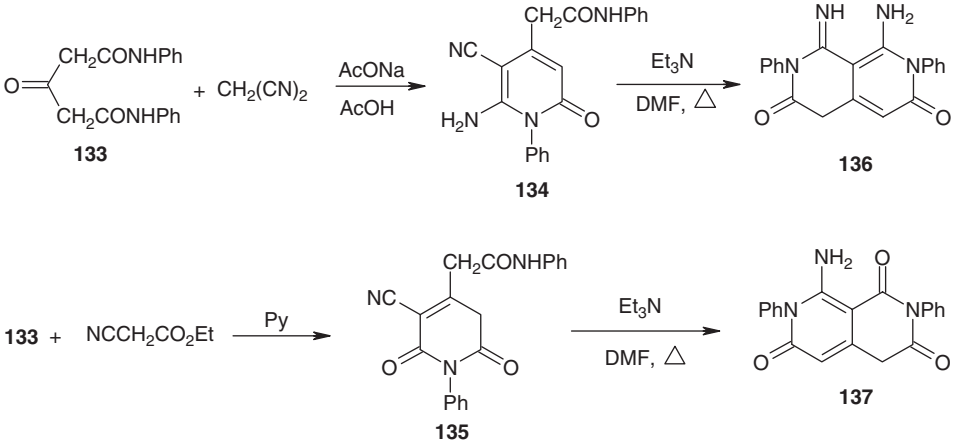
Benzo[*b*][1,3]benzodioxolo[5,6-*h*][2,6]naphthyridine was prepared via a multistep synthetic sequence starting from 3,4-dimethoxyacetanilide, 1,3-benzodioxol-5-amine, benzaldehyde and $MeCOCH{=}CH_2$. This naphthyridine was assayed for inhibiting cell growth against a number of human cancer cell lines, such as RPMI 8402, CPT-K5 and U 937 (2003PIAWO2003051289).



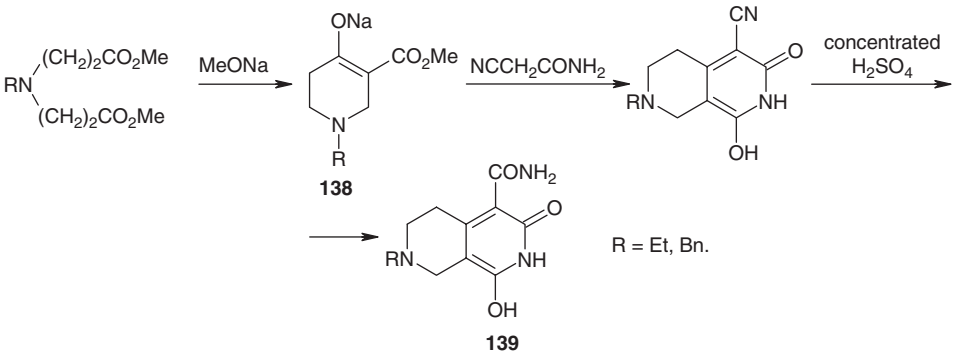
The reaction of 1,6-dialkyl-1,6-diazacyclo-3,8-diynes with different organic solvents (cyclohexa-1,4-diene, 9,10-dihydroanthracene or cyclooctane) as scavengers or with such reagents as HCl or MeOH proceeds with high regioselectivity to give derivatives of 1,2,3,5,6,7-hexahydro-2,6-naphthyridine (1994AG(E)2470, 1997LA1179).

E. 2,7-Naphthyridines

Various approaches to the synthesis of 2,7-naphthyridines are available. Thus, the dianilide of 3-oxoglutaric acid **133** reacted with malononitrile in the presence of sodium acetate to give pyridone derivative **134**, whereas the reaction of **133** with ethyl cyanoacetate in pyridine afforded tetrahydropyridinedione derivative **135**. The compounds **134** and **135** underwent cyclization upon heating with triethylamine in DMF to form substituted 2,7-naphthyridine-3,6-diones **136** and **137**, respectively (1989JPR745).

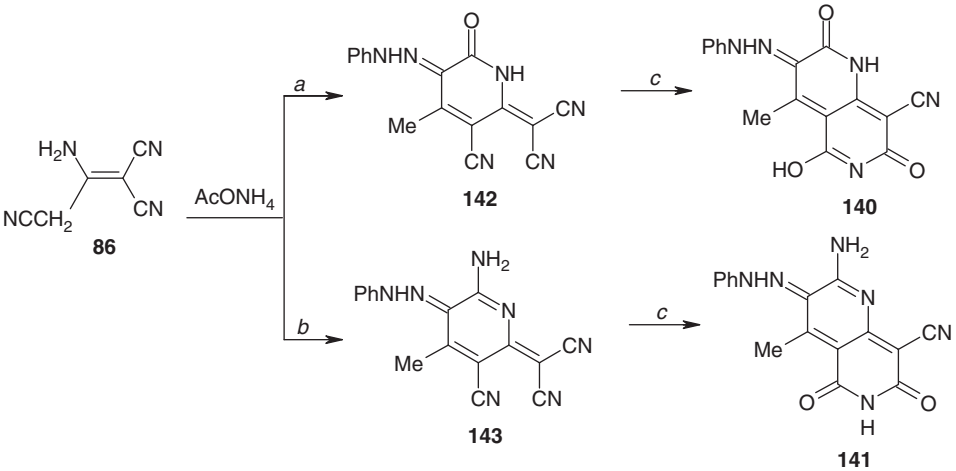


Dieckmann cyclization of *bis*(2-methoxycarbonylethyl)alkylamines under the action of sodium methoxide gave sodium salts of 4-hydroxy-3-methoxycarbonyltetrahydropyridines **138**. Condensation of the latter with cyanoacetamide afforded 4-cyano-1-hydroxy-5,6,7,8-tetrahydro-3-oxo-2,7-naphthyridines whose hydrolysis gave 4-carbamoyl derivatives **139** exhibiting antiarrhythmic activity (1996KFZ13).



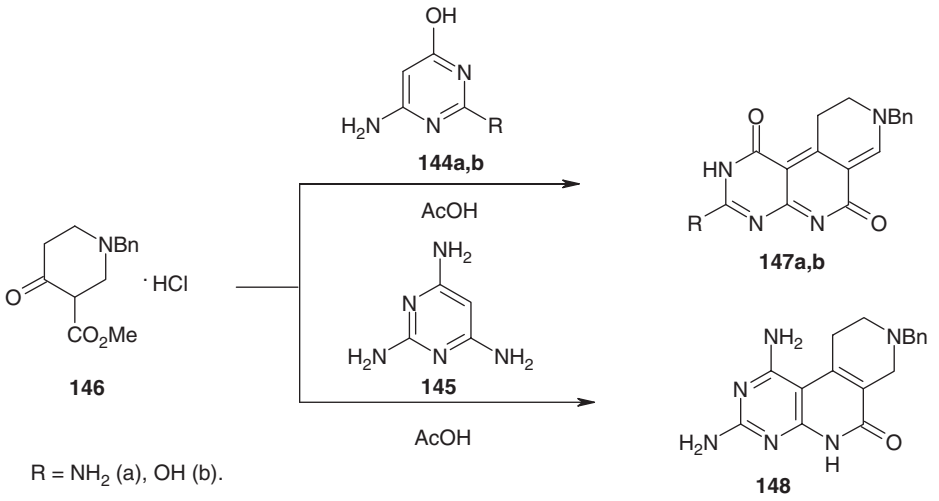
One procedure for the preparation of alkyl-substituted 2,7-naphthyridines involves acylation of alcohols, ketones or alkenes in the presence of $AlCl_3$ followed by treatment with ammonia. However, these reactions are not necessarily regioselective. Thus, the reactions of acetyl chloride with *tert*-butyl alcohol or isobutylene in the presence of $AlCl_3$ followed by NH_4OH gave 1,3,6,8-tetramethyl-2,7-naphthyridine along with other products (1984BSF449, 1986IZV688).

Naphthyridinediones **140** and **141** have been synthesized using reactions of 3-amino-4,4-dicyanobut-2-enenitrile **86** with α-diketone monophenylhydrazones. Cyclization of intermediate dinitriles **142** and **143** was performed with a mixture of AcOH and HCl (1996JCR(S)434).

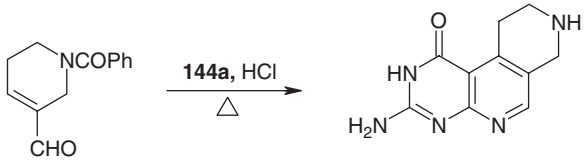


(a) PhNHN=C(Ac)CO_2Et; PhNHN=C(Ac)CN; (c) AcOH, HCl.

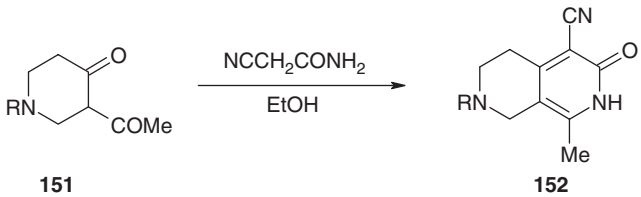
Refluxing aminopyrimidines **144a,b** and **145** with methyl 1-benzyl-4-oxopiperidine-3-carboxylate **146** in glacial acetic acid provided pyrimido[4,5-*c*]-2,7-naphthyridin-6-ones **147a,b** and **148**. The compounds **147b** and **148** inhibit *in vitro* growth of malignant leukemia cells (1984JHC873).



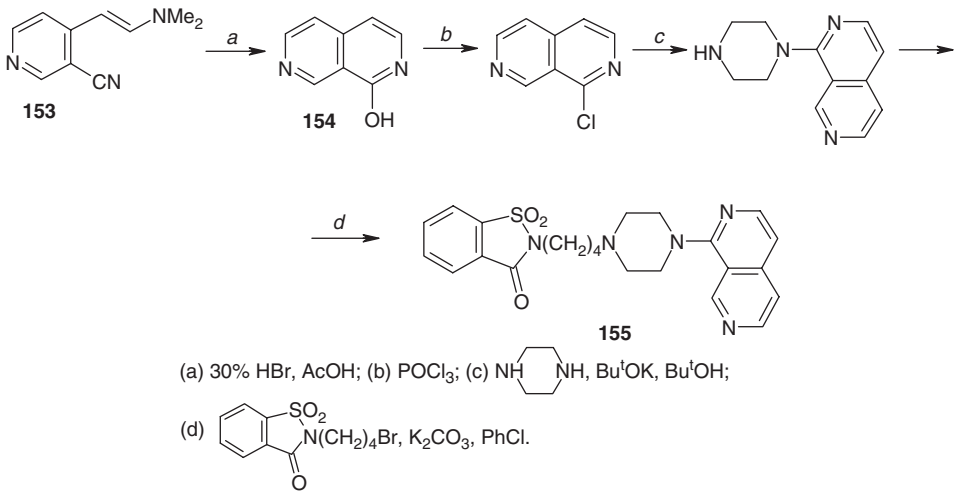
A similar condensation of the aminopyridine **144a** with hydrogenated 3-formylpyridine **149** in the presence of HCl in ethanol results in tetrahydropyrimido[4,5-*c*]-2,7-naphthyridine **150** mixed with its 7-benzoyl derivative (1985JHC1153, 1987JHC123).



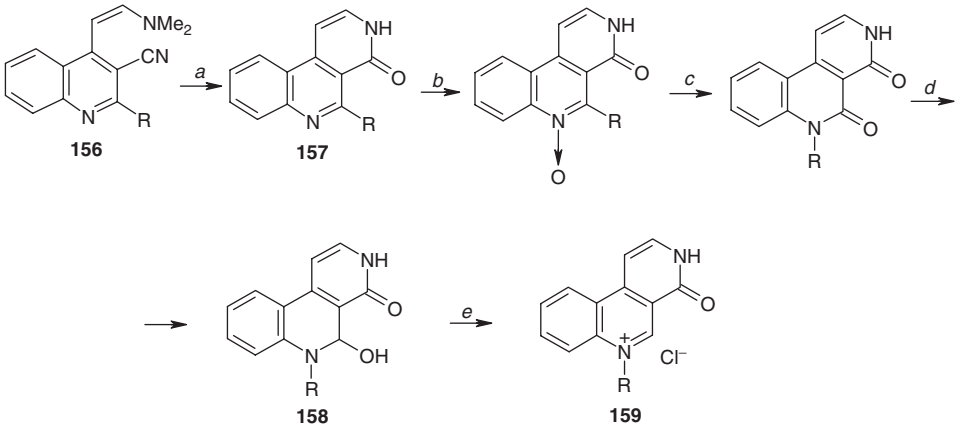
Refluxing 1,3-dicarbonyl compounds **151** with cyanoacetamide in ethanol in the presence of piperidine gives 2,7-naphthyridine derivatives **152**, used as components of formulations for the treatment of diseases of blood circulation (1990JAP01/279884).



Yet another reaction used in the synthesis of 2,7-naphthyridine derivatives involves intramolecular cyclization of enamino nitriles under the action of acid catalysts. Thus compound **153** underwent cyclization to form 1-hydroxy-2,7-naphthyridine **154**, used in the synthesis of sedative agent **155** (1988USP4859671).

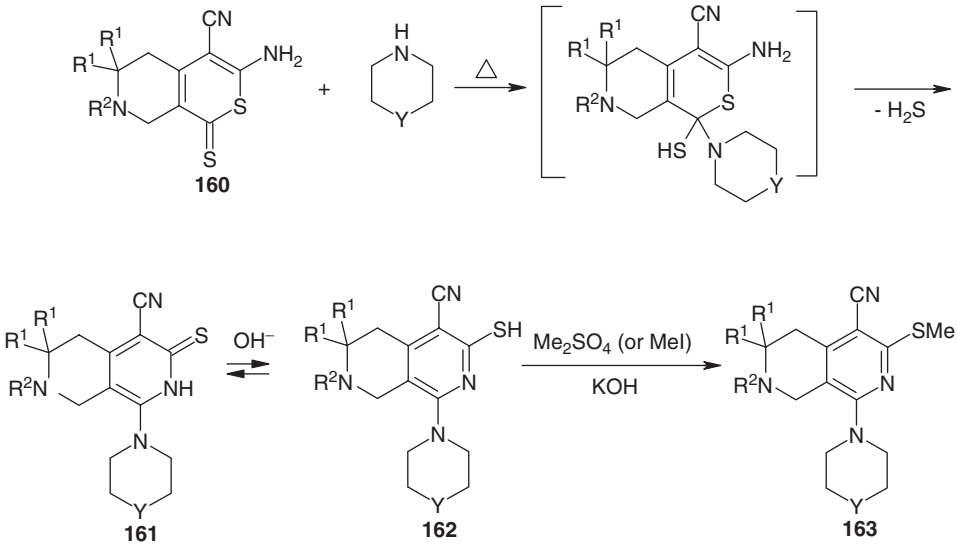


Analogous cyclization of enamino nitrile **156** in PPA afforded benzo[*c*][2,7]naphthyridine **157**, which was converted into perlolinium chloride **158** (herbaceous alkaloid perloline **159**) (1985CZ139).



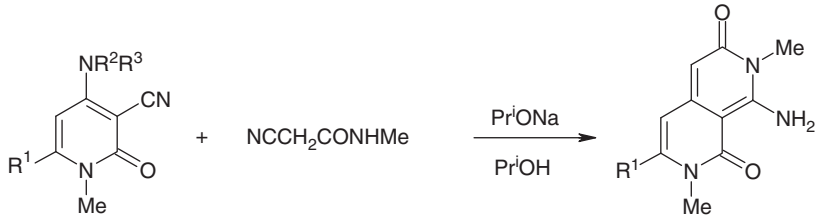
R = 3,4-$(MeO)_2C_6H_3$; (a) PPA; (b) 3-$ClC_6H_4CO_3H$; (c) hv, MeOH; (d) $[MeO(CH_2)_2O]_2AlH_2Na$; (e) HCl.

Yet another approach to the synthesis of 2,7-naphthyridines involves recyclization of pyridinothiopyranothiones and pyridinopyranones. Thus recyclization of thiopyranothiones **160** upon heating with morpholine, piperidine or piperazine in anhydrous ethanol proceeded through nucleophilic attack of the amine on the thiocarbonyl group, cleavage of the C(1)–S bond of the thiopyran ring and rearrangement to form finally 2,7-naphthyridine-3(2*H*)-thiones **161**. It was demonstrated that **161** in the crystalline state exists in equilibrium with the thiol **162**. Their methylation with Me_2SO_4 or MeI in aqueous or ethanolic solutions of KOH produced thiomethyl derivatives **163** exhibiting antibacterial activity (1993KFZ29).



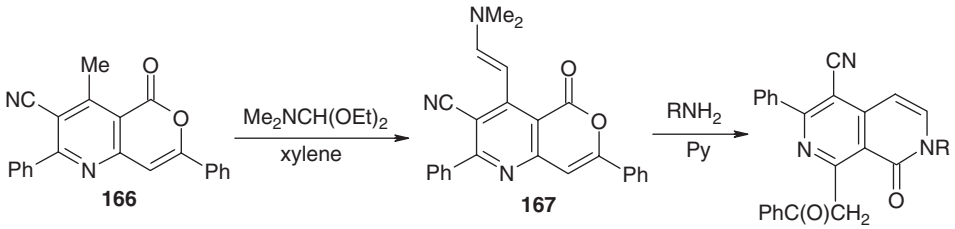
R^1= H, Me; R^2 = Me, $CH_2CH{=}CH_2$; Y =O, CH_2, NH.

The reaction of 4-dialkylaminopyridones **164**, containing a *β*-enaminoamide fragment with *N*-methylcyanoacetamide is accompanied by replacement of the amino group followed by cyclization to give 2,7-naphthyridine **165** (1982S214).

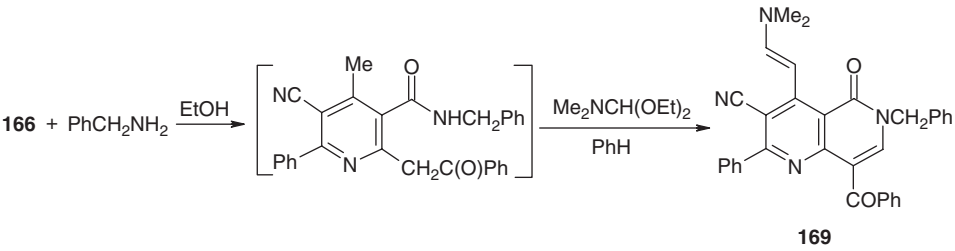


R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^2 =Et, Ph, CH_2Ph, $CH_2CH(OEt)_2$; R^3= H, $CH_2CH_2OCH_2CH_2$.

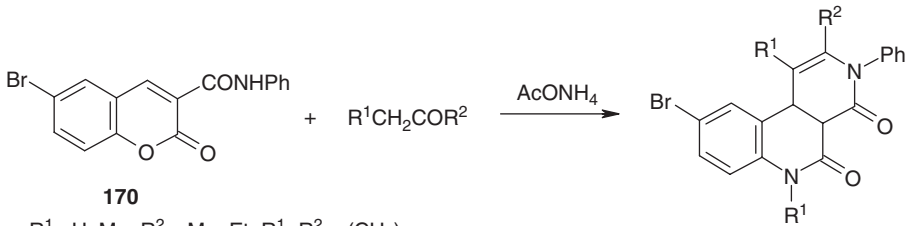
Condensation of substituted pyrano[4,3-*b*]pyridine-5-one **166** with dimethylformamide dimethyl acetal in xylene yielded enamine **167**, which underwent recyclization to 2-alkyl-5-cyano-8-phenacyl-2,7-naphthyridin-1(2*H*)-ones **168** on treatment with primary amines (1997IZV1079). A change in the sequence of addition of the reagents to the pyranone **168** (first, treatment with benzylamine and then condensation with dimethylformamide dimethyl acetal) resulted in 8-benzoyl-3-cyano-4-(2-dimethylaminovinyl)-2-phenyl-1,6-naphthyridin-5(6*H*)-one **169**.



R = Pr, Bn.

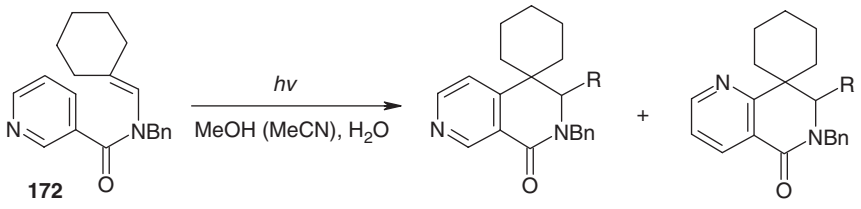


The reactions of 3-(phenylcarbamoyl)coumarin **170** with ketones in the presence of ammonium acetate in ethanol at 20 °C or in the absence of a solvent at 170 °C yielded benzo[*c*][2,7]naphthyridines **171** (1985MI1).



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

UV irradiation of *N*-aroyleneamide **172** in methanol or aqueous acetonitrile afforded a mixture of regioisomeric spirocycloadducts **173** and **174**. The solvent was not involved in the reaction performed in cyclohexane, *R*=H in **173** and **174** (1991T7301).



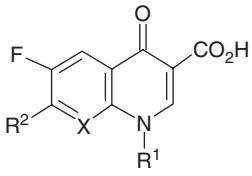
R = OMe, OH.

Some other approches to the synthesis of 2,7-naphthyridines and their fused analogs were described (1984BSF2454, 1984S1052, 1987AKZ587, 1987JOC2935, 1987KGS989, 1987KGS1696, 1991AP105, 1991EGP279246, 1992JHC971, 1993JHC157, 1994AP539, 1994T5807, 1994TL3195, 1995JCS(P1)979, 2002MI1).

F. 1,8-Naphthyridines

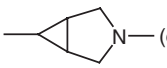
Of the six isomeric pyridopyridines, 1,8-naphthyridine derivatives have been studied the most during the last 20 years. This class of compounds has attracted considerable attention primarily because the 1,8-naphthyridine skeleton is present in many compounds which have been isolated from natural substances and exhibits various biological activities. The number of publications (including patents) devoted to the chemical and biological properties of 1,8-naphthyridines which were issued over this period is substantially larger than the number of studies on all other types of isomeric pyridopyridines published in the last 90 years. In the last three years, about 1000 publications appeared, including more than 200 patents. Most of these studies were devoted to specific aspects of biological activity assays of 1,8-naphthyridine derivatives.

Among 1,8-naphthyridine derivatives, 6-fluoro-substituted 1,8-naphthyridin-4-ones, which are aza analogs of fluoroquinolones, have attracted the most attention in the last 20 years. Fluoroquinolone- and fluoronaphthyridonecarboxylic acids provided the basis for the design of highly efficient antibacterial drugs, such as norfloxacin **175a** (1999MI2), pefloxacin **175b** (1971CR37), ciprofloxacin **175c** (1982MI1), enoxacin **175d** (1987CPB2280), trovafloxacin **175e** (1996MI2, 1998MI2, 1998S739, 1999MI3), etc.

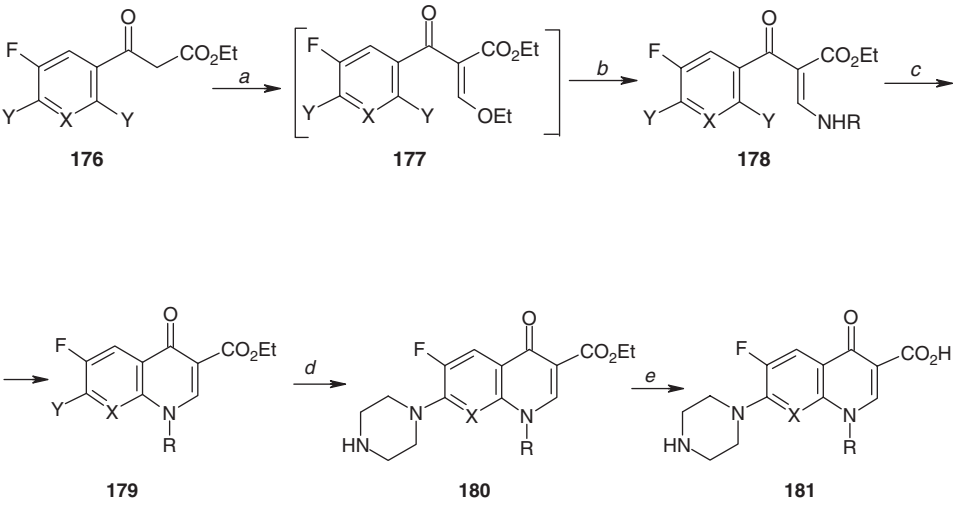


175a-e

X = CH: R^1= Et, R^2= piperazin-1-yl (a), N-methylpiperazin-1-yl (b); R^1= cyclo-C_3H_5, R^2= piperazin-1-yl (c);

X = N: R^1= Et, R^2= piperazin-1-yl (d); R^1= 2,4-$F_2C_6H_3$, R^2= N_2N  (e).

Fluoronaphthyridones are similar not only in their biological activity but also in other properties to fluoroquinolones, whose chemistry has been studied in considerable detail (1983MI1, 1983MI2, 1984MI1, 1991MI3, 1996BSB683). The most commonly used method for the synthesis of fluoro-substituted 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid is based on approaches developed for preparing fluoroquinolone analogs (1985JHC1033, 1985JMC1558, 1985GEP3248506, 1985JAP6028964, 1986JMC2363) and can be represented by the following scheme:



176 177 178 179 180 181

X = N (a), CH (b), CF (c); Y = Cl, F;

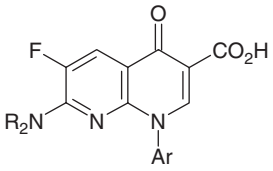
R = Et, Pr^i, cyclo-C_3H_5, Bu^t, CH_2=CMe,4-FC_6H_4;

DBU is diazabicyclo[5.4.0]undec-7-ene;

(a) $HC(OEt)_3$, Ac_2O; (b) RNH_2, EtOH; (c) NaOH, dioxane;

(d) $NH(CH_2CH_2)_2NH$, DBU, MeCN; (e) 1) NaOH, H_2O, Δ 2) H^+.

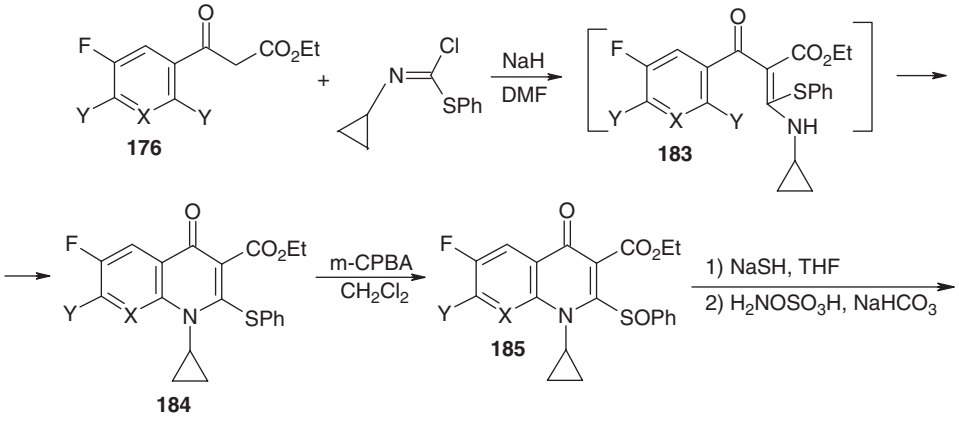
Condensation of ethyl (2,6-dichloro-5-fluoronicotinoyl)acetate **176a** and analogous benzoyl derivatives **176b,c** with ethyl orthoformate in acetic anhydride followed by the reaction of intermediates **177** with a small excess of amine yields the corresponding enamino ketoesters **178a–c**. Heating enamines **178b** with sodium hydride in dioxane gives ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylates **179b**. Cyclization of enamines **178a**, which can be carried out according to three procedures, viz., by reaction with sodium hydride in dioxane, with potassium carbonate in acetonitrile or with *tert*-butylammonium fluoride in THF, affords naphthyridones **179a** in good yields (1984JMC292, 1985GEP3248506, 1985JAP6028964, 1985JHC1033, 1985JMC1558, 1986GEP3508816, 1986JMC2363, 1988CPB1223, 1989JMC537, 1990JHC1191, 1991JMC29). The replacement of the hydrogen atom at position 7 of **179a** under the action of amine in acetonitrile (in some cases, in the presence of DBU as a base) gives rise to esters **180a**, which are hydrolyzed to form acids. This procedure was used for the synthesis of naphthyridonecarboxylic acids **181a** (*R*=Et (1984JMC292), Pr^i (1985JMC1558), isoprenyl (1988CPB1223), Bu^t (1989JMC537), cyclopropyl 1986GEP3508816), 4-fluorophenyl (1986JMC2363)), derivatives of thiazolo-, oxazolo- and imidazolo[3,2-*b*][1,8]naphthyridines (1990JMC2012). Ester **176a** was also used as the starting compound in the synthesis of the previously unknown 7-substituted 6-fluoro-1-(1- or 2-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids **182**, which possess pronounced (comparable to that of the drug ataverdine) anti-HIV-RT activity (1998JHC17).



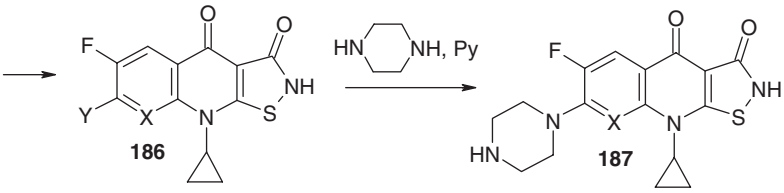
182

Ar = 1-naphthyl, 2-naphthyl; R_2NH = piperazine, 2-methylpyperazine, N-methylpiperazine, (2R,6S)-2,6-dimethylpiperazine, (3S)-3-aminopyrrolidine.

The high synthetic potential of esters **176** is also exemplified by their reactions with thioformates. For example, the reaction of ethyl 2,6-dichloro-5-fluoronicotinoylacetate **176a** with phenyl *N*-cyclopropyliminochlorothioformate in the presence of one equivalent of sodium hydride in xylene proceeds through intermediate **183a** to give ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-2-phenylthio-1,4-dihydro-1,8-naphthyridine3-carboxylate **184a** in 51% yield (1988CPB1223). An analogous treatment of ethyl 2,3,4,5-tetrafluorobenzoylacetate **176c** produces ethyl 1-cyclopropyl-6,7,8-trifluoro-4-oxo-2-phenylthio-1,4-dihydroquinoline-3-carboxylate **184c** in 42% yield. Oxidation of 3-carboxylic esters **184a,c** with *m*-chloroperoxybenzoic acid (*m*-CPBA) affords ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-2-phenylsulfinyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate **185a** (83% yield) or ethyl 1-cyclopropyl-6,7,8-trifluoro-4-oxo-2-phenylsulfinyl-1,4-dihydroquinoline-3-carboxylate **185c** (78% yield), respectively. The regiospecific replacement of the sulfinyl group of sulfoxide **185a** with freshly prepared sodium hydrosulfide in aqueous THF gives a 2-mercapto derivative, whose treatment (without purification) with hydroxylamine-*O*-sulfonic acid in the presence of sodium bicarbonate affords the hydrosulfamino derivative. The latter undergoes cyclization to form 7-chloro-9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydroisothiazolo[5,4-*b*][1,8]naphthyridine-3,4-dione **186a** (67% yield). The reaction of naphthyridinedione **186a** with an excess of piperazine produces 9-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-2,3,4,9-tetrahydroisothiazolo[5,4-*b*][1,8]naphthyridine-3,4-dione **187a** in 98% yield. An analogous sequence of transformations of quinolinedione **186c** gives 9-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione **187c** (74%). Naphthyridinedione **187a** and quinolinedione **187c** exhibit higher antibacterial activity compared to ciprofloxacin **175c** (1988CPB1223).

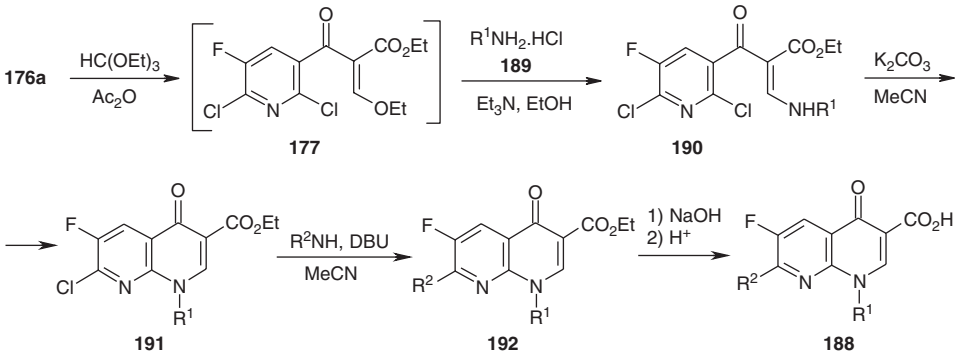


176 **183** **184** **185**



X = N, Y = Cl (a); X = CF, Y = F (c).

With the aim of studying their structure–antibacterial activity relationships, a series of new 7-substituted 6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids **188** containing fluoro-substituted *tert*-butyl groups at the N(1) atom was synthesized (1984JMC1543, 1989JMC537, 1989MI3, 1990JMC1344, 1991JMC29). For example, the reaction of intermediate **177** (*R*=N, *Y*=Cl) derived from ester **176a** with amines **189** in the presence of triethylamine in ethanol produces enamines **190**, whose treatment with K_2CO_3 in acetonitrile results in their cyclization to esters **191**. Condensation of the latter with amines upon refluxing in acetonitrile in the presence of DBU yields esters **192**, whose alkaline hydrolysis gives naphthyridonecarboxylic acids **188**. The latter exhibit high *in vitro* antibacterial activity against four types of Gram-positive bacteria and eight types of Gram-negative bacteria (1991JMC29). Examples of naphthyridonecarboxylic acids **188** are given in Table 1.



189: R^1= Bu^t, FCH_2CMe_2, $(FCH_2)_2CMe$, $(FCH_2)_3C$.

Ethyl (2-chloroquinolyl-3-carbonyl)acetates **193** served as the starting compounds for the preparation of benzo[*b*][1,8]naphthyridines **194–196** (1991FRP2642070, 1991FRP2642071) possessing high antibacterial activity against Gram-positive bacteria. These compounds are used for the treatment of skin staphylococcus infections and water purification and also as preservatives and decontaminants.

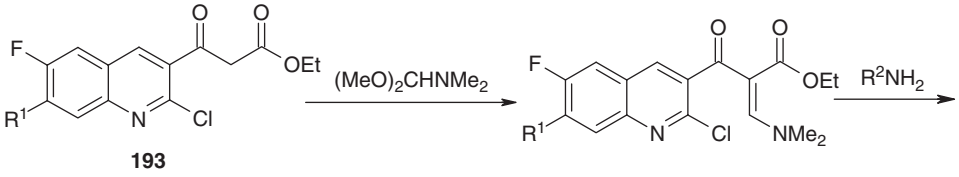
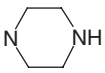
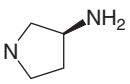
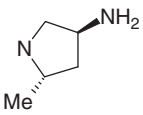
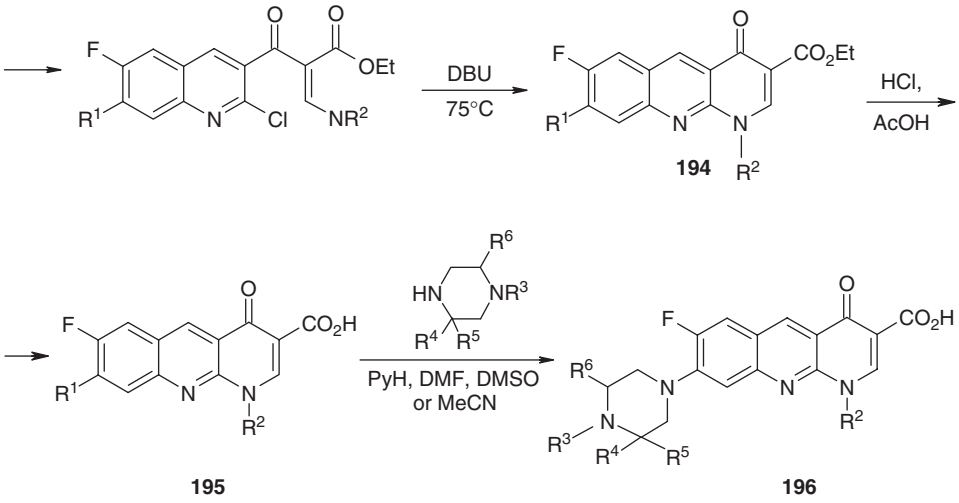


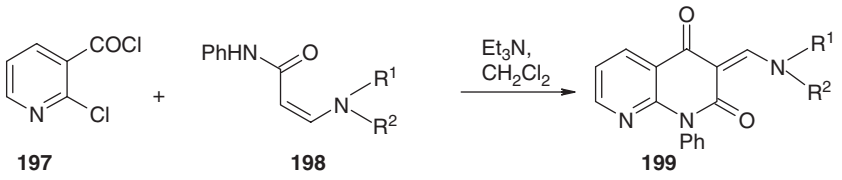
Table 1. Substituted 1,8-naphthyridinecarboxylic acids **188**

R^2	R^1	Yield (%)	Reference
	Bu^t	—	1985EURP132845
	FCH_2CMe_2	70	1987JHC1333
	$(FCH_2)_2CMe$	30	1987JHC1333
	$(FCH_2)_3C$	89	1987JHC1333
	Bu^t	—	1998MI3693, 1998AF185668
	FCH_2CMe_2	60	1987JHC1333
	$(CH_2F)_2CMe$	50	1987JHC1333
	$(CH_2F)_3C$	84	1987JHC1333
	Bu^t	—	1998MI4694
	FCH_2CMe_2	46	1987JHC1333
	$(FCH_2)_2CMe$	76	1987JHC1333
	$(FCH_2)_3C$	79	1987JHC1333
	FCH_2CMe_2	65	1987JHC1333
	$(FCH_2)_3C$	78	1987JHC1333



R^1= F, Cl; R^2= Me, MeO, cyclo-C_3H_5; R^3=H,Alk, AlkO; R^4, R^5, R^6= H, Alk.

2-Chloronicotinoyl chloride **197** is widely used as the starting compound in the synthesis of various 1,8-naphthyridine derivatives (1985UKZ750, 1990USP4810708, 1992USP4988705, 1993USP5116840, 1994MI1, 1994USP5126352, 1994USP5179093). For example, its reactions with substituted 5-aminoacrylic acid anilides **198** produce aminomethylidene-1,8-naphthyridine-2,4-diones **199** (1994USP5179093).



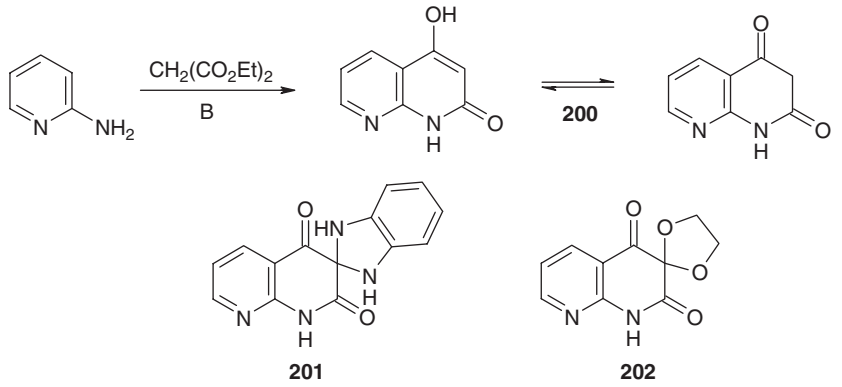
197 198 199

R^1= H, Me; R^2= Me, Et, CH_2Ph, 2-methylpyrid-6-yl

1,8-Naphthyridine-4-ones were prepared in a one-pot reaction of chloride **197** with $Me_2NCH{=}CHCO_2Et$, followed by amine in the presence of excess Et_3N in MeCN (2003JOC4598).

2-Aminopyridine and its derivatives are often used as the starting compounds in the synthesis of 1,8-naphthyridine derivatives (1984JIC888, 1984MI2, 1985EJMC381, 1985JAP60112790, 1985JOC2407, 1986FRP2567520, 1986JAP60126284, 1986JIC345, 1986JIC443, 1986JIC984, 1987JIC193, 1987JIC443, 1987JIC488, 1987JIC709, 1987JIC710, 1987TL5833, 1988CCC643, 1988CPB4403, 1988FRP2592649, 1988FRP2592650, 1988FRP2592651, 1988FRP2592652, 1989CCC1716, 1989IJC362, 1989MI4, 1990KGS643, 1991FRP2641783, 1991GEP3907938, 1991JIC85, 1992JCS(P1)1747, 1992S798, 1993JOC6625, 1993MI1, 1993S152, 1994JIC765, 1994TL1995, 1994PIAWO9412499, 1995H1001, 1995JHC1595, 1995T6941, 1996H53 1997EUP0670320, 1997JMC2266, 1997JMC3049, 2001S103).

For instance, the reaction of unsubstituted 2-aminopyridine with diethyl malonate in the presence of bases produced naphthyridinedione **200**, which exists as two tautomeric forms (1993MI1, 1994JIC765). Halogenation of compound **200** under various conditions (SO_2Cl_2, $POCl_3$, Br_2, I_2) gives both 3-mono- and 3,3-dihalogen derivatives. The reaction of the latter with *o*-phenylendiamine and ethylene glycol forms spiro-fused heterocycles **201** and **202**, respectively (1994JIC765).

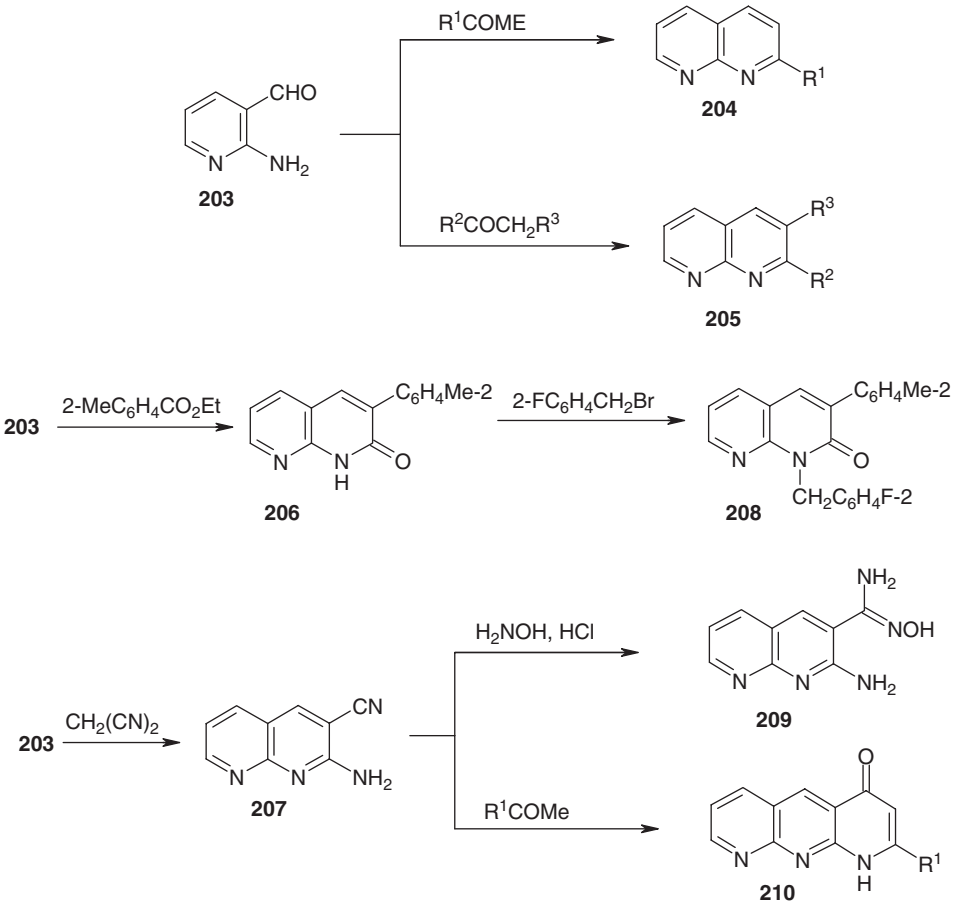


201 202

B is a base.

Substituted 2-aminopyridines, in particular, 2-amino-3-formylpyridine **203** and its derivatives, possess much higher synthetic potential (1984JIC888, 1985JOC2407, 1986JIC345, 1986JIC443, 1986JIC984, 1987JIC488, 1987JIC709, 1987TL5833, 1989CCC1716, 1989IJC362, 1989MI4, 1992JCS(P1)1747, 1992S798, 1993JOC6625,

1995T6941, 2001IJC713, 2001OL1101, 2001S103). For example, condensation of pyridine **203** in ethanol in the presence of piperidine base with compounds containing an active methylene group as well as with aldehydes, acyclic and cyclic ketones and diketones yielded 1,8-naphthyridines **204–207**, which were used as the starting compounds for the synthesis of derivatives **208–210** (1986JIC345, 1986JIC443, 1987JIC488, 1987JIC709, 1987JIC710, 1989CCC1716, 1989IJC362, 1991GEP3907938). Naphthyridines **204** exhibit antibacterial and antihelminthic activities and are used in the synthesis of fungicides (1986JIC443, 1987JIC488, 1987JIC710, 1989CCC1716, 1989IJC362). Compounds **205** are intermediates in the synthesis of some hypotensive drugs (1991JIC85). Naphthyridine **209** possess herbicidal properties and is used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops (1991GEP3907938). 1,8-Naphthyridin-2-one derivative **208** is used for the treatment of memory disorders, in particular, Alzheimer's disease (1997EUP0670320).

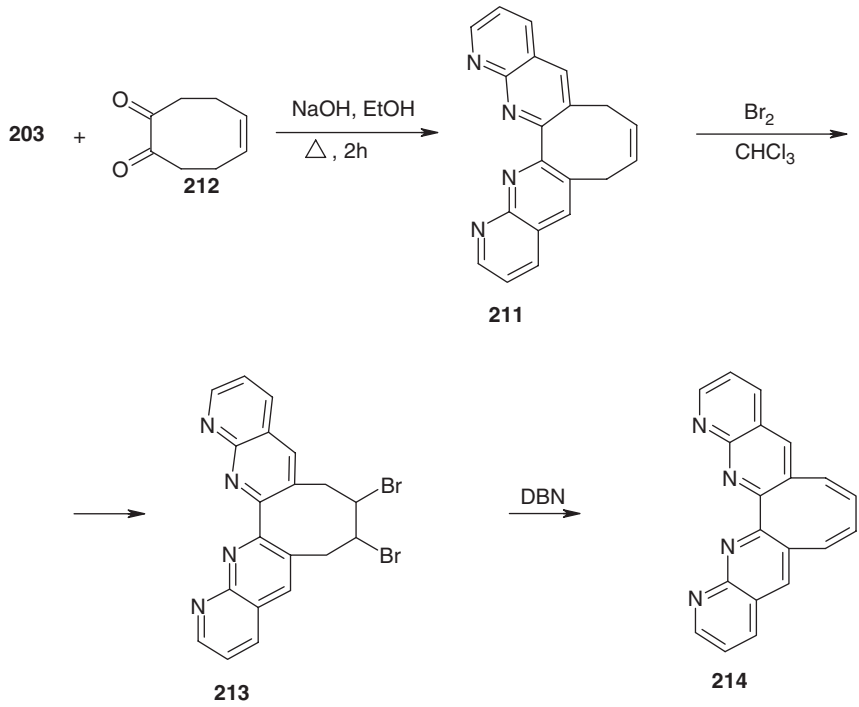


R^1 = 1-naphthyl, 2-pyridyl, 2-furyl, 2-thienyl, 2- HOC_6H_4, CH=CHPh; R^2 = Me, Ph;

R^3 = Ph, COPh, CONHPh, MeCO.

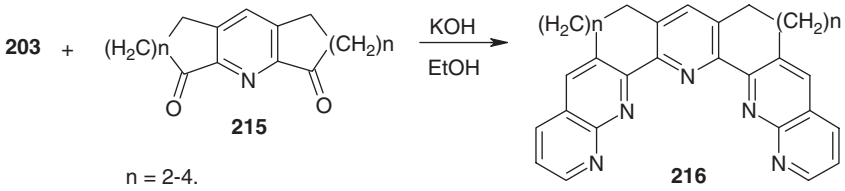
There are numerous examples of the use of 2-amino-3-formylpyridine **203** in the synthesis of substituted 1,8-naphthyridines and their fused analogs (1986JIC345, 1986JIC443, 1989CCC1716, 1989IJC362, 1994TL1995).

The same aminoaldehyde **203** was successfully used in the synthesis of polyannulated 1,8-naphthyridines. For example, 7,10-dihydrocycloocta[2,1-*b*:3,4-*b*′]di[1,8]naphthyridine **211** was prepared by the reaction of **203** with cyclooct-5-ene-1,2-dione **212** in ethanol in the presence of NaOH. The reaction of **211** with bromine in chloroform followed by debromination of adduct **213** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in toluene or dimethyl sulfoxide (DMSO) produced cycloocta[2,1-*b*:3,4-*b*′]di[1,8]naphthyridine **214**, which is a new promising ligand system (1987JIC709, 1989IJC362). The complex formation of ligand **214** with Cu(II) ions was studied.



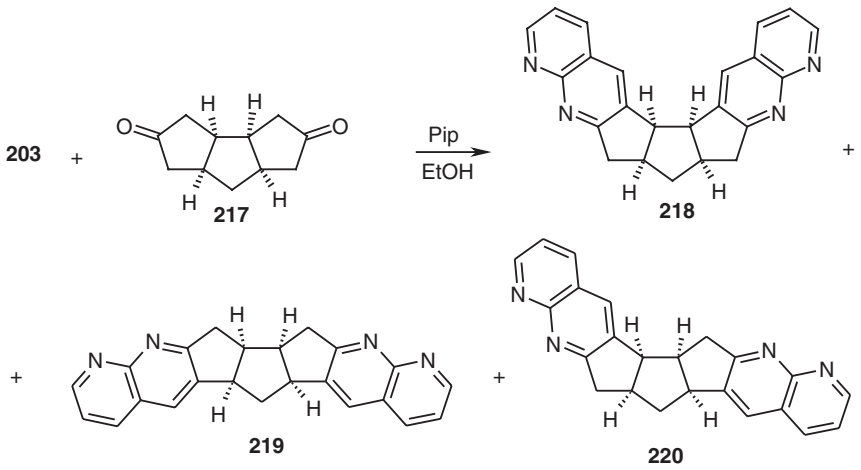
DBN is 1,5-diazabicyclo[4.3.0]non-5-ene.

Friedlander condensation of aminoaldehyde **203** with cyclic diketones **215** gives heptaannulated heterocyclic systems **216** (1985JOC2407).



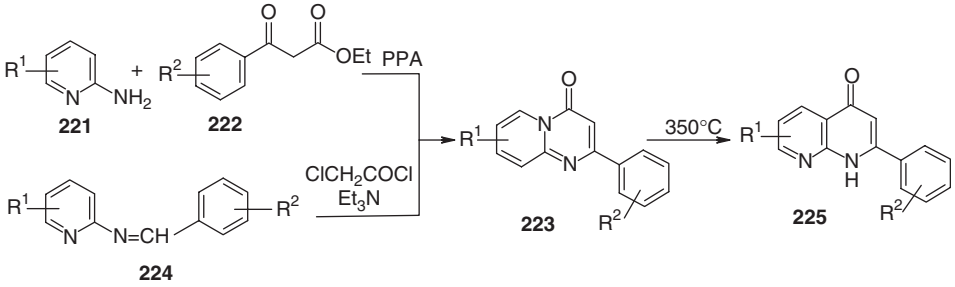
n = 2-4.

Analogous condensation **203** with dione **217** in ethanol in the presence of piperidine base afforded a mixture of polyannulated bisnaphthyridines **218–220** in a total yield of 82% (1992JCS(P1)1747).



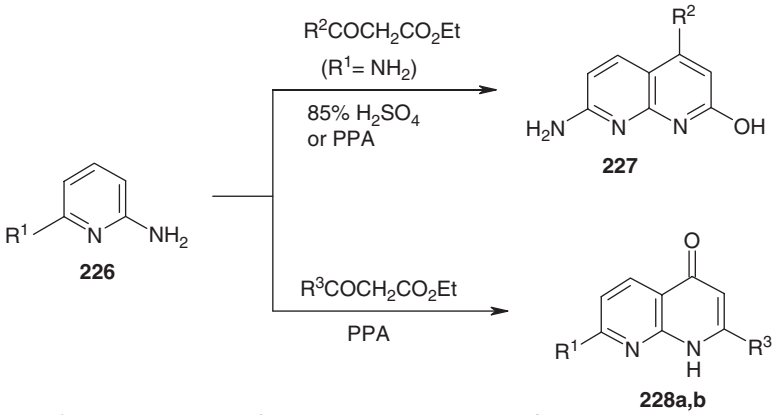
Under analogous conditions, substituted α-aminopyridinealdehydes react with activated and nonactivated ketones according to a cascade heterocyclization scheme to form various 1,8-naphthyridine derivatives in satisfactory yields (1986FRP2567520, 1988FRP2592649, 1988FRP2592650, 1988FRP2592651, 1988FRP2592652, 1992S798, 1993JOC6625, 1993S152, 2001S103, 2002IJC(B)1894).

With the aim of designing new potential antitumor drugs procedures were developed for the synthesis of substituted 2-aryl-1,8-naphthyridin-4(1*H*)-ones using substituted 2-aminopyridines **221** and ethyl benzoylacetates **222** as the starting compounds (1997JMC2266, 1997JMC3049). Their condensation in the presence of PPA affords the corresponding pyridopyrimidinones **223**. Compounds **223** were also prepared by cyclization of Schiff bases **224** with monochloroacetyl chloride in the presence of triethylamine. The subsequent thermal rearrangement of pyridopyrimidinones **223** at 350 °C gives 2-phenyl-1,8-naphthyridines **225**. An analogous approach was also used for the preparation of the corresponding 2-naphthyl-substituted 1,8-naphthyridinones (1991FRP2641783).



R^1 = H, Me, Cl, Br; R^2 = H, Me, F, Cl.

Condensation of 2-aminopyridines **226a,b** with β-ketoesters or dicarboxylic esters is a promising approach for the synthesis of 1,8-naphthyridines. The reaction is carried out at high temperature in PPA or Dowtherm (1982JHC1017, 1984AJC1065, 1986FES926, 1987SC319, 1988GEP3644825, 1990JA8024, 1990JCS(P1)2409, 1990JHC881, 1991GEP3907937, 1992JHC559, 1998JHC1231). For example, this procedure was used for the synthesis of 7-amino-2-hydroxy-1,8-naphthyridines **227** (1990JHC881) and naphthyridones **228** (1982JHC1017, 1987SC319).

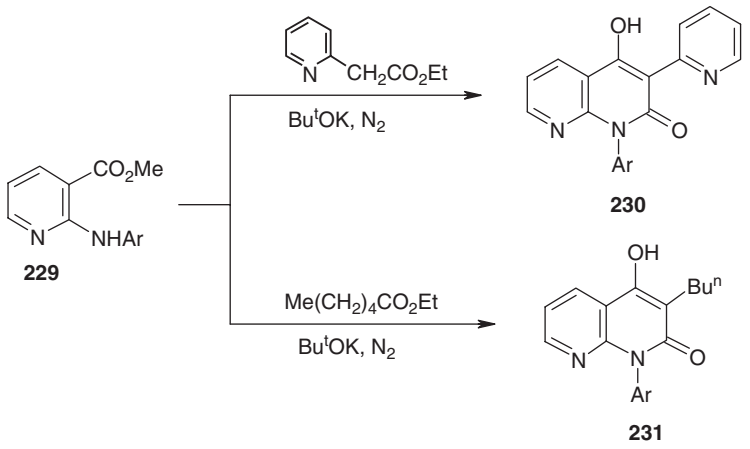


R^1= Me (a), NH_2 (b); R^2= Me, Pr, CF_3, $ClCH_2$, Ph; R^3= Me. Ph.

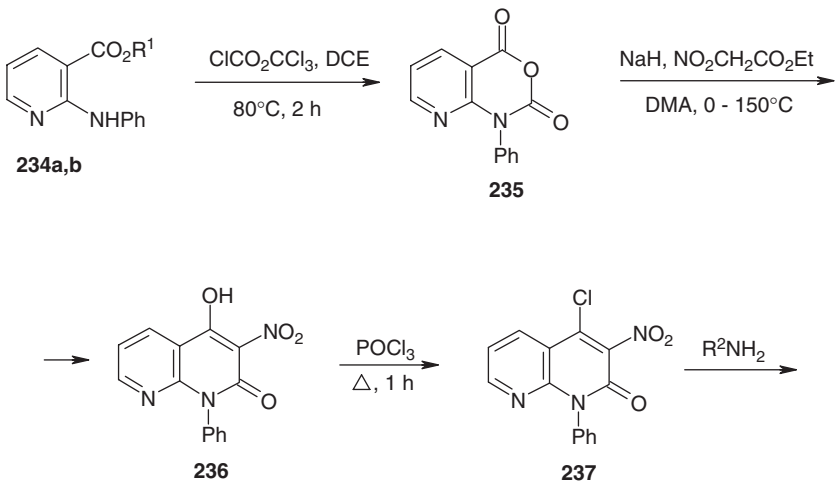
Naphthyridine **227** (R^2=$ClCH_2$) was covered by a patent as an agent reducing the phytotoxicity of herbicides belonging to cyclohexenones or phenoxyacetic acids (1991GEP3907937). Naphthyridone **228** (R^3=Me) was used as an intermediate in the synthesis of compounds possessing antimalarial activity against *Plasmodium vinckei vinckei* (1984AJC1065).

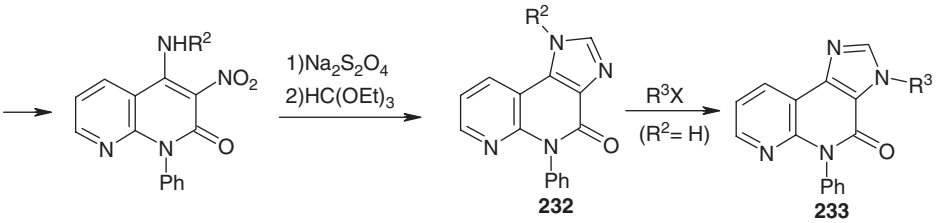
Other 2-aminopyridines were also successfully used in the synthesis of substituted 1,8-naphthyridines (1982JHC1017, 1985EJMC381, 1986T687, 1986ZN105, 1989MI5, 1990JCS(P1)2409, 1991GEP3911064, 1991MI4, 1993JHC909, 2002S1912, 2003PIA-WO2003082870).

Procedures were developed for the synthesis of various 1,8-naphthyridin-2-one derivatives based on condensation of methyl 2-arylaminonicotinates **229** and carbonyl compounds containing an activated methylene group. This method was used, for example, for the preparation of naphthyridones **230** and **231** exhibiting anti-allergic, anti-inflammatory and antiulcerative actions (1984USP4492702, 1986USP4551463, 1987JMC2270, 1987USP4596809, 1987USP4628055, 1987USP4632923, 1987USP4684727, 1988USP4652564, 1989MI5, 1989USP4775524, 1989USP4782067, 1991S571, 1991USP4897487, 1991USP4916131, 1993USP5037826, 1993USP5079360, 1994USP5180823).



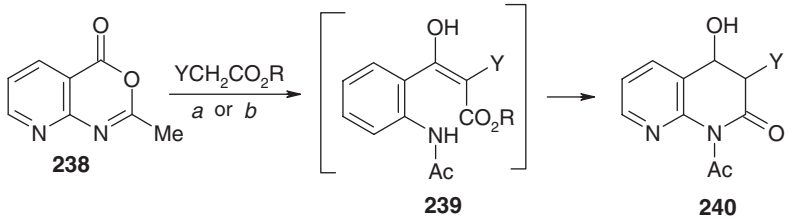
A convenient regioselective procedure was developed for the synthesis of new heterocycles, viz., 5-phenyl-1*H*- **232** and 5-phenyl-3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones **233**, starting from 2-phenylaminonicotinic acid **234a** or its methyl ester **234b** (1985JHC193, 1991JHC2029, 1992JMC1130, 1992JMC2863, 2001JOC4413). Treatment of ester **234** with trichloromethyl chloroformate in 1,2-dichloroethane at 80 °C affords *N*-phenyl-3-azaisatinic anhydride **235**. The reaction of the latter with sodium hydride and ethyl nitroacetate in *N*,*N*-dimethylacetamide produces 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one **236**. Chlorination of naphthyridone **236** with phosphorus oxychloride gives chloride **237**, which is transformed into the target naphthyridines by successive amination, reduction and cyclization. Imidazonaphthyridones **232** and 233 are new nonsteroid anti-inflammatory drugs possessing activity analogous to that of glucocorticoids.





R^1= H (a), Me (b); R^2= H, Et, Pr^i, Bn; R^3= Me, Et, Pr^i, Bu^n, Bu^t, C_6H_{13}, Bn, $CH(Me)C_6H_5$;
X = I, Cl, Br; DCE is 1,2-dichloroethane; DMA is N,N-dimethylacetamide.

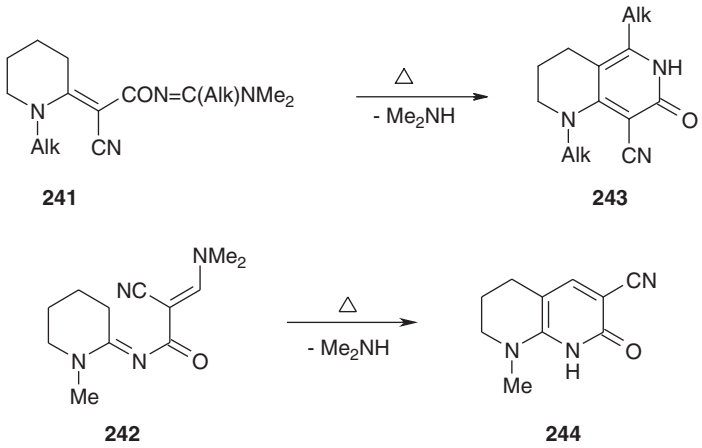
A new efficient procedure was proposed (1988JMC2108, 1988AKZ687, 1991MI4, 1991MI5, 1994JMC1327, 1994MI2) for the synthesis of 3-substituted 1,8-naphthyridine-2,4-diones, which are of considerable pharmacological interest. The reaction of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one **238** with compounds containing an active methylene group in the presence of potassium *tert*-butoxide or *tert*-butyl alcohol or in the presence of sodium hydride in anhydrous benzene produces 3-substituted 1-acetyl-1,2,3,4-tetrahydro-1,8-naphthyridine-2,4-diones **239** in yields up to 87% (1997JCS(P1)1487). Evidently, the reactions proceed through intermediates **240**.



Y = EWG, R = Alk;
(a) Bu^t OK, Bu^t OH, 20°C; (b) NaH, PhH, 20°C.

Amines of the isoquinoline series can be used as starting compounds for the preparation of benzoannulated 1,8-naphthyridines (1984AJC1135, 1986AJC667, 1990AJC1469, 1991AJC481, 2002MI2, 2003MI3).

Enamino amides **241** and **242**, containing a *β*-enaminocarbonyl fragment, are promising starting compounds in the synthesis of hydrogenated naphthyridines **243** and **244** (1976KGS1509, 1977KGS1106, 1977KGS1523, 1978KGS355, 1980KGS416, 1980KGS1120, 1981KGS215, 1981KGS1283, 1982RCR119, 1983RCR377, 1985KGS929, 1986KGS364). Study of the kinetics of these reactions demonstrated that the rate of cyclization of **241** is much higher than that for the amidine **242**, due to the more pronounced delocalization of the positive charge in the amidine system compared to the enamine system (1977KGS1523, 1982RCR119, 1983RCR377).



Some other approches to the synthesis of 1,8-naphthyridine and its derivatives were described (1985UKZ750, 1986JCS(P1)753, 1987AP285, 1987MI2, 1988JOC5379, 1990JCS(C)7, 1990JHC189, 1990USP4859669, 1991EUP430485, 1991LA1215, 1991USP4996212, 1991ZOR2424, 1992MI2, 1993H1541, 1993JCR(S)8, 1993S111, 1996JOC4136, 1997TL115, 1998TL9237).

III. Physicochemical Properties of Naphthyridines

Data on the structures, physicochemical properties and reactivities of isomeric naphthyridines published up to 1984 inclusive, have been analyzed in sufficient detail in reviews (1970AHC123, 1983AHC95, 1983AHC147, 2000RCR201, 2001RCR299, 2004RCR637).

A. Structure

An X-ray diffraction study was first performed on unsubstituted 1,5- and 2,6-naphthyridines (1959G2328, 1966MI1, 1970AHC123). The transition from pyridine to naphthyridines is accompanied by a shortening and lengthening of C–C bonds approximately equal to that observed on passing from benzene to naphthalene. In addition, the N–C bonds in naphthyridines were found to be shorter than such a bond in pyridine. Also, the pyridine nitrogen atom in 2-(cyclohex-2-enylthio)quinuclidinepyridine has a short non-valence contact with the C=C bond of the cyclohexene fragment (1989MI6).

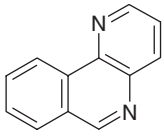
X-ray diffraction analysis was also used to determine the structure of several 1,5-, 1,7-, 1,8- and 2,6-naphthyridine derivatives (1970AHC123, 1983AHC95, 1983AHC147, 1985CPB5551, 1987AX2198, 1988CJC2981, 1990AX2198, 1995AX(C)978, 1995JCS(P1)465, 1996M391, 1997PIAWO9639406, 1998AX781, 1998HCA507, 1998ICA129, 1998ICA237), 5-amino-7-benzylseleno-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-1,2-dimethyl-1,4-dihydro-1,6-naphthyridine (2002KGS1263),

2-nitroso-1,3-diphenyl-1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridine (2003AX(C)o153), 5-amino-4-(4-dimethylaminophenyl)-2-(4-methoxyphenyl)-7-(pyrrolidin-1-yl)-1,6-naphthyridine-3-carbonitrile (2003AX(E)o200), 3,5-dichlorobenzo[*h*][1,6]naphthyridine (2003JHC255) and 6-(3-iodopropyl)benzo[*f*][1,7]naphthyridium iodide(2003AX1178).

B. Quantum-Chemical Calculation

Since the 1950s, quantum-chemical methods have been used to elucidate structure–property relationships in the naphthyridine series (1949JCS971, 1957MI1, 1958JOC20413, 1960JCS1946, 1962JCS493, 1965JCP2658, 1966JCP2139, 1966JSP25, 1967MI1, 1968JOC1384, 1972MI1, 1972MI2, 1973JCS(P1)1024, 1976JCS(P1)19, 1985CPB5332, 1987MI3, 1991MI6, 1997JHC765, 1997MI3, 1998LA2601). The intensities of bands in the UV spectra of naphthyridines have been found to be correlated with the energies of the lower unoccupied molecular orbitals (1960JCS1946, 1962JCS493, 1966JSP25); quantum-chemical calculations have also been used in ^{1}H and ^{13}C NMR spectroscopy (1966JCP2139, 1972MI1, 1972MI2, 1973JCS(P1)1024, 1976JCS(P2)19, 1997JHC765) and for a comparison of the total π-energy and delocalization energy of naphthyridines and naphthalene (1967MI1, 1968JOC1384). Other results include a determination of π-electron distribution (1958JCS204, 1968JOC1384), elucidation of correlations of the total π-electron energy with specific features of electrophilic (1968JOC1384) and nucleophilic (1958JCS204, 1968JOC1384) substitution and with the hyperfine splitting constants in their ESR spectra (1966JCP2139).

The influence of the structure of benzo[*h*]naphthyridines **245**–**247** and their amino derivatives on their reactivity, charge distributions, excitation energies and the oscillator strengths have been calculated. The calculation was carried out by a semi-emperical self-consistent field method in the Pariser–Parr–Pople π-electron approximation with allowance for the configurational interaction between single excited states and by the Hückel method. The results are in satisfactory agreement with their UV spectra (1991ACH267). The populations of the atomic π-orbitals, the order of π-bonds and the frequency and oscillator strengths for a three-electron transition in naphthyridines **245**–**247** and their salts **248**–**250** were also calculated. By comparing the calculated and experimental spectra, correlation coefficients for the relation $v_{calc} = av_{exp} + b$ were determined (1989ACH187).



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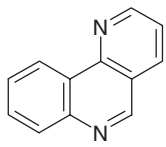

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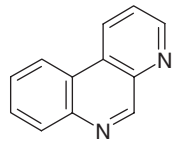

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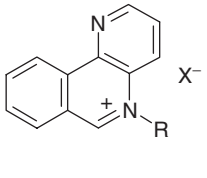

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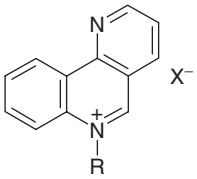

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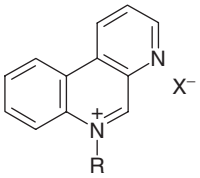


250

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

In recent years, quantitative structure–biological activity relationships for 5-acetyl-1,6-naphthyridin-2(1*H*)-one (1996MI3), 6-[2-(4-arylpiperazino)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines (1985CPB5332), 5-amino-2,4-diphenyl-7-(pypyrrolidin-1-yl)-1,6-naphthyridin-8-carbonitryle (1998AX781) and 7-substituted 1,4-dihydro-4-oxo-1-(2thiazolyl)-1,8-naphthyridin-3-carboxylic acids (2002JMC5564) have been established and complexes of antitumor antibiotics – naphthyridinomycins – with DNA have been studied by molecular modeling methods (1991MI6).

The UV spectral parameters of six isomeric formyl-substituted 4,6-benzo-1,5- and -1,6-naphthyridines were calculated (1998MI5).

C. Spectroscopy

Spectroscopic techniques (UV, IR, ^1H and ^{13}C NMR) are widely used not only to identify naphthyridines but also to elucidate fine points concerning their structures (1970AHC123, 1983AHC147).

Thus, the UV spectra of 1,5-, 1,6-, 1,7- and 1,8-naphthyridines **1**–**4** are fairly similar to one another and contain three separate groups of bands, analogous to the bands displayed in the spectra of quinoline and isoquinoline. However, the spectra of 2,7- and 2,6-naphthyridines **5** and **6** differ both from each other and from the spectra of any other naphthyridines (1960JCS1790, 1970AHC123). The UV spectra of 4-hydroxy-1,5-naphthyridine (1967MI2) and of a large number of substituted 1,8-naphthyridines (1958M5) have been analyzed in detail. In order to disclose the influence of substituents on the absorption spectra, UV spectra of 1,8-naphthyridines monosubstituted at positions 2 (Me, Cl, Br, OEt, SMe, NH_2, OH, SH), 3 (Me, Cl, Br, NO_2, NH_2) and 4 (Me, Cl, Br, OMe, OEt, OH, SH) have been studied (1987MI4).

Transmission and absorption spectra of 1,8-naphthyridine **2** in the range of 50,000–20,000/cm have been investigated in solution and in various mixed crystals at 4.2 and 300 K (1987MI3). The pattern of the band corresponding to the $\pi \rightarrow \pi^*$ transition was found to be similar to that observed in the spectrum of the related naphthalene molecule with allowance for perturbation induced by the replacement of carbon by nitrogen. The position of the long-wavelength $\pi \rightarrow \pi^*$ band at about 27,000/cm agrees with the theoretical predictions based on extended Hückel calculations. The bands at about 31,600–31,900/cm were assigned empirically to the second $\pi \rightarrow \pi^*$ transition (1987MI3).

With the aim of elucidating the influence of substituents on their absorption spectra, the UV spectra (in methanol) of 1,8-naphthyridines monosubstituted at position 2 (Me, Cl, Br, OMe, OEt, OH or SH as the substituent) were examined (1987MI4).

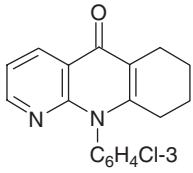
The solvatochromism in 1,6- and 1,7-naphthyridine derivatives has been studied in solvents of different polarity and hydrogen bond donor and hydrogen bond acceptor abilities (2003SA1399).

All bands in the IR spectra of several substituted 1,5-naphthyridines have been assigned; the spectrum of 1,5-naphthyridine **1** was compared with the spectrum of 5-substituted quinoline (1963MI1). IR spectroscopy was used to study the keto–enol tautomerism of 4-hydroxy-1,5-naphthyridine in solution and in the solid state; it was found that the keto form predominates in polar solvent and the enol form in non-polar solvent (1967MI2).

Study of the IR and Raman spectra of 1,6- and 1,8-naphthyridines permitted the assignment of all 42 fundamental vibrations of these two heterocyclic systems (1973JSP401).

Data on the ^{1}H NMR spectra (chemical shifts and spin–spin coupling constants) for the naphthyridines **1–4** and **6** can be found in the literature (1965JCP2658, 1965JHC393, 1965TL1117, 1965TL2737, 1966CI(L)1557, 1966JCS315, 1966JCS750, 1966JOC3055, 1967JCS377, 1967JCS1564, 1967JHC284, 1967JOC832, 1967JOC2616, 1968JHC561, 1968JOC1384, 1976JCS(P2)19, 1983AHC147, 1984JHC817, 1985CPB5332, 1987MI3, 1997JCS(D)4257, 1997MI1). The chemical shifts observed in the ^{13}C NMR spectra of the naphthyridines **1–6** were compared with those for quinoline and isoquinoline (1972MI1, 1972MI2, 1976JCS(P2)19, 1983AHC147).The resonance signals in the ^{1}H NMR spectrum of 2-(2′-pyridyl)-1,8-naphthyridine were completely assigned using homonuclear 2D *J*-resolved NMR spectroscopy (1984JHC817).

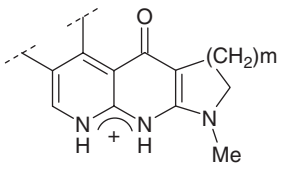
According to its ^{1}H NMR spectroscopic data, 1,8-naphthyridone **251** are chiral and exists as short-lived interconvertable atropoisomeric enantiomers, which form diastereomeric complexes with the shift-reagent [(*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol]. The enantiomers were isolated in their individual forms. The racemization constant is 0.213/min at 37 °C. The activation energy is $E_a = 21.6\,\text{kcal mol}^{-1}$ (1996MI4).



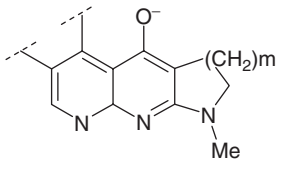
251

Protonation of naphthyridones **252** was studied by UV and ^{1}H and ^{13}C NMR spectroscopy (1990KGS643). Protonation occurs to give the cationic form **A**. In 70% DMF, the ionization constants of naphthyridones **252** depend on the size of the saturated cyclic fragment of the molecules, which is associated with steric factors

such as a change in steric accessibility of the polar groups of the cationic (**A**) and anionic (**B**) forms to solvation (1990KGS643).



252 A



252 B

m = 1 - 3.

The behavior of derivatives of the isomeric naphthyridines **1**–**4** under electron impact has been studied and the main fragmentation pathways have been indentified (1967JHC547, 1970AHC123, 1987MI5, 1989MI7). Mass spectrometry was used for the investigation of the structures and decomposition of the isomeric $[M–HCN]^-$ and $[M–2HCN]^-$ ions formed upon fragmentation of naphthyridines and benzoazines (1989MI8). The $[M–2HCN]^-$ ions can exist as two isomeric forms, one of which is typical of naphthyridines, whereas the other is characteristic of benzoazines.

High-resolution photoelectron spectra of the naphthyridines **1**–**6** have been described (1972MI3).

Polarized phosphorescence spectra of 1,5-naphthyridine **1** (1959MI1, 1973MI2, 1981JSP345) and the ESR spectrum of 1,6-naphthyridine **3** (1975MI1) and hexahydro-1,8-naphthyridinetetrazole were recorded (1998MI6).

A number of publications deal with the capacity for ionization (including the pK_a values) of the naphthyridines **1**–**4** and their derivatives (1954JCS234, 1954JCS505, 1954MI, 1956JCS1294, 1960JCS1790, 1963JCS4237, 1967JCS377, 1970AHC123).

The electric dipole moment of 1,8-naphthyridine in benzene was determined (4.10 D) (1988MI2).

The pattern of deuterium distribution in isotope exchange products of 1,8-naphthyridine and its methyl-, hydroxyl-, amino- and nitro derivatives indicates that the rate and pathway of this process depend on the pH of the medium as well as the nature and position of substituent (1988ACH267). In neutral D_2O and a D_2O–DCl mixture, hydrogen atoms are replaced with deuterons exclusively at positions 2 and 7. In D_2O solutions containing NaOD, hydrogen atoms are replaced with deuterons in all positions of the naphthyridine system. In neutral D_2O, the replacement of the protons in monomethyl-substituted 1,8-naphthyridines occurs predominantly in the *ortho* positions with respect to the nitrogen atoms (positions 7 and 2, 7). The high reactivity of these positions is determined by the inductive effect of the substituent.

IV. The Reactivity of Naphthyridines

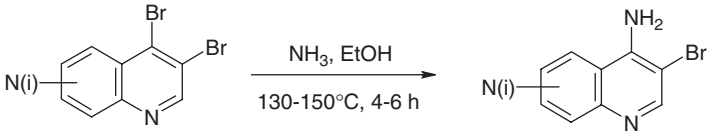
Reactions of naphthyridines including electrophilic substitution (bromination, nitration), nucleophilic substitution (amination, metallation), reduction, complexation, etc., have been considered comprehensively in reviews (1970AHC123,

1983AHC147). In yet another review, attention is focused on the reactivity of naphthyridines toward *N*-nucleophiles (1983AHC95). Here, we survey the data on the reactivity of naphthyridines published over the last 20 years.

Electrochemical reduction of naphthyridines **1**–**6** has been reported (1976MI1, 1978MI1).

On exposure to UV radiation in the presence of sodium nitrite, 3-amino-1,6-naphthyridine-4(1*H*)-one eliminates a nitrogen molecule being thus converted into 5-azaindole-3-carboxylic acid (1958MI1, 1960JCS1794).

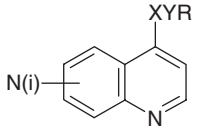
Nucleophilic substitution of bromine at position 4 in 3,4-dibromonaphthyridines **253a–c** on treatment with a saturated alcoholic solution of ammonia in an autoclave affords 4-amino-3-bromo-*N*(1),*N*(*i*)-naphthyridines **254a**–**c** (1983MI3).



253a-c **254a-c**

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

The naphthyridine derivatives **255a–c**, possessing fungicidal activity, have been synthesized using nucleophilic substitution of the halogen atoms in isomeric halo naphthyridines. These products can also be employed for combating exo- and endo-parasites in agriculture and cattle breeding, for wood protection, and as preservatives for paints, varnishes and cutting fluids during metal working (1995GEP4308014).

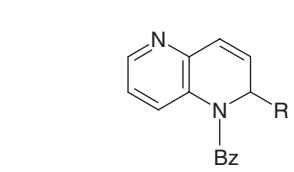


255a-c

i = 5 (a), 6 (b) 7 (c); X = O, S, SO, SO_2;

Y is alkenyl or a single bond; R is cycloalkyl or piperidin-2-yl.

In recent years, nucleophilic addition reaction has been widely used for the synthesis of various derivatives of isomeric naphthyridines. For example, nucleophilic addition of indole to 1,5-, 1,6- and 1,8-naphthyridine derivatives in the presence of benzoyl chloride in toluene or DMF yields, depending on the temperature and reactant ratio, hydrogenated mono- (**256**–**265**) or *bis*-(3-indolyl)naphthyridines **259**–**264** (1985MI2, 1986KGS1218, 1986MI3). Hetarylation includes the *in situ* formation of *N*-acyl heteroaromatic cations and the addition of nucleophiles to them. Aromatization of the N-acylated hydrogenated naphthyridine derivatives **259** and **264** on treatment with tetrachloroquinone affords the same compound, naphthyridine **265**.



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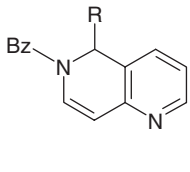

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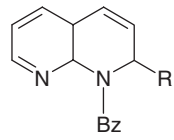

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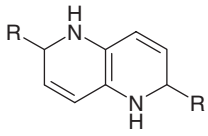

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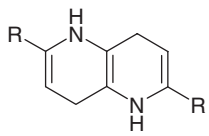

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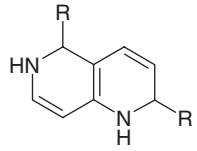

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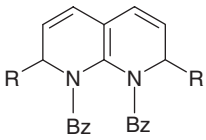

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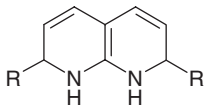

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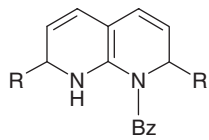

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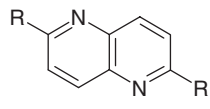


265

R is 3-indolyl.

Refluxing *N*(1),*N*(*i*)-naphthyridin-4(1*H*)-ones **266a–d** in DMSO gives 1-methylthiomethyl naphthyridine derivatives **267a–d**, which depress microbial growth (1984PLP125299, 1986KGS1218, 1986PLP125298, 1986PLP125310). Similar methylthiomethylation of naphthyridin-2(1*H*)-ones **268a–d** has resulted in N-substituted *N*(1),*N*(*i*)-naphthyridin-2(1*H*)-ones **269a–d** (1984MI3).

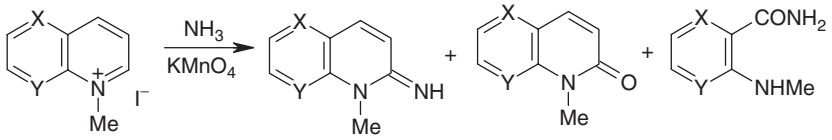
266a-d **267a-d**

268a-d **269a-d**

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

Treatment of 1-methyl-*N*(1),*N*(*i*)-naphthyridinium iodides **270a,b** with liquid ammonia in the presence of potassium permanganate gives mixtures of imino **271a,b**

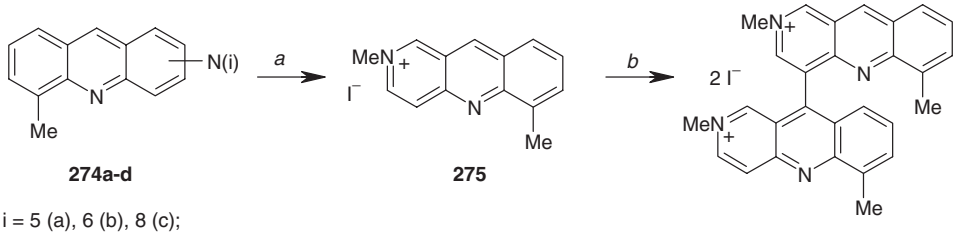
and oxo **272a,b** derivatives of dehydronaphthyridines and vicinal methylaminopyridinecarboxamides **273a,b** (1985JHC765).



270a,b **271a,b** **272a,b** **273a,b**

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

The kinetics of N-methylation of benzonaphthyridines **274a–d** with methyl iodide in DMSO has been studied (1993AJC1909). The salt **275**, formed from the naphthyridine **274b**, slowly dimerizes in a 10% aqueous solution of DMSO to give **276**.

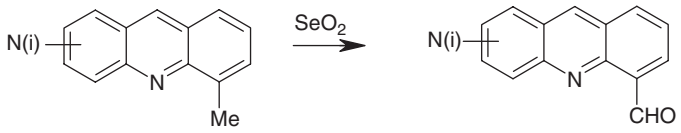


274a-d **275** **276**

i = 5 (a), 6 (b), 8 (c);

(a) i = 6, MeI, $MeCO_2Et$, Δ, 0.5 h; (b) DMSO - H_2O (1: 9), 10 h.

The methyl group in benzo[2,3]naphthyridines **274a–d** can be easily modified. Thus refluxing these compounds with SeO_2 in chloro-, 1,2-dichloro- or 1,2,4-trichlorobenzene gives aldehydes **277a–d**, which serve as the starting compounds for the synthesis of diverse functional derivatives of benzonaphthyridines (1992JHC1197, 1993AJC987, 1994JMC593). Oxidation of the compounds **274a–d** to the aldehydes **277a–d** and further oxidation to the corresponding acids are the key stages of the synthesis of compounds, which are the aza analogs of the potential antitumor preparation, *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide.



274a-d **277a-d**

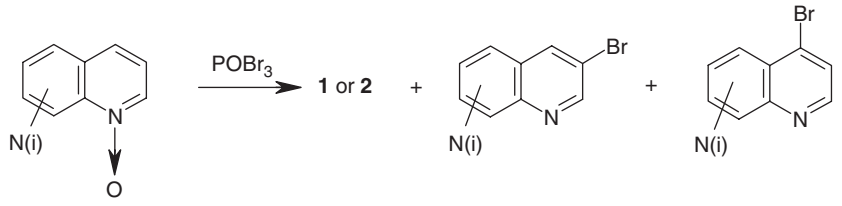
i = 5 (a), 6 (b), 8 (c);

Dipolar 1,3-cycloaddition of various dienophiles to naphthyridinium ylides, generated *in situ* by dehydrobromination of the corresponding quaternary salts, has been studied; this gives rise to benzo[*h*]pyrrolonaphthyridines (1984M1101, 1987JPR529, 1988ACH491, 1990ACH711, 1991PLP149212, 1991PLP149332, 1995M227).

Quaternization of naphthyridines **245–247** (1988ACH267, 1990PLP144778, 1996PLP165956) (the compounds **245** and **246** were prepared by the Skraup method (1988ACH267) and **247** was synthesized by photocyclization of diazastilbene (1998OPP481)) induced by alkyl, aryl or benzyl halides gave quaternary salts **248–250**. The salts **248** and **249** exhibit bactericidal and fungicidal activities (1988ACH267).

The formation of *N*-ylides of the benzonaphthyridinium series upon dipolar 1,3-addition of benzonaphthyridine *N*-oxides to dimethyl acetylenedicarboxylate at room temperature has been reported (1996AJC523).

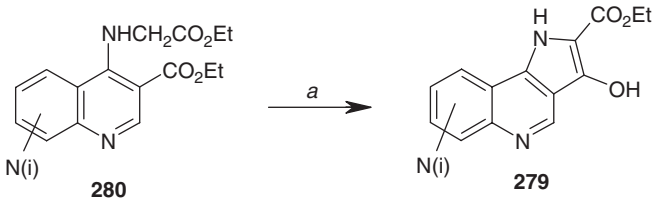
Treatment of *N*-oxides **278a,b** with $POBr_3$ affords a mixture of 1,5- (**1**) or 1,8-naphthyridines (**2**) with their brominated derivatives. A similar mixture of products is also formed when $POBr_3$ reacts with 1,5-naphthyridine *bis*(*N*-oxide) (1991MI7).



278

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

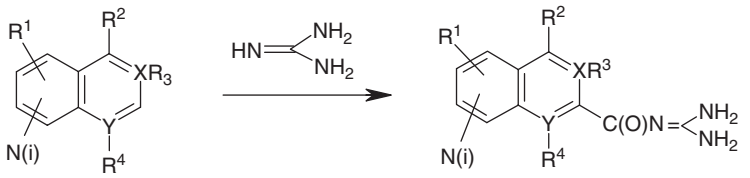
Carboxylic acid derivatives **279** of the pyrrolonaphthyridine series – potential preparations for treatment of degenerative, ischemic and autoimmune diseases – have been synthesized using intramolecular cyclization of ethyl (3-ethoxycarbonylnaphthyridin-4-ylamino)acetates **280** induced by potassium *tert*-butoxide in a toluene–^{t}BuOH mixture (1994EUP587473).



280 **279**

(a) Bu^{t}OK, PhMe, Bu^{t}OH, 20 h.

The reaction of naphthyridinecarboxylic acids **281** with guanidine in the presence of carbonyldiimidazole in anhydrous THF results in hetaroylguanidines **282**, which can be used for the therapy of heart diseases, for surgical operations and organ transplantation, for the diagnostics and treatment of hypertension and proliferative diseases (1986GEP3508816).



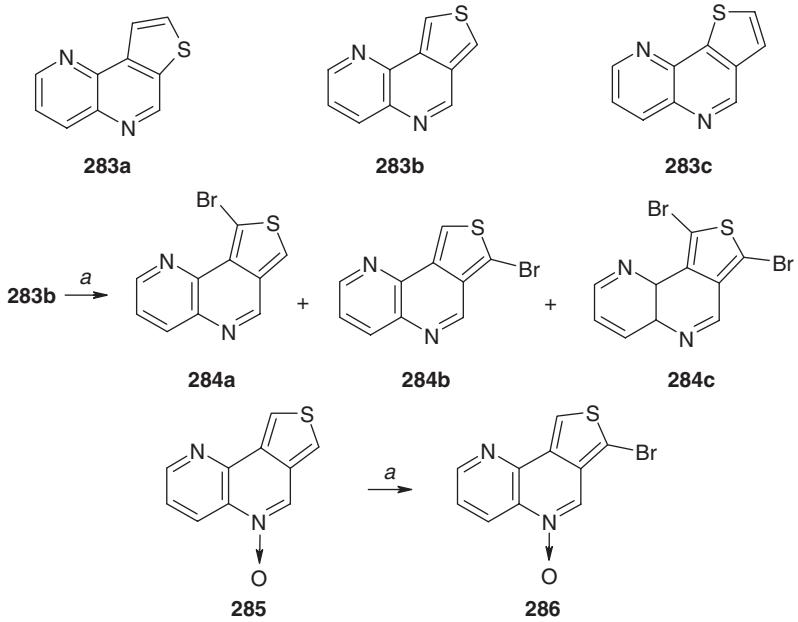
281 **282**

R^1, R^2= H, Hal, Alk, alkenyl, alkynyl, CN, Alk_F;

R^3, R^4= H, Hal, Alk, Alk_F, AlkO, Alk_2N, $CON{=}C(NH_2)_2$ or none;

X = N, Y = C; X = C, Y = N.

The chemical properties of 1,5-naphthyridines and the possibility 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 **283a–c** and their *N*-oxides with tetrabutylammonium perbromide or bromine in the presence of $SOCl_2$ was investigated (1994H331). The reactions involving *N*-oxides proceed with higher regioselectivity. Thus bromination of thienonaphthyridine **283b** with tetrabutylammonium perbromide afforded a mixture of halogeno derivatives **284a–c**, whereas bromination of its *N*-oxide **285** under the same conditions gave rise to bromide **286** in 55% yield (23% of the initial compound remained unconsumed).



283a **283b** **283c**

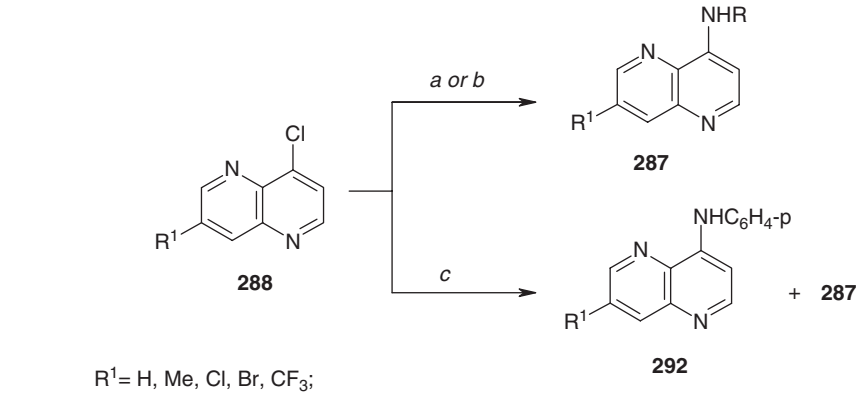
284a **284b** **284c**

285 **286**

(a) 1.2 equiv. BuN_4^+, 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 (1985AJC459, 1984AJC2469, 1985AJC905, 1986AJC51, 1988AJC1727, 1990AJC1175, 1991AJC151, 1991AJC677, 1991JHC1997, 1993AJC1695, 1993LA471, 1994AJC1143, 1994USP5110347, 1995USP5240916). Thus, substituted 1,5-naphthyridin-4-ylamines **287** were prepared by the reaction of 4-chloro-1,5-naphthyridines **288** with aminophenols **289–291** (1988AJC1727, 1990AJC1175, 1991AJC151) or by the Mannich reaction of 8-(4-hydroxyphenylamino)naphthyridines **292** (1985AJC905, 1986AJC51).



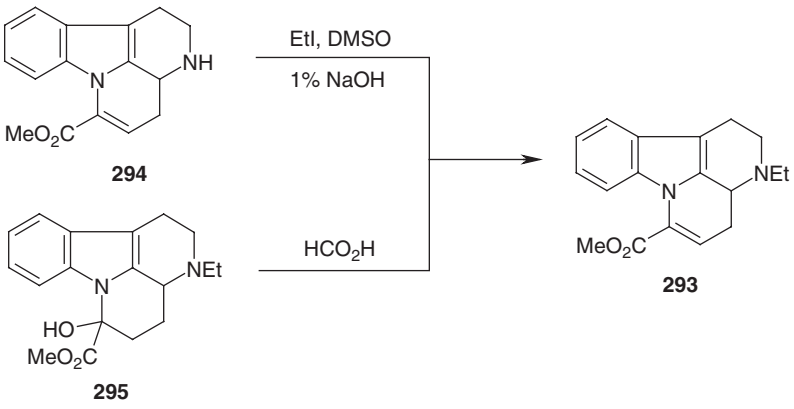
(a) H_2NR^2, MeOH (EtOH), HCl, Δ; (b) $AcNHR^2$, MeOH (EtOH), HCl, Δ;

(c) 4-$HOC_6H_4NH_2$.HCl, MeOH, Δ; (d) CH_2O, HNR_2^3, EtOH, Δ.

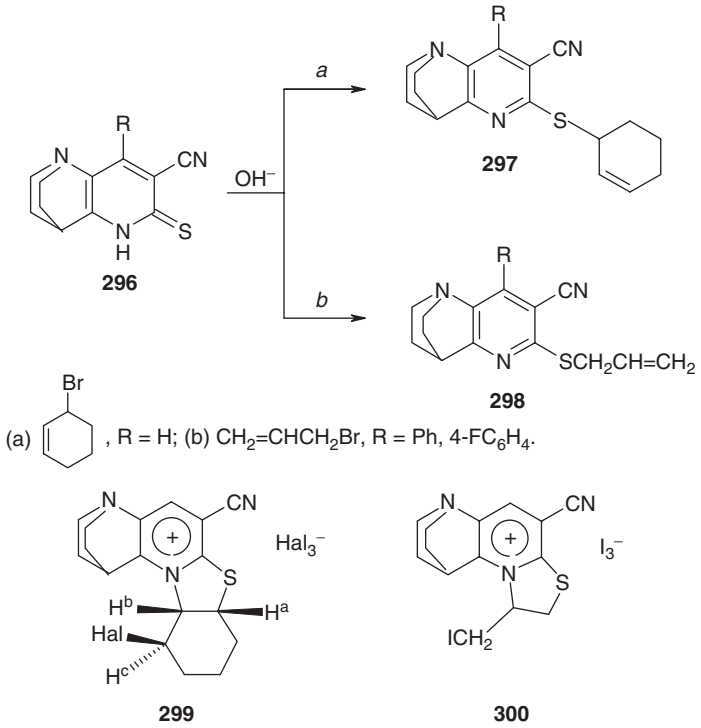
The compounds **287** exhibit antimalarial activity both *in vitro* and *in vivo*. This activity is less pronounced in the case of R^1=Br or CF_3 and R^2=Me or Et (1990AJC1175, 1991AJC151).

(7-Bromo-1,5-naphthyridin-4-yl)(piperidin-2′-yl)methanol, which is a potential antimalarial drug of a new type, was synthesized in four steps starting from 4,7-dibromo-1,5-naphthyridine (1993AJC1695).

Methyl (±)-3-ethyl-2,3,3*a*,4-tetrahydro-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine-6-carboxylate **293** possessing psychostimulating activity was prepared by the alkylation of ester **294** with iodoethane in DMSO or by dehydration of hydroxyl derivative **295** (1988FRP2590990).

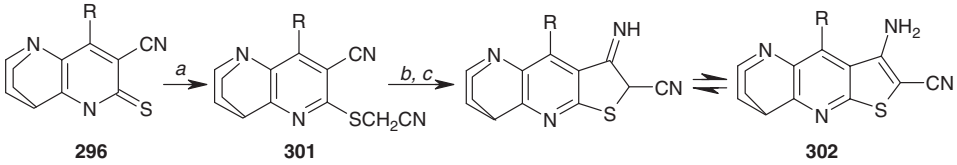


Regioselective alkylation of quinuclidinopyridine-2(1*H*)-thiones **296**, containing a 1,5-naphthyridine fragment, with 3-bromocyclohexene or allyl bromide in the presence of a base affords the corresponding 2-(cyclohex-2-enylthio)- **297** and 2-allylthio derivatives **298**. Halogen-induced quaternization of these products yields salts **299** and **300** with high regio- and stereoselectivity (1989KGS557, 1989ZOR1980, 1989MI6, 1991MI9).



2-Cyanomethylthio derivatives **301**, prepared by the alkylation of **296** with chloroacetonitrile, cyclize under Thorpe–Ziegler conditions to give the corresponding

thieno[2,3-*b*]pyrido[3,2-*e*]quinuclidines **302**, containing a 1,5-naphthyridine fragment (1989ZOR1980).

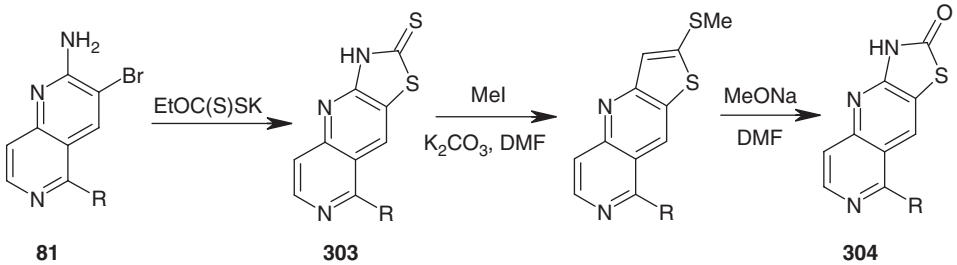


296 **301** **302**

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

The reactivity of various derivatives of 1,6-naphthyridines has been studied.

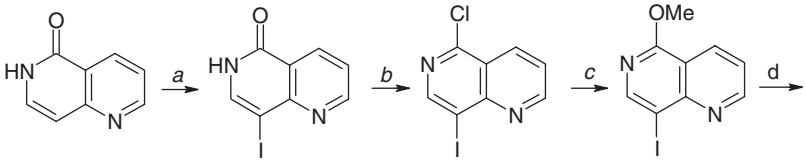
Condensation of 2-amino-3-bromo-1,6-naphthyridines **81** with potassium *O*-ethyl xanthate in *N*-methylpyrrolidone afforded thiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thiones **303** whose subsequent methylation and hydrolysis in the presence of sodium methoxide afforded thiazolonaphthyridones **304** inhibiting adenosine-3′,5′-cyclophosphate phosphodiesterase (cAMP PDE III) (1995JMC2546).



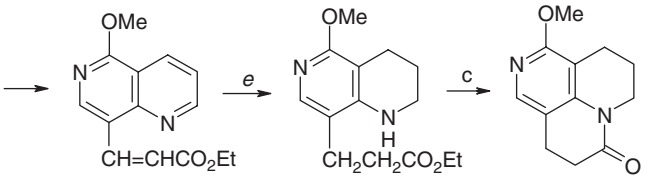
81 **303** **304**

R = Me, Et, Pr^n, Bu^t, Ph, p-$NO_2C_6H_4$.

The hydrogenated pyrido[3,2-*ij*]-1,6-naphthyridin-6-one **305** was synthesized from 1,6-naphthyridin-5(6*H*)-one **306** in six steps (1986CPB2018). The key stage of the scheme consists in the Heck reaction of 8-iodo-1,6-naphthyridine **307** with ethyl acrylate. Reduction of the double bond in the resulting derivative **308** and cyclization of **309** under the action of sodium methoxide complete the synthesis. The structural fragment in **305** is present in the alkaloid matrine (sophocarpidine) found in dried roots of several plants belonging to the genus *Sophora*.



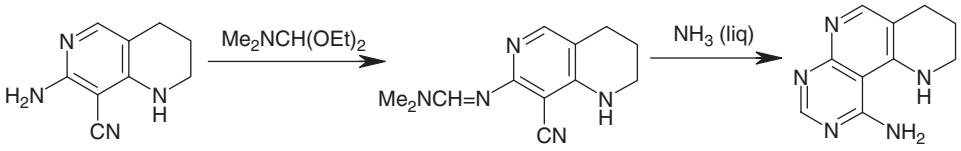
306 **307**



308 **309** **305**

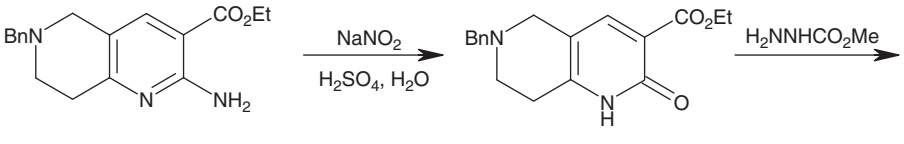
(a) I_2, 4M NaOH, 80°C, 4 h; (b) $POCl_3$; (c) MeONa, MeOH;
(d) CH_2=$CHCO_2Et$, $Pd(OAc)_2$, Et_3N, MeCN; (e) H_2, PtO_2, MeOH.

Condensation of 7-amino-8-cyano-1,2,3,4-tetrahydro-1,6-naphthyridine **310** with dimethylformamide diethyl acetal afforded azomethine **311**. Its treatment with ammonia gave 1-amino-7,8,9,10-tetrahydropyrimido[4,5-*h*][1,6]naphthyridine **312** (1984KGS1287).

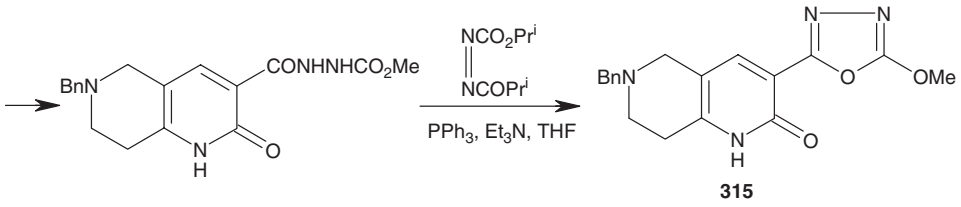


310 **311** **312**

Diazotization of the amine of **313** with sodium nitrite in 10% H_2SO_4 afforded naphthyridinone **314**, used as the starting compound in the synthesis of the antagonist of benzodiazepine receptors **315** (1993USP5367078, 1994USP5424433, 1994USP5424434).

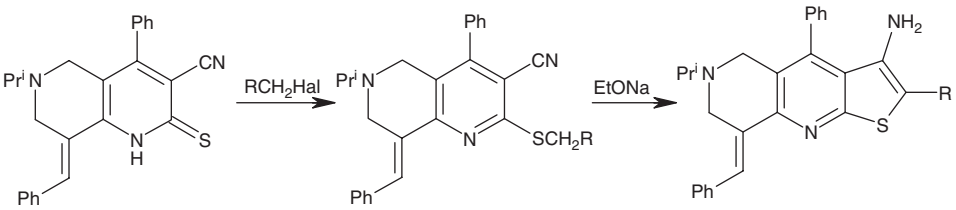


313 **314**



315

Treatment with sodium ethoxide of thioethers **316**, prepared by the reaction of 1,2,5,6,7,8-hexahydro-1,6-naphthyridine-2thiones **317** with halo ketones, esters, amides or nitriles, resulted in the synthesis of thieno[2,3-*b*]-1,6-naphthyridines **318** (1993BCJ3716).

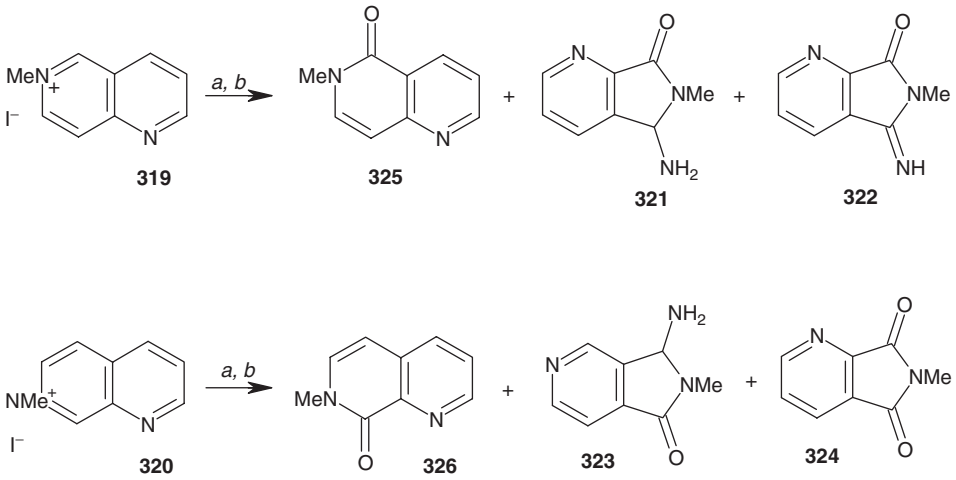


R = MeCO, PhCO, EtO_2C, $CONH_2$, CONHPh, CN, $CONHC_6H_4Me$-p, $CONHC_6H_4OMe$-p, $CONHC_6H_4COMe$-p.

A study of the reaction of 3-chloro-4-cyanobenzo[*b*][1,6]naphthyridine with nucleophilic reagents was described (2002RCB2121).

Some aspects of the reactivity of 1,7-naphthyridine derivatives are reported.

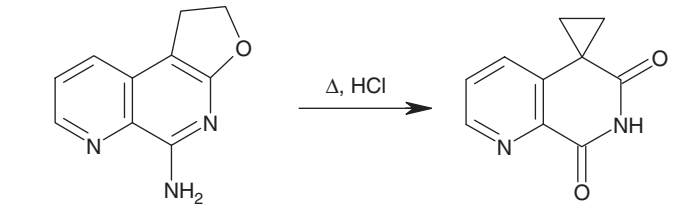
6-Methyl-1,6-naphthyridinium iodide **319**and 7-methyl-1,7-naphthyridium iodide **320** react with liquid ammonia and $KMnO_4$ with ring contraction as the predominant pathway yielding 4-azaindole derivatives **321**–**324** together with the oxo derivatives of the corresponding dihydronaphthyridines **325** and **326** (1985JOC3435).

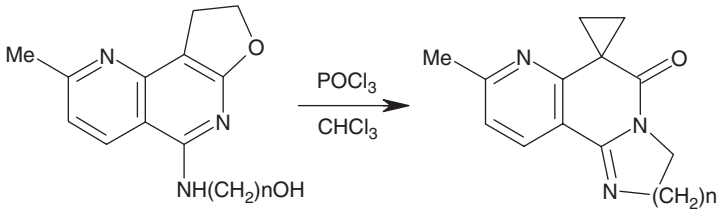


(a) NH_3 (liq), $KMnO_4$, - 33°C, (b) OH^-; (c) NH_3 (liq).

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 (1988MI5).

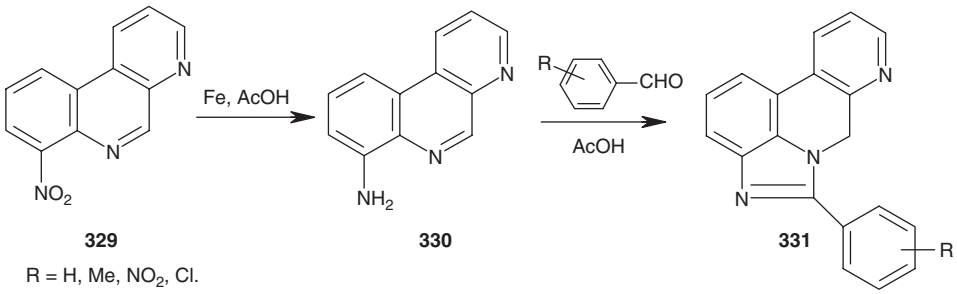
The rearrangement of the amine of 1,2-dihydrofuro[3,2-*f*][1,7]naphthyridine produced naphthyridine derivatives **327** containing the spirocyclopropane fragment (1995H2565). The reaction of analogous 1,2-dihydrofuro[2,3-*h*][1,7]naphthyridine derivatives containing the hydroxyalkylamino group with $POCl_3$ afforded imidazo[2,1-*f*]- **328a** or pyrimidino[2,1-*f*][1,7]naphthyridinones **328b** bearing the spirocyclopropane fragment (1996JHC49).





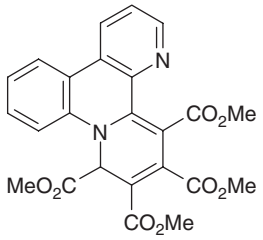
n = 1 (a), 2 (b).

Reduction of 7-nitrobenzo[*f*][1,7]naphthyridine **329** with iron in 80% acetic acid gave amine **330**, whose condensation with aromatic aldehydes afforded benzoimidazo[4,3-*fg*][1,7]naphthyridines **331** exhibiting antibacterial and antifungal activities (1993AJC1115, 1996PLP167956).

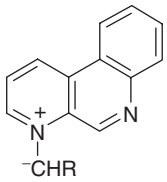


R = H, Me, NO_2, Cl.

The reactivity of 4,6-benzo[*h*][1,7]naphthyridine in Diels–Alder reactions with maleic acid and dimethyl acetylenedicarboxylate was examined. The reaction afforded adduct **332** (1996MI5). 6-Ethoxycarbonyl- **333a** and phenacylmethylides **333b** were used as 1,3-dipolar reagents in reactions with methacrylic acid, methyl methacrylate, butyl vinyl ether, methyl vinyl ketone, maleic anhydride and dimethyl acetylenedicarboxylate (1996MI5, 1999AJC149).



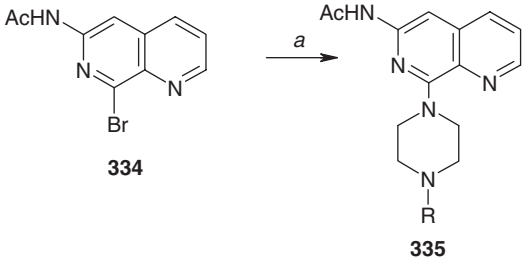
332



333a,b

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

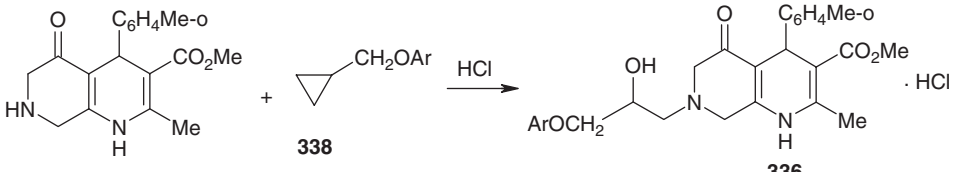
The reactions of 6-acetamido-8-bromo-1,7-naphthyridine **334** with substituted piperazines in the presence of NaH afforded 6-acetamido-8-(4-*R*-piperazin-1-yl)-1,7-naphthyridines **335** possessing anti-inflammatory, antiarrhythmic, cardiotonic, vasodilatory, broncholytic, diuretic and antichlolinergic activities (1986USP4690924, 1988JAP62-30780, 1989JAP63-48277, 1990USP4866176).



334 **335**

R = H, $(CH_2)_2OH$, CHO, Ar; (a) N⬡N-R, $EtO(CH_2)_2OH$, NaH.

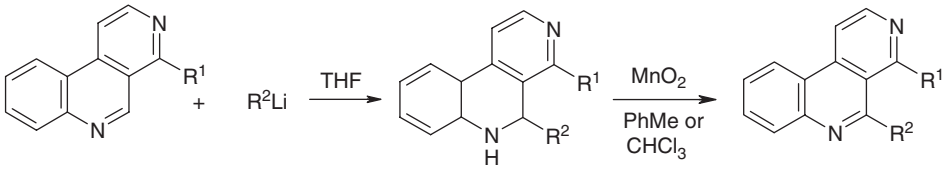
The hydrochloride of the derivative of 1,7-naphthyridine-3-carboxylic acid **336**, which lowers high blood pressure, was prepared from **337** and oxirane **338** on refluxing in MeOH followed by saturation of the reaction mixture with HCl (1984USP4551534).



337 **338** **336**

3*H*-pyrrolo[2,3-*c*][1,7]- and 3*H*-pyrrolo[2,3-*c*][2,6]naphthyridines were prepared by the dihydroxylation of the alkenyl group of the 1-substituted 4-alkenyl-3-amino analogs of 1,7 and 2,6-naphthyridines followed by oxidative cleavage of the resulting diols (2002A61).

Dehydrogenation of 5,6-dihydro derivatives of 2,7-naphthyridines **339**, prepared by the addition of organolithium compounds to 4-substituted benzo[*c*][2,7]naphthyridines **340**, afforded naphthyridines **341** (1995JCS(P1)979).

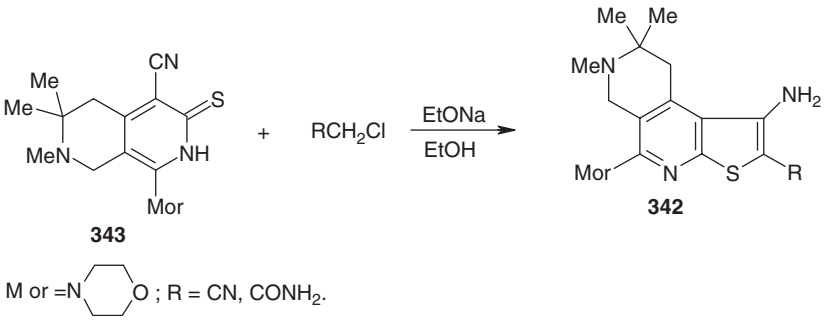


340 **339** **341**

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

A series of 1-substituted and 1,4-disubstituted 2,6-naphthyridines were prepared by base-mediated intramolecular cyclization of pyrrolo[2,3-*c*][2,6]naphthyridines by palladium catalyzed amination (2003A40).

Substituted tetrahydrothieno[2,3-*c*][2,7]naphthyridines **342** were prepared by the reaction of naphthyridinethione **343** with derivatives of chloroacetic acid in ethanol in the presence of sodium ethoxide (the Thorpe–Ziegler reaction). Their properties were investigated (1995MI2, 1996KGS512, 1997MI2).



343 **342**

M or =N O ; R = CN, $CONH_2$.

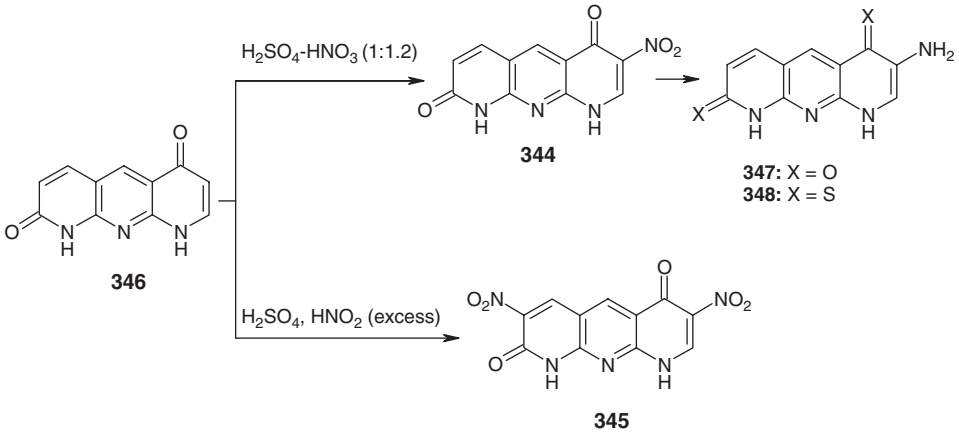
An unexpected conversion of 3-acetyl-1-chloro-2,7-naphthyridine into 3-ethenyl-2,7-naphthyridine by treatment with hydrazine is reported (2001MI1).

The synthesis and biological activity of 2-(alkoxycarbonyl)thieno[2,3-*c*]-2,7-naphthyridine and isothiazolo[4,5-*b*]-2,7-naphthyridine derivatives have been described (2002MI3, 2002MI4).

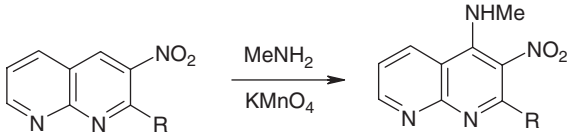
Among nitrogen-containing heterocyclic systems containing the 1,8-naphthyridine fragment, the pyrido[2,3-*b*][1,8]naphthyridine (1,9,10-antyridine), which are triaza analogs of anthracene, have attracted considerable attention. Earlier, these compounds have been synthesized according to multistep procedures starting from pyridine derivatives, such as 2,6-diaminopyridine (1935USP2002280, 1947MI1, 1966G103, 1970JHC875) and 2,6-diamino-3,5-diformylpyridine (1977JOC3410), etc. (1966G1443, 1967G1274). Later, 1,8-naphthyridine derivatives became easily accessible (1986JIC345, 1987JIC709, 1998JHC1231), which made it possible to simplify procedures.

A similar transformation of 1,9,10-anthyridines is also described. 7-Nitroanthydrine-2,6-dione **344** or 3,7-dinitroanthyridine-2,6-dione **345** can be prepared by nitration of anthydrine-2,6-dione **346** with various amounts of a mixture of concentrated sulfuric and nitric acids. Treatment of nitro derivative **344** with sodium

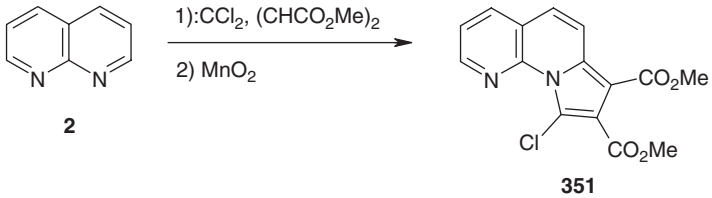
dithionite (in 5% NaOH) gives 7-aminoanthyridine-2,6-dione **347** in quantitative yield. The reaction with phosphorus pentasulfide in anhydrous pyridine produces 7-aminoanthydrine-2,6-dithione **348** (1972JHC801).



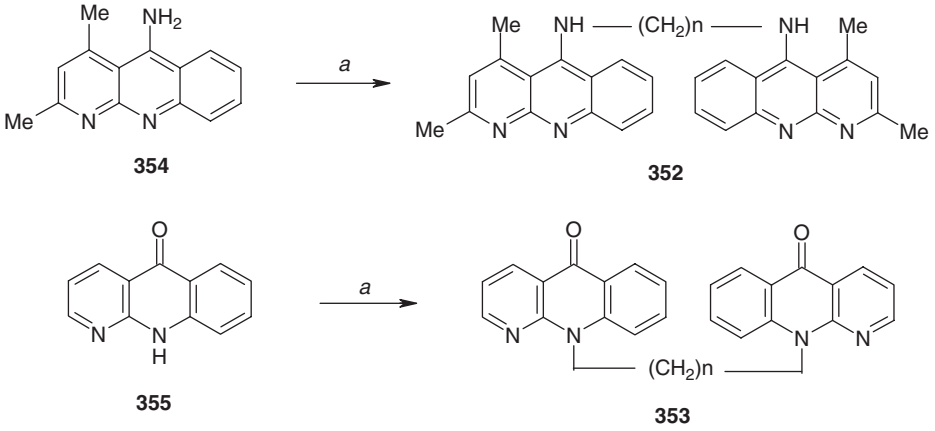
3-Nitro-1,8-naphthyridines **349** and their derivatives were subjected to amination at position 4 using liquid ammonia and potassium permanganate (1983JHC9) or liquid methylamine and potassium permanganate (1996KGS1652, 1997LA2601, 2000CJC950) as aminating systems. Amination of naphthyridines **349** affords 4-methylamino3-nitro-1,8-naphthyridines **350** in 50–90% yields (1996KGS1652, 1997LA2601). Quantum-chemical calculations demonstrated that the reaction is controlled by the interaction of frontal molecular orbitals of the reagents.



The reaction of 1,8-naphthyridine **2** with dichlorocarbene and dimethyl maleate followed by oxidation of the mixture containing the intermediate cycloadduct with manganese dioxide produced dimethyl 1-chloro[1,2-*a*][1,8]naphthyridine-2,3-dicarboxylate **351** in 11% yield (1998ZOR754).



New bisnaphthyridines **352** and **353** containing the 5-amino-2,4-dimethylbenzo[*b*][1,8]naphthyridine or benzo[*b*][1,8]naphthyridone chromophores were synthesized in a phase-transfer system by the reaction of aminobenzonaphthyridine **354** or dihydrobenzonaphthyridone **355** with alkylene dibromides (2000JHC1289). Such bisintercalates are of interest as potential antitumor drugs.



354 **352**

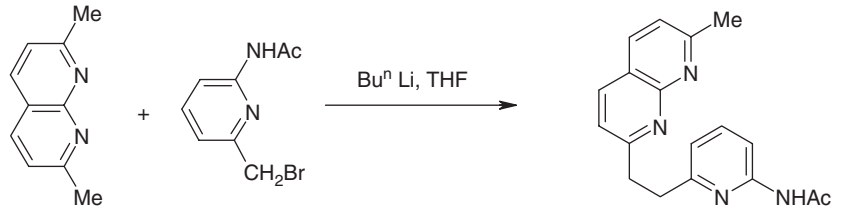
355 **353**

n = 3, 6, 8, 10 ; (a) $Br(CH_2)nBr$, TBAB, PhMe,50% KOH, Δ;

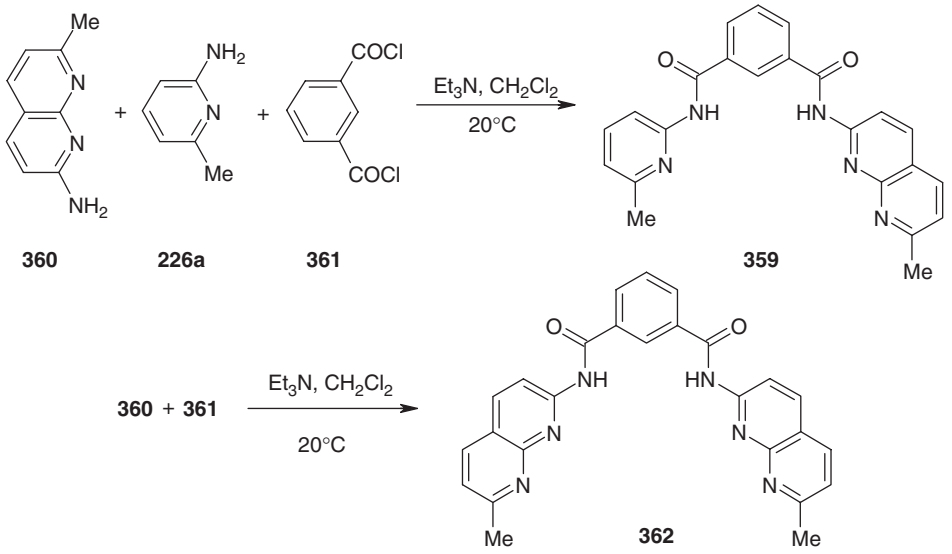
TBAB is tetrabutylammonium bromide.

Procedures were developed for the synthesis of new types of simple receptors based on substituted 1,8-naphthyridines. These receptors serve as carriers for the transport of biologically important organic substrates (urea, amino acids, hydroxy acids) into cells (1999JIC661, 2001T4987, 2002EJOC4063).

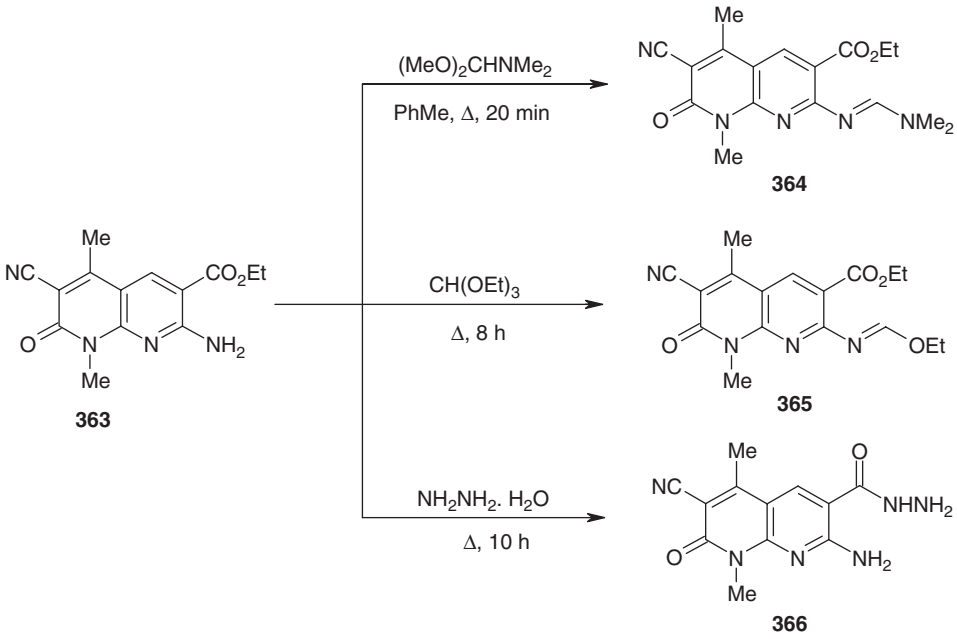
N-{6-[2-(7-methyl[1,8]naphthyridin-2-yl)ethyl]pyridine-2-yl}acetamide **356** was prepared by the reaction of 2,7-dimethyl-1,8-naphthyridines **357** with *n*-butyllithium and 2-*N*-acetylamino-6-bromomethylpyridine **358**. Another carrier, viz., *N*-(7-methyl[1,8]naphthyridin-2-yl)-*N*′-(6-methylpyridin-2-yl)isophtalamide **359**, was synthesized from 2-amino-7-methyl-1,8-naphthyridine **360**, 2-amino-6-methylpyridine **226a** and isophthaloyl chloride **361** in dry dichloromethane in the presence of triethylamine. *N*,*N*′-*bis*(7-methyl[1,8]naphthyridin-2-yl)isophthalamide **362** was prepared from naphthyridines **360** and chloride **361** under analogous conditions. Isophthalamides **359** and **362** were used for the determination of L-(+)tartaric acid as complexes (1:1) soluble in chloroform (1999JIC661, 2001T4987).



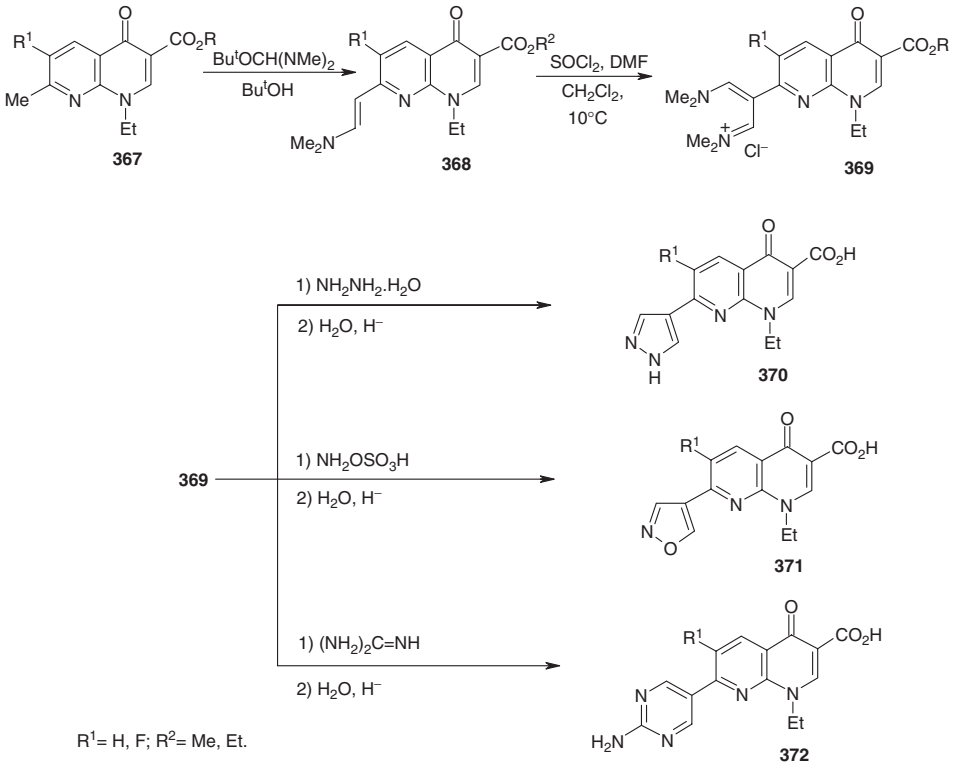
357 **358** **356**



With the aim of searching for synthetic approaches to new 1,8-naphthyridin-2-one derivatives, transformations of ethyl 7-amino-1,4-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-6-carboxylate **363** were studied. Refluxing this compound with *N*,*N*-dimethylformamide dimethyl acetal in dry toluene afforded 7-[(*N*,*N*-dimethylaminomethylene)amino]-1,8-naphthyridinone **364**. The reaction of naphthyridone **363** with triethyl orthoformate produced ethoxymethyleneamino derivative **365**. The reaction with hydrazine hydrate gave 7-amino-3-cyano-1,4-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-6-carbohydrazide **366** (2001S103).



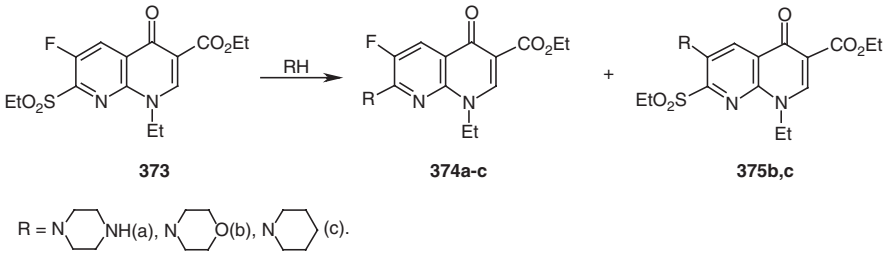
In the last 20 years, considerable attention has been given to the variation of substituents in a different position of a molecule (predominantly at position 7 in particular) for the purpose of preparing new active fluoroquinolone and fluoronaphthyridone antibacterial drugs for oral administration (1984JHC673, 1985MI3, 1985MI4, 1986JMC394, 1986JMC445, 1986MI2, 1987JAP6272686, 1987JHC215, 1987MI6, 1988JHC479, 1989JHC1147). For example, esters of nalidixic acid **367** were used for this purpose (1988JHC479, 1989JHC1147). The reactions of these esters with *tert*-butoxybisdimethylaminomethane in Bu^{t}OH produce enamines **368**. The addition of the Vilsmeier reagent derived from DMF and thionyl chloride leads to the formation of enamines **369**. Treatment of the reaction mixture with hydrazine hydrate, hydroxylaminosulfonic acid or guanidine followed by hydrolysis of the reaction mixture gives pyrazolyl- **370**, isoxazolyl- **371** and pyrimidinyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic derivatives **372** (1989JHC1147).

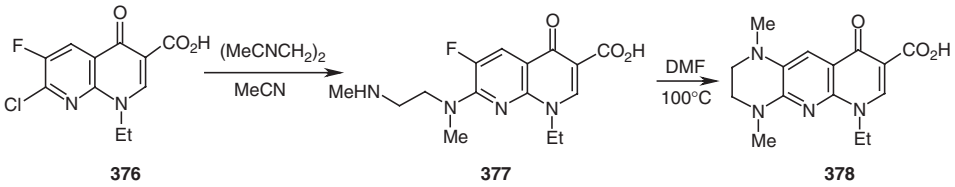


367 **368** **369** **370** **371** **372**

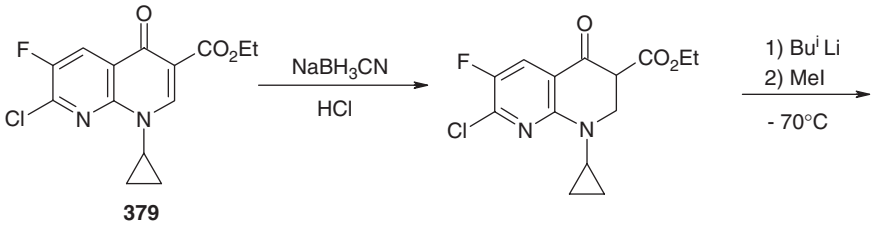
The reaction of ethyl 1-ethyl-7-ethylsulfonyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate **373** with piperazine is accompanied by the replacement of the 7-ethylsulfonyl group to form 7-piperazino derivative **374a** in good yield (1984JHC673). Treatment of ester **373** with morpholine and piperidine leads to the replacement of the atom at positions 6 and 7 to give substituted derivatives **374b,c** and **375b,c** (1988JHC479). The reaction of 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid **376** with *N*,*N*′-dimethylethylenediamine

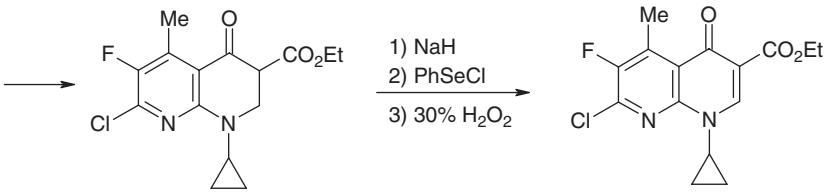
in acetonitrile produces {*N*-methyl-*N*-[2-(methylamino)ethyl]}aminonaphthyridine **377**, which readily undergoes cyclization upon heating in DMF to give 6-ethyl-1,4-dimethyl-9-oxo-1,2,3,4,6,9-hexahydropyrazino[2,3-*b*][1,8]naphthyridine-8-carboxylic acid **378** (1988JHC479).





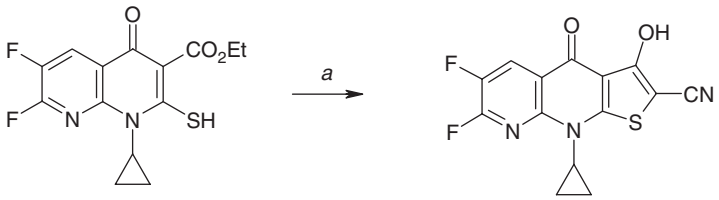
Selective reduction of the C(2)=C(3) bond in naphthyridone **379** followed by treatment with ^{i}BuLi in THF and methylation affords compound **380**. Subsequent regeneration of the double bond occurs as a result of successive selenation, oxidation and *syn*-elimination to form naphthyridone **381** (1991JHC541). Earlier, an analogous scheme has been used for the synthesis of ethyl 7-chloro-1-ethyl-6-fluoro-2-mrthyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (1989JHC1675).





380 **381**

Thieno[2,3-*b*][1,8]naphthyridone **382** exhibiting antimicrobial and antitumor actions was synthesized starting from the 2-mercapto derivative of naphthyridone **383** (1993JAP3223289).

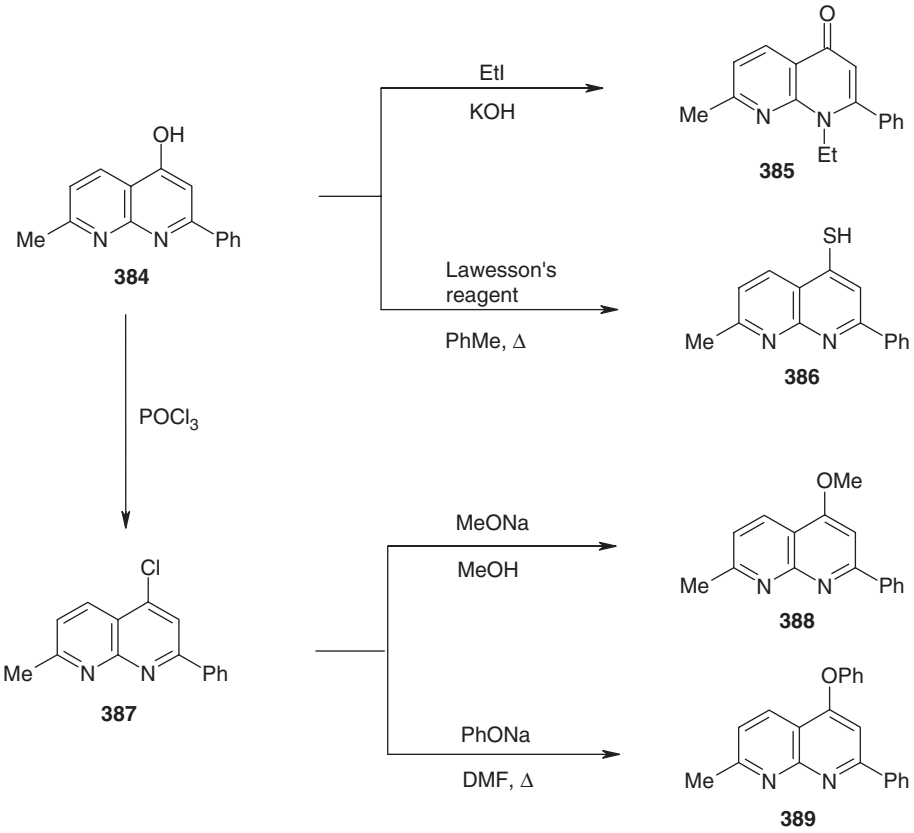


382 **383**

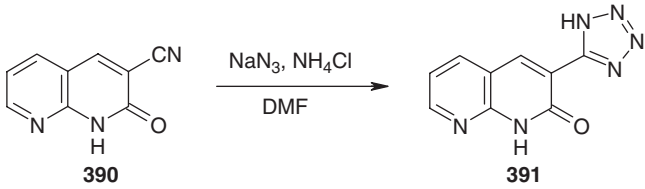
(a) 1) $BrCH_2CN$, THF, $NaHCO_3$; 2)$NaHSO_3$, THF, H_2O.

Procedures for the synthesis of compounds containing a five-membered heterocycle with a linearly fused 1,8-naphthyridine fragment (thiazolo[5,4-*b*]- (1979CPB410), imidazolo[4,5-*b*]-, triazolo[4,5-*b*]- (1980CPB235), oxazolo[5,4-*b*]-, thiadiazolo[5,4-b]-, isothiazolo[5,4-*b*]-, pyrazolo[3,4-*b*]-, thieno[2,3-*b*]-, furo[2,3-*b*]-1,8-naphthyridines (1980CPB761, 1984CPB4914)) were described and the antibacterial activity of these compounds was studied.

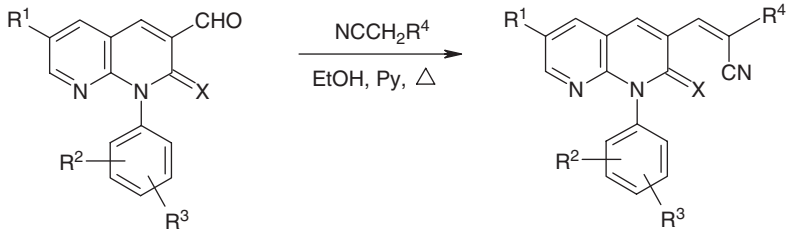
It was found (1994PHA878) that 1,8-naphthyridine derivatives could react with adenosine receptors of subtypes A_1 and A_{2A}. These stimulated studies on the synthesis and the biological activities of various functionalized (particularly, at positions 1, 2, 4 and 7) naphthyridines. Alkylation and nucleophilic substitution of these compounds was studied. 7-Methyl-2-phenyl-1,8-naphthyridin-4-ol **384** is alkylated at position 1 with EtI and KOH in aqueous ethanol to form 1-ethyl-7-methyl-2-phenyl-1,8-naphthyridin-4(1*H*)-one **385** (1978FES315, 2000JMC2814). Refluxing naphthyridone **384** with Lawesson's reagent in toluene affords 7-methyl-2-phenyl-4thiol-1,8-naphthyridine **386**. Treatment of 4-chloronaphthyridine **387** (prepared by the reaction of naphthyridone **384** with $POCl_3$) with sodium methoxide in methanol gave 4-methoxy-7-methyl-2-phenyl-1,8-naphthyridine **388**. Refluxing compound **387** with PhONa in DMF produced 7-methyl-4-phenoxy-2-phenyl-1,8-naphthyridine **389**. A series of other 1,8-naphthyridine derivatives were also prepared and their properties as A_1, A_{2A} and A_3 adenosine receptors were studied (2000JMC2814).



Along with substituted 1,8-naphthyridin-4-ones, derivatives containing the carbonyl group at position 2 were subjected to various transformations (1989USP4735948, 1995USP5281610, 1996USP5364859). For example, the reaction of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile **390** with sodium azide and ammonium chloride in DMF produced tetrazolyl-1,8-naphthyridin-2-one **391**, which was covered by a patent as an antiallergic drug (1989USP4735948).



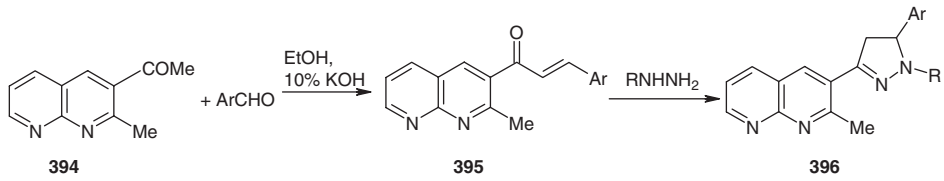
Numerous 3-(2-cyanovinyl)-substituted 1,8-naphthyridines **392** were prepared by refluxing 1,8-naphthyridine-3-carbaldehydes **393** with substituted acetonitriles in alcohol in the presence of catalytic amounts of pyridine. Compounds **392** were covered by a patent as promising starting compounds for the synthesis of new drugs for the treatment of cancer, psoriasis and atherosclerosis (1996FRP2706898).



393 **392**

R^1= H, AlkO, OH, Hal; R^2, R^3= H, AlkO, AlkS, CF_3, OH, NO_2, CN, Hal;
R^4= Py, $CONH_2$, $CSNH_2$; X = NH, O, S.

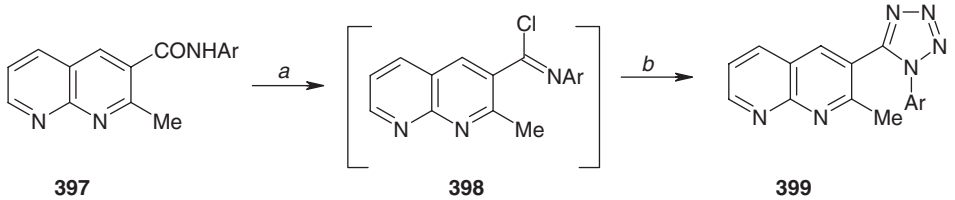
Claisen–Schmidt condensation of 3-acetyl-2-methyl-1,8-naphthyridine **394** with aromatic aldehydes occurs in ethanol in the presence of KOH to give cinnamoyl-substituted 1,8-naphthyridines **395**. The latter undergo cyclization with hydrazine hydrate or phenylhydrazine to form 3-(5-aryl-2-pyrazolin-3-yl)-1,8-naphthyridines **396a** (62–84% yields) or 3-(5-aryl-1-phenyl-2-pyrazolin-3-yl)-2-methyl-1,8-naphthyridines **396b** (64–86% yields), respectively, which exhibit pronounced antifugicidal activity (1988CCC1543).



394 **395** **396**

R = H (a), Ph (b); Ar = Ph, 3 - MeC_6H_4, 4 - MeC_6H_4, 2 - $MeOC_6H_4$, 4 - $MeOC_6H_4$, 4 - HOC_6H_4, 2 - ClC_6H_4, 4 - ClC_6H_4, 3 - $NO_2C_6H_4$, 4 - $Me_2NC_6H_4$.

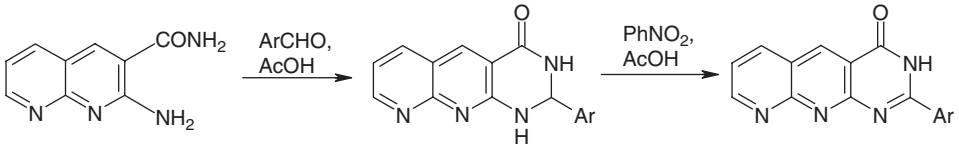
N-aryl-2-methyl-1,8-naphthyridine-3-carboxamides **397** with $POCl_3$ gave imidoyl chloride **398** and then with sodium azide afforded 3-(1-aryl-1*H*-terazol-5-yl)-1,8-naphthyridines **399** (1988CCC1539) (see also Ref. (1990ACH45, 1990JIC691, 1990JIC691, 1990MI1, 1995IJC(B)734, 1995IJC(B)1035)).



397 **398** **399**

Ar = 2 - MeC_6H_4, 3 - MeC_6H_4, 4 - MeC_6H_4, 2 - $MeOC_6H_4$, 3 - $MeOC_6H_4$, 4 - $MeOC_6H_4$, 2 - ClC_6H_4, 3-ClC_6H_4, 4 - ClC_6H_4, 3 - $NO_2C_6H_4$;
(a) $POCl_3$, 120°C, 3 h; (b) NaN_3, AcONa, Me_2CO, H_2O, 20°C, 24 h.

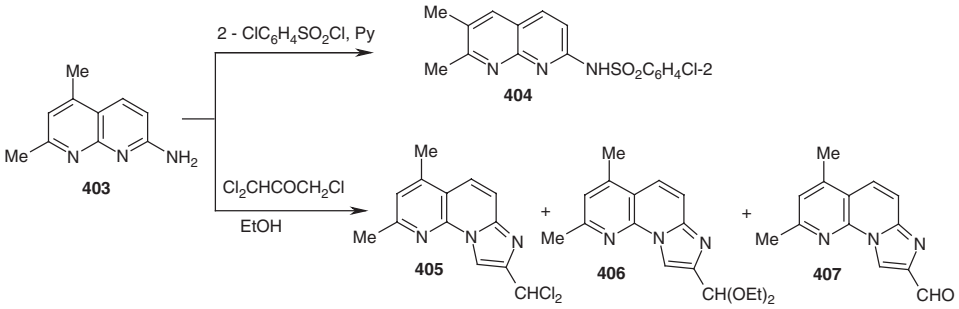
Condensation of 2-amino-1,8-naphthyridine-3-carboxamide **400** with aromatic aldehydes in glacial acetic acid affords 2-aryl-1,2,3,4-tetrahydropyrimido[4,5-*b*][1,8]naphthyridin-4-ones **401**, whose oxidation with nitrobenzene in glacial acetic acid gives 2-arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones **402**. Compounds **402** were also synthesized without isolation of naphthyridones intermediate **401** formed by condensation of amide **400** with aromatic aldehydes on refluxing in a mixture of nitrobenzene and glacial acetic acid (1987IJC(B)1194).



400 **401** **402**

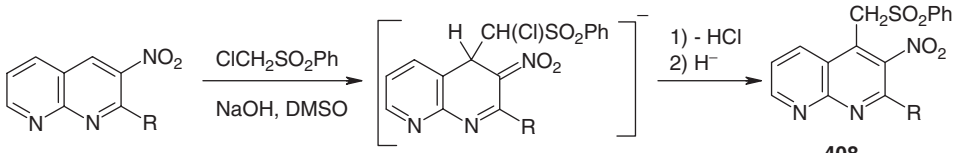
Ar = Ph, 2 - MeC_6H_4, 4 - $MeOC_6H_4$, 2 - $MeOC_6H_4$, 4 - $MeOC_6H_4$, 2 - ClC_6H_4, 3 - ClC_6H_4, 4 - ClC_6H_4, 2 - $NO_2C_6H_4$, 3 - $NO_2C_6H_4$, 4 - $Me_2NC_6H_4$.

The reaction of 2-amino-5,7-dimethyl-1,8-naphthyridine **403** with 2-chlorophenyl sulfonylchloride produces sulfonamide **404**, which possesses herbicidal and growth-controlling properties (1990GEP3804990). Condensation of amine **403** with trichloroacetone affords a mixture of angular imidazo[1,2-*a*][1,8]naphthyridines **405–407** (1992JHC691).



403 **404** **405** **406** **407**

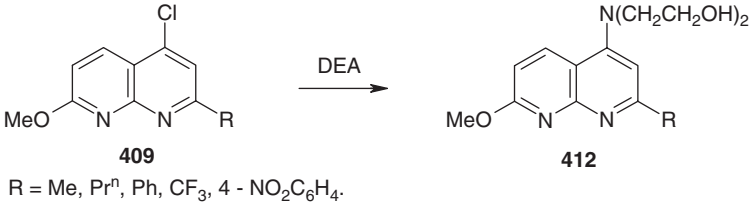
Substituted 3-nitro-1,8-naphthyridines **349** with chloromethylphenyl sulfone produce 3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridines **408** in high yields. Quantum-chemical calculations by the MNDO method demonstrated that the pathway, like that of amination, is determined not by charge control but by the interaction between the HOMO of the nucleophile and the LUMO of the substrate (1991JHC1075).



349 **408**

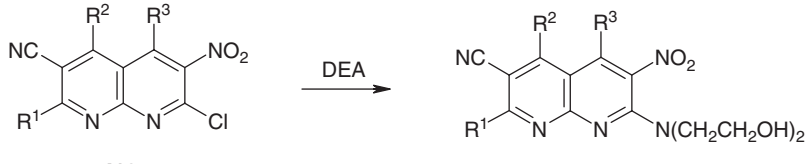
R = H, D, Pr^n, Ph, CF_3, 4 - $NO_2C_6H_4$.

Treatment of chloronaphthyridines **409–411** with diethanolamide (DEA) (120 °C) afforded the corresponding *bis*-(2-hydroxyethyl)amino derivatives **412–414**. However, the expected antitumor activity of these compounds was not revealed (1984JHC417).



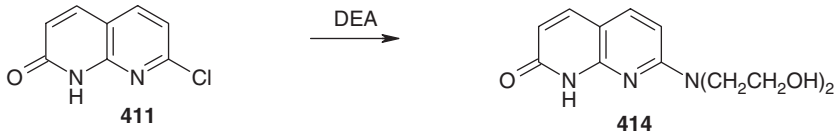
409 **412**

R = Me, Pr^n, Ph, CF_3, 4 - $NO_2C_6H_4$.



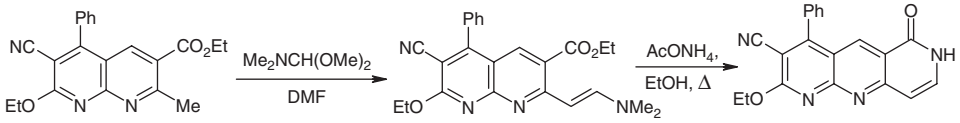
410 **413**

R^1= Me, NH_2, OH; R^2 = H, Me; R^3 = H, Ph.



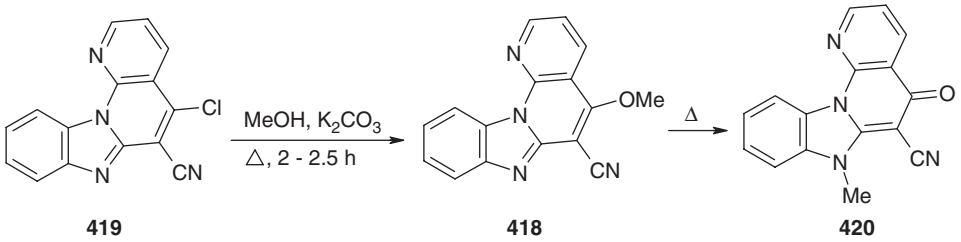
411 **414**

Ethyl 3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine-6-carboxamide **415** with dimethylformamide dimethyl acetal produced enamine **416**. Subsequent refluxing of the latter with ammonium acetate in ethanol leads to cyclization to form tricyclic naphthyridine **417** (1995H111).

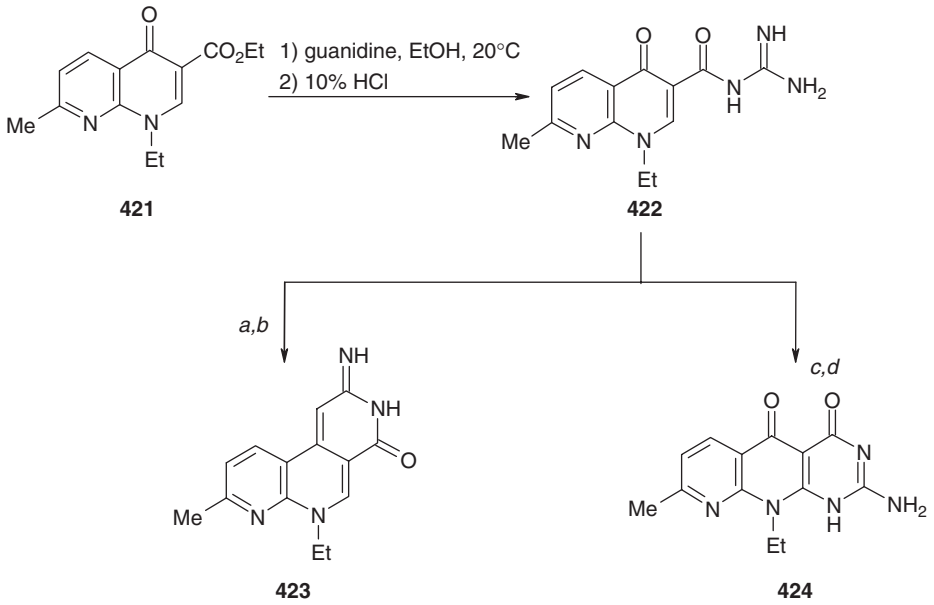


415 **416** **417**

A study (1989KGS273) was devoted to the transformations of a tetracyclic system containing fused naphthyridines and a benzimidazole ring. 5-Methoxybenzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile **418** was prepared from 5-chlorobenzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile **419** with methanol and potassium carbonate. Upon heating to its melting point in DMF or in the absence of the solvent, compound **419** undergoes migration of the methyl group from the O to the N atom of the benzimidazole fragment to give 7-methyl-5-oxo-6-benzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile **420**.



In studies of 1,8-naphthyridine derivatives possessing potential biological activities, a procedure was devised for the synthesis of a new tricyclic system containing the 1,8-naphthyridine fragment, viz., pyrimido-1,8-naphthyridines (2000MI1, 2001JHC467). The synthesis involves condensation of commercially available guanidine carbonate with ethyl naldixate **421** to form *N*-[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]guanidine–hydrochloride **422**. After preneutralization with 10% NaOH, guanidine **422** readily undergoes cyclization to form the angularly tricyclic system, viz., 6-ethyl-2-imino-8-methyl2,3,4,6-tetrahydropyrimido[5,4-*c*][1,8]naphthyridin-4-one **423**, which was isolated as the hydrochloride (2001JHC467). Treatment of guanidine **422** with an excess of sodium hydride in dry DMF at 20 °C afforded 2-amino-10-ethyl-8-methyl-1,4,5,10-tetrahydropyrimido[5,4-*b*][1,8]naphthyridine-4,5-dione **424**, also isolated as the hydrochloride.



(a) EtOH, △, 1 h; (b) HCl; (c) NaH, DMF, 20°C; (d) 10% HCl.

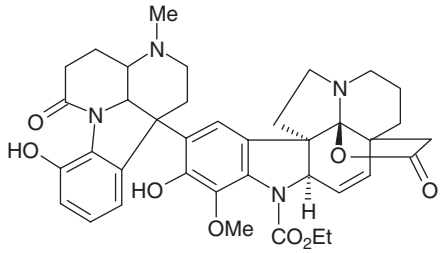
4-Halo-1,8-naphthyridin-2(1*H*)-ones, readily available from 2-chloronicotinic acid, were subjected to Suzuki coupling with aryl boronic acids to give a diversity of 4-aryl-1,8-naphthyridin-2(1*H*)-ones ((2003T6021).

Recently, an efficient and rapid method for the synthesis of different derivatives of 1,8-naphthyridines in the solid state under microwave irradiation has been described (2002IJC113, 2002MI5, 2002KFZ465, 2003SC73, 2003SC127, 2003SC1067, 2003SC2377, 2003IJC1170, 2003IJC(B)1750, 2003IJC(B)1753). Mainly the products are obtained in excellent yields and in a high state of purity.

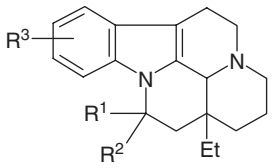
V. Biological Activity and Other Practical Properties

In the last decade, complex heterocyclic systems containing a naphthyridine fragment have been synthesized and their reactions giving functionalized naphthyridines have been investigated. The biological activities of naphthyridine derivatives have been studied the most.

1,5-Naphthyridine derivatives, like other isomeric pyridopyridines, have been found in many natural substances and were used for the construction of a series of effective medicines. Recently, the previously unknown dimeric indole alkaloid cimiciduphytine **425** containing the 1,5-naphthyridine fragment (1991H1461) and derivatives of eburnane alkaloids **426** exhibiting hypotensive and pain-relieving activities have been isolated from naturally occurring sources. These compounds are suitable for the treatment of cerebral circulation disturbance (1985CZP216622, 1985SWP646166, 1986FRP2562894, 1986GEP3409185, 1986JAP60-248688, 1993LA221).



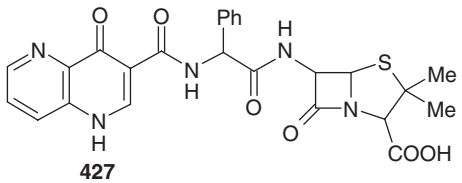
425



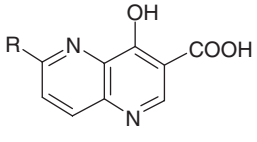
426

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

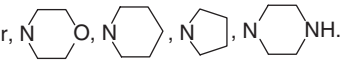
A derivative of penicillanic acid **427** was covered by a patent as an antibiotic (1991GEP279887). Derivatives of hydroxy acid **428** were covered by a patent as antihelminthics (1985JAP59-93080).



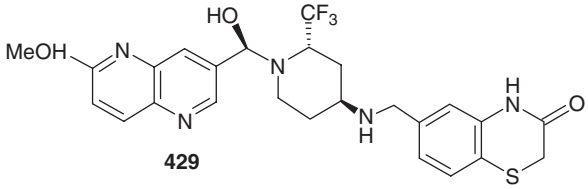
427



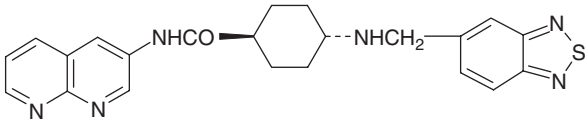
428

R = OEt, OPr, 

1,5-Naphthyridine derivatives **429** (2003PIAWO2003064421) and **430** (2003PIAWO2003087098) were prepared to treat bacterial infections.



429



430

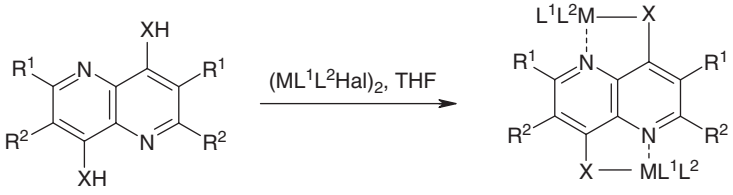
N-(1,5-naphthyridin-4-yl)piperidine-4-carboxamide is an antibacterial agent (2003PIAWO2003010138).

N-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide are inhibitors of HIV integrase and inhibitors of HIV replicant (2003PIAWO2003062204).

Derivatives of annulated benzoindolo-1,5-naphthyridines attempting to improve memory were described (1985FRP2548667, 1987BCJ3797). These are benzo[*b*][1,5]naphthyridines, which are analogs of inhibitors of neurokinin NK_1-receptors. Various 1,5-naphthyridine derivatives, in particular, 2-naphthyridinecarboxamide, possessing antiviral activity were also reported (1999PIAWO9929318).

A library of *bis*(6-chloro-2-methoxyacridin-9-yl) and *bis*(7-chloro-2-methoxybenzo[*b*][1,5]naphthyridin-10-yl) analogs was synthesized to explore the effect of structurally diverse linkers on PrP^{Se} replication in scrapie-infected neuroblastoma cells (2003MI4).

Complexes **431** of Group IB or VIII metals with 1,5-naphthyridine derivatives **432** were synthesized (1993GEP4105386). Compounds **431** are used for the preparation of singlet oxygen. These serve as sensitizers in photoinitiation of polymerases and electrophotography and as redox catalysts in organic reactions.



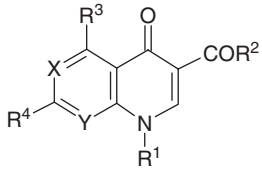
432 **431**

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.

Considerable recent attention has been focused on procedures for the modification of 1,6-naphthyridine derivatives with the aim of searching for new biologically active compounds. Compounds **433**, including 1,6-naphthyridine derivatives as well as

octahydronaphthyridines **434** are of interest from the pharmacological standpoint (1985CPB4402, 1985JAP58-7626, 1991USP5180719, 1993USP5281703, 1996PIA-WO9412173). Thus, **433** possess low toxicity and are used as components of drugs for prophylaxis and treatment of infectious diseases caused by various pathogenic bacteria (1985CPB4402, 1985JAP58-7626, 1991USP5180719, 1993USP5281703). Octahydronaphthyridines **434** are used in the treatment of depression or in cases of abstinence (1996PIAWO9412173).

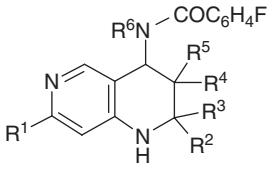


433

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.



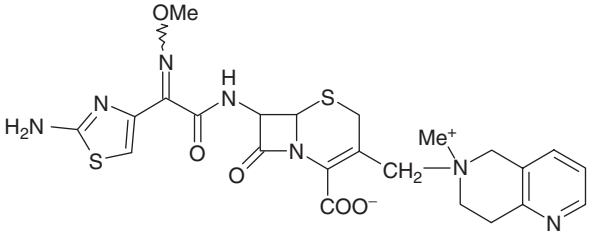
434

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 **435**, active with respect to both Gram-positive and -negative bacteria (1986JAP59-219292).



435

Recently, 1,4-dihydro-4-oxo-1,6-naphthyridine and 8-methylbenzo[*b*]naptho[*f*][1,6]naphthyridine derivatives have also been described as antibacterial agents (1997MI2, 2003MI5).

1,4-Dihydro-5-isopropoxy-2-methyl-4-(2-trifluoromethylphenyl)-1,6-naphthyridine-3-carboxylic esters are efficient components of cytokinin inhibitors (1998JAP10182462).

1,6-Naphthyridine-2-carboxylamides were covered by patents as drugs used in the therapy and prophylaxis of cytomegalovirus infection (1997PIAWO9734894).

1,6-Naphthyridine derivatives were prepared as anticonvulsive agents (1999PIAWO9854184, 2003MI6), tachykinin NR_3-receptor (1999PIAWO9900388), 5-HT receptor (2003JMC138) and benzodiazepine receptor (1999PIAWO9903857) antagonists.

A series of novel 1,6-naphtyridine derivatives were prepared as potential inhibitors of human topoisomerase I (2003JMC2254), farnesyltransferase inhibitors (2003USP2003199544), p38 mitogen-activated protein kinase inhibitors (2003MI7), SYK kinase inhibitors (2003PIAWO2003057695) and spleen tyrosine kinase inhibitors (2003MI8).

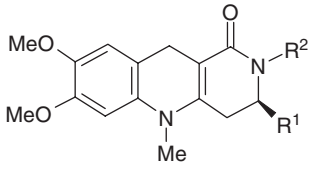
2-Substituted 6-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acids (2003JMC1049), 5*H*-dibenzo[*c*,*h*][1,6]naphthyridine derivatives (2003MI9) and 5,6,7,8-tetrahydro-1,6-naphthyridin-2(1*H*)-one derivatives (2003USP2003199542) were prepared as potential anticancer agents.

Benzo[*c*][1,6]naphthyridine derivatives were covered by a patent as agents for the treatment of male impotence and female sexual dysfunction (2003USP2003158184). A series of 1,6-naphthyridine derivatives was synthesized as potential antimalarials (2002MI5) and antidiabetics 2003PIAWO2003027113).

5-Substituted 8-hydroxy-1,6-naphthyridine-7-carboxamides are useful as HIV integrase inhibitors for the treatment of HIV infection (AIDS) (2003JMC453, 2003PIAWO2003016309, 2003PIAWO2003016315, 2003PIAWO2003016294, 2003PIAWO2003077850, 2003PIAWO2003086319, 2003PIAWO2003077857).

Acyl-substituted octa(deca)hydro-1,8-naphthyridines were synthesized as derivatives of matrine- and allomatryne-type alkaloids, and the structure–activity relations were examined by the acotic acid-induced abdominal contraction test (2003MI10, 2003MI11).

A novel class of stable, reactive and highly enantioselective chiral biomimetic NADH derivatives **436** were prepared (2003T4911).



436

R^1 = Me, Ph; R^2 = CH_2Ph, CH_2CH_2OMe, $(CH_2)_3OH$, CH_2CH_2OH, $CH_2CH_2P(O)(OEt)_2$.

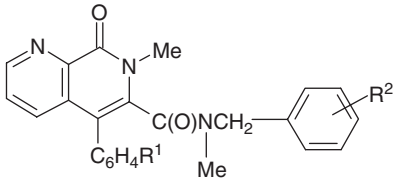
The reaction of mesityl oxide with malononitrile gave 5-amino-7-(pyrrolidin-1-yl)-2,4,4-trimethyl-1,4-dihydro-1,6-naphthyridine-8-carbonitrile. The non-linear optical studies of this pyridinenitrile derivative showed a high value while that of nicotinonitrile was low (2003T3761).

The new ligand systems related to the previously described DOTTADs have been generated in a simple one-step reaction 6-methyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6*H*-[1,6]naphthyridin-5-one-3-carboxylic acid, an example of semi-DOTTAD (2003MI12).

The 1,3,4,5-tetrahydrobenzo[*c*][1,6]- and -1,7-naphthyridin-6-ones are presented as a patent class of PARp-1 inhibitors (2003MI13).

1,7-Naphthyridine derivatives were prepared as antibacterial agents (2003MI14, 2003PIAWO2003091253) and covered by patents as pharmaceutically active compounds (1985USP4596873, 1985USP4618678, 1997PIAWO9703074, 1997PIAWO9748368, 1998PIAWO9818796, 2003PIAWO2003014119, 2003PIAWO2003014120, 2003PIAWO2003039544, 2003USP20036531475).

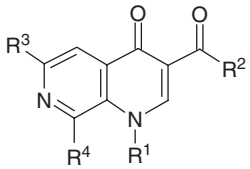
Compounds **437** are new strong neurokinin NK_1-receptor antagonists (1995JMC3106).



437

R^1 = H, 4-Me, 4-F; R^2 = 3,5- $(CF_3)_2$, 2-MeO, 2-Cl, 2,5-Cl_2.

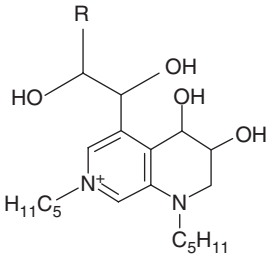
1,7-Naphthyridone derivatives **438** were covered by patents as antibacterial agents (1991CCC2420, 1992MI3, 1992MI4) and derivatives **439** as antidiabetic drugs (1994EUP563797).



438

R^1= H, Et, Bn; R^2= OH, OAlk;

R^3, R^4= Hal, Me_2N, OAlk.



439

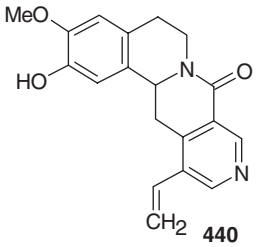
R = H, $HOCH_2CH(OH)$.

The data on different biological activities exhibited by a series of 1,7-naphthyridine derivatives have also been reported (1985USP4596873, 1985USP4618678, 1996MI5, 1997PIAWO9703074, 1997PIAWO9748368, 1998JAP10109989, 1998PIAWO9818796, 2003MI14, 2003PIAWO2003091253, 2003PIAWO2003014119, 2003PIAWO2003014120, 2003PIAWO2003039544, 2003USP20036531475).

2-Methoxy-12-methoxycarbonyl-2,6,8,9-tetrahydro-1*H*-indolo[7a,1*a*][2,6]naphthyridine isolated from the seeds of *Erythrina melanacantha* Harms can be used in the

treatment of different forms of hypertonia and as an inhibitor of thrombocyte agglutination (1986GEP3336194).

In a number of studies, the 2,7-naphthyridine fragment was found to be a component of alkaloids alangimaridine **440** (1987CJC2362), isolamarine **441** (1990T7893), alamardine **442** and epi-alamardine (1994M1397), nauclefine **443** (1987T5761, 1994H445), naulafine **444** (1988H2289), normalidine **445** (1991H1143), eudistones **446** (1991JOC5369), cystodytins **447–449** (1991JA8016), kuanoniamines **450** (1992JOC1523), merdine **451** possessing fungistatic activity (1992MI5), alkaloids **452** and **453** exhibiting high antifungal and anticancer activities (1991USP5182287) and other biological compounds, such as sampangine **454** possessing antibacterial activity (1990USP5128344, 1991USP5227383), the biosynthetic precursors of camptothecin **455** exhibiting anticancer activity (1990T2747), an analog of olivecin **456** (1992MI6) and benzo derivatives **457** suitable for the treatment of asthma and lowering of blood pressure (1985USP4478834). The data on antispasmodic (1989MI9) and neurotropic (1997KFZ34) activities of 2,7-naphthyridine derivatives were also reported.



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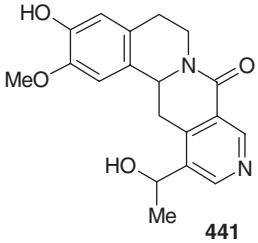

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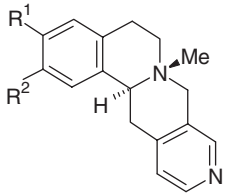

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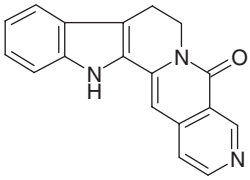

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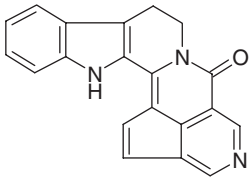

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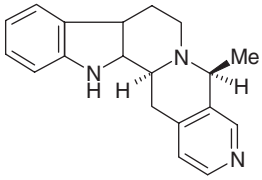

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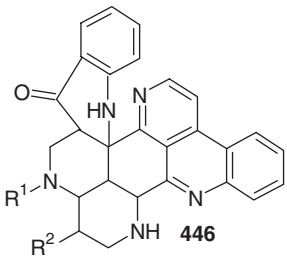

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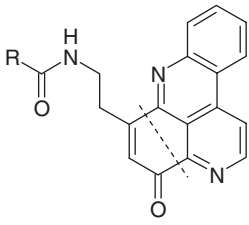

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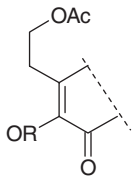

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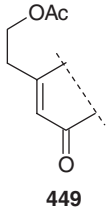

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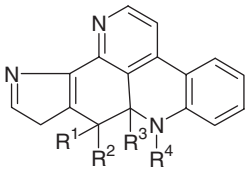

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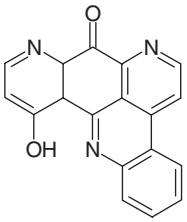

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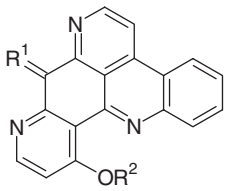
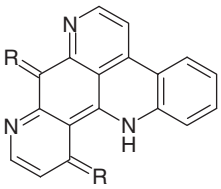


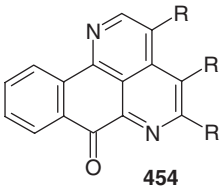
452

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



453

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



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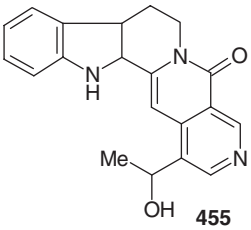

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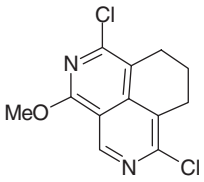

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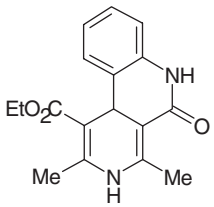
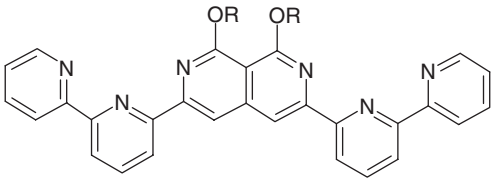


457

Enzymological and pharmacological properties of 2-(2-methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphenyl-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carboxylic acid methyl ester hydrochloride, a new phosphodiesterase type 5 inhibitor, were studied *in vitro* and *in vivo* (2002MI6).

The synthesis and crystal structure of the $[Co_4(L)_4H_2(PF_6)_6]$ complex, using an unusual *bis*(bipyridinyl)dimethoxynaphthyridine ligand **458**, is described (2003CC336).



458

In the last decade, complex heterocyclic systems containing the 1,8-naphthyridine fragment have been synthesized and their reactions giving functionalized naphthyridines

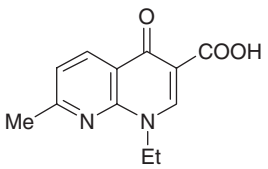
have been investigated. The biological activities of 1,8-naphthyridine derivatives have received the most study. A detailed consideration of these studies is beyond the scope of the present review. For completeness, this review contains a bibliography, including patents and papers, published over the last 20 years, except for those in which 1,8-naphthyridine derivatives are used only in specific biochemical assays.

The activities of 1,8-naphthyridine derivatives are listed in Table 2. Several examples of the biological properties of this class of compounds are cited below.

6-Fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid derivatives possess a very broad spectrum of biological activities, in particular, antibacterial action. Many compounds of this class exhibit high activity against various Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538P, CMX 686B, FDA 209P JC-1; *S. epidermidis* 3519, IAM 1296; *Streptococcus faecium* ATCC 8043, *S. pyogenes* 930) and Gram-negative bacteria (*Escherichia coli* Juhl, KC-14, K12 C600; *Enterobacter aerogenes* ATCC 130048; *Klebsiella pneumoniae* 8045, PCI-602; *Pseudomonas aeruginosa* EZ, 5070, K799/WT; *Acinetobacter* CMX 669, AC54) (1986JMC2363, 1990JMC2012).

These properties stimulated research to modify the 1,8-naphthyridine system by introducing various substituents using standard synthetic approaches. Biological activities of the compound synthesized were tested, most publications being devoted to the problems of the analysis of toxicity, synergism of action in various mixtures, elucidation of fine details of physiological action, etc. These aspects are beyond the scope of the present review, where only a bibliography of recent studies on fluoro-substituted 1,8-naphthyridines is given. Among these publications, numerous papers and patents concered with the antibacterial drugs enoxacin **175d** and trovafloxacin **175e** are noteworthy (see Ref. (2004RCR637)). In the literature, (particularly patents), other derivatives of fluorine-containing 1,8-naphthyridines have been described. For example, the review (1998DF1199) was devoted to the synthesis, pharmacology, pharmokinetics and metabolism of 6-fluoronaphthyridinecarboxylic acids. Antibacterial and antimicrobial activities of these compounds were studied. These problems were also covered by many recent patents (see Ref. (2004RCR637)).

Voluminous literature on 1,8-naphthyridine derivatives containing no fluorine is available. Explosion of interest in this class of heterocyclic compounds dates back to 1962, when Lesher and co-workers (1962MI1, 1963BLP612258) synthesized 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid **459** (nalidixic acid) possessing strong antibacterial activity. The pharmacological properties of this compound are still being studied (see Ref. (2004RCR637)).



459

With the aim of prolonging the action of nalidixic acid **459**, which is used, in particular, for the treatment of infectious diseases, acid **459** was subjected to esterification

Table 2. Biological activities of 1,8-naphthyridine derivatives

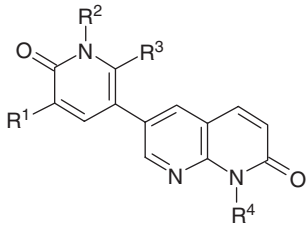
Activity	Reference
Antibacterial	1985JHC1029, 1985USP4477449, 1986GEP3508816, 1986USP4510000, 1987FRP2583418, 1987JAP61126082, 1988CPB1223, 1988FRP2595355, 1988GEP3635062, 1989GEP3632222, 1990GEP3816119, 1990JHC1527, 1991GEP3808118, 1992H2301, 1992HUP199465, 1992JAP03223289, 1995GEP4234078, 1996MI6, 1997EUP763359, 1997JMC3584, 1997PIAWO9708191, 1997PIAWO9731919, 1997SPP2095809, 1997USP5591766, 1998EJMC697, 1998IJC(B)139, 1998IJC(B)894, 1998MI7, 1998JAP1007568, 1998USP5776944, 1999JAP1112279, 1999JAP1160578, 1999PIAWO9900393, 1999PIAWO9907704, 1999PIAWO9910351, 2000JHC109, 2000KOP9701159, 2000MI2, 2000MI3, 2000PIAWO0037467, 2001IJC(B)43757, 2001IJC(B)619, 2002F631, 2003IJC(B)192, 2003IJC(B)636, 2003IJC(B)658, 2003IJC(B)1746, 2003PIAWO2003032962
Antimicrobial	1986PLP125298, 1986PLP125310, 1987PIAWO8607537, 1988USP4735949, 1996MI7, 1999JAP11147883, 2000EJMC1021, 2000MI3, 2002JHC877, 2003MI15
Antiviral	1997PIAWO9638445, 1998PIAWO9807428, 1999PIAWO9902527, 1999PIAWO9915508
Anti-inflammatory	1986FRP2567520, 1990USP4916229, 1997PIAWO0912546, 2000EJMC1021, 2002PIAWO2002094823, 2002PIAWO2002100859, 2003PIAWO2003018579
Antitumor	1992JAP03223289, 1995PIAWO9425438, 1997JAP09221424, 1997PIAWO0912546.
Antiulcerative	1986FRP2567520
Anticancer	2002MI7
Antihypertensive	1989USP4617308, 1997EJMC955, 1998EJMC383, 1998PIAWO9823615
Antidiabetic	1997PIAWO0912546, 2003PIAWO2003027112
Anticonvulsive	1986FRP2567887
Antithrombotic	1992H2301, 1993PIAWO9210191, 1994USP5281612, 2000EJMC1021, 2000F603, 2001F311
Antiatherosclerotic	1997PIAWO0912546, 1998GEP1962743
Analgetic	1986FRP25675201 1996PIAWO9601260, 2003JAP2003081946
Immunostimulating	1986FRP2567887, 1989USP4617308, 1990USP4916229 1994USP5215996
Various receptor antagonist	1987PIAWO8607359, 1993PIAWO9210492, 1994PIAWO9404505, 1997CPB1642, 1997PIAWO0912546, 1997PIAWO9637475, 1997PIAWO9704755, 1997PIAWO9835967, 1997USP5591766, 1998PIAWO9808840, 1998PIAWO9818795, 1998PIAWO9839322707, 1999PIAWO9907704, 2000JMC2814, 2001EUP1065207, 2001PIAWO0130779,

Table 2 (*continued*)

Activity	Reference
	2002CPB1050, 2002F783, 2002PIAWO2002102374 2003JMC1144, 2003JMC4790, 2003PIAWO2003006464842, 2003PIAWO2003040143, 2003PIAWO2003048154

with xanthine using dicyclohexylcarbodiimide in DMSO. The ester proved to be rather efficient against *S. aureus* 209P (1990MI2).

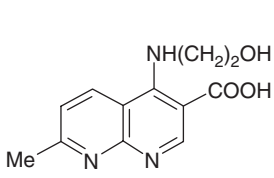
Naphthyridines **460** containing substituted pyridones at position 6 are used as components of cardiotonic drugs (1990USP4866074).



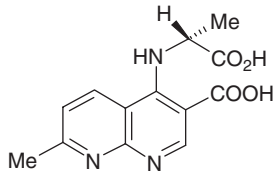
460

R^1 = H, Alk, AlkO, CHO, CN, NO_2, NH_2; R^2, R^3, R^4= Alk, Ar.

The inotropic activities of 4-(2-hydroxyethylamino)-7-methyl-1,8-naphthyridine-3-carboxylic acid **461** and its chiral methyl derivative **462** were compared with those of known drugs having an analogous action (isoproterenol, adrenaline, histamine, etc.) with the use of isolated samples of guinea pig myocardium. Biological assays demonstrated that compounds **461** and **462** are similar to heart glycosides in many respects (1991AP600, 1994AF937).

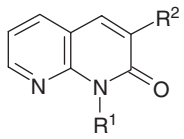


461



462

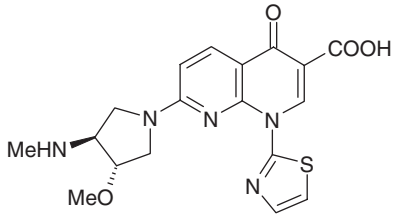
Substituted 1,8-naphthyridin-2(1*H*)-ones **463** were tested as selective phosphodiesterase inhibitors (1994BPB498) (see also (2002CPB1050, 2003JAP2003012671)).



463

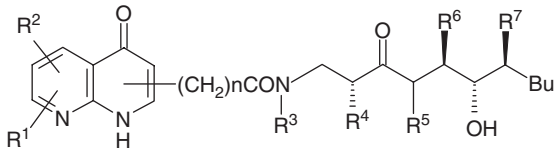
R^1 = Me, $(CH_2)_2Pr^i$, $(CH_2)_3OAc$, in-C_5H_{11}, Allyl, 2-$FC_6H_5CH_2$;
R^2 = H, Me, Ph, 2-Py, $(CH_2)_4OH$, $CH_2CH(OH)Me$.

The new antitumor drug Ag-7352 **464** was designed based on 1,8-naphthyridin-2-one-3-carboxylic acid (1999MI4, 1999MI5). An efficient stereospecific procedure was specially developed for the synthesis of (*S*,*S*)-3-methoxy-4-methylaminopyrrolidine, the key reagent in the synthesis of naphthyridine **464** (2001TA1793).



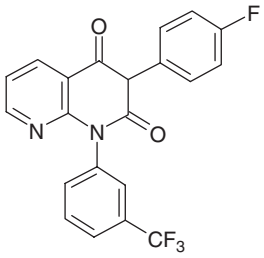
464

Numerous substituted naphthyridines were studied and N-terminal aminohydroxy derivatives of *β*-amino acids **465** were demonstrated to inhibit rennin (1994USP5179102, 1994USP5215996). Naphthyridinedione **466** stimulates carotene biosynthesis (1986FES827, 1990FES385, 1991MI8); (*E*)- and (*Z*)-*O*-(diethylamino)ethyl oximes of naphthyridine series **467** are potential drugs for local anesthesia (1990FES385). 1,8-Naphthyridine derivatives **468** exhibit high antihypertensive activity (1986FES827).



465

R^1, R^2 = H, Alk, OH, OAlk, Ar, CO_2H, NH_2; R^3, R^4 = H, Alk;
R^5 = H, Alk, cyclo-Alk, Bn; R^6 = Alk, cyclo-Alk, Ph;
R^7 = H, OH, OAlk, cyclo-Alk, NH_2.



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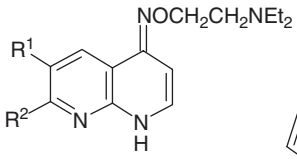
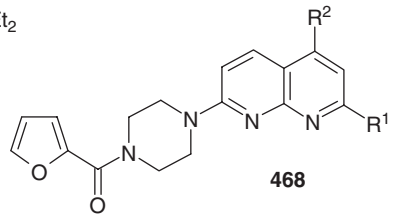


467

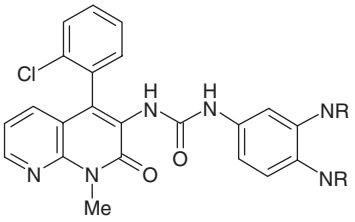
R^1 = H, Br;
R^2 = Me, OMe, OEt, Br.



468

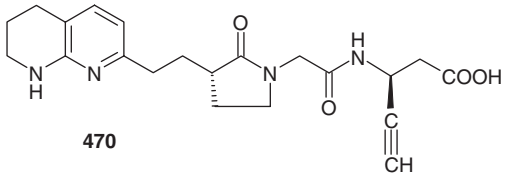
R^1 = H; R^2 = OH, OMe, NH2;
R^1 = R^2 = Me, CF_3.

Of numerous compounds of the naphthyridine series covered by patents as various receptor inhibitors, cholesterol acyl transferase inhibitors **469** (1993PIAWO9210191, 1994USP5281612), integrin receptor antagonist **470** and **471** (1987PIAWO8700752, 1993PIAWO9210492, 1997PIAWO9704755, 1997PIAWO0912546, 1997PIAWO9835967, 1998PIAWO9808840, 1998PIAWO9818795, 1998PIAWO9831359), victonectin receptor antagonist **472** (1997PIAWO9637475) and others (see Refs. in Table 2) are worthy of note.

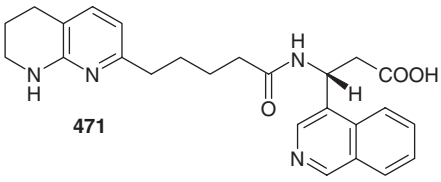


469

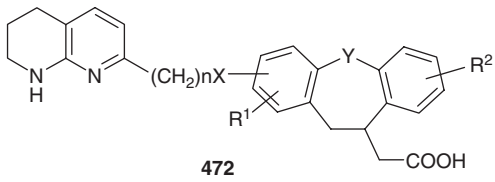
R = H, Alk, cyclo-Alk, Alkenyl.



470



471

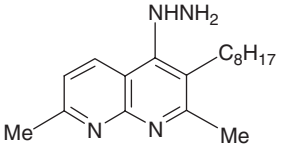


472

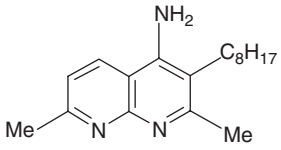
R^1 = H, Hal, C_1-C_6-Alk; R^2 = H, C_1-C_6-Alk;
X = Y = O, CH_2; n = 2, 3.

1,8-Naphthyridine **227** (R^2=$ClCH_2$) was covered by a patent as an agent reducing the phototoxicity of herbicides belonging to cyclohexenones or phenoxyacetic acids (1991GEP3097937). Naphthyridone **228** (R^3=Me) was used as an intermediate in the synthesis of compounds possessing antimalarial activity against *P. vinckei vinckei* (1984AJC1065).

Compounds **473** and **474** in doses of 0.1–5 kg ha^{-1} exhibit fungicidal activity against phytopathogenic fungi (particularly, *Phycomyceten*) and are efficient against *Phytophthora infestans* on tomatoes and potatoes as well as against *Pseudoperonospora cubenis* on cucumbers (1988GEP3644825).



473



474

Owing to the presence of two geminal endocyclic nitrogen atoms, the 1,8-naphthyridine molecule is more promising for interactions with various biological receptors, coordination to metal ions and other intermolecular contacts compared to other isomeric pyridopyridines and the majority of known nitrogen heterocycles. In the immediate future, it is hoped that new regio- and stereoselective procedures will be developed for the introduction of pharmacophoric groups at different positions of the naphthyridine molecule with the use of cascade heterocyclization and combinatorial chemistry for the design of more efficient medical drugs possessing prolonged action or improved pharmacokinetic characteristics. In particular, the design of the so-called dual action antibiotics, viz., systems consisting of β-lactam antibiotics of the penicillin and cephalosporin series and fluoroquinolonecarboxylic or fluoronaphthyridonecarboxylic acid derivatives, holds promise.

Complexes of the antitumor antibiotics naphthyridinomycines with DNA were investigated by molecular mechanics methods (molecular simulation) (1991MI6). It was found that the nature of the substituent at the C(11) atom as well as the stereoconfiguration of the C(7) center are of importance for biological activity of naphthyridinomycins. The antibacterial activities of various substituted 1,8-naphthyridines (1998MI7), including 2-phenyl-1,8-naphthyridin-4-one derivatives, were calculated using the QSAR method (2000MI4).

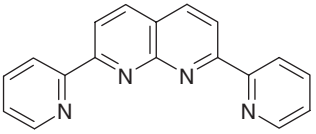
A spectrophotometric procedure (1989MI10) and a modified gas-chromatographic method (1987MI7) were devised for the analysis of nalidixic acid **459**. Drug forms for intramuscular injection (1990GEP3902079) and sublimed drugs for parenteral use (1994USP5188833) are available. These drug forms contain the gyrase inhibitor from 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives as the active component.

The complexation properties of naphthyridines are widely used for analytical purposes, primarily, in medicine. A highly sensitive diagnostic was proposed (1987AX2198) for bacterial infectious diseases based on scanning electron microscopy. Complexes of antibiotics of the naphthyridin-4-one series or their salts with ^{99m}Tc, ^{67}Ga, ^{111}In, ^{113m}In and other radionuclides are used for revealing inflammatory focus. These compounds are involved in parenteral drug forms (1994BRP2262937).

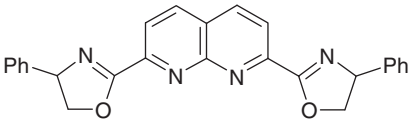
In recent years, 1,8-naphthyridine derivatives have attracted growing interest as promising ligand systems, which coordinate metal ions of different groups of the periodic table, such as Cu (1984IC3633, 1992JOC2215, 1998ICA129), Au

(1997JCS(D)4257, 2002JHC829), Zn (1998HCA507, 1998JCS(D)873, 2000IC3365), Hg (2001NJC63), Mo (1998ICA237, 1998JCR(S)538), Re (2003EJIC255), Fe (1999ACS230, 2003IC6447), Co (1992AX(C)625), Ni (1998BCJ1279), Ru (1985IC4214, 1997JCS(D)4561, 1999AG362), Rh (1986ICAL1, 2001JAP2001199922, 2003ICA190), Pd (1986IC1514), Pt (1986IC1514, 1999ICA72), Eu and Tr (1996IC7345). The crystal structures of some complexes were studied by X-ray diffraction analysis.

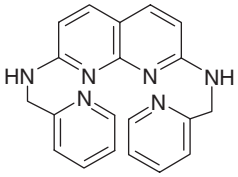
Various ligands based on 1,8-naphthyridines, including polydentate binuclear (compounds **475** (1992JOC2215), **476** (1999MI6), **477** (1998HCA491)) and other compounds (2000JOC2838, 2000T8245), are used for complexation with these metal ions.



475

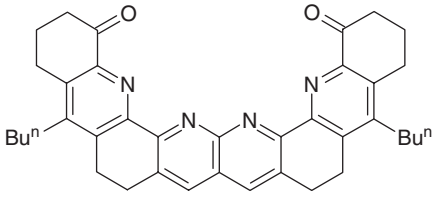


476

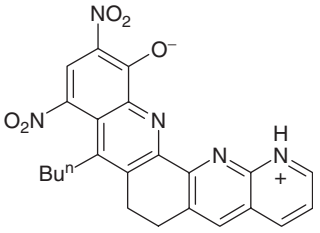


477

Polycyclic compound **478**, which forms stable complexes with urea, guanidine, amidines and their derivatives, is covered by patents (1991USP15030728, 1994USP5283333). These complexes were used in a biological investigation. Receptor betaine molecule **479** was constructed for diagnostic tests for blood (serum) creatinine and renal insufficiency.

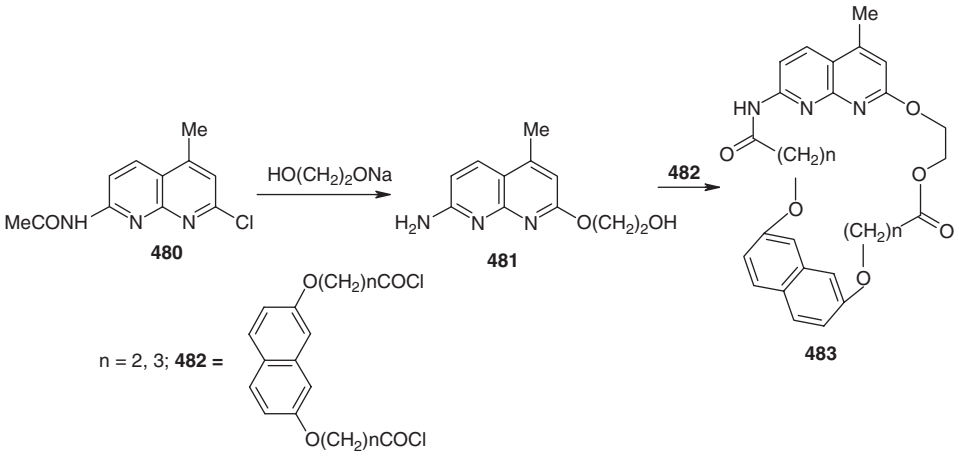


478

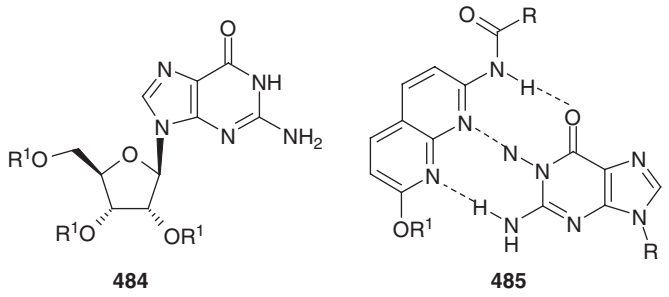


479

New guanine receptors were prepared based on 7-acetylamino-2-chloro-4-methyl-1,8-naphthyridine **480** (1988CC765). Amino alcohol **481** was prepared by the reaction of compound **480** with an excess of sodium 2-hydroxyethoxide. Compound **481** reacts with dicarboxylic acid chlorides **482** under high dilution conditions to form naphthyridine macrocycles **483**.



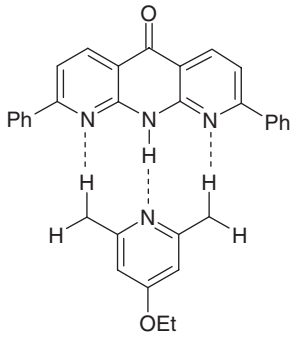
The addition of 2′,3′,5′-tri-*O*-pentanoylguanosine **484** to a solution of macrocyclic compound **485** in $CDCl_3$ causes pronounced changes in the ^1H NMR spectra of both compounds: the resonances of the NH and NH_2 groups are shifted downfield, whereas all six resonances of the naphthalene system are shifted upfield. The assumed (1988CC765) structure of the complex consists of two molecules linked via three hydrogen bonds (analogous to the structure of complex **485**) and the naphthalene system forms a complex with guanine. The association constant of compounds **483** and **484** is four times as high as that of the guanine complex with unsubstituted 1,8-naphthyridine.



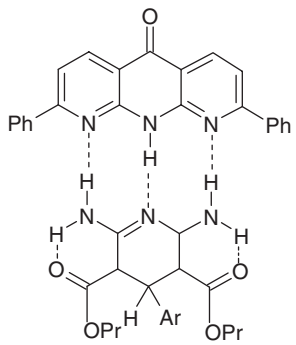
R^1 = C(O)Bu^n; R^2 = H, MeCO, Pr^{n}CO; R^3 = Cl, OEt, $O(CH_2)_2OH$.

The structures of other complexes based on 1,8-naphthyridine and pyrido[2,3-*b*][1,8]naphthyridine (1,9,10-anthyridine) derivatives containing three hydrogen bonds each were established (1987SC319, 1987JA7531, 1988CC765, 1989JA3744, 1990JA2008, 1991GEP3907937, 1991JA2810, 1992JA4010, 1993JOC6625).

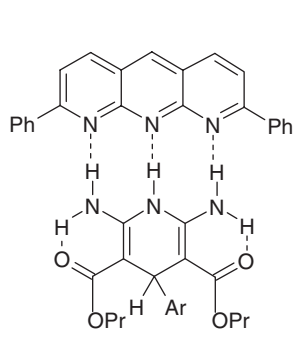
1,9,10-Anthyridine was used for the synthesis of analogous stable complexes **486–488** (1992JA4010).



486

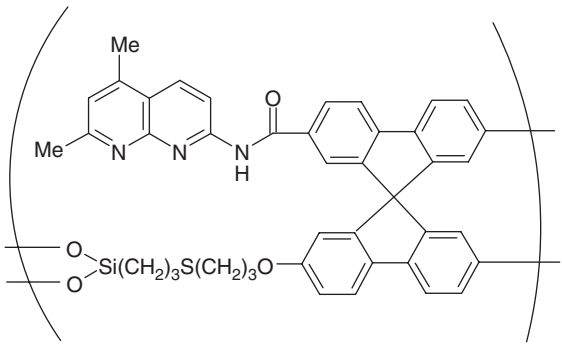


487



488

1,8-Naphthyridine derivatives were used for the preparation of polysiloxanes. New chiral stationary phase **489** was constructed on the basis of 2-*N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide (1997HCA897).



489

VI. Conclusion

Analysis of the data on the synthesis, chemical properties and biological activities of the six isomeric pyridopyridines (1,5-, 1,6-, 1,7-, 1,8-, 2,6- and 2,7-naphthyridines) published over the last 20 years is indicative of a lively interest in different aspects of their chemistry. This interest is generally associated with the practical utility of their derivatives possessing a very broad spectrum of biological activities. The present data, devoted to the biological activities of naphthyridine derivatives, will hopefully be of interest to organic chemists and biologists.

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