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Volume 77

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

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Preface

The first two chapters in this volume continue the survey of heteroaromatic tautomerism that was the topic of Volume 76 of *Advances in Heterocyclic Chemistry*. This whole subject was first dealt with comprehensively in Volumes 1 and 2 of our series, which date back to 1963 and 1964. The area was updated in a special supplementary volume of the series that appeared in 1976 but is now seriously out of date. The chapters in Volume 76 deal with a general introduction and the tautomerism of five-membered monocyclic rings systems.

In the present volume, the first chapter covers the tautomerism of rings with three, four, and seven or more members and is authored by Professor R. Claramunt of the Open University (Madrid, Spain) together with Dr. J. Elguero (Madrid, Spain) and Dr. A. R. Katritzky (University of Florida, U.S.A.)

The second chapter deals with rings systems which comprise two or more fused five- or six-membered heterocyclic rings. It is authored by Dr. I. Shcherbakova of NPS Pharmaceuticals, Salt Lake City, U.S.A., together with Drs. Elguero and Katritzky.

The final chapter, which will complete our survey of heteroaromatic tautomerism with a survey of monocyclic compounds with six-membered rings, will appear in a subsequent volume.

The other chapters in the present volume cover a variety of topics.

The synthesis and properties of azafulvalenes are covered in a comprehensive review by Professor R. Beckert (Friedrich Schiller University, Germany).

Over the last decade *N*-(1-haloalkyl)pyridinium salts and analagous compounds have been developed as important synthetic reagents. In a joint contribution from the Universities of Friedrich Schiller, Germany, and Mons, Belgium, Professors E. Anders and J. J. Vanden Eynde and Dr. K. Wermann give an authoritative account of these interesting and important compounds.

Progress in the chemistry of three- and four-membered rings containing two sulfur atoms has been rapid in the past few years. An updated survey of the chemistry of dithiiranes, 1,2-dithietanes, and 1,2-dithietes is now provided from a major center in this area by Professor J. Nakayama and Dr. A. Ishii (Saitama University, Japan).

In the next chapter of this volume, Professors M. Woźniak (Cracow University of Poland) and H. van der Plas (University of Wageningen, The Netherlands) survey the interesting chemistry of nitronaphthyridines.

The final chapter in the present volume is the third of a triad of reviews of 1,2,4-triazolopyrimidines, and it covers 1,2,4-triazolo[1,5-*c*]pyrimidines. As with the first and second part of this series (which appeared in Volumes 73 and 75, respectively), it is authored by Professor M. A. E. Shaban and Dr. A. E. A. Morgaan (Alexandria University, Egypt).

ALAN R. KATRITZKY

ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Tautomerism Involving Other Than Five- and Six-Membered Rings

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The results reported in this chapter owe much to those described in *Comprehensive Heterocyclic Chemistry* (CHEC-I), Volumes 7 ("Small and Large Rings", edited by W. Lwowski) [84CHEC-I(7)1, 84CHEC-I(7)47, 84CHEC-I(7)195, 84CHEC-I(7)449, 84CHEC-I(7)491, 84CHEC-I(7)593, 84CHEC-I(7)653, 84CHEC-I(7)709] and 4 ("Five-Membered Rings with One O, S or N atom", edited by C. W. Bird and G. W. H. Cheeseman) [84CHEC-I(4)377] as well as in *Comprehensive Heterocyclic Chemistry II* (CHEC-II), Volumes 1A ("Three-Membered Rings") [96CHEC-II(1)1, 96CHEC-II(1)61, 96CHEC-II(1)173, 96CHEC-II(1)347], 1B ("Four-Membered Rings") [96CHEC-II(1)911, 96CHEC-II(1)1113], and 9 ("Seven-Membered and Larger Rings with Fused Derivatives", edited by G. R. Newkome) [96CHEC-II(9)1, 96CHEC-II(9)113, 96CHEC-II(9)139, 96CHEC-II(9)151, 96CHEC-II(9)403, 96CHEC-II(9)459].

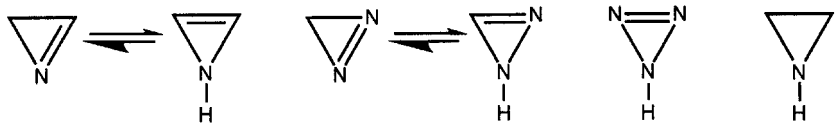
The tautomerism of heteroaromatic compounds is intimately related to the problem of aromaticity and antiaromaticity (87MI1, 94MI1), this being especially true for the compounds of this chapter, which are borderline between these showing Hückel behavior and polyenic compounds (nonaromatic).

I. Microcycles (Three- and Four-Membered Rings)

A. Tautomerism Not Involving Functional Groups

1. *Three-Membered Rings*

It is known that unsaturated three-membered nitrogen heterocycles display tautomerism involving nonaromatic and antiaromatic (i.e., 4π systems) forms. In all cases, the nonantiaromatic tautomer is the most stable: 1-azirine **1a** and 1-diazirine **2a.** Nonetheless, antiaromatic tautomers are known, for instance, triazirines **3.**



1a **1b** **2a** **2b** **3** **4**

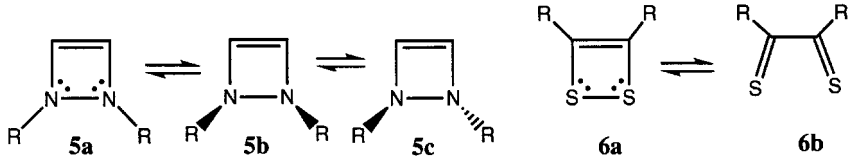
The case of azirines **1** has been of considerable theoretical interest (73MI50403, 73CC688; 80PAC1623; 91JA3689; 93CB2337, 93JA11074, 93JPC5553). Tautomer **1a** has been calculated to be 140–180 kJ mol^{-1} more stable than planar tautomer **1b,** as the antiaromaticity of **1b** is relieved by nitrogen pyrimidalization (tilt angle = 72.1°, inversion barrier 170–190 kJ mol^{-1}). The antiaromaticity of 1*H*-azirine is removed upon protonation, thus accounting for the high basicity of **1b** (87JCP6484; 93JA11074). The

equilibrium in diazirines **2** (and their protonated species) has also been examined theoretically (73MI50403; 93JA11074, 93JPC4239).

A comparison between aziridine **4,** as a model of nonaromatic structure, 1*H*-azirine **1b,** 1*H*-diazirine **2b,** and triazirine **3** using 6-31G*/MP3 calculations leads to the following values for the N-H inversion barriers: **4,** 86.2 (experimental value 80 kJ mol^{-1}); **1b,** 190.4; **2b,** 160.2; and **3,** 246 kJ mol^{-1} [89JCC468]. The difference in inversion barrier values between **1b** and **2b** was attributed to a decrease in the antiaromaticity of the latter. The antiaromaticity of **1b** was examined subsequently by the same authors [89JST(201)17].

2. *Four-Membered Rings*

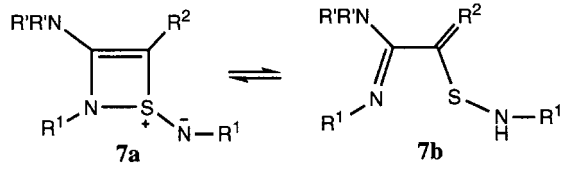
When comparing three- and four-membered heterocycles, one must keep in mind the formal possibility of obtaining 6π-systems using a double bond and two heteroatom electron lone pairs, as in 1*H*,2*H*-diazetine **5** (also called Δ^3-1,2-diazetine and 1,2-dihydro-1,2-diazete). This compound could exist in a planar form (**5a**) and in two nonplanar forms, the *syn* (**5b**) and the *anti* (**5c**). Several *ab initio* calculation papers have been devoted to compound **5** [77JA1949; 87JA6290; 89JST(201)17; 92JOC2040]; for instance, **5c** has been calculated (STO-3G) to be more stable than **5b** by 20 kJ mol^{-1} (77JA1949).



The case of 3,4-bis(trifluoromethyl)-1,2-dithiete (**6a,** R = CF_3) was discussed in the previous edition of *The Tautomerism of Heterocycles* (76AHCS1). This compound presents an interesting case of ring-chain isomerism between the "aromatic" structure **6a** and the ring-opened tautomer, 1,2-dithioglyoxal (or 1,2-dithione) (**6b**). However, when R = Bu^t the stable isomer is the cyclic one (**6a**) as shown by the absence of C=S signal in ^{13}C NMR (expected near 250 ppm) [82JCR(S)314]. It is well known that Bu^t groups extraordinarily stabilize ring-strained structures; this effect has been called the "corset-effect."

Previous extended Hückel calculations on the bis(trifluoromethyl) derivative **6** show the favored isomer to be **6b,** while the CNDO/2 method favors **6a** [75JCS(P2)559]. More recent *ab initio* calculations for different R substituents show that electron-releasing substituents favor the ring-opened dithione (**6b**), whereas electron-withdrawing substituents favor the cyclic structure (**6a**) (80JA6687). These conclusions are supported by electron diffraction (ED) (76JA899) and photoelectron (PE) spectral data

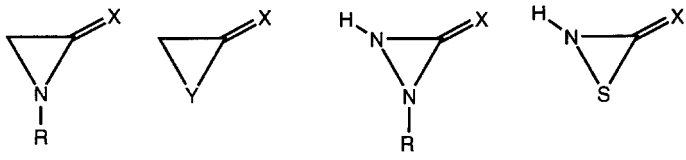
(83HCA801). The problem is fascinating for theoretical chemists and many papers have been devoted to **6,** including calculations on the cis, trans, and gauche forms of **6b** [87JCC389; 89JA7651; 90JA7529, 90ZC176; 91CPL(177)175]. An excellent summary on this problem is given in the review of Schulz and Schweig (88MI289). 1,2-Oxathiete, the mono-oxygen analoge of **6a,** has never been observed: only the α-thioketone is present in all solvents (76JOC2498).



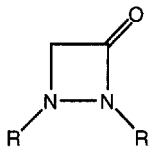
Gotthardt *et al.* (87CB747, 87CB751) reported a curious case of ring-chain isomerism which is intermediary between those of **5** and **6,** although the positive charge on the sulfur makes **7a** nonaromatic, at least without assuming increase in the sulfur valence. When R^2 is a phenyl ring, **7a** is stable; on the other hand, when R^2 is a CH_2R group, a proton is transferred to the nitrogen atom and the open form **7b** is isolated.

B. Compounds with Potentially Tautomeric Groups

In the case of three-membered rings, when the tautomerism involves an antiaromatic functional tautomer (hydroxy, amino, mercapto), the nonaromatic (oxo, imino, thio) tautomer is always the only form observed even in the most unfavorable case (alkylidene vs alkyl): **8** (X = O, NR′, CHR′R″), **9** (Y = O, S; X = O, NR′, CHR′R″), **10** (X = O, NR′), and **11** (X = NR′). For instance, **8** (R = H, X = O) has been obtained as a matrix-isolated species and the geometry and vibrational frequencies were reproduced by *ab initio* calculations (94JA60). Compound **9** (Y = S, X = NH) has been calculated (RHF/6-31G* and MP2/6-31G*) (90JPC1335; 91JOC5651) and the resulting geometry successfully compared with that of a substituted thiiranimine [82AG(E)694].



In the case of four-membered rings where the endocyclic double bond leads to an aromatic tautomer, this possibility was never observed for functional tautomers like 1,2-diazetidin-3-ones **12** and 1,2-dioxetanone **13.** The geometry of this last compound (essentially planar) has been calculated at the 4-31G level (81JA1292).



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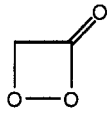

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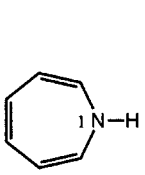
II. Cycles of Medium Size (Seven- to Nine-Membered Rings)

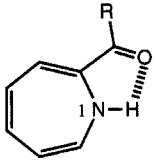
A. Tautomerism Not Involving Functional Groups

Heterocyclic aromaticity requires a planar, or nearly planar, conjugated system containing $4n+2$ π electrons. The Hückel condition often can be met utilizing the system's π-bonds and n electron pairs but planarity often cannot be achieved because of increased strain in going from puckered to planar geometries. Aromatic heterocyclic systems are known with 7 to 21 ring members. Still, a great many heterocycles having the right number of electrons are polyenic rather than aromatic, due to the excessive energy required to achieve near planarity. For instance, spectroscopic and X-ray crystallographic data portray **14** as a cyclic polyalkene having no propensity to attain planarity (81ACR348).

1. *Azepines*



14a



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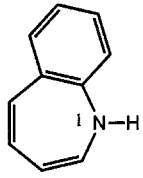

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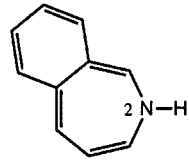

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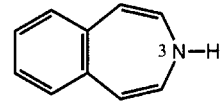

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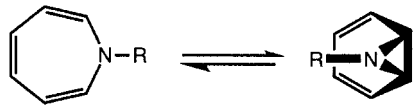
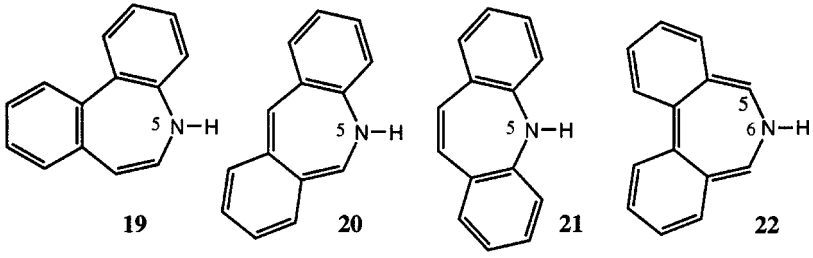
Among azepines and their benzo derivatives, antiaromatic 1*H*-azepine **14a** is known as a very unstable (even at −78°C in $CDCl_3$ solution) red oil which in the presence of acid or base rearranges to the marginally

more stable colorless 3*H*-azepine [80AG(E)1016; see also 84MI(37)171; 97JCS(P2)2015]. The 1*H*-tautomer can be stabilized using an intramolecular hydrogen bond (IMHB) as in compound **15** [81JCS(CC)399]. Nonaromatic 2*H,* 3*H,* and 4*H*-azepines have all been characterized by ^{1}H NMR spectroscopy [84RTC225; 94JCS(P1)1753]. 1*H*-1-Benz[*b*]azepine (**16**) was known only as N-substituted derivatives [80AG(E)1015, 80TL3403] until Gonzalez described a series of 1*H*-3-acyl derivatives and proved their structure by IR and ^{1}H NMR [93BSF143]. 2*H*-2-Benz[*c*]azepine (**17**) is known only as nonaromatic 1*H,* 3*H,* and 5*H* derivatives (74JOC3070; 75JA4682; 77HCA1644). 3*H*-3-Benz[*d*]azepine (**18**) derivatives are known as both *N*-alkoxycarbonyl derivatives and 1*H*-tautomers [78H(11)401; 81HCA373].



14b **14c**

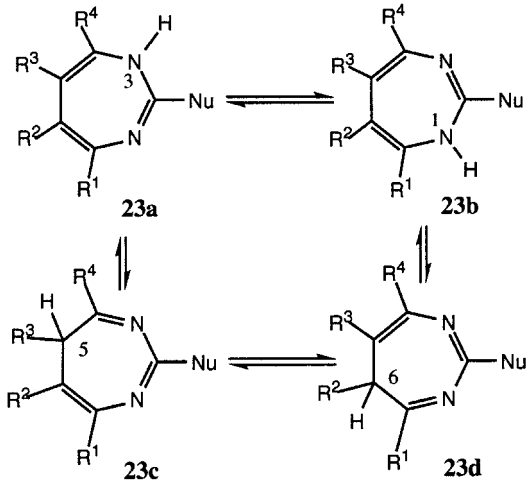
Prinzbach and Limbach have studied the valence isomerism between *N*-substituted azepines **14b** and benzeneimines **14c** (76CB3505); although **14b** is much more stable (actually it is the only form detected by ^{1}H NMR), the compound could react, depending on R, as **14c** with diazomethane. Later, Prinzbach *et al.* reported the study of the equilibrium **14b** (90%)/**14c** (10%) in the case of R = *p*-tosyl [the compound has the following C-substituents: 3,6-dichloro-4,5-di(methoxycarbonyl)]; in the solid state (X-ray) only **14b** is present [86CB616].



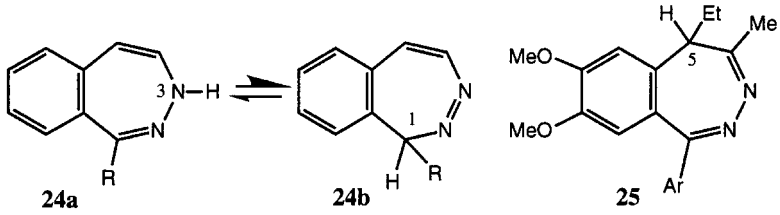
19 **20** **21** **22**

Of the four dibenzazepines, 5*H*-dibenz[*b,d*]azepine (**19**), 5*H*-dibenz[*b,e*]azepine (**20**), 5*H*-dibenz[*b,f*]azepine (**21**), and 6*H*-dibenz[*c,e*]azepine (**22**), only **21** is known as such (74CRV101; 84JHC197), while **22** exists as the nonaromatic 5*H*-tautomer (81LA240).

2. *Diazepines and Triazepines*

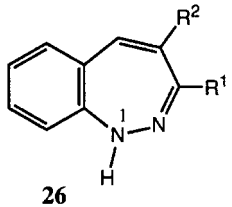


One of the most interesting and original results in this section is the synthesis and structural characterization of 1*H*-1,3-diazepines **23** by Wentrup *et al.* [98JCS(P1)2247]. The Nu substituent is usually OR or NR_2 and R^1, R^2, R^3, and R^4 are H or CH_3. Although the authors did not distinguish between **23a/23b** and **23c/23d** tautomers, they established the existence (depending on Nu and R's) of the antiaromatic NH forms and the nonaromatic CH forms. In the case of Nu = OCH_3 and all R's = H, the ^1H and ^{13}C NMR data (four different protons and four different carbons not including those of the C-Nu) proved unambiguously that there is no "annular" prototropy between **23a** and **23b.**



1*H*-2,3-Benzodiazepines (**24b**) exist as such and not as the antiaromatic 3*H*-tautomers **24a** [73JCS(P1)2543; 83H2173]. A different tautomer (5*H*) was observed for Tofizopam (**25**) using ^1H and ^{13}C NMR (74CB3894) and X-ray structure analysis [86JST(147)143]. The same behavior is observed

for 3*H*-1,2-benzodiazepines [75JCS(P1)102; 79JCS(P1)1433]. 3*H*-1,2-Diazepines exist as mixtures in equilibrium of nonaromatic isomeric 3*H*-tautomers [79JCS(P1)2209]. On the other hand, 1*H*-1,2-benzodiazepines (**26**) [77JCS(P1)2092; 78S603; 79JCS(CC)803, 79S380], 3*H*-1,3-benzodiazepines (**27**) (83H2173), and 5*H*-dibenzo[*d*,*f*][1,3]diazepines (**28**) are known to be stable (83CB1822).



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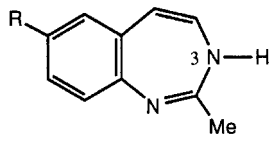

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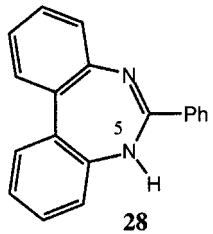
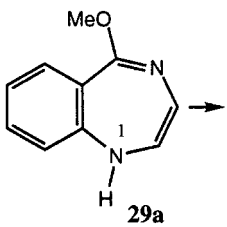
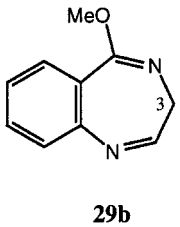


28

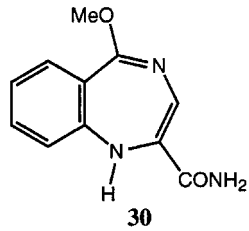
An interesting case involving 1,4-benzodiazepines has been reported (87CPB4676; 90CPB2919). While **29a** is unstable, the presence of an amide group at C-2 (**30**) or C-9 (**31**) made these compounds stable crystalline solids and it was suggested that this stability is a result of an intramolecular hydrogen bonding (IMHB) between the 1-NH and the adjacent amide group. Compound **29a** is converted into the more stable 3*H* isomer **29b** on stirring with an excess sodium methoxide in methanol (87CPB3182). As pointed out in the previous edition (76AHCS1), 1,5-benzodiazepines exist as nonaromatic diimines [98AHC(71)1]; this tautomeric form has been used by Lloyd *et al.* (98T667) to explain the flash vacuum pyrolysis (FVP) of these compounds. Okamoto and Ueda (75CPB1391) have reported that 4-amino-1,5-benzodiazepine-3-carbonitrile exists as the 1*H*-tautomer, but this result needs further support.



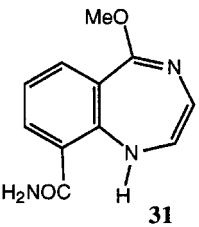
29a



29b



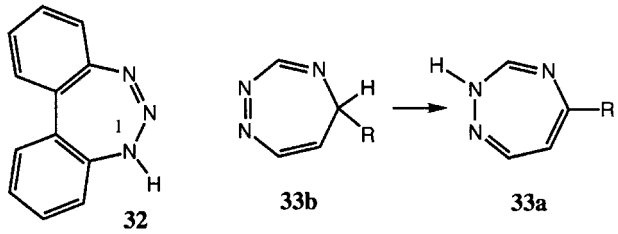
30



31

The only known example of 1,2,3-triazepine (**32**) behaves as a reactive cyclic triazene with a high degree of masked diazonium character [74JCS(P1)1248]. 2*H*-1,2,4-Triazepine (**33a**) has been obtained from the 5*H*-tautomer (**33b**) by a 1,5-hydrogen shift (74CC45, 74TL2303), this being one of these rare cases that an antiaromatic tautomer **33a** is more stable than the nonaromatic one **33b.** But it must be noted that these 2*H*-1,2,4-tri-

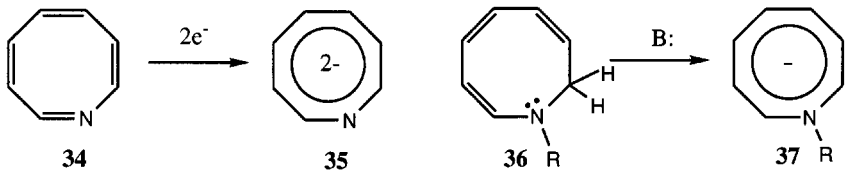
azepines are rather unstable and undergo thermal decomposition at temperatures as low as 80°C in some cases; moreover, they are probably nonplanar structures, therefore, not truly antiaromatic systems.



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

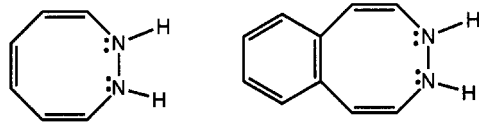
3. *Azocines, Diazocines, and Azonines*

Fully unsaturated azocines are π-equivalent heterocyclic analogs of cyclooctatetraene. Addition of two electrons to the completely unsaturated azocine (**34**) can lead to a dianion **35** and removal of a proton from a dihydroazocine (**36**) to the monoanion **37.** Both the mono- and the dianions are 10π-electron systems, corresponding to "π-equivalent" and "π-excess" analogs of cyclooctatetraenide [84CHEC-I(7)653]. Aromatic dianions related to **35** have been fully characterized by ^{1}H and ^{13}C NMR (87TL2517).



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

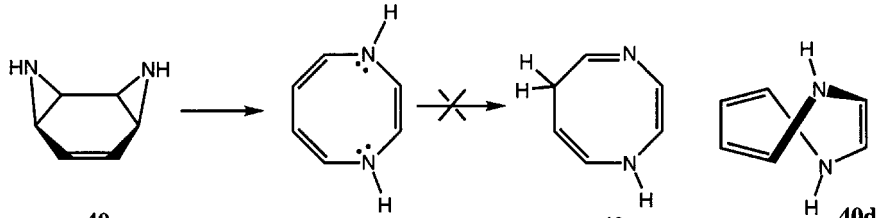
1,2-Dihydro-1,2-diazocine (**38**) and 3,4-dihydro-3,4-benzodiazocine (**39**) continue to arouse theoretical interest related to their possible aromaticity [89AHC(45)185], although the most recent work considers **38** as a saddle point on the reaction coordinate leading to ring opening (91RRC333).



38 **39**

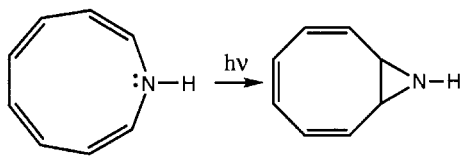
The parent 1,4-dihydro-1,4-diazocine (**40b**) has been thoroughly characterized by Prinzbach and Vogel and their colleagues [79AG(E)962, 79AG(E)964; 80CB3161; 83CB2492; 87TL2517]. Compound **40b** was ob-

tained by valence isomerization of a *cis*-diaza-bis-σ-homobenzene ("*cis*-benzenediimine" **40a**). Detailed analyses of the NMR data for **40b** are consistent with a planar (and not twisted like **40d**) delocalized diatropic, i.e., aromatic, structure (10 π-electrons), which was confirmed by crystallography. Chemical evidence for the aromatic character of **40b** is provided by its stability to acid and base. No tautomerization to imine forms such as **40c** is detectable in NMR experiments, which is an indication of a lower limit of about 84 kJ mol^{-1} for the stabilization energy. Gayoso (86IJQC1599) has reported MNDO calculations on the structure of diazocine **40.**



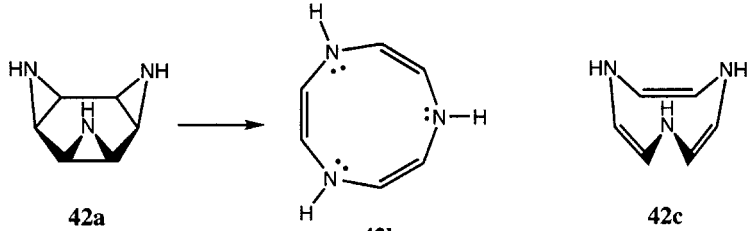
40a **40b** **40c** **40d**

Anastassiou has summarized in two reviews the knowledge about 1*H*-azonine (**41a**) [72ACR281; 78AHC(23)55]. Compound **41a** as well as its salts ($N^- M^+$) are aromatic compounds which exist as such and not as imine polyenic forms. This compound demonstrates a valence isomerism **41a/41b** similar to that of 1*H*-azepine (**14a/14c;** see Section II,A,1); the transformation **41a** $\rightarrow$ **41b** occurs upon irradiation. 9-Azabicyclo[6.1.0]nona-2,4,6-triene **41b** displays no tendency to thermal isomerization to **41a** at ambient temperature (72ACR281).



41a **41b**

Finally, there is a series of publications by Prinzbach and co-workers on 4,7-dihydro-1*H*-1,4,7-triazonine **42b** (80CB3127, 80CB3161, 88CB757, 89AG1386). This compound, obtained by a $3\sigma \rightarrow 3\pi$ isomerization of **42a** (*cis*-triaza-tris-σ-homobenzene or "*cis*-benzene triimine," its valence isomer) is a nonaromatic, nonplanar 12π-electron system, better represented as **42c.**

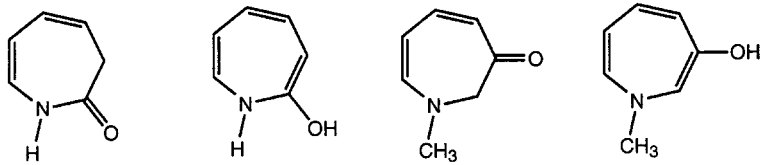


42a **42b** **42c**

B. Compounds with Potentially Tautomeric Groups

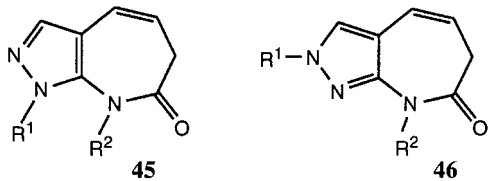
1. *Azepines*

1*H*-Azepin-2-ones (**43a**) and 1*H*-azepin-3-ones (**44a**) exist as such and not as hydroxy tautomers **43b** and **44b** [73HCA1852; 90JCS(P1)3159].



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

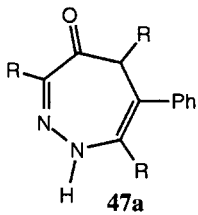
Lynch has prepared a large collection of pyrazoloazepinones, **45** and **46;** all of them exist in the nonaromatic CH_2 form (79CJC3034).



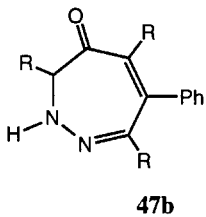
45 **46**

2. *1,2-Diazepines*

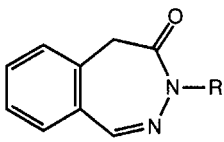
A well-studied case of tautomerism is that of 1,2-diazepin-4-ones: tautomers **47a** and **47b** were characterized by ^{13}C NMR, the former being the most stable (85JOC2141). 3,5-Dihydro-4*H*-2,3-benzodiazepin-4-ones exist as **48a** and not as 4-hydroxy tautomers **48b** (74JHC401).



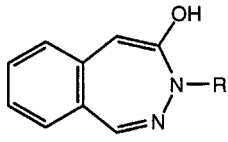
47a



47b



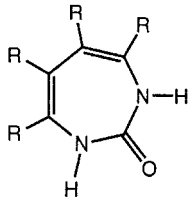
48a



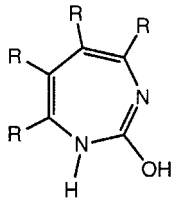
48b

3. *1,3-Diazepines*

Wentrup's paper [98JCS(P2)2247] contains one of the very few contributions to the tautomerism of functionalized 1,3-diazepines. 1,3-Dihydro-1,3-diazepin-2-ones (**49a**) exist as such and not as hydroxy tautomers **49b** (^{1}H and ^{13}C NMR in DMSO solution and IR in the solid state).



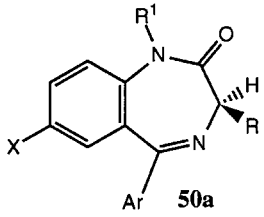
49a



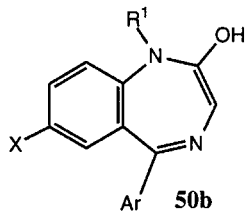
49b

4. *1,4-Diazepines*

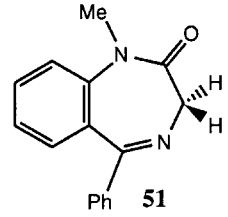
The compounds discussed in this subsection are by far the most studied of all types of heterocycles considered in Section II,B, partly due to the contributions of Aversa and Essassi groups but certainly also because of the pharmaceutical importance of many 1,4-benzodiazepinones. Compounds **50a,** representatives of which are Lorazepam and Oxazepam, have been studied extensively but no evidence has been found for the OH tautomer **50b** (82EA141, 86BSF797, 88BSF889, 94SC2899). Several spectroscopic techniques have been used; for instance, ^{1}H NMR spectroscopy of compound **50a** (R = CH_3, X = Cl, R^1 = H) has been used to determine its conformation (methyl pseudoequatorial) (79JHC757), similar studies were carried out for compounds with R = H (79OMR593), while ^{13}C NMR spectroscopy has been used to characterize the benzodiazepine **51** [82OMR134, 96CHEC-II(9)151].



50a

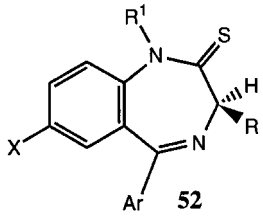


50b

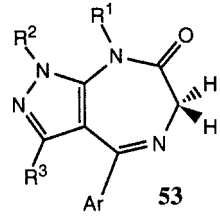


51

Absolute predominance of nonaromatic CH tautomers is also the situation for benzothiazepinones **52** (88BSB387, 89BSB405, 97JHC953) and pyrazolodiazepinones **53** (77JMC1562).

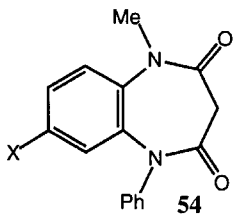


52

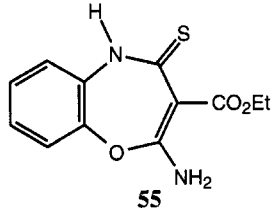


53

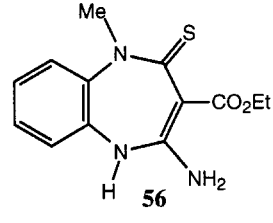
Clobazam (**54,** X = Cl) and related compounds (X = H, X = CF_3) exist in the dioxo tautomeric form [80JHC551, 87JCS(P2)1071], as do the analogous pyrazolo[3,4-*b*][1,4]diazepinediones (89JHC949). These conclusions were mainly based on careful ^{1}H NMR studies including the use of lanthanide shift reagents (LSR).



54

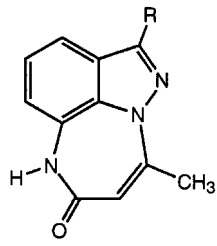


55



56

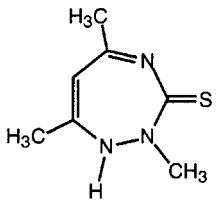
A careful ^{1}H and ^{13}C NMR study of 1,5-benzoxazine and 1,5-benzodiazepine shows that these compounds exist in the amino-thione forms **55** and **56,** respectively. Compound **55** displays a solvent-dependent amino/imino tautomerism (92MRC673). Tricyclic compounds **57,** analogous to the bicyclics discussed above have been described; they exist in the tautomeric form shown below (87BSB399, 92BSB995, 96BSB345).



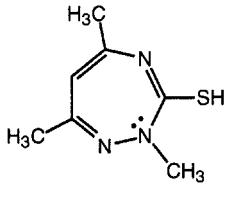
57

5. *Triazepines*

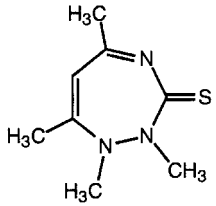
These derivatives quite generally exist in the oxo or thioxo tautomeric forms. Monocyclic compounds are rare; for instance, Lavergne *et al.* reported that compound **58** exists as the thioxo tautomer **58a** and not as the more antiaromatic mercapto tautomer **58b** on the basis of the similarity of the ^{1}H NMR spectra of **58** with that of **59** (80RTC301).



58a

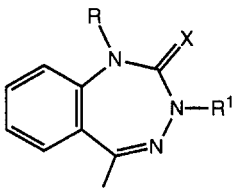


58b

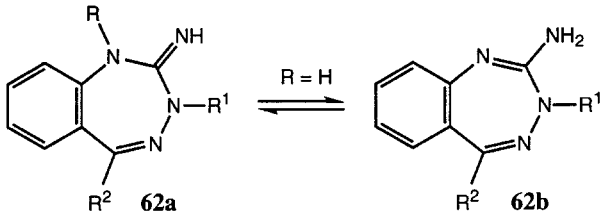


59

Some examples of benzotriazepines are reported below; most were studied by Morgenstern. Thus, **60** (74JPS838, 92PHA25) and **61** (92PHA25, 96PHA458) exist as depicted; the imino form **62a** is observed only when R ≠ H; otherwise, **62b** is stable (89PHA690, 90PHA434).

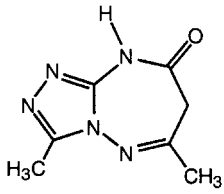


60, X = O
61, X = S

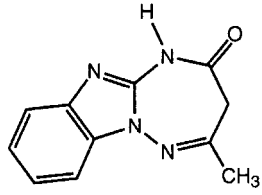


62a **62b**

Some triazepinones in which one of the nitrogen atoms belongs to a fused azole moiety have been reported. For instance, compound **63** was prepared (74JHC751) and its X-ray structure determined (75CSC317). Similarly, ^{1}H and ^{13}C NMR spectra and X-ray structural determination of **64** revealed that this compound exists as a 3*H*-tautomer with the 1,2,4-triazepine ring in a distorted boat conformation (88T7185).



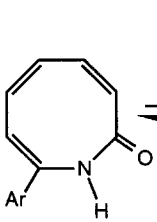
63



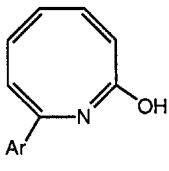
64

6. *Azocines, Diazocines, and Azonines*

The tautomeric equilibrium of azocinones **65** has been studied by ^{1}H NMR, IR, and UV spectroscopy (90JHC1323). Dioxo derivatives of diazocines all exist as such, as illustrated by the analgetic **66** (75MI37) and the extensively studied dibenzo[*b,f*][1,4]diazocines (**67**) [81JCS(P1)988].



65a



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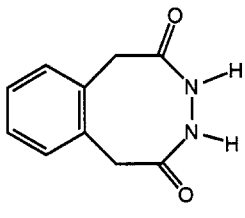
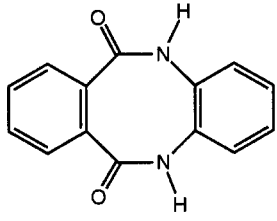
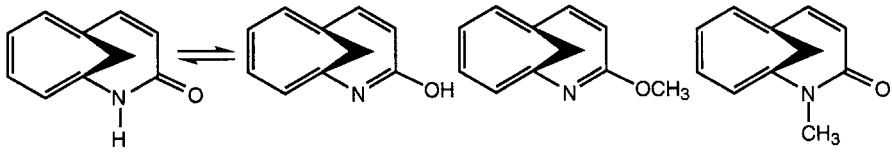


66



67

Katritzky *et al.* have studied, using pK_a measurements, the tautomerism of aza[10]annulenone (2-azabicyclo[4.4.1]undeca-4,6,8,10-tetraen-3-one) **68** (93H2483). Comparison of the pK_a's of **68** and of model compounds **69** and **70** suggests that **68a** is the dominant tautomer (p$K_T = -0.70$). This implies a significantly diminished preference for the oxy form in compound **68** compared to 2-pyridone (p$K_T = -3.0$). This result indicated that aza[10]-annulenones **68a** and **70** should be viewed as 6π-homoaromatic species. ^{1}H NMR spectra support this conclusion (93H2483).



68a **68b** **69** **70**

III. Macrocycles

A. Porphyrins

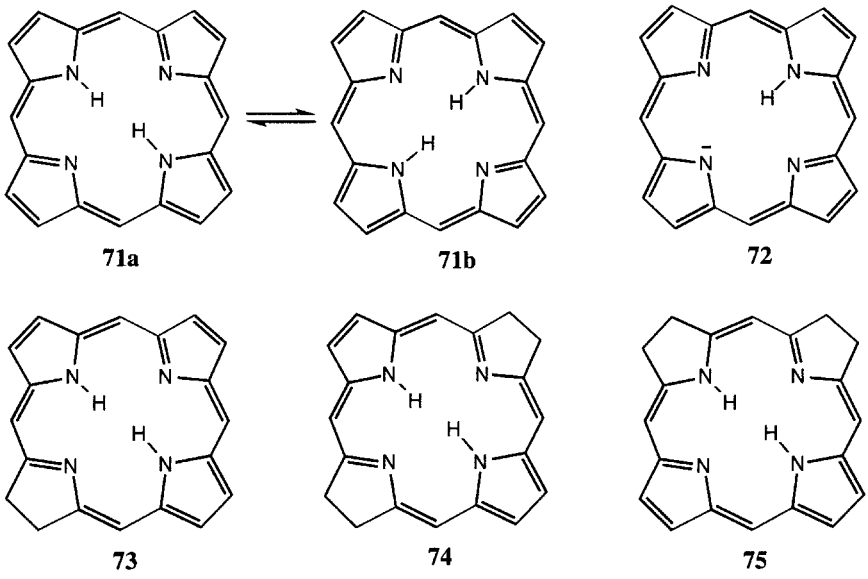
This is one of the most actively developing and closely watched fields of heterocyclic tautomerism—only the study of purines and pyrimidines is of comparable contemporary interest. The number of references is so high that many relevant works have had to be neglected, whereas in other sections of this chapter relatively minor contributions have been commented on because they pertained to a field where few contributions are available. The selection criteria were (1) all pertinent authors are quoted at least once, (2) full papers are preferred to communications or letters, and (3) recent works are preferred to earlier ones because they usually quote the previous publications.

There are several reasons for this great interest in the tautomerism of porphyrins (which could justify its own review): (1) their biological significance, (2) their applications in material science ("hole burning" is related to their tautomerism), (3) the simplicity of the system (annular tautomerism involving *intramolecular* proton transfer both in solution and in the solid state), and (4) the possibility of elucidating the kinetic processes in great detail.

The macrocyclic core of porphyrin systems **71** is highly conjugated and a number of effective resonance forms can be written. There are nominally 22 π-electrons but only 18 of these can be included in any one conjugative path (for a modern discussion on this topic, see references 98AGE177 and 99CEJ267). Chlorins (**73,** dihydroporphyrins), bacteriochlorins (**74,** tetrahydroporphyrins), and isobacteriochlorins (**75,** tetrahydroporphyrins) also have full 18-π delocalization available, though the number of possible resonance forms is reduced.

Porphyrin systems therefore obey Hückel's rule in having $4n + 2$ ($n = 4$) π-electrons in a planar, cyclic, conjugated array. Both major tautomeric forms have delocalization pathways with opposite N-Hs (trans tautomers), as shown in **71a** $\rightleftharpoons$ **71b.** It is already known (76AHCS1) that tautomers with inner hydrogens adjacent (cis tautomers) are much less stable, playing an important role only in the mechanism of proton transfer in porphyrins and phthalocyanines.

In porphyrin H_2P (**71**, also known as porphine) the tautomerism is "degenerate"; i.e., tautomers **71a** and **71b** are identical. Also, in the anion HP^- **72,** the four tautomers are all degenerate; the kinetics of proton transfer have been studied. In chlorins, bacteriochlorins, and isobacteriochlorins, all the tautomers are different, but all the evidence indicates that the most stable tautomers are those with the inner protons in a trans disposition, represented by **73, 74,** and **75,** all having an 18-π-delocalized system. Gossauer's pentaphyrin, a 22-π-electron pentapyrrole macrocycle with two inner hydrogen atoms, should also be prone to annular tautomerism [83JCS(CC)275].



For porphyrins and phthalocyanines, chemists use in their publications abbreviations which, although not always consistent, are necessary to avoid the long names of these compounds. The code H_2 means that we are dealing with the free base; if the central hydrogens are partly or totally replaced by deuterium, we use HD or D_2. For instance, in the case of porphyrins, besides H_2P, the following abbreviations will be used in this review: HP^- (anion of porphine), H_2TPP (tetra-*meso*-phenylporphyrin), H_2TTP (tetra-*meso*-*p*-tolylporphyrin), H_2TRP [tetra-*meso*-alkylporphyrin, R = methyl (Me), propyl (Pr), butyl (Bu), hexyl (He)], H_2TPPC (31,51-cyclo-51-ethyl-10,15,20-tripropylporphyrin), H_2OEP (octaethylporphyrin), H_2OETNP (tetranitrooctaethylporphyrin), H_2DPP (dodeca-phenylporphyrin), H_2ACP [acetylporphyrin, 8-acetyl-3,13,17-tris(2-methoxycarbonyl)-ethyl)-2,7,12,18-tetramethylporphyrin], H_2C (chlorin), H_2TPC (tetra-*meso*-phenylchlorin), H_2TPrC (tetra-*meso*-propylchlorin), H_2Bc (bacteriochlorin), H_2TPBc (tetra-

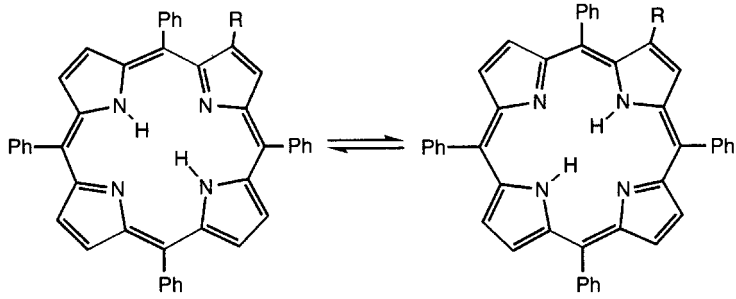
meso-phenylbacteriochlorin), H_2iBc (isobacteriochlorin), H_2TPiBc (tetra-*meso*-phenylisobacteriochlorin), and H_2COMiBc (5-cyano-2,2,8,8,12,13,17,18-octamethylisobacteriochlorin).

Since this notation is not systematic, some ambiguities can occur; for instance, H_2TMeP is for some authors (and in this chapter) tetra-*meso*-methylporphyrin but for some others it is 2,3,10,12-tetramethylporphyrin. For the last-mentioned compound, we use its full name.

1. *Static and Dynamic Studies in Solution*

The tautomerism of *meso*-tetraphenylporphyrins was discovered by Storm and Teklu (72JA1745). Abraham and Smith reported one of the first modern studies of the tautomerism of porphyrins using as substrate the readily available H_2TPP [75JCS(P2)204]. They measured the kinetic parameters ($\Delta G^{\ddagger}_{303}$ = 51.4 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 38.5 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −42 J K^{-1} mol^{-1}) using ^{1}H (at 100 MHz) and ^{13}C DNMR in $CDCl_3$. From these values and an isotopic effect, k_{HH}/k_{DD} = 12, they concluded that the double-proton transfer involves the cis tautomer; i.e., it is a two-step mechanism and not a concerted one. Eaton and Eaton studied a series of derivatives of H_2TPP (the four *meso*-phenyl rings bearing different substituents) showing that these substituents have little influence on the tautomerism rates (77JA1601).

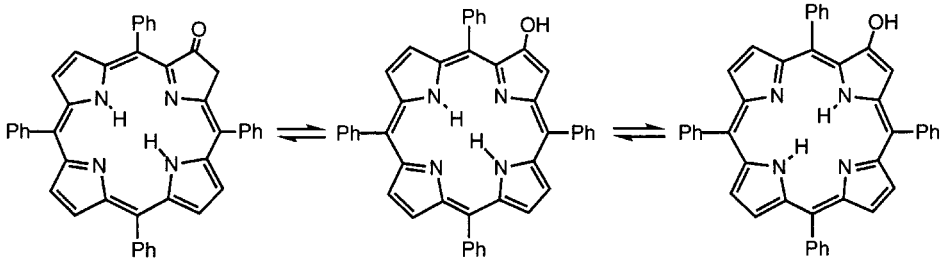
Afterward, Crossley and Sternhell published a series of significant papers dealing with the thermodynamic and kinetic aspects of a series of porphyrins and chlorins. First, they describe the annular tautomerism of H_2TPP derivatives bearing one substituent at the β-position (86JA3608). Using ^{1}H NMR data at 400 MHz in either CD_2Cl_2 or $CDCl_3$, they proved that tautomer **76a** is dominant when R = NO_2, CHO, Cl, Br, OMe, CN, NHCOMe, SPh, OCOPh, or OH, whereas **76b** is the major tautomer when R = CH:CH_2, CH_2OH, NH_2, Me, iPr, or nBu. These substituent effects do not follow any known scale, probably due to differential *peri* steric effect between R and the closest Ph substituent.



76a **76b**

Kinetic aspects of the above equilibrium were studied by the same authors (87JA2335). Due to the asymmetry of the equilibrium, two activation barriers were expected (the forward **76a** → **76b** and the backward **76b** → **76a**) but, in fact, there are four barriers, since in going from **76a** to **76b** it is possible to use a clockwise (left–right) or a counter clockwise path (up–down). Besides differences due to the asymmetry of the double-well, the clockwise and anticlockwise barriers are quite different, 46.6 kJ mol^{-1} and 56.7 kJ mol^{-1} (they were measured by ^1H NMR spectroscopy at 400 MHz). The authors have also measured an isotopic effect (k_{HH}/k_{DD} = 30, probably exaggerated) and concluded that there is a simultaneous migration of two protons involving a symmetric transition state with no evidence of proton tunneling (87JA2335).

They also described an interesting case of a porphyrin displaying simultaneously annular and functional tautomerism, very common in the azole series but very rare in porphyrins (88JOC1132). The only tautomers observed, **77a–77c,** have an 18-atom 18-π-electron structure similar to that of [18]diazaannulene. The relative amounts of tautomers **77a–77c** are solvent dependent; for instance, in toluene-d_8 and in CD_2Cl_2 they are **77a** (53 and 78%), **77b** (29 and 13%), and **77c** (18 and 9%).



77a **77b** **77c**

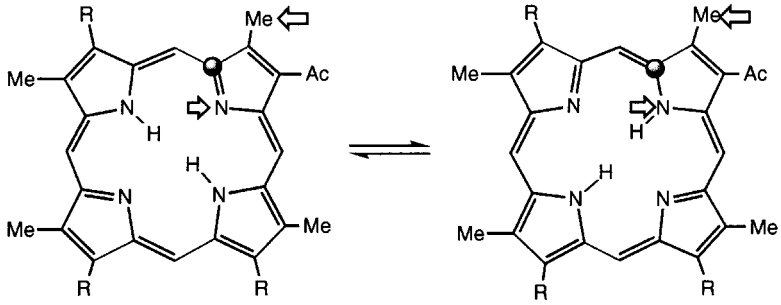
Two more recent papers by the same group described the use of the allylic $^4J_{Me,H}$ coupling constant for determining the structure of a bacteriochlorin (type **74,** the only example with a [18]annulene periphery) (92JA3266) and studied the tautomeric equilibrium analogous to **76a**/**76b** using the fact that tautomerism involving N-deuterated porphyrins is much slower than that for NH analogs (92JOC1833).

Smith *et al.* determined the activation barrier for H_2OETNP by ^1H NMR in CD_2Cl_2 at 300 MHz ($\Delta G^{\ddagger}_{273}$ = 55.2 kJ mol^{-1})(94JA3261) and found it to be similar to that measured for NH tautomerism in other free-base dodecasubstituted porphyrins (90JA8851, 92JA9859, 93IC1716). Finnish authors have reported a detailed study of the tautomerism of a natural chlorin,

bonellin, **81.** Using high-level NMR experiments and semiempirical calculations (AM1 and PM3) they were able to determine the activation barrier ($\Delta G^{\ddagger}_{297}$ = 60.2 kJ mol^{-1} in $CDCl_3$) for a stepwise tautomerization going through the fully aromatic *cis* tautomers (similar to the mechanism proposed by Abraham and Smith [75JCS(P2)204]) and the less aromatic *trans* tautomer (99JOC432). By means of ^{1}H NMR (500 MHz, $CDCl_3$) Chinese authors determined the free energies of activation of four mono-*meso*-substituted octamethylporphyrins [94MI(12)231], which are in the range 61.0 kJ mol^{-1} (R_{meso} = *o*-hydroxybenzyl) to 53.6 kJ mol^{-1} (R_{meso} = ferrocenyl).

Using ^{1}H NMR spectroscopy and $^{15}N_x$– (*x* is generally 4 but sometimes 3) labeled porphyrins, (the label introduction is expensive and synthetically demanding, but is very important to suppress ^{14}N broadening and to obtain ^{1}H–^{15}N coupling constants) Limbach and co-workers published a series of notable papers on the tautomerism of porphyrins (86JA3856; 89AGE76; 91JA3550; 92BBPC821; 93JA4554; 94AGE2215, 94JA6593; 96JA7231).

Isotope effect between the HH, HD, DH, and DD isotopomers was used as an important tool to determine the mechanism of the double-proton transfer. For concerted degenerate double-proton transfers in the absence of tunneling, the rule of the geometrical mean (RGM) should hold in good approximation, which states that $k_{HH}/k_{HD} = k_{DH}/k_{DD}$. Tunneling may lead to a breakdown of this rule but the relation $k_{HH} > k_{HD} = k_{DH} > k_{DD}$ should remain valid. In the absence of secondary isotope effects the relation $k_{HH} \gg k_{HD} = k_{DH} \approx 2\,k_{DD}$ should hold for a stepwise pathway, even if tunneling is involved.



78a **78b**

In collaboration with Djerassi, Limbach *et al.* studied H_2ACP, which was prepared in two isotopic modifications, namely $^{15}N_3$ and $^{13}C_2$ labeled (86JA3856; 93JA4554). The single ^{14}N nitrogen atom was that of the pyrrole ring bearing the acetyl group; in the same ring, the carbon atom of the

methyl group and one of the ring carbons (gray dot) were labeled with ^{13}C. The acetyl group exerts a big influence on the tautomeric equilibrium of this porphyrin: **78b** is much less stable than **78a** (5.8 kJ mol^{-1}). The use of ^{13}C NMR with the $^{13}C_2$ labeled compound allowed observation of the minor tautomer at low temperatures. The tautomeric equilibrium constant **78a/78b** depends on the temperature according to a van't Hoff plot (the entropic contribution is negligible). Using ^{1}H NMR of the $^{15}N_3$-labeled sample allows determination of the rates for the different species H_2ACP, HDACP, and D_2ACP; analysis of the KIE showed that the tautomerization proceeds stepwise (in relative values, if $k_{HH} = 16$, then $k_{HD} = 1$, $k_{DH} = 4$, $k_{DD} = 0.84$). It is important to note that the rates determined using ^{1}H-NMR and those determined using ^{13}C NMR are consistent. There are two kinds of activation energies, about 40 kJ mol^{-1} for HH and DH and about 52-54 kJ mol^{-1} for HD and DD.

The comparative studies of H_2TPP, H_2TPC, H_2TPBc, and H_2TPiBc were discussed in two further publications (89AGE76; 91JA3550). There, the discovery of the proton tautomerism in H_2TPC and H_2TPiBc was reported (proton transfer in H_2TPBc is very slow). The barrier for H_2TPC is 61.3 kJ mol^{-1}, which is 20 kJ mol^{-1} higher than in H_2TPP. The proton transfer in H_2TPiBc is fast because the ground state is less aromatic than the *cis* intermediate. H_2TPBc does not undergo intramolecular tautomerism, which would take place via zwitterionic intermediates (89AGE76). The case of H_2TPC was later studied in detail (91JA3550). Measurements and modeling of isotope effects in terms of a stepwise double-proton transfer in an asymmetric potential well were carried out using ^{1}H DNMR at 90 MHz in tetrachloroethane-d_6. It was shown that the asymmetry of the potential well leads to substantial differences in the HH/HD/DD isotope effects; thus the activation energy for the HH isotopomer is 58.4 kJ mol^{-1} while that for the HD species is 61 kJ mol^{-1} (91JA3550). The case of H_2TPP was studied in more detail later using ^{1}H DNMR at 300 MHz in toluene-d_8 and ^{13}C DNMR at 75 MHz in THF-d_8 (92BBPC821). In this last paper on H_2TPP, the authors describe its non-Arrhenius behavior at low temperatures and interpret it as thermally activated tunneling.

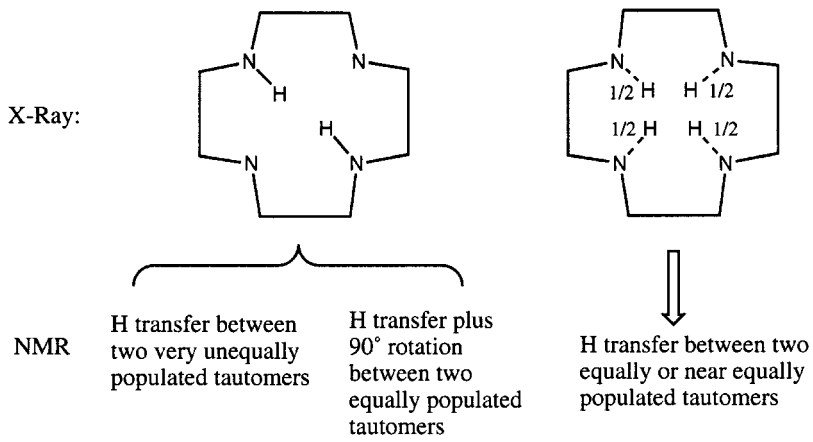
The three most recent papers of Limbach's group dealt with porphine **71** and its monoanion **72.** $[^{15}N_4]HP^-$ **72** was generated from $[^{15}N_4]H_2P$ **71** using phosphazenes as bases; compound **71** shows dynamic proton transfer between the four inner nitrogens. Using ^{1}H NMR at 500 MHz in THF-d_8, the authors showed that this process is much faster than that in H_2P, the reason being that there is no longer the "bottleneck" of the cis tautomer (see Section III,A,2) (94AGE2215). Measurements of the kinetic HH/HD/DD isotope effects of H_2P tautomerism in the solution and the solid state were reported in (94JA6593). The data obtained by these measurements both in

the solid state and in solution fall on the same Arrhenius plot, which confirms the remarkable fact of the absence of isotopic effects in H_2P tautomeric equilibrium. The isotope effects ($k_{HH}/k_{DD} \approx 17$ and $k_{HD}/k_{DD} \approx 1.9$) are typical for degenerate intramolecular double-proton transfer reactions involving two consecutive single-proton transfer steps via a cis intermediate. Finally, the first observation of kinetic tritium isotope effects by ^1H DNMR (500 MHz. toluene-d_8) was reported for H_2P in 96JA7231. These results, $k_H/k_D \approx 11.4$, $k_D/k_T \approx 3.4$, confirm the conclusion of the previous paper regarding the mechanism, including the tunneling process.

2. *Static and Dynamic Studies in the Solid State by NMR*

The solid-state behavior of porphyrins, as studied by both NMR and crystallography, are discussed in reference to Scheme 1.

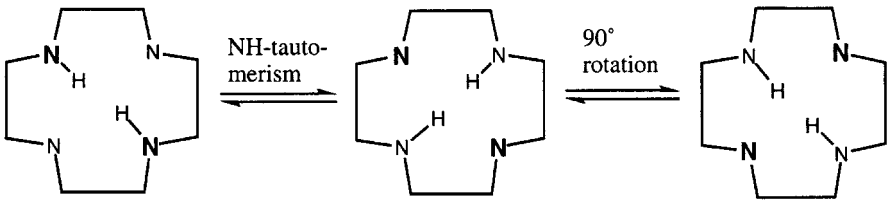
When X-ray crystallographic studies disclose a structure showing proton disorder (four "half-protons") and NMR studies show a temperature-dependent dynamic phenomenon, the explanation is not controversial: this is a case of crystallographic proton disorder due to the double transfer of hydrogens. On the other hand, when the inner hydrogens located by X-ray crystallography appear localized, but NMR shows that a dynamic process is taking place, two explanations are possible: either the transfer involves very differently populated tautomers (the minor one being not "seen" by crystallography) or the transfer is followed by a 90° rotation of the whole molecule around the symmetry axis perpendicular to the plane of the ring. This last explanation was suggested by Frydman in a series of four papers (88JA336, 88JA5651; 89JA7001; 92JPC4753).



SCHEME 1.

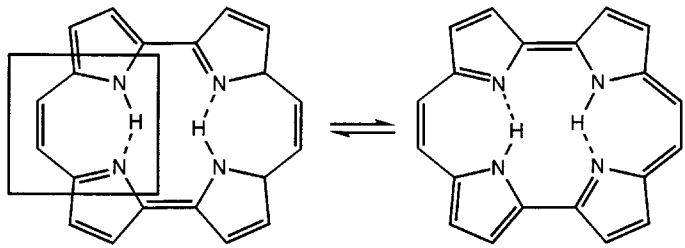
Different solid-state NMR techniques (^{13}C CPMAS NMR, the second moment of the ^{1}H signal, the spin-lattice ^{1}H relaxation time in the rotating frame $T_{1\rho}$) were combined to reach the conclusion that in the case of porphine H_2P the double-proton transfer is followed by a 90° rotation within the crystal (see Scheme 2).

According to Frydman, this mechanism is necessary to account for the fact that hydrogen atoms appear localized in one of the X-ray structures of porphine (72JA4144), while all NMR techniques show that the double-proton exchange is present in this compound (89JA7001). In the publications mentioned above, Frydman and Olivieri first studied the porphyrins H_2P, H_2TMeP, H_2TPrP, H_2TBuP, and H_2THeP using ^{13}C CPMAS NMR methods and measured the barriers to the double-proton transfer in H_2P (47.7 kJ mol^{-1}), H_2TPrP (50.2 kJ mol^{-1}), and H_2THeP (53.1 kJ mol^{-1}) (88JA336). In their second paper, they also explained that the case of H_2P ($K_T = 1$) is exceptional in porphyrins since other porphyrins have tautomers with different populations due to crystal effects; they have determined ΔH for H_2TTrP (5.4 kJ mol^{-1}) and H_2OEP (5.8 kJ mol^{-1}) (which corresponds to populations about 90–10%) and found that both tautomers have their protons diagonally positioned, the difference in stability being a typical crystal effect [kinetic solid-state effects, KSSE (88JA5651)]. In their key publication, the model of hydrogen transfer/90° in-plane jumps was postulated for the case of H_2P, both jumps occurring with the same rate (about 10^3 Hz, $E_a = 37.7$ kJ mol^{-1}); the authors concluded that the rotations are probably absent in bulky molecules like H_2TTP (89JA7001). In the last of Frydman's publications on this subject (92JPC7001), he reported the proton-transfer barrier for D_2P ($E_a = 46.0$ kJ mol^{-1}) being 8.3 kJ mol^{-1} higher than that for H_2P, an increase similar to one reported for H_2TPP (77JA1601, 82FAR229). A priori, one could expect that deuteration would increase the hydrogen transfer barrier but that the rotation rate should remain constant; actually, according to Frydman, both barriers increase simultaneously because the rotation occurs only when hydrogen transfer leads to a less stable crystal structure.



SCHEME 2.

A series of publications of the Limbach group also deals with the tautomerism of porphyrins in the solid state (82FAE229; 84JA4059; 87AGE934, 87BBPC941; 94JA6593; 96JA11101) (for their studies in solution, see Section III,A,1), but covers a longer period than Frydman studies. Limbach used mainly ^{15}N CPMAS NMR spectroscopy with $^{15}N_4$-labeled samples. Employing not lineshape analysis but magnetization transfer experiments in the rotating frame, Limbach compared H_2TPP and H_2TTP, which behave identically in solution (see Section III,A,1) but not in the solid state; the hydrogen transfer rate in H_2TTP is the same in the solid state as in solution, but that of H_2TPP is different (84JA4059). This difference was assigned to the fact that H_2TTP displays hydrogen transfer between two identically populated states while H_2TPP (triclinic polymorph) shows hydrogen transfer between two very unequally populated tautomers (see Scheme 1). This means that H_2TTP should present four "half-protons" in the X-ray structure (Scheme 1), as was confirmed subsequently for monoclinic H_2TTP (85JA2978). The case of H_2P was examined in a later paper and the rate for the double-hydrogen transfer, k_{HH}, was measured at different temperatures (this rate was calculated assuming a symmetric double-minimum potential), which yielded $E_a = 39$ kJ mol^{-1} (87AGE934) [compare with the value of 34.7 kJ mol^{-1} determined by Frydman (88JA336)].



79a **79b**

In the same paper, Limbach *et al.* (87AGE934) reported the study of the compound related to porphyrins, porphycene **79.** Porphycene behaves very differently from H_2P in ^{15}N CPMAS DNMR experiments. Its behavior was explained assuming that the four porphycene tautomers (two cis and two trans) are present in the crystal and interconverting very rapidly due to short N-H…N distances in the "seven-membered" pseudorings.

In (87BBPC941), Limbach made a major contribution to understanding crystalline and amorphous environments using compounds that in the gas phase show symmetric double minimum potentials. Several compounds were used to illustrate the periodic (crystal) and random (glass) distortions of the potential surface, among them H_2P and porphycene. The seminal paper on the tautomerism of porphyrins in the solid state is that of Limbach

and Vogel in 1994 (94JA6593). The dynamic processes present in monoclinic porphine were completely disentangled using H_2P, HDP, and D_2P samples. Frydman hypothesis of rotational jumps was examined, but Limbach and Vogel found no evidence for this (they presented the correct exchange model including 16 different molecular states, see Fig. 1). It was pointed out that the only difference between the structures of porphine proposed in two previous publications by Webb and Tulinsky is that the earlier publication (65JCP3100) presumed hydrogen disorder over the four nitrogens, while in the later article (72JA4144) the inner hydrogen atoms were found to be localized in a trans disposition. Limbach and Vogel discussed these suggested structures and concluded that the porphine molecules are very tightly packed, which would make 90° molecular jumps very slow processes. Moreover, unambiguous evidence of a stepwise mechanism and a tunnel contribution was obtained (94JA6593).

In summary, it was concluded that no effect of phase was indicated by comparing measurements of the kinetic HH/HD/DD isotope effects of the porphyrin tautomerism in the liquid and the solid states. In both phases the process is degenerate within the margin of error. The absence of isotope effects indicates a stepwise processes in both phases. Together with the data obtained by Butenhoff and Moore (88JA8336; 90JPC7847), this proves that at low temperatures the tautomer interconversion takes place by tunneling via the *cis*-porphyrin intermediate. The activation energy corresponds, at low temperatures, to the energy difference between the *cis*- and the *trans*-porphyrins. The HH/HD/DD isotope effects of the solid-state tautomerism indicate a symmetric profile for the proton transfer, as in the liquid state. These effects are not in agreement with a double-proton transfer along an asymmetric reaction pathway followed by a fast molecular rotation, as proposed by Frydman.

Definitive proof of the structure of porphine in the solid state awaits a variable-temperature crystallographic (X-ray or neutron diffraction) study; the analysis of the anisotropic displacement factors (ADP) should disclose any rotational motion or its absence as well as determine the positions of the inner hydrogens. A search in the September 1998 version of the Cambridge Structural Database [CSD (91MI187)] showed that the only structures of porphine (codename PORPIN) were obtained in 1965 and 1972.

The latest Limbach paper reviewed here reported a study of the monoanion of porphine HP^- and its deuterated DP^- and tritiated TP^- counterparts both in solution and in the solid state (96JA11101). One of the motivations for undertaking these difficult series of experiments was to provide theoreticians with a simpler model (one hydrogen transfer between four degenerate sites, including tunneling effects) than that of H_2P (see Section III,A,5). Many interesting conclusions were reached in this work, one is that liquid and solid state rates for the hydrogen transfer at a given temperature

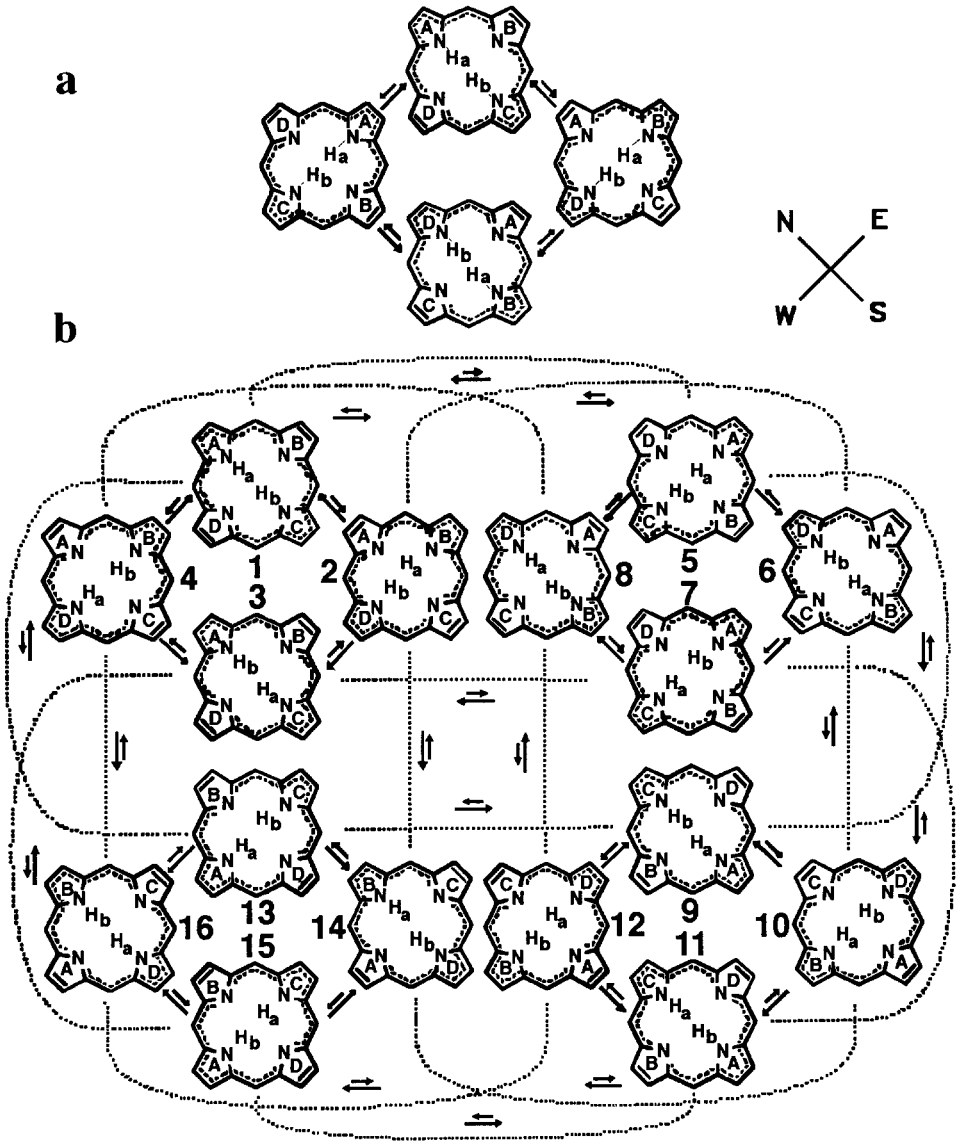


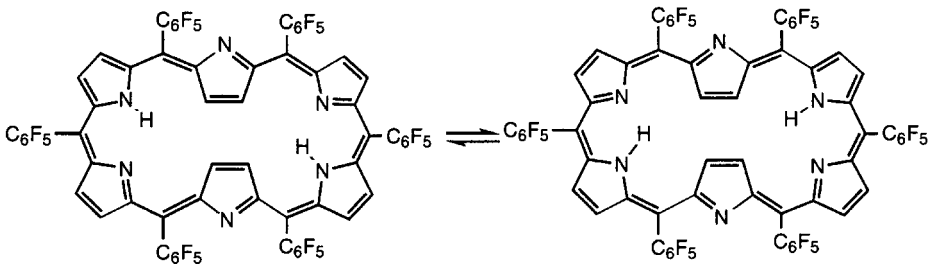
FIG. 1. Combined proton tautomerism and 90° rotation of porphyrin molecule in the solid state. (a) Reduced scheme proposed by Frydman *et al.* (89JA7001). (b) Complete scheme according to Limbach *et al.* (94JA6593).

are similar (those for TP^- have been obtained only in solution for obvious reasons). The H transfer in the anion is much faster than that in the parent neutral compound in contrast with the D and T transfers, which are only slightly accelerated.

3. *Static Studies in the Solid State by Crystallography*

Determination of the X-ray structure of monoclinic H_2TTP (85JA2978) led to discussion of the possibility of locating the inner hydrogens using the fact that the endocyclic angle C-N(H)-C = 109.8° while that of C=N-C = 105.8°. Since in monoclinic H_2TTP the C-N-C angle = 107.8° (the average value), there is 50:50 proton disorder. This conclusion was based on earlier crystallographic study of porphyrins (80JA2823). Proton disorder in X-ray structures of porphyrins remains an exceptional finding; in most porphyrins, including those studied by Smith (see below), the NH protons shows no disorder and are located in trans position [98AX(C)662].

Smith *et al.* have explored the relationship between conformational and tautomeric aspects in nonplanar porphyrins. They first determined the conformation of highly substituted porphyrins by X-ray crystallography and then used high-field ^{1}H NMR to measure some kinetic processes. For instance, it was found that H_2OETPP is a severely saddle-shaped molecule which shows two dynamic processes, one of lower energy, the proton transfer ($\Delta G^{\ddagger}_{293}$ = 57 kJ mol^{-1}), and other of higher energy ($\Delta G^{\ddagger}_{383}$ = 76 kJ mol^{-1}) (90JA8851). H_2DPP also shows these two processes, but the activation energies are reversed: $\Delta G^{\ddagger}$ = 54 kJ mol^{-1} and 46 kJ mol^{-1} for NH tautomerism and inversion of the saddle conformation, respectively (92JA9859). These authors also reported the X-ray structure of a chlorin derivative, which showed the expected trans disposition of the inner protons situated on the aromatic pyrrole rings (see formula **73**) [93JCS(P2)11].



80a **80b**

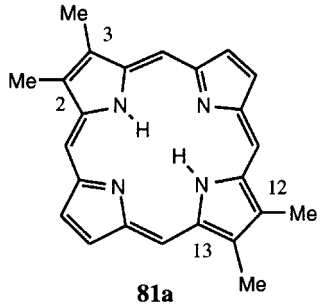
The X-ray structure of *meso*-hexa(pentafluorophenyl)hexaphyrin **80** found to be an expanded *trans*-porphyrin was reported recently by Aveiro's group. In the ^{1}H NMR, the two NH protons appear at −1.98 ppm and the four "inside" pyrrole CH protons as a singlet at −2.43 ppm, while in the ^{19}F NMR, just two kinds of pentafluorophenyl groups were observed in a 2:1 ratio (99CC385). These results indicate that in solution compound **80** exists in a rapid equilibrium between **80a** and **80b.**

4. *UV, Fluorescence, and Photoisomerization*

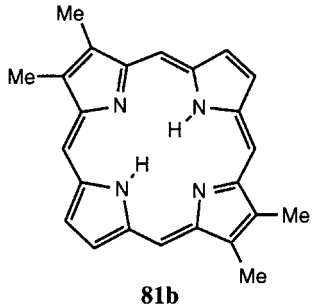
Photochemical hole burning (PHB) has been attracting increasing attention in recent years. PHB applied to frequency-domain memory studies can contribute to big improvements in the information-storage field. PHB can be utilized for realizing high-resolution site-selectivity spectroscopy (96MI1). Deuterated free-base porphyrins are much less efficient for hole formation than hydrogenated free-base porphyrins, supporting the idea that the rate-determining step is the tautomerism of central protons of free-base porphyrins. This tautomerism, determined using PHB, is supposed to proceed via the lowest triplet state, T_1 (93CM366).

It is well-known that *para* substituents on the phenyl groups of H_2TPP have no influence on the tautomerism rates in the ground state (see Section III,A,1). In the case of PHB, there seems to be only a small substituent effect on Φ_{PHB} (the quantum efficiency for hole burning) through modification of the relative energy of T_1 (93CM366).

This field has been studied extensively by Russian authors, including Solov'ev (Solovyov) and Chernook and Shul'ga (86MI74) using Shpol'skii matrices at very low temperatures. Thus, Solov'ev demonstrated that the high-energy form of chlorin (**73b,** see Section III,A,6) can be generated by photoisomerization of the lower energy form **73a** and is metastable at the temperature of liquid helium (84JAS73). The photoinduced conversion of H_2TPPC, an asymmetric porphyrin, was reported by Shul'ga and Chernook as the trans → trans isomerization [85CPL(120)63]. The same group described the fluorescence spectra of both tautomers of 2,3,12,13-tetramethylporphyrin **81a** and **81b;** they demonstrated that the photo-tautomer with fluorescence in the shorter wave region is **81a** while the tautomer with fluorescence in the longer-wave region corresponds to **81b** (85MI529).



81a



81b

Similar studies were carried out on H_2TPrC (90JAS381) and on $H_2COMiBc$ (in hexane at 4.2 K) [92SA(A)155]. In the last study, the existence of cis and trans isomers of similar stability in the case of bacterio-

chlorins was demonstrated. Finally, Kuz'mitskii published a kinetic model of slow photo-induced tautomerization of free porphyrin bases, taking into account both ground and excited (singlet and triplet) states (96MI1783). He showed that free porphyrin bases undergo NH tautomerism in the triplet state even at temperatures as low as liquid helium.

Friedrich has studied the free-base cytochrome *c* in a glass state at 1.6 K (96MI77). In general, for free-base protoporphyrins it can be safely assumed that the hole-burning photoreaction is based on a light-induced rearrangement of the inner protons. This type of reactions has been verified for all free-base porphyrin molecules [92MI(61)381].

Burkhalter has studied the room-temperature solutions of two synthetic H_2iBcs which have dual fluorescence resulting from two different tautomers, the *trans*-**75** and the cis tautomers, involving both aromatic pyrrole rings (87JPC3228). The trans tautomer is the most stable and emits at 585 nm (0-0 band) while the cis one emits in the red region (635 nm). Using *meso*-porphyrin-horseradish peroxidase, a small protein, Friedrich and Fidy studied photoinduced prototropic tautomerism in protein crevices [91MI(59)305]. They carried out these studies using *meso*-porphyrin IX bound to the apoperoxidase heme pocket and hole-burning techniques and demonstrated that more than four tautomers are necessary to explain the experimental results [92MI(61)381]. The four tautomers (not identified) are populated within the protein under the influence of irradiation or thermal treatment, and the existence of a fifth and six tautomers is also likely [95MI(69)577]. Moreover, the relative populations of the tautomers change upon deuterium substitution (94JPC2210). A subsequent publication of the same group describes hole-burning Stark experiments on cytochrome *c,* in which the iron atom of the heme was removed (H_2C c) based on a light-induced rearrangement of the two inner protons [96MI(71)77].

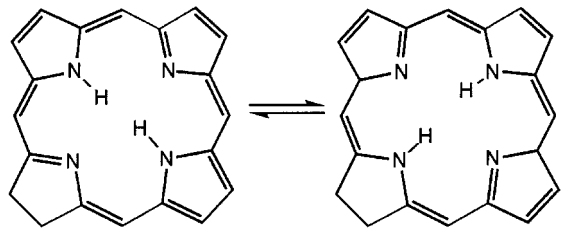
Butenhoff *et al.* discovered the near-infrared (NIR)-induced tautomerism of H_2P embedded in a hexane Shpol'skii matrix [90SA(A)519] and gave a detailed description of its vibrational photochemistry (90JPC7847).

5. *Photoelectron Spectroscopy (UPS, XPS) and Circular Dichroism*

Ghosh *et al.* reported that the XPS (X-ray photoelectron spectra) of porphyrins distinguishes the unprotonated (N 1s peak at 398.6 eV) from the protonated central nitrogens (N 1s at 400.7 eV) in octakis(*N*,*N*-diethylcarboxamido)porphyrin (93JOC6932). The observation of a pair of MCD (magnetic circular dichroism) bands of opposite sign within the transition of monoacetylporphyrins is probably related to the existence of an equilibrium between tautomers (83TL2433).

6. *Theoretical Calculations of Stability and Proton Transfer*

In 1980, Kuzmintsky (Kuz'mitskii) and Soloyov published the results of CNDO/2 calculations on the proton transfer in H_2P [80JST(65)219]. Although the method is now obsolete, the main facts of the tautomerism of porphyrins were correctly reproduced: (1) the trans isomer **71** is more stable than the cis one (calculated difference is 36 kJ mol^{-1}), (2) the stepwise mechanism via the cis isomer is much lower in energy than concerted double-proton transfer, (3) the process is phase independent, and (4) tunneling is necessary to explain the experimental results. Using a semiclassic treatment (the so-called "golden rule") Siebrand and Wildman agreed with the previous authors. They also concluded that the trans–cis barrier is approximately equal to the difference in energy between these two tautomers (about 40 kJ mol^{-1}), and they reproduced the H/D isotope effects and estimated the tunneling effects [88CPL(143)395].



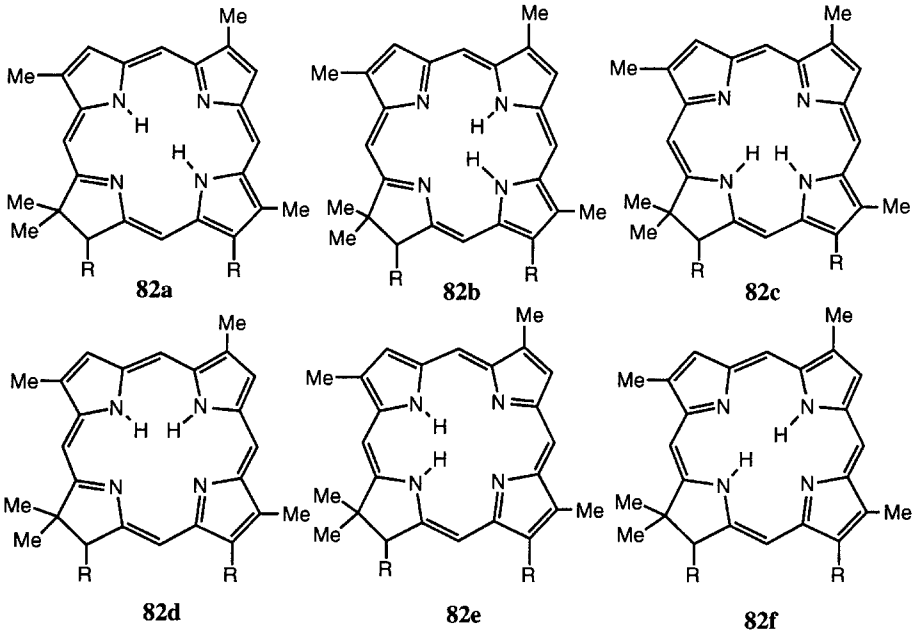
73a **73b**

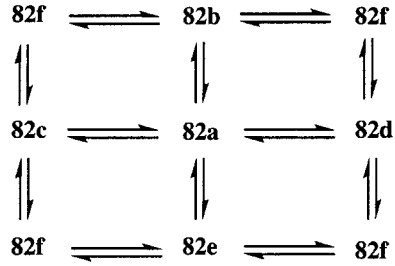
Numerous important contributions from Gassman, Almlöf, and Ghosh include studies of chlorin **73** tautomerism (93JPC10964). The **73a** and the **73b** forms of H_2C have both been observed experimentally (see Section III,A,4), although it is well established that **73a** is the predominant tautomer (see Sections III,A and III,A,3). Using a local density functional (LDF) at the MP2/DZP2 level, they calculated the **73a/73b** difference to be 39 kJ mol^{-1}.

In the search for molecular wires, Reimers and Crossley calculated, at the MP2 level, the four stationary points of H_2P **71** hypersurface (94JPC11878). The trans isomer **71a** (or **71b**), is 42 kJ mol^{-1} lower in energy than the corresponding cis isomer, the transition state (TS) between the trans and the cis isomer amounts to 70 kJ mol^{-1}, and the second-order saddle point (SS) connecting the trans tautomers **71a** and **71b** is higher in energy than TS. Subsequently, they published a detailed account of the tautomerism of H_2P where they depicted the complete hypersurface of the proton transfer using a six-parameter Fourier-series potential (95JA2855). Indirect estimates place the cis isomer ca. 20–35 kJ mol^{-1} in energy higher than the corresponding trans isomer (88JA8336); therefore the Ghosh and Almlöf value, 32 kJ mol^{-1}, also a MP2 calculation, is close to the experimental value (95JPC1073).

Ghosh discussed the tautomerism of porphyrins in three important papers [97JPC(B)1496, 97JPC(B)3290, 97JPC(B)5459]. In the first he reported the transition state (TS) for HP^- (49.5 kJ mol^{-1}), which correlates with experimental results (94AGE2215); in particular, the calculations reproduce the lowering of the barrier in going from H_2P to HP^- (see Sections III,A,1 and III,A,2). One very significant geometrical aspect is that the N_4 core of the TS has a distinctly trapezoidal (or roughly rectangular) shape in contrast to the nearly square N_4 core of HP^- [97JPC(B)1496]. The second paper discussed the cis–trans tautomerism of isobacteriochlorin **75** (represented in the trans form). According to the calculations, the two tautomers of **75** are energetically equal [97JPC(B)3290]; this is in accord with the simultaneous spectroscopic detection of both cis and trans tautomers for unsubstituted H_2iBc (92JPC6189). The last paper discusses tetrapyrrolic porphyrin isomers with additional *E* and *Z* CH=CH double bonds but the calculations have been done only for the trans tautomers [97JPC(B)5459].

Using the master equation approach, Brackhagen and Meyer discussed the circular motion of the hydrogen atom in the plane of the porphyrin anion ring system (98BBPG303). Assuming rectangular displacement of the pyrrole rings [97JPC(B)1496], they succeeded in reproducing the H, D, and T isotope effects of HP^-. Until now this is the most complete treatment of the kinetic aspects of a tautomerism phenomenon.

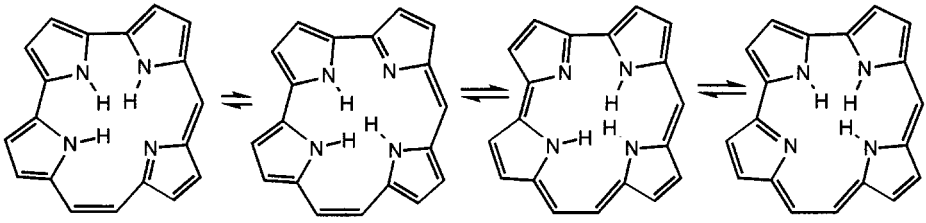




SCHEME 3.

An MP2 study of the tautomerism of a natural chlorin, bonellindimethylester **82** (R = $CH_2CH_2CO_2Me$), was reported recently (99CEJ267). The energies of the six possible tautomers were calculated as well as all the interconversion barriers. As in all chlorins, the most stable tautomer is **82a** (the relative energy values for the other tautomers are given in kilojoules per mole in parentheses), followed by **82d** (32.0), **82f** (37.7), **82b** (37.9), **82c** (69.3), and **82e** (72.3). The barriers to all the interconversion paths were also calculated (see Scheme 3) (for instance 50.6 kJ mol^{-1} from **82a** to **82d**) as well as chemical shifts (absolute shielding values) of **82** and H_2P (99CEJ267). The results of the chemical shift measurements obtained do not agree with a previous study by Schleyer (98AGE177).

Ghosh and Jynge have carried out a theoretical study of the tautomerism of corroles using a LDF (local density functional) theory (97CEJ823). Among the studied corroles are H_3[1.1.1]Cor, H_3[2.0.1]Cor, *cis*-H_3[3.0.0]Cor, and *trans*-H_3[3.0.0]Cor presenting two tautomers and the most complex case of H_3[2.1.0]Cor **82** with four different tautomers. According to these authors, the stability decreases in the following order (the energy differences in kilojoules per mole are indicated in parentheses): **83a** (0.0) > **83b** (11.4) > **83c** (21.7) > **83d** (27.5).



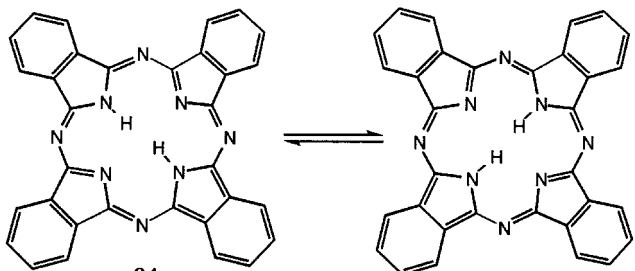
83a **83b** **83c** **83d**

7. *Theoretical Calculations of Electronic Spectra*

Ghosh and Almlöf published many articles discussing the XPS (X-ray photoelectron spectroscopy) and UPS (ultraviolet photoelectron spectra) and the corresponding ionization potentials of porphyrins using high-level calculations. These topics are indirectly related to the tautomerism of porphyrins (for an example see 94IC6057 and 95JA4691).

B. Phthalocyanines

Phthalocyanines (**84**) are tetrabenzotetraazaporphyrins; compound **84** is often designed as H_2Pc. Phthalocyanines display "autotropic" tautomerism **84a** ⇌ **84b** similar to that of porphyrins. According to our previous review (76AHCS1), there is fast proton exchange between **84a** and **84b** in the solid state. Gouterman was one of the first to carry out theoretical calculations (EHT) on the electronic spectra of these compounds, characterized by the Q and B (or Soret) bands. The splitting of the Q bands was assigned to the existence of phthalocyanines as mixtures of two tautomers with internal N-H···N hydrogen bonds (72TCA62); more recently electronic transitions were calculated at the *ab initio* level by Almlöf (94JA1932).

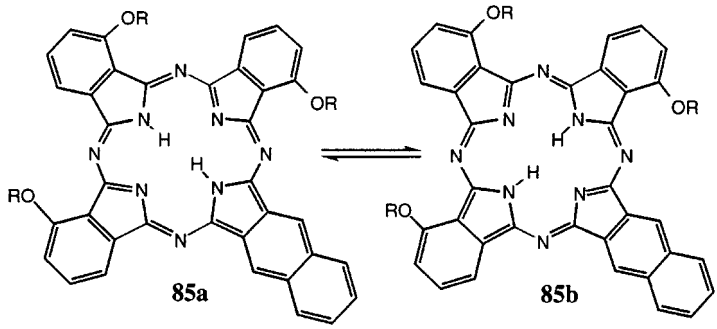


84a **84b**

Major contributions to the tautomerism of phthalocyanines have been made by: Limbach, Yannoni, and Wehrle on the use of ^{15}N CPMAS NMR to study these compounds in the solid state [85JMR159; 89CP(136)223]; Chen, Rieckhoff, and Voigt concerning the spectral properties (fluorescence and Zeeman effect in Shpol'skii matrices) of phthalocyanines at very low temperatures [82JCP3424; 89MP1439; 90SA(A)1601; 91SA1023; 94SA797; 96JCP8210]; and Mendoza and Torres on the synthesis and study of compounds related to **84** but with one or two 1,2,4-triazole rings replacing the isoindole moieties (triazolophthalocyanines) [89JCS(P2)797;

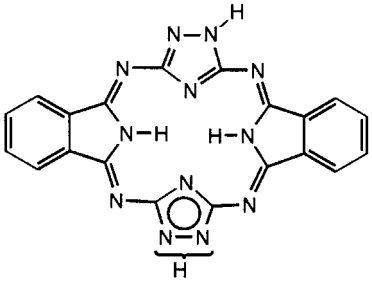
94JCS(CC)1525; 95ICA(230)153, 95LA495]. Other significant contributions are those of Cook [NMR in solution (91MRC1053)] and Renge (spectral hole burning [97JPC(A)6202]).

Cook *et al.* described the ^{1}H and ^{13}C NMR spectra of 1,4,8,11,15,18,22,25-octaalkylphthalocyanines in $CDCl_3$ at room temperature. They pointed out that the signal of the quaternary carbon linked to two nitrogens is observed at 22.5 MHz (149.5 ppm) but not at 100 MHz (91MRC1053) and assigned the absence of the latter to time averaging due to a slow double-proton transfer between octa-substituted **84a** and **84b.** Limbach, who discovered the solid-state proton tautomerism of phthalocyanine (85JMR159), later studied the behavior of H_2Pc in the solid state using ^{13}C CPMAS NMR (see also 86JA6072) and, preferentially, ^{15}N CPMAS NMR of a ^{15}N-enriched sample. He observed a fast thermally activated proton transfer in both crystalline modifications (α and β) and, at the same time, excluded molecular rotation of H_2Pc. The α-modification shows a quasisymmetric proton potential ($\Delta H \sim 0$), while in the β-modification this degeneracy is lost ($\Delta H =$ 1.3 kJ mol^{-1}) [89CP(136)223]. For "doubly stable" molecules with two degenerate molecular sites in the gas phase, either the crystal (depending on its structure) can retain the degeneracy or the two tautomers, **84a** and **84b,** can become different in energy. The rate of the proton transfer depends on the geometric arrangement of the inner nitrogen atoms; thus, it is faster in the β-phase ($E_a = 32.3$ kJ mol^{-1}) than in the α-phase ($E_a = 39.8$ kJ mol^{-1}). Substantial but different tunnel contributions to the reaction rate are observed in both phases.



Rieckhoff and Voigt reported the fluorescence of H_2Pc in a Shpol'skii matrix (in a mixture of α-chloronaphthalene and *n*-octane) at 4.2 K. They observed a splitting (65 cm^{-1}) of the stable doublet of H_2Pc (14475 and 14411 cm^{-1}) pertaining to the nondegenerate S_1 state, i.e., Q_x, the lowest excited singlet. This can be ascribed to the existence of H_2Pc molecules in

two tautomeric states **84a** $S_1^{(1)}$, the less energetic of which **84b** $S_1^{(2)}$ is obtained by rotating the two inner hydrogens 90° about the molecular axis with respect to $S_1^{(1)}$. Chen, Rieckhoff, and Voigt measured the double-fluorescence lifetimes for these two tautomeric species in a glass state, proving that the tautomers are situated in an asymmetric double-well potential (two-level system, TLS), which is a necessary condition for photochemical hole burning (89MP1439). Later, they described the $S_0^{(1)} \rightarrow S_0^{(2)}$ photochemical transformation in H_2Pc [90SA(A)1601] and discussed the hole-burning technique where the population of a specific tautomer (**84a** or **84b**) was selectively bleached to create an "optical hole" in the background absorption (91SA1023). In subsequent papers they described the single quantum mechanical proton tunneling in the ground state (for tetra-4-*tert*-butylphthalocyanine, TBH_2Pc) at temperatures from 4.2 to 77 K for tautomers embedded in hexadecane matrices (94SA797) and Zeeman studies of both tautomers of H_2Pc (96JCP8210). Renge *et al.* proposed mixed phthalonaphthalocyanines such as **85** (R = $CH(iPr)_2$) as low-temperature photochroms for spectral hole burning (97JPC6202). These compounds **85** exist in two tautomeric forms and the authors determined that the more stable tautomer (educt form) has one proton attached to the naphthopyrrole ring (**85a**) while the less stable tautomer (product form) has the structure **85b.** They determined for a series of compounds the percentage of the less stable form trapped at 10 K (between 2 and 10%) and at room temperature (between 8 and 30%) and the barriers to proton transfer (e.g., 520 cm^{-1}, i.e., 6.2 kJ mol^{-1} for **85**).



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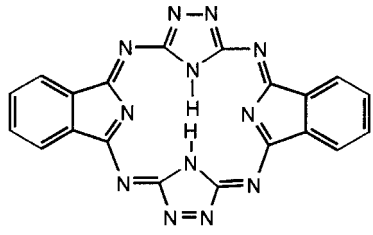
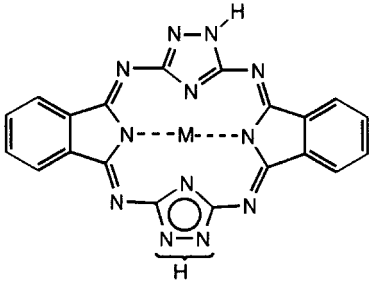


87

Mendoza and Torres and later Torres alone carried out systematic studies of the consequences of replacing an isoindole ring by a 1,2,4-triazole one. A first attempt to introduce two triazole subunits gave the dihydro 20-π ring **86** instead of the 18-π system **87** [89JCS(P2)797]. All attempts to oxidize **86** into **87** failed. Compound **87** was calculated to be less stable than

86 because it implies the destruction of the aromaticity of one of the triazole rings. The tautomerism of **86** is as represented in the scheme; the relative positions of the protons in the triazole rings (1*H* and/or 2*H,* but never 4*H*) are not known. A metal present in the cavity (**88;** M = Mn, Co, Ni, Cu) complexes with the isoindole nitrogen atom and NH's of triazole rings always stay outside the cavity (1*H* and/or 2*H*) (95LA495).



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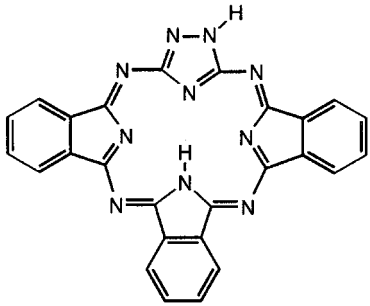

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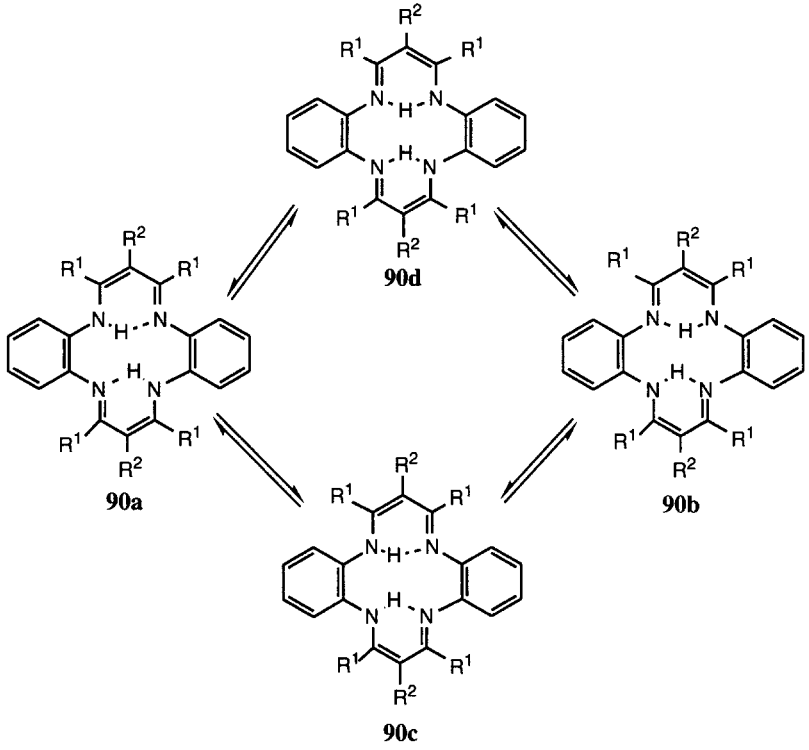
More recently, activity in the field of the preparation of phthalocyanine-like compounds useful in material science concentrated on compounds containing only one triazole subunit (triazolophthalocyanines) **89** [94JCS(CC)1525; 95ICA(230)153]. These aromatic compounds (without or with metals in the cavity) present a problem of annular tautomerism of triazoles, but as yet it is known only that the NH is outside the cavity.

C. Large Rings

This section deals with dibenzotetraaza[14]annulene (1,8-dihydrodibenzo[*b,i*] [1,4,8,11]tetraazacyclotetradeca-4,6,11,13-tetraene) derivatives **90,** in particular with the tetramethyl derivative (R^1 = CH_3, R^2 = H) called TTAA by Limbach [87AGE247, 87BBPC941, 87JA929; 90JMR592; 94JPC843; 97AGE247]. Compounds **90** display annular tautomerism related to that of porphyrins (see Section III,A) and phthalocyanines (see Section III,B). Compounds **90** can exist in four tautomeric forms, two degenerate pairs (unless the substituents R^1 are different). The study of **90** is a cornerstone of modern tautomerism studies because it treats all the novel facets by high-level physicochemical techniques: proton transfer in the solid state, dynamic solid-state NMR, kinetic parameters, ordered crystalline vs disordered glassy state, X-ray crystallography, and *ab initio* calculations.



Limbach and co-workers have studied in particular two compounds: the dimethyl derivative DTTA **90** (R^1 = H, R^2 = CH_3) and the tetramethyl derivative TTAA **90** (R^1 = CH_3, R^2 = H). TTAA is a useful "thermometer" for ^{15}N NMR studies in the solid state (90JMR592). DTTA exists in a tautomeric equilibrium between **90a** and **90b** (the two other tautomers are not significantly populated); the interconversion involves intramolecular jumps of two protons between **90a** and **90b,** which are nondegenerate in the crystal (94JPC843). The analysis of the data led the authors to the conclusion that there is a stepwise double-proton transfer with thermally activated single-proton tunneling along an asymmetric double minimum potential (97AGE247). This result is in contrast to that obtained for solid TTAA, where all four tautomers were observed (87JA929). These differences were assigned to the planar nature of DTAA (dark red) and the twisted nature (caused by repulsion of the four methyl groups) of TTAA (yellow) (87BBPC941). The problem has been investigated by Crayston *et al.* using ^{13}C CPMAS NMR spectroscopy. Although their conclusions generally agree with those of Limbach, they also proposed that the proton transfer is coupled with a rapid 90° rotation of the whole molecule about either of the two C_2 axes in the molec-

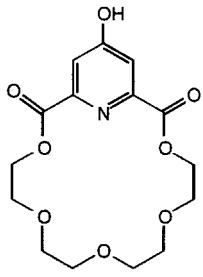
ular plane [95JCS(P2)809]; this is related to the Frydman approach to the tautomerism of porphyrins (see Section III,A). The tautomerization is rapid on the ^{1}H NMR time scale in toluene-d_8 and the equilibrium cannot be frozen at −90°C for **90** (TAA, $R^1 = R^2 = H$) [95JCS(P2)343].

DTTA, TTAA, and related compounds, including the parent compound TAA, have been repeatedly studied using X-ray crystallography. The location of N–H protons on opposite nitrogens (**90a**/**90b**), the near-planar structure of DTAA, and the saddle shape of TTAA are all confirmed [91JCS(P2)1845; 95JCS(P2)343 and references therein]. The existence of geometrical differences between DTAA (C_{2h}) and TTAA (C_{2v}) is necessary to account for the IR and resonance Raman spectra of these compounds; the spectra were assigned using *ab initio* 3-21G calculations (96JPC5252).

D. Supramolecular Structures

We do not discuss in detail the cases of tautomerism of heterocycles embedded in supramolecular structures, such as crown ethers, cryptands, and heterophanes, because such tautomerism is similar in most aspects to that displayed by the analogous monocyclic heterocycles. We concentrate here on modifications that can be induced by the macrocyclic cavity. The so-called "proton-ionizable crown ethers" have been discussed in several comprehensive reviews by Bradshaw *et al.* [90H665; 96CSC(1)35; 97ACR338, 97JIP221]. The compounds considered include tautomerizable compounds such as 4(5)-substituted imidazoles; 1*H*/4*H*-1,2,4-triazoles; 3-hydroxypyridines; and 4-pyridones.

Such modifications can be produced either in the kinetic aspects (proton transfer) or in the equilibrium constant. Both effects are mediated by intramolecular hydrogen bonds. For instance, Navarro *et al.* (93MI69) showed that the rate of proton transfer between the two nitrogen atoms of pyrazole (annular tautomerism) is considerably reduced in macrocycles containing oxygen or nitrogen atoms in the macroring.



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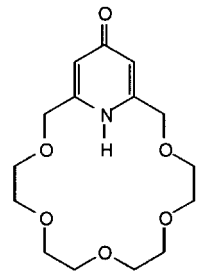

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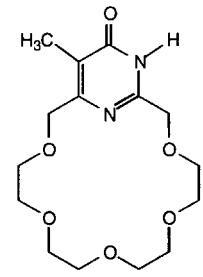

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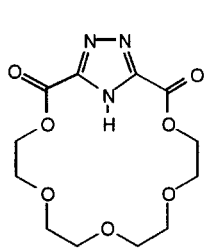

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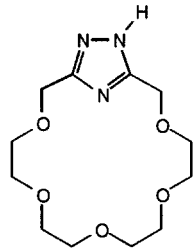

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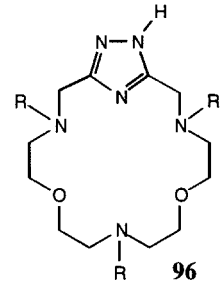
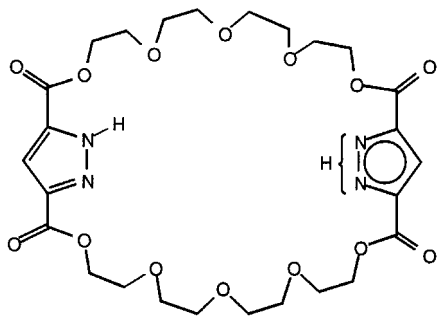


96

As far as tautomerism is concerned, the most interesting of Bradshaw's results is the way in which the tautomerism of pyridones and 1,2,4-triazoles is modified in crown esters and crown ethers. Crown ethers **92** and **95** display the "normal" tautomerism, i.e., as in ordinary pyridone and 1*H*-1,2,4-triazole, while the esters **91** and **94** exist as the "rare" 4-hydroxypyridine and 4*H*-1,2,4-triazole tautomers respectively (85JOC3065). The X-ray structural studies of **91** · $1H_2O$ (85JOC4865), **92** (86JHC353), **94** (85JOC3065), and **95** (86JHC361) confirmed the tautomerism of these compounds in the solid state (see also 97ACR338 and 97JIP221). It was also shown that the pyrimidono-crown ether **93** exists in the "normal" oxo form (97JIP301), the "normal" tautomer was also observed for the aza-crown ether **96** (91JHC773). This different behavior was explained by Bradshaw (97ACR338) as being caused by the much more strong acidic character of the crown esters with respect to the ethers: **91** (pK_a = 8.49), **92** (pK_a = 10.98), **94** (pK_a = 8.4), and **95** (pK_a = 9.55). This explanation rings true for the hydroxypyridine **91** stabilization. In the case of 1,2,4-triazole, the problem needs further investigation because **94** and related compounds are the only 4*H*-triazole tautomers known so far. Mendoza *et al.* have also reported macrocycles related to **95** with the same tautomeric structure (94JOC6539, 94TL7669).



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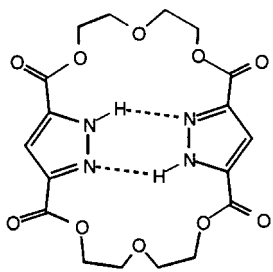

98

Another important contribution to this section is a long series of publications by Navarro and co-workers on macrocycles containing two NH–pyrazole units. Depending on the size of the cavity, the annular tautomerism of each pyrazole is independent, as in (**97**) [88JCS(CC)1365], or correlated, as in (**98**) (94T4765; 97JOC2684). The same was observed for the compounds similar to **98** but with NR instead of O in the macrocycle (93TL3159).

IV. Summary and Conclusions

The only way (other than specific theoretical calculations) to rationalize tautomerism is using the concept of aromaticity and its opposite, antiaromaticity. Because this concept cannot be unambiguously applied to small and large rings, the interpretation and rationalization of such tautomerism have not made much progress since our previous review (76AHCS1). In "microcycles" the ring is too small to sustain the aromatic sextet efficiently and in "macrocycles," with the ring size increasing, the polyenic character of the heterocycle predominates. Only for the tautomerism of porphyrins and phthalocyanins has major progress been achieved as is discussed comprehensively in this review.

Acknowledgments

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Tautomerism of Heterocycles: Condensed Five–Six, Five–Five, and Six–Six Ring Systems with Heteroatoms in Both Rings

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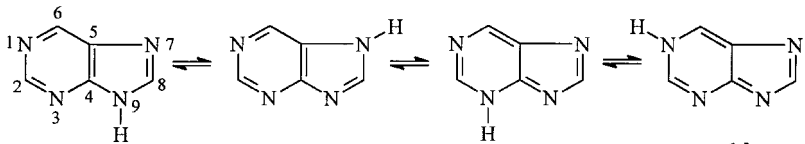
I. [5.6]Bicyclic Compounds (76AHCS1, p. 502)

A. Purines

1. *Tautomerism Involving Only Annular Nitrogen Atom*

a. *Theoretical Calculations.* The predominant existence of purine as the N(9)H (**1a**) and N(7)H (**1b**) tautomers was well established in early studies (76AHCS1, p. 502): in solution, both **1a** and **1b** are present but N(7)H is the only tautomer in the crystal.



1a **1b** **1c** **1d**

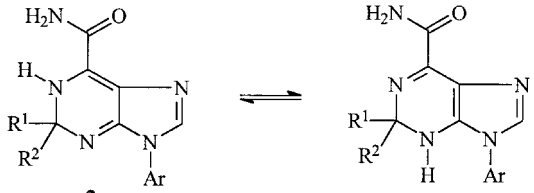
Semiempirical calculations yield the comparable energies for **1a** and **1b** while the N(3)H (**1c**) and N(1)H (**1d**) tautomers are much less stable. A major difficulty in those calculations was the choice of the correct geometry. It was shown recently by Broo and Holmén [96MI(211)147] that there are relatively large differences between the calculated geometry of N(7)H purine (**1b**) (*ab initio* with MP2/6-31G* basis set) and the X-ray crystallography data (65AX573). It was proposed that the crystal geometry is not representative of a free purine molecule due to the hydrogen bonding in the crystal between neighboring species. SCF/3-21G [91SA(A)187] and SCF/6-31G** equilibrium geometries for purine have been reported [94JPC2813; 96THE(366)185], which also showed significant differences with the crystal geometry. The relative equilibrium energies for N(9)H and N(7)H tautomers, as calculated by *ab initio* at various levels [90THE(208)35; 94JPC2813; 96MI(211)147], gave similar results: in vacuum, **1a** is favored by 3.9 kcal mol^{-1}; in aqueous solution, **1b** is stabilized relative to the N(9)H form by less than 1 kcal mol^{-1}. The dipole moments have been calculated for MP2/6-31G** (96JPC2813) and SCF/6-31G** [96THE(366)185] geometries: 3.65 D (**1a**) and 5.97 D (**1b**), but experimental values are not available. Due its higher dipole moment, the N(7)H tautomer should be more stabilized in polar media. Static dipole polarizabilities have been reported for

the 7*H* and 9*H* tautomers [96THE(366)185], which can be used to evaluate various aromaticity indices.

b. *Spectroscopy Studies.* Data on N(9)H–N(7)H tautomerism in a non-interacting environment have been obtained by IR matrix isolation (in neon, argon, or nitrogen; cf. 000AHC(76), Ch. 1, Section VII,B) combined with theoretical *ab initio* studies. The experimental IR spectra of purine were first interpreted as two tautomers **1a** and **1b** existing in almost equal proportions [85JST(131)333]. Later it was shown that the splittings of the IR bands observed for purine were due to "matrix effects," and the N(9)H tautomer with the lower dipole moment is the only one detected in the inert gas matrices [89CPL(157)14; 94JPC2813]. Gas-phase UV photoelectron studies indicated that the spectra of purine are much more similar to the spectra of the 9-methyl rather than the 7-methyl derivative, and this also suggested the dominance of the N(9)H tautomer (80JA4627). Thus, the earlier conclusion from MO calculations of almost equal stabilities of 7*H*- and 9*H*-purines in the vapor phase (76AHCS1, p. 504) has been reconsidered.

Fourier transform IR (FT-IR) and Raman (FT-R) spectra for purine and its D- and ^{15}N-substituted analogs have revealed that the N(7)H tautomer is present almost exclusively both in the solid and in aqueous solution, although a few weak bands may be assigned to the N(9)H tautomer in aqueous solution [94MI(25)233]. Resonance Raman (RR) studies also shown the predominance of 7*H*-purine in aqueous solution [95JST(355)147]. Quantitative experimental results for the solution tautomerism of purine have been obtained from ^{1}H, ^{13}C, and ^{15}N NMR measurements (75JA4636; 82JA3162, 82JA4167). In contrast to the FT-IR, FT-R, and RR data, these studies suggested equal amounts of 7*H*- and 9*H*-purine in aqueous solution and about 40% of the 7*H*-tautomer in DMSO. ^{1}H and ^{13}C NMR chemical shifts have been evaluated to determine the stack formation (dimers and/or trimers) due to the solvent effect and concentration (80JA525). The UV studies in ethanol suggested that the N(9)H tautomer forms dimers at high concentrations through hydrogen bonding, whereas 7*H*-purine does not [88JST(174)83].

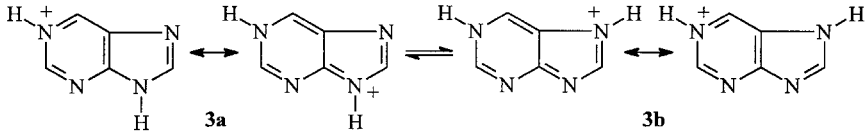
An interesting example of desmotropy (cf. Chapter 1, Section V,D,2) has been reported for dihydropurines **2a** and **2b:** both tautomers have been fully characterized by ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallography [94JCS(P2)1949].



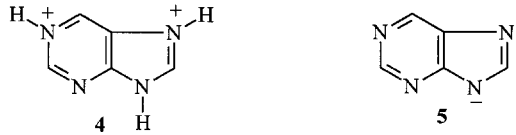
2a **2b**

The low-temperature ESR spectrum of the anion radical of purine disclosed that about 45% of the spin density is localized at position 6 (80BCJ1252), although a single very broad signal for N(7) and N(9) did not allow discussion of the tautomerism.

c. *Cation and Anion Structures.* It was concluded from early NMR studies (76AHCS1, p. 504) that monoprotonation of purine results in **3a** and/or **3b** and that the cation **4** is formed on diprotonation.



3a **3b**



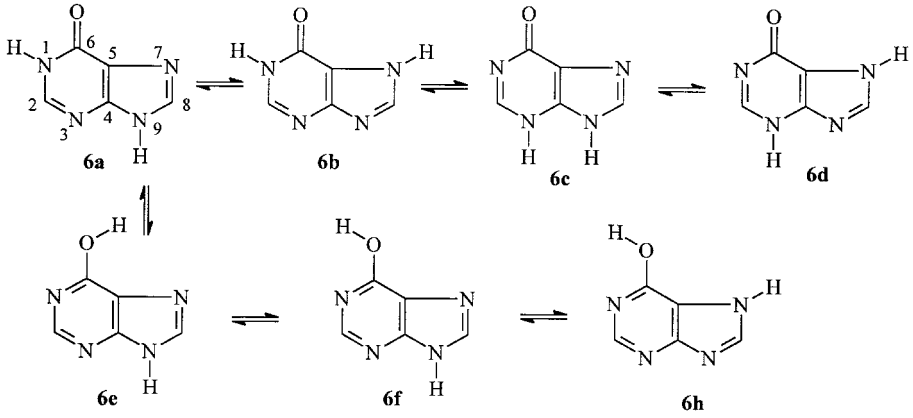
4 **5**

Most recent ^{15}N, ^{1}H, and ^{13}C NMR spectroscopy studies are in accord with the previous data on the principal protonation sites of purine: such results have been reported for the cations in H_2SO_4, CF_3COOH, or FSO_3H with an ~1:1 ratio of **3a** and **3b.** In addition, the anion **5** has been described in aqueous solutions of NaOH or NaOD (82JA4167; 83CB2001). The ^{15}N chemical shifts and ^{15}N-^{1}H and ^{1}H-^{13}C coupling constants for purine and its 7- and 9-methyl derivatives have been assigned at various p*H*. The protonation of purine nucleotide models at N(7) and the C(8)H acidity of the purine cations have been performed by *ab initio* (STO-3G) calculations on neutral, N(7)-protonated, and C(8)-deprotonated purine (85JA2952). It was found that the nature of substituents on the pyrimidine ring has a significant effect upon N(7) basicity of neutral purine and upon C(8)H acidity of N(7)-protonated purine.

Optical detection of magnetic resonance (ODMR) was attempted for measurements of the p*H* effects on the triplet state of purine to investigate the protonation site of purine at low temperatures (78JA7131). The ODMR spectrum did not show the presence of more than one triplet state at liquid helium temperatures. Since the protonated tautomers 1*H*,9*H* (**3a**) and 1*H*,7*H* (**3b**) have similar bond structures, their triplets should have similar zero-field parameters and are thus not easy to distinguish by ODMR.

2. *Oxopurines*

a. *Annular and Functional Group Tautomerism.* The tautomerism of 2-, 6-, and 8-monooxopurines was surveyed in the previous review (76AHCS1, p. 503). The discussion was based on semiempirical calculations and NMR, UV, and IR spectroscopy data with the evident restrictions of the methods developed by the mid-1970s. Since then, no significant data appeared on 2- and 8-oxopurines while 6-oxopurine (**6**), or hypoxanthine, was a subject of intensive investigations due to its biologically important role in interaction with xanthine oxidase (97JA3007).

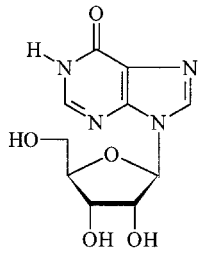


In the solid state, neutral hypoxanthine exists as the 1*H,*9*H* tautomer **6a,** and X-ray crystallography data indicated N(9)-H(9)···N(7) intermolecular hydrogen bonding in the crystal lattice [88AX(C)732]. Since Pullman and Pullman studied the 2-, 6-, and 8-oxopurines by MO methods (76AHCS1, p. 504, and references therein), a few detailed *ab initio* studies have appeared on 6-oxopurine tautomerism. In agreement with the earlier data, practically identical stabilities were found at the 6-31G**, MP2, and DFT(B3LYP) levels for the 1*H,*9*H* (**6a**) and 1*H,*7*H* (**6b**) forms [93THE(279)173; 96JOC5964; 97JPC(A)8309]. Geometry optimizations and molecular and electron properties calculations of the 14 possible tautomers of neutral hypoxanthine have been reported at the DFT level [97JPC(A)8309]. Seven tautomers (**6a–6h; 6e** and **6f** are rotamers) were considered in a final study at the SCF and MP2 levels after screening in the stepwise elimination protocol (energy considerations) (96JOC5964). It was found that the lactim tautomers **6e–6h** are more stable than 3*H*-oxo forms

6c and **6d.** The most stable tautomers are **6b, 6a,** and **6f,** and, according to the relative stabilities determined at the MP2/6-31+G(d,p) level, the population of these forms in the gas phase is 81, 18, and 1%, respectively (96JOC5964). This agrees with the experimental evidence gained from UV photoelectron spectra, which clearly indicated that 1*H,*7*H* tautomer **6b** is more stable than **6a** in the gas phase (80JPC1006). Tautomeric equilibrium constants at different temperatures have been reported for all hypoxanthine tautomers in the gas phase [97JPC(A)8309]. IR spectral studies of hypoxanthine in an Ar matrix assumed the predominant existence of the 1*H,*7*H* and 1*H,*9*H* tautomers **6a** and **6b** with a small contribution of a enolic form [87THE(158)275], and the calculated IR spectra confirmed this conclusion [97JPC(A)8309]. The calculated equilibrium geometries, dipole moments, and static dipole polarizabilities have been reported for the 1*H,*7*H* and 1*H,*9*H* tautomers [96THE(366)185]. Due to the higher dipole moment, the 1*H,*9*H* form **6a** should be stabilized in polar media. Indeed, solvation greatly modulates the tautomerism of hypoxanthine. The most relevant effect is the solvent-induced stabilization of the 1*H,*9*H* form **6a** (96JOC5964). 3*H* Tautomers **6c** and **6d** are also stabilized upon solvation but they are still disfavored with respect to **6a** and **6b;** the enol tautomers are destabilized in polar solvents. The ^{1}H and ^{13}C NMR spectroscopy data indicate that hypoxanthine exists as the 1*H*–oxo forms **6a** and **6b** in almost equal concentrations in aqueous solution (85CJC3053), but that in DMSO-d_6 the concentrations of **6a** and **6b** are 42 and 58%, respectively (75JA4636).

b. *Cation Structures.* Hypoxanthine is well established to monoprotonate at the imidazole ring (71CR439; 85CJC3053), and recent results suggest that N(7) is the protonation site [90MI(39)277]. The X-ray crystallographic study of hypoxanthinium hydrochloride [69AX(B)1608] and nitrate monohydrate [90AX(C)340] concluded that the nitrogen atoms N(1), N(7), and N(9) carry a proton. The cation geometry calculated by *ab initio* (6-31G**) [93THE(279)173] agreed well with the crystallographic data. The choice of the position of the second protonation of hypoxanthine is restricted to N(3) or O(6). Study of the protonation equilibria of hypoxanthine by UV and ^{1}H and ^{13}C NMR spectroscopies in aqueous sulfuric and perchloric acids (85CJC3053) showed that the second protonation occurred at N(3); p*K* values were calculated.

c. *Inosine.* Inosine, a 9-substituted 6-oxopurine, is the N(9)H fixed tautomer. The N(9)-substituted purines are models for residues of purine nucleotides, which are the building blocks of nucleic acids.

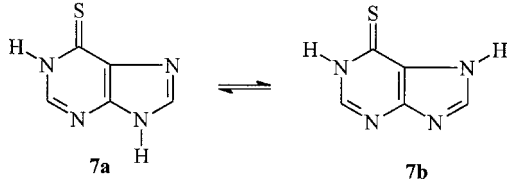


Inosine

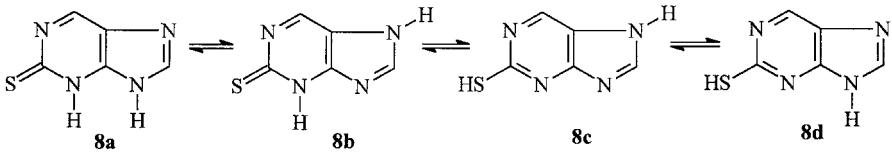
The equilibrium of the four tautomeric forms of inosine was discussed in the previous survey (76AHCS1, p. 509). In agreement with the earlier data, the 6-oxo tautomer was later reported to exist almost exclusively in the gas phase and in solution [IR and UV: 78ZN(C)876; ^{13}C NMR: 75JA4627; 76JA4736]. The most recent IR and ^{1}H and ^{13}C NMR studies of 9-benzocrown substituted hypoxanthine in the solid state and in polar aprotic solutions have confirmed the predominance of the lactam form (96ZOB798). In connection with the determination of the water affinities (log*P*) of nucleic acid bases, 9-methylhypoxanthine was studied in terms of the changed hydrophilic character on lactim–lactam tautomerism [81MI(20)3024]. The results concluded that the oxo form is ~1000-fold more abundant than the hydroxy tautomer at equilibrium.

3. *Purinethiones*

In addition to the rather scattered data reported in the previous survey (76AHCS1, p. 510), a few new studies appeared on purine-6- and -2-thiones. The MO calculations of solvent effects (AM1-SM1 and AM1-SM2) on the tautomerism of 6-thiopurine indicated that 1*H*,9*H*-tautomer **7a** is greatly stabilized in aqueous solution [94THE(309)137]. The same results were obtained experimentally from UV and ^{1}H and ^{13}C NMR studies (75JA3215, 75JA4627, 75JA4636).



7a **7b**



8a **8b** **8c** **8d**

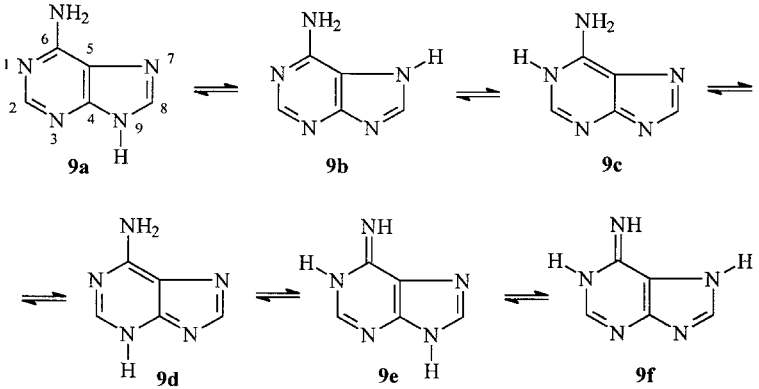
MO studies (AM1 and AM1-SM1) on the tautomerism and protonation of 2-thiopurine have been reported [95THE(334)223]. Heats of formation and relative energies have been calculated for the nine tautomeric forms in the gas phase. The proton affinities were determined for the most stable tautomers **8a**–**8d.** The pyrimidine ring in the thiones **8a** and **8b** has shown a greater proton affinity in comparison with the imidazole ring, or with the other tautomers. In solution, the thione tautomers are claimed to be more stabilized by solvent effects than the thiol forms, and the 3*H*,7*H* tautomer **8b** is the most stable. So far, no additional experimental data or *ab initio* calculations have been reported to confirm these conclusions.

4. *Aminopurines*

Tautomerism of 6-aminopurines, or adenines, has been discussed in the previous survey on the base of the data then available (76AHCS1, p. 513). The 2- and 8-aminopurines were only briefly mentioned due to few experimental data. Recent investigations disclosed that 2-aminopurine can readily replace adenine in base pairs with thymine and also forms moderately stable pairing with cytosine [86MI(14)5869; 88MI(16)5631; 96MI(35)4026]. Thus, the tautomerism of adenine and 2-aminopurine can contribute to the molecular mechanism of point mutation postulated by Watson and Crick in the early 1950s: the introduction of mismatched pairs into DNA leads to mutation, and such pairs can be formed by "rare" tautomers (53MI737, 53MI964). Confident discussion of this mechanism was previously not available due to indefinite data obtained from the low-level theoretical and ambiguous experimental studies. The recent explosive development of computational methods, which can accurately calculate the properties of the species that are not experimentally available, has triggered a growing interest in the tautomerism of aminopurines.

a. *N-Unsubstituted Adenines: Neutral Species.* It was well established that the amino forms **9a**–**9d** are preferred for aminopurines, although earlier data did not easily distinguish between the lowest energy 9*H* (**9a**) and 7*H* (**9b**) forms of adenine. No experimental evidence was reported for the lowest energy "rare" imino forms **9e** and **9f** in the previous survey (76AHCS1, p. 517). *Ab initio* calculations with HF/STO-3G

and 3-21G, SCF-3-21G, and MP2/6-31G and 6-31G* basis sets have since been performed for the evaluation of the geometry and energy in the adenine series [79TCA129; 87JA7629; 88JA2353; 89CPL(156)61; 90JPC1366, 90THE(208)35; 94JPC2813, 94THE(305)139; 97JPC(A)4361; 98JPC(A)526].



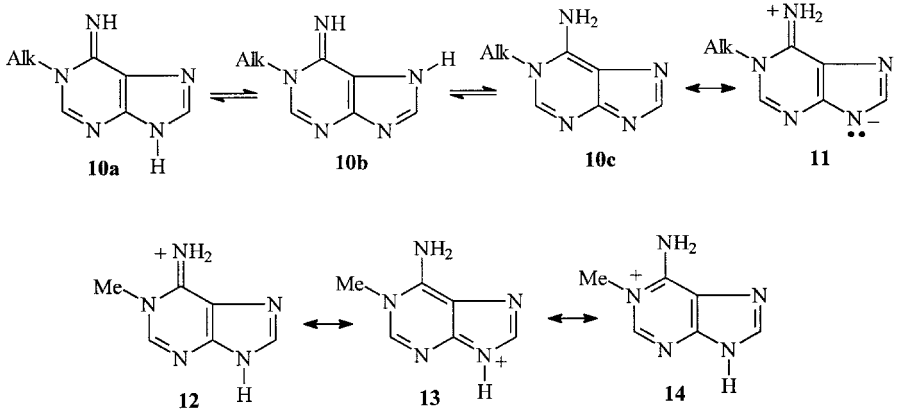
The 9*H* form **9a** was found to be of lowest total energy, in agreement with most experimental results. The 7*H* tautomer **9b** has the second lowest total energy, and the energy difference between the ground states of **9a** and **9b** is 12 kcal mol^{-1} (79TCA129). The calculations predict a large difference between the energy of the most stable "rare" (imino form **9e**) and "normal" (amino form **9a**) tautomers (ca. 14.5–16.5 kcal mol^{-1}), while the estimated free energy associated with spontaneous mutation is about 6 kcal mol^{-1}. This indicates that an amine–imine tautomerization of adenine is probably not the process primarily responsible for spontaneous mutations. The calculations of hydrogen bonding energies for the "rare–normal" and "normal–normal" pairing schemes of adenine–adenine, adenine–guanine, and adenine–thymine also disclosed that the "normal" (amino) form of adenine is more likely to play a role in the mutational mechanism [77MI(4)197; 90THE(237)151]. In polar solvents, the amino tautomer **9a** should still predominate over the imino form **9e** due to the energy differences, even though the latter has a slightly higher calculated dipole moment [90THE(208)35]. Indirect arguments, such as comparison of p*K* values for the methylated adenines [69MI(40)307], have led to the conclusion that in solution **9a** predominates over **9e** by a factor of about 10^5. In the experimental studies, only the 9*H* and 7*H* amino tautomers **9a** and **9b** have been detected. Adenine is a mixture of about 20% 7*H* form and 80% 9*H* form in water (75JA2369), in DMSO-d_6 (75JA4636; 82JA4167), and in a PVA ma-

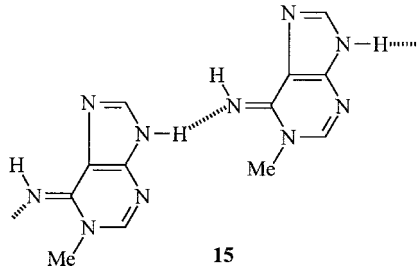
trix [97JPC(A)4361], but in the gas phase and in inert gas matrices the 9*H* tautomer is highly dominant [IR: 78ZN(C)876; 89JPC(156)61, 89JST(194)239; 94JPC2813; 96JPC3527; MW: 89CPL(156)61; UV: 78ZN(C)876; 80JA4627]. This dependence on solvent polarity is to be expected, as the 7*H* tautomer has a substantially larger dipole moment than the 9*H* tautomer [95MI(22)113]. Studies of electronic transitions in adenine have shown that the N(9)H form **9a** and the photochemically produced N(3)H tautomer **9d** contribute to the absorption spectra [94THE(305)139], whereas the luminescence properties of adenine are dominated by the highly fluorescent minor N(7)H tautomer **9b** [80MI(31)323].

b. *Cations of N-Unsubstituted Adenines.* In the previous survey (76AHCS1, p. 515) it was generally accepted that the N(1) protonated adenines predominate, although some controversy was discussed. Recent X-ray crystallographic studies showed that protonation of the ring-N atoms in N^6-mono- and N^6,N^6-disubstituted adeninium hemisulfate hydrates may occur at N(1) or at N(9) (93ACSA38). For some other compounds, the protonation was also reported at N(1) and N(9) [78MI263; 84ACSA(A)485], as observed for the unsubstituted adeninium ion in solid state [74AX(B)166; 81AX(B)140]. In several compounds with various anions the protonation occurred at N(3) and N(7) [83ACSA(A)353; 85MI(15)651; 89ACSA493, 89ACSA882], and in one case it was found to be at N(3) and N(9) [86ACSA(B)226]. It was suggested that the protonation of the ring atoms in adenines depends on the nature of the ion to which the two NH groups are hydrogen bonded and hence on the strength of the hydrogen bonds in the crystal. When both NH groups are linked to the anions, directly or through a water molecule, N(1),N(9) protonation is preferred. When one group is bonded to an anion, and the other to a neighboring adeninium ion, N(3),N(7) protonation occurs. In the latter case, the higher stability of the hydrogen bond to the adeninium ion seems to compensate the lower stability of the bond from NH(7) to the anion. Raman and IR spectral studies of adenine hydrochloride indicated the N(1) protonated species (87MI83). Del Bene has calculated the protonation energies for adenine using *ab initio* SCF methods (83JPC367) and reported that protonation at N(1) is slightly preferred over protonation at N(3) in the gas phase. The N(7) position was shown to be the least probable protonation site [82JST(78)1], but it is protonated below p*H* 1, yielding the dication (76AHCS1, p. 515). *Ab initio* studies (STO-3G) on the influence of substituents at C(2) and C(8) on proton affinities have been reported (85JA2952). The ^{15}N NMR spectroscopy data on the protonation of adenine in aqueous solution indicated N(9) protonation (83JA2050). The fluorescence of acidified solutions of adenine was found to be due to a minor N(7)H tautomer, as in the case of

neutral adenine, and this tautomer carries a proton or a hydrogen both at the 7 and 9 positions (82JPC49).

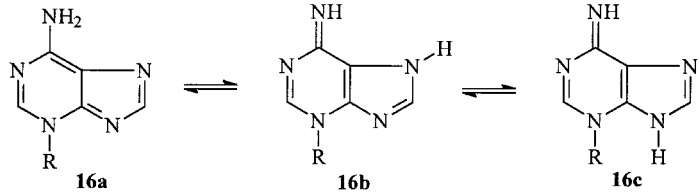
c. *1-, 3-, 7-, and 9-Substituted Adenines: Neutral Species and Cations.* Fragmentary evidence for the existence of 1-methyladenine in the imino form **10a** was discussed in the previous survey (76AHCS1, p. 514). IR and Raman spectral data have since provided clear evidence for the tautomeric stability of the 9*H* imino form **10a** and for structure **12** for the protonated imino compound, which can be in resonance with **13** and **14** [87MI(18)83]. The neutral imino form **10a** is assumed to be stabilized by the hydrogen bonds as shown for **15.** As the result, the dipolar tautomer **11,** which can resonate with the corresponding neutral form **10c,** was postulated on the basis of UV, IR, and ^{13}C NMR spectral data for 1-alkyladenines in solution and in the solid state (77JA7027). FT-IR studies and *ab initio* calculations (SCF/6-31++G**) of the IR spectra determined that the imino tautomer **10a** is largely predominant in Ar matrices, although 9% of the 7*H* imino form **10b** and 5% of the amino tautomer **10c** were also detected [96SA(A)383]. Pivovarov *et al.* reported the exclusive existence of the imino tautomer **10a** in Ar matrix but only semiempirical calculations were used in their analysis [95SA(A)843, 95MI(40)1189]. Studies in solutions have demonstrated the dependence of imine–amine equilibrium on the polarity of the solvent. IR spectra of 1-methyladenine in water indicated the presence of a considerable amount of the imino tautomer **10a** along with the dominant amino form **10c** [95MI(40)1189]. Detailed IR, UV, and ^{13}C NMR studies demonstrated the predominance of the imino form **10a** in nonpolar solvents but the preferred existence of the amino tautomer **10c** in aqueous solution with $K_{[\mathbf{10a}]/[\mathbf{10c}]} = 10^{-2}$ (77JA7027).





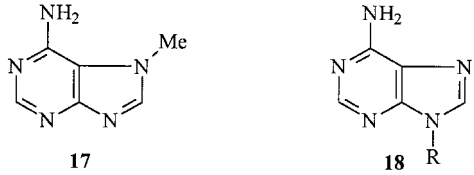
15

For 3-alkyladenines **16,** the equilibrium strongly favors the amino form **16a** irrespective of the environment [IR and UV (solutions): 77JA7027; IR (gas phase): 78ZN(C)876], which is consistent with the data reported earlier (76AHCS1, p. 514).



16a **16b** **16c**

Polarized IR spectra in PVA film, and the calculated (SCRF) spectra of 7-methyl- and 9-methyladenine, **17** and **18** (R = Me) respectively, have demonstrated that they exist as the amino forms shown [97JPC(A)4361].

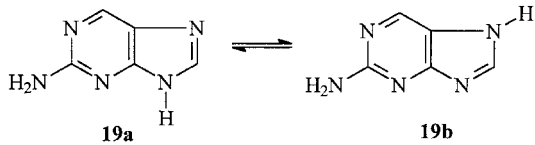


17 **18**

In agreement with the previous observations (76AHCS1, p. 515), 9-substituted adenines **18,** or adenosines, have been shown to exist predominantly in the amino form in the gas phase, in solution, and in the solid state. Protonation mainly occurs at N(1) [IR and UV: 78ZN(C)876, 89JST(194)239; neutron diffraction: 80AX(B)1424; *ab initio* geometries: 96MI(211)147, and energies: 87JA7629, 89MI(291)365; p*H*-dependent laser Raman spectroscopy: 87JA7634; spectropolarimetry: 95MI(28)824]. An interesting example of tautomerism has been described for N^6-methoxyadenosine: in solution, an equilibrium mixture of amino and imino tautomers with

comparable populations has been detected by ^{1}H NMR spectroscopy [93MI(46)207] (cf. 000AHC(76), Ch. 1, Section VI,C). Each tautomer pairs with a different complementary base, thus providing for the first time a suitable model system for the "rare" adenosine form in the studies on mutagenesis.

d. *2-Aminopurines.* 2-Aminopurine (**19**) is an isomer of adenine, but little data were available on it at the time of the previous review (76AHCS1, p. 519). Recent *ab initio* (MP2 and DFT) calculations showed that in the gas phase, the 9*H* tautomer **19a** has about 4 kcal mol^{-1} lower enthalpy of formation than the 7*H* form **19b,** which predicts <1% of the 7*H* tautomer at room temperature [96MI(211)147].

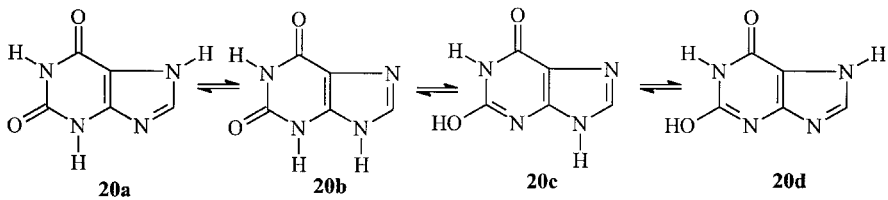


19a **19b**

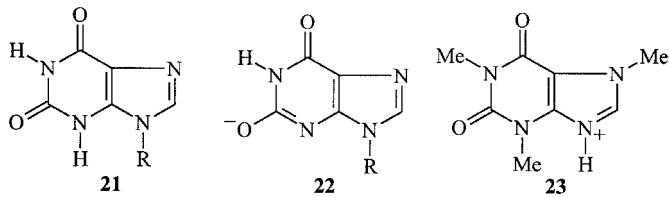
The luminescence properties of 2-aminoadenine are due to the minor N(7)H tautomer, and the geometries of both the ground and the lowest singlet state have been calculated by the CIS *ab initio* method (98JPC526). UV absorption, fluorescence, and excitation spectra have been described for aqueous solutions at different p*H* values [91SA(A)1685]. Several studies of DNA dynamics using 2-aminopurine as an intrinsic probe of helix motion have been performed with fluorescence anisotropy [87MI(15)9011; 89MI(28)9095]. Using linear dichroism, fluorescence anisotropy, and ordinary and magnetic circular dichroism techniques, the near-UV spectra of a few 2-aminopurines have been resolved into contributions from four moderately strong $\pi \rightarrow \pi^*$ transitions and one weak $n \rightarrow \pi^*$ transition (97JA3114). ^{15}N NMR studies of 2-aminopurine deoxynucleoside have targeted its amine–imine tautomerism in water and DMSO-d_6 [89MI(8)23], but no traces of the imino form were detected. The IR spectrum of 2-amino-9-methylpurine has been characterized in terms of transition energies, intensities, and transition moments directions both experimentally (PVA film) and computationally [97JPC(A)4361]. Protonation of 9-substituted 2-aminopurines was shown to occur at the N(1) site. The interaction energy for the 2-aminopurine–cytosine pair was calculated using the STO-3G basis set, and pairing of the amino ("normal") tautomer of 2-aminopurine with the imino ("rare") form of cytosine was found to be preferred, at least at that level of calculation [88THE(179)451].

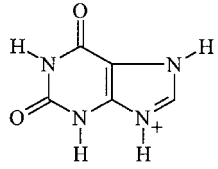
5. *Purines Containing Two Potential Tautomeric Groups*

a. *2,6-Dioxopurines (Xanthines).* Although the majority of purine derivatives exist essentially as 1*H*,9*H* tautomers, for neutral xanthine the 1*H*,3*H*,7*H* form **20a** was postulated to be dominant in solution (76AHCS1, p. 519). Theoretical study of xanthine at various *ab initio* levels [93THE(279)173; 95MI(14)287; 96MI(10)535; 97JA3007] has shown a clear preference for the dioxo tautomers **20a** and **20b,** both in the gas phase and in aqueous solution. Although more stable than other mono- and dihydroxy tautomers, the monohydroxy forms **20c** and **20d** are still strongly disfavored comparing to **20a** and **20b.** The 7*H*-dioxo form **20a** is about 8–9 kcal mol^{-1} more stable than **20b,** and thus the high level calculations are in good agreement with the data reported previously by semiempirical methods (76AHCS1, p. 519). Optimized geometries of neutral, protonated, and coordinated xanthine have been reported with MIDI [93THE(279)173] and 6-31G** [95MI(14)287; 96THE(366)185] basis sets. The theoretical results are in good agreement with the few crystallographic investigations of metal complexes of neutral and anionic xanthine, which elucidated the potential coordination capacity of the imidazole nitrogen atom N(9) (92IC3728). Dipole moments and static dipole polarizabilities have been calculated for the 7*H* and 9*H* tautomers **20a** and **20b** [95MI(14)287; 96THE(366)185].

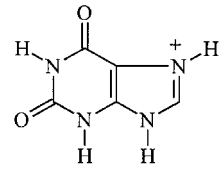


The tautomerism and ionization of xanthosine (**21**), a 9-substituted xanthine, have been studied by IR spectroscopy in aqueous solution [83MI(2)231]. The diketo structure **21** was shown to exist below p*H* ~5, and the 2-enolate anion **22** at neutral and slightly basic p*H*.





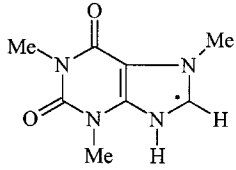
24a



24b

The protonation of xanthine and 1,3,7-trimethylxanthine, or caffeine, has been studied in H_2SO_4 solutions by UV and ^1H and ^{13}C NMR spectroscopies (85CJC3053). In agreement with the previously reported data (76AHCS1, p. 520), caffeine is protonated at N(9) to give **23.** The first protonation of xanthine on the imidazole ring with formation of **24a** or **24b** seems to be well established (71CR439; 85CJC3053). There is no experimental evidence regarding the second protonation of xanthine and caffeine.

An interesting example of the N(9)–C(8) prototropic tautomerism has been reported for the caffeine radical by pulse radiolysis studies in aqueous solution: the transformation of the heteroatom-protonated electron adduct **25** into the carbon-protonated tautomer **26** occurred spontaneously in neutral media [95JCS(F)615].



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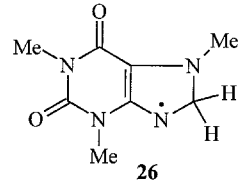

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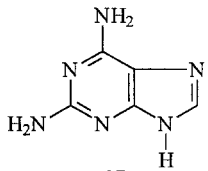
b. *Diaminopurines.* UV absorption, fluorescence, and excitation spectra of 2,6-diaminopurine (**27**) have been studied in aqueous solutions at different p*H* [91SA(A)1685]. UV spectra were interpreted as $\pi \rightarrow \pi^*$ transitions for **27,** and N(7) was excluded as a protonation site. It was established by ^1H NMR spectroscopy that for the *N*-methoxy analog, the imino (usually "rare") form **28a,** and the amino (usually "normal") tautomer **28b** exist in DMSO-d_6 in a 9:1 ratio [98MI(26)1144] (cf. Section I,A,4,c).



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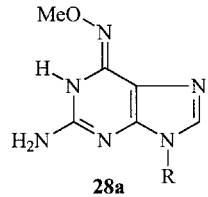
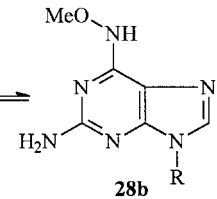
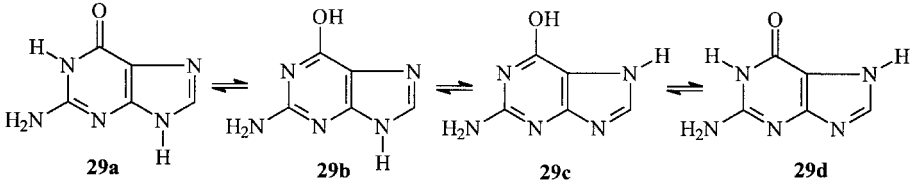


28a



28b

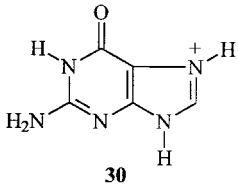
c. *Guanines (2-Amino-6-oxopurines).* Both in aqueous solution and in the crystalline state, guanine has long been well known to exist as an oxo–amino tautomer, presumably **29a,** although the N(9)H–N(7)H tautomerism remained in doubt. Semiempirical calculations also predicted that the oxo forms are the most stable (76AHCS1, p. 523). Earlier UV photoelectron studies of guanine and 7- and 9-methylguanine in the gas phase concluded the predominance of the 1*H*,7*H*-oxo tautomer **29d** but the existence of the lactim forms had not yet been considered (80JPC1006). For the imine–amine tautomerism, the most recent *ab initio* studies on 1,7-dimethylguanine reported the large energy difference between the amino–oxo and imino–oxo tautomers in favor of the amino form [98JST(442)201]; no experimental evidence exists for this type of tautomerism in guanines.



The latest *ab initio* calculations have demonstrated that the predictions of the tautomeric preferences in the guanine system are sensitive to the basis set used and degree of correlation included. Thus, the majority of high-level calculations yielded almost equal energy values in the gas phase for 9*H*- and 7*H*-oxo tautomers **29a** and **29d,** respectively [79TCA129; 86THE(135)253; 89CPL(161)185; 90CPL(174)347, 90THE(208)35; 94CPL(225)265; 95THE(331)147; 96JA6811; 97MI(65)759]. The results from 3-21G to MP4/6-311++G(d,p) levels reported the predominance of the oxo forms **29a** and **29d** over the 9*H*-hydroxy tautomer **29b,** which had a lower energy than the 7*H*-hydroxy tautomer **29c.** However, at least three different tautomers of guanine are observed in the IR isolated matrix experiments (see below). The analysis of experimental data and *ab initio* studies, and the results on the tautomeric stability with large basis sets and higher order electron correlation contributions, have been reported by Leszczynski *et al.* [90CPL(174)347; 90THE(208)35; 91CJC1705; 97MI(65)759; 98JPC(A)2357]. It was found that (1) three tautomers, **29a, 29b,** and **29d,** are located within 2.4 kcal mol^{-1} on the potential energy surface of guanine; (2) energy barriers for the proton transfers from oxo to hydroxy forms are larger than 35 kcal mol^{-1} in the gas phase; and (3) due to

a large difference in dipole moments, the 9*H*-oxo form **29a** is predicted to be stabilized in polar solvents. These conclusions agree well with the experimental data. Thus, IR studies on guanine and 9- and 7-methylguanine have reported that in low-temperature matrices, the amino–oxo (**29a**) and the amino–hydroxy (**29b**) tautomers are present in almost equal amounts [85JST(131)333; 87JST(156)29; 88CPL(153)39; 89JST(194)239; 90JST(222)345; 91CJC1705; 93SA(A)1727]. The amino–hydroxy tautomer occurs as two different rotamers, and, in a low-temperature argon matrix, the ratio of their concentrations is sensitive to UV irradiation. This ratio relaxes to an equilibrium value after irradiation is stopped (91CJC1705). The electronic transitions of guanine have been studied by Jug and Mishra [94THE(305)139], and the contributions of two oxo forms, **29a** and **29d,** and of the hydroxy tautomer **29b** to the absorption spectra have been deduced. Surface-enhanced Raman spectroscopy (SERS) studies were reported for the electrodynamic behavior of the guanine derivatives [96MI(27)533]. SER spectra on a gold colloid indicated that guanine and 7-methylguanine absorb mainly in their oxo forms, adopting a perpendicular arrangement on the gold surface, whereas 9-ethylguanine lies nearly flat on this support with the evidence of 7*H*-hydroxy tautomer. The existence of 9-substituted guanines or guanosines in abnormal hydroxy forms had been reported earlier (76AHCS1, p. 525). In accord with the previous results, the 1*H,*9*H* tautomer **29a** has been confirmed to predominate in polar solvents [96JA6811, 96MI(10)535; 97MI(65)759]. Fluorescence, absorption, and fluorescence excitation spectra of guanine and 7-methylguanine strongly suggested that the luminescence from guanines is mostly due to the minor 1*H,*7*H* tautomer **29d** [80MI(31)323]. The appearance of guanine in the "rare" (lactim) form in an inert environment may have important biological implications in the "rare-normal" pairing related to spontaneous mutations (cf. Section I,A,4,a). The energies calculated for the pairs involving the hydroxy tautomer of guanine are comparable for the G-T "wobble" pair, suggesting that these rare pairs might occasionally be observed [77MI(4)197; 90JA2008, 90THE(237)151].

Theoretical studies have concluded that N(7) of guanine possesses the strongest basicity and thus, in agreement with the previous data (76AHCS1, p. 524), forms monocation **30** in the gas phase and in solution [78MI(7)261; 85JA2952, 85CJC3053; 96JA6811]. A second protonation at N(3) yields the dication **31,** and the p*K* values both for the first and second protonation have been determined (85CJC3053). IR and Raman spectroscopy studies confirm the earlier data (76AHCS1, p. 524) on the formation of the monoanion **32** in basic solutions [78MI(7)261].



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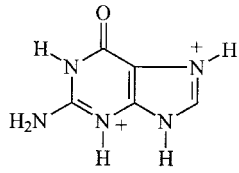

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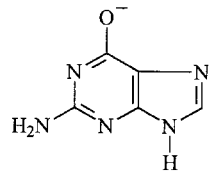
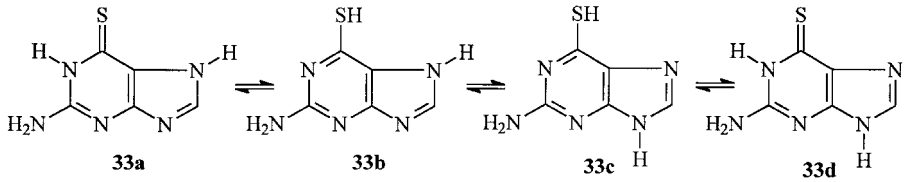


32

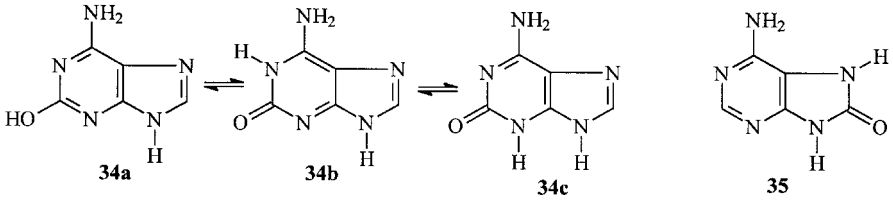
d. *Thioguanine.* The biological relevance of guanine and its sulfur analog has accelerated theoretical and experimental studies on thioguanine. The existence of 6-thioguanine as the N(7)H thione **33a** in the solid state was demonstrated by X-ray analysis (76AHCS1, p. 525) and by IR and Raman solid-state studies [91SA(A)819]. This is unlike guanine, which occurs as the N(9)H oxo species in the solid state (cf. Section I,A,5,c).



33a **33b** **33c** **33d**

Recent investigation of the IR spectrum of 6-thioguanine in an argon matrix showed that, similarly to guanine, the N(9)H thiol form **33c** is predominant (about 85%) over the N(7)H thione **33a** [95MI(41)300]. This is in agreement with the *ab initio* calculations in a noninteracting environment [93JPC3520; 94THE(311)37; 95JOC969; 97JPC(A)4753], whereas in polar solvents the N(7)H thione **33a** was initially predicted to dominate (95JOC969). However, recent high-level *ab initio* calculations by Leszczynski *et al.* [97JPC(A)4753] suggest the existence of N(9)H thiol **33c,** N(9)H thione **33d,** and N(7)H thione **33a** in a 98 : 18 : 1 ratio of tautomer concentrations in aqueous solution. Interestingly, the calculated dipole moment for the thione **33d** is roughly twice as large as that of the most energetically favored tautomer (the thiol **33c**), but no direct correlation is seen between dipole moment and stability for the SCRF model calculations (cf. 000AHC(76), Ch. 1, Section III,D). Experimental UV absorbance and luminescence studies confirm the existence of at least two distinct thione chromophores, and these data were used to determine that 6-thioguanine is present in DNA in the N(9)H form **33d** [97JPC(A)4753]. *Ab initio* (SCRF) studies on protonation of 6-thioguanine predicted that the N1(H),7H,9H thione and two thiol forms exhibit close stability in the gas phase, but only the N1(H),7H,9H thione form is expected in aqueous solution (95JOC969).

e. *2- and 8-Oxoadenines.* The geometry and electronic properties of 2- and 8-oxoadenines have been calculated by a high-level *ab initio* method [95JPC9702; 97THE(397)167]. The most stable forms are the enol–amino **34a** for 2-oxoadenine, or isoguanine, and the oxo–amino **35** for 8-oxoadenine, both with the fully aromatic pyrimidine ring. The existence of form **35** is in agreement with NMR observations in solution and in the solid state [77JA3250; 91MI(19)1041]. The existence of the hydroxy (**34a**) and oxo (**34b**) tautomers has been implicated in the UV and NMR spectroscopy studies of isoguanine (76ZN361) and isoguanosine (95HCA1843). The tautomerism of isoguanine is solvent dependent: the oxo form **34b** dominates in polar solvents, whereas nonpolar ones favor the hydroxy form **34a.** Although the N(3)H tautomer **34c** has not been detected by spectral studies, the investigation of the thermodynamics of duplex formation in two unnatural nucleotide systems consistently suggested its existence (93HCA259; 96AGE1537; 97JA4640).



6. *Conclusion*

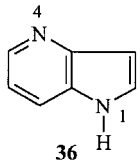
The explosive interest in purines which arose in the 1950s following publication of the Watson–Crick model (Section I,A,4) has continued. Whereas much of the basic chemistry of purines was explored by the 1980s, there is a steady and continuing interest in purine-base chemistry including *de novo* purine nucleotide biosynthesis, improvements in methods for calculating and measuring interaction energies, new studies of tautomeric forms, and refined X-ray data. These new developments are heading toward the information which could provide the experimental proof for the Watson and Crick postulate on the molecular mechanism of point mutation.

B. Azaindoles

1. *Annular Tautomerism*

a. *Monoazaindoles.* The four possible monoazaindoles **36–39** all possess the indole structures shown as reported in the previous survey

(76AHCS1, p. 528). *Ab initio* (STO-3G) calculations of the geometry, charge distribution, and gas-phase basicity of azaindoles concluded that the structure of five-membered ring is almost unaffected by the position of the aza-N atom (83T2851).



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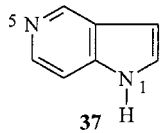

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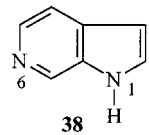

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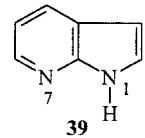
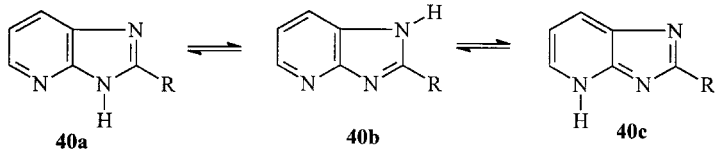


39

A N(1)H–N(7)H phototautomerism of 7-azaindole (**39**) has been proposed to involve dimer formation (76AHCS1, p. 529). A study on the thermal or tunneling mechanism of the proton transfer in the excited state suggests that a tunneling mechanism does not need to be involved (80JA3259). The excited-state intermolecular double-proton transfer in 7-azaindole in water, alcohols, and in carboxylic acids has been studied extensively, and three main mechanisms along with the references cited are presented in 000AHC(76),. Ch. 1 (Section VIII and Table XIV). In addition, more data on acid catalysis and on solvation dynamics in a variety of alcohols are available on 7-azaindole (91JPC10359; 94JPC8801) and on 1-, 2-, 3-, and 4-azacarbazoles (91JCP4074; 97JOC5104). The mechanism of phototautomerization for 7-azaindole is similar to that for flavins (**152**) (cf. Section III,D).

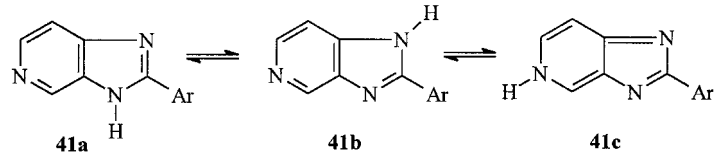
In agreement with the previous data on the protonation site in azaindoles (76AHCS1, p. 529), an example of monoprotonation of 3-aryl substituted 6-azaindoles at the pyridine ring has been demonstrated by UV spectroscopy [88JCS(P2)1839].

b. *Imidazopyridines.* A previously inconclusive choice between the tautomers of imidazo[4,5-*b*]pyridines (**40**) (76AHCS1, p. 529) has been resolved by ^{1}H and ^{13}C NMR studies: the 3*H*-form **40a** (R = H*)* is the major component in the equilibrium (87MRC16). Two-dimensional NMR experiments described the presence of two tautomers in DMF, 3*H*-form **40a** and 1*H*-tautomer **40b,** in a 2 : 1 ratio (93H971). Methoxymethylation of this tautomeric mixture resulted in 3- and 1-alkylated products in a 4 : 1 ratio. It was concluded that the overall site selectivity toward methoxymethylation appears to be governed by the relative reactivity of individual nucleophilic sites rather than tautomeric composition in solution. No spectroscopic evidence has been reported for the theoretically possible 4*H* tautomer **40c.**



40a **40b** **40c**

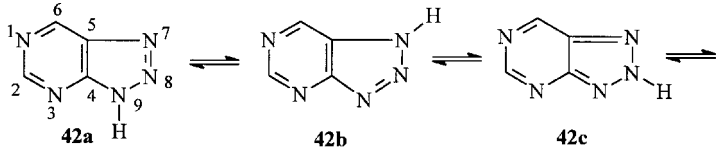
A detailed analysis of the ^{13}C NMR spectra of imidazo[4,5-*c*]pyridine (**41**) concluded that the 1*H* tautomer **41a** predominates (89MRC992).



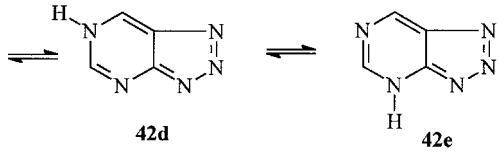
41a **41b** **41c**

The pyridine nitrogen atom remains the center for predominant protonation of both imidazo[4,5-*b*]- and imidazo[4,5-*c*]-pyridines **40** and **41,** respectively [88JCS(P2)1839; 90MRC573].

c. *8-Azapurine.* No experimental data are available on 8-azapurine but this system has been studied theoretically. Early semiempirical calculations (76AHCS1, p. 530) predicted that the relative stability of the three studied tautomeric forms follows the order N(9)H (**42a**) > N(7)H (**42b**) > N(8)H (**42c**), with **42c** about 30 kcal mol^{-1} less stable than the other two. Later CNDO/2 calculations showed that N(1) and N(3) are the most basic centers in the neutral species and hence one can expect that the N(1)H and N(3)H forms will be stabilized in the corresponding monocation [75AX(B)1751; 77JA4119]. Recent *ab initio* (HF/3-21G*) calculations concluded that in the gas phase, the stability order for the tautomers is N(9)H (**42a**) > N(8)H (**42c**) > N(7)H (**42b**) > N(3)H (**42e**) > N(1)H (**42d**) [96THE(365)63]. The use of the SM2 solvation model predicted the stability of tautomers in aqueous solution as N(8)H (**42c**) > N(9)H (**42a**) > N(7)H (**42b**) > N(1)H (**42d**) > N(3)H (**42e**).

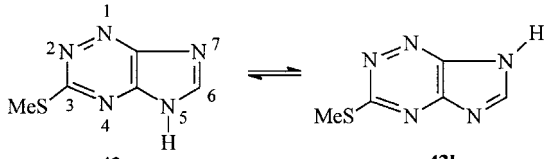


42a **42b** **42c**



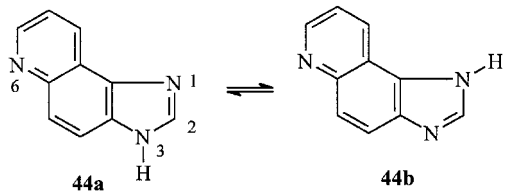
42d **42e**

d. *Imidazotriazines and -quinolines and Indoloquinoxalines.* For imidazo[4,5-*e*]-*as*-triazine, the 5*H* tautomer **43a** predominates (69%) over the 7*H* form **43b** in DMSO-d_6, as was determined by ^{13}C and ^{15}N NMR studies [86JCS(P2)931]. In the monocation, protonation occurs mainly at N(1) [88JCS(P2)1839].



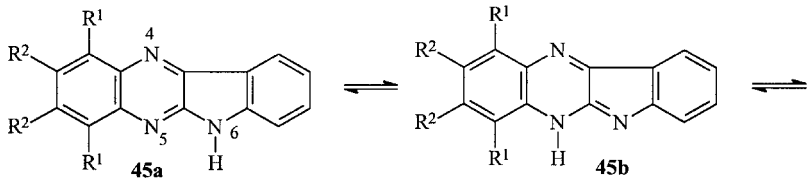
43a **43b**

Ab initio calculations (STO-3G) on imidazo[4,5-*f*]quinolines have shown that in all cases (neutral, anionic, mono-, and dicationic) the 3*H* form **44a** is favored over the 1*H* form **44b** [93THE(279)167].

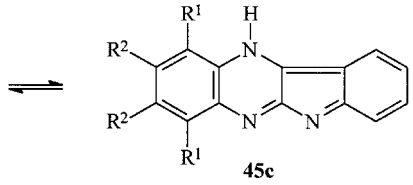


44a **44b**

Indolo[2,3-*b*]quinoxalines could theoretically exist as three tautomers **45a**–**45c.** UV studies have concluded the predominance of the 6*H* form **45a** (83CHE974).

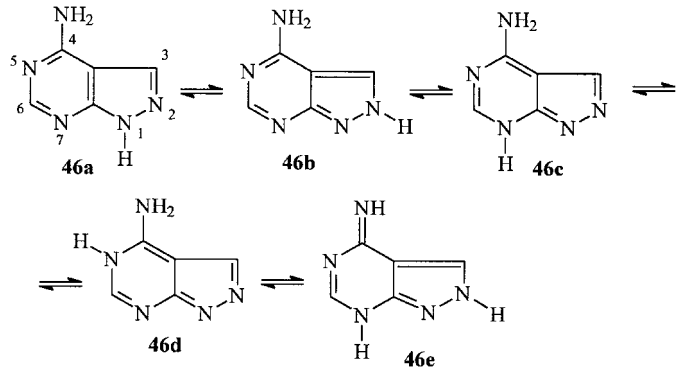


45a **45b**



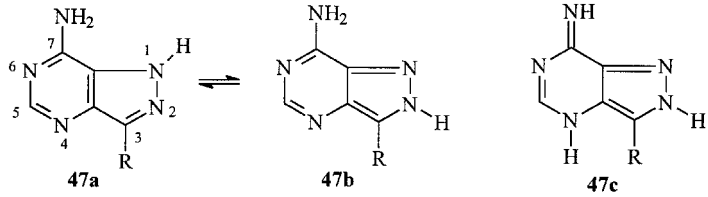
45c

e. *Aminopyrazolopyrimidines.* 4-Aminopyrazolo[3,4-*d*]pyrimidines (**46**) and 7-aminopyrazolo[4,3-*d*]pyrimidines (**47**) strongly prefer amino structures (similarly to 4-aminopyrimidine) and exhibit annular tautomerism. Neutral 4-aminopyrazolo[3,4-*d*]pyrimidine exists in water in two tautomeric forms, 1*H* (**46a**) and 2*H* (**47b**) with $K_{[46a]/[46b]} = 0.1$ at 10°C (76JA7257). The interconversion of two forms is catalyzed by H^+ or OH^- and proceeds through either an intermediate cation or the anion. ^{13}C NMR spectroscopy determined that the monocation is formed by protonation of the 1*H* tautomer **46a** at N(5). Comparisons with the corresponding methylated derivatives in temperature-jump experiments suggested small amounts of the 7*H* form **46c** ($\sim 10^{-3}$) and 5*H* tautomer **46d** ($2 \cdot 10^{-4}$). The latter in water has a partial imino structure **46e** with $K_{[46d]/[46e]} = 10$.



46a **46b** **46c** **46d** **46e**

7-Aminopyrazolo[4,3-*d*]pyrimidine moiety (**47**) is present in several nucleosides of both biological and synthetic origins. Among them, formycin (**47,** R = 3β-D-ribofuranozyl) is of particular interest as a C-nucleoside analog of adenosine.



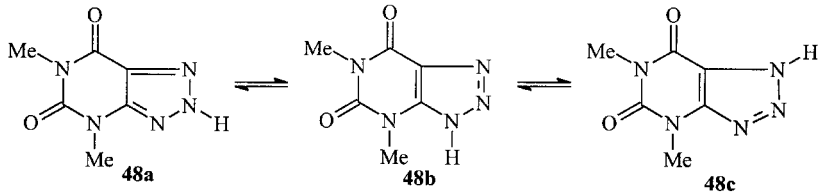
47a **47b** **47c**

Ab initio calculations with STO-3G [89MI(291)365] and 4-31G* (90JOC753) basis sets suggested that the 1*H* form of formycin (**47a**) is the most stable. The X-ray structural data on formycin [73MI(12)1196] detected the N(1)H tautomer **47a.** NMR studies clearly demonstrated the existence of a N(1)H–N(2)H tautomerism in solution, the 1*H* form being the most abundant (73JA4761, 73JHC431; 76JA4736). At physiological pH, formycin was found as a mixture of **47a** and **47b** with 94% predominance of the 1*H* form [94MI(13)481]. Wierzchowski and Shugar have reported the detailed study on the luminescence spectra, which distinguished the tautomers **47a** and **47b** by the location of the emission maxima [82MI(35)445]. Also, the proton migration in the excited state of formycin has been observed, which constitutes one of the few examples of phototautomerism in heterocycles similar to 7-azaindole (cf. Section I,B,1,a) and flavins (cf. Section III,D). So far, no evidence of any imino form (e.g., **47c**) has been reported.

Protonation at N(4) and N(6), and deprotonation at N(1) have been described for formycin [90JOC753; 94MI(13)481]. The X-ray structural data on protonated formycin are surprisingly heterogeneous: whereas formycin hydrobromide was reported as the N6(H),2H form [74AX(B)1511], 3′-deoxyformycin hydrobromide was detected as the N4(H),1H tautomer [87AX(C)2358].

f. *2-Azaadenine.* High-level *ab initio s*tudies on 2-azaadenine suggested, similarly to adenine (cf. Section I,A,4,a), that the N(9)H–amino form is preferred both in the gas phase and in aqueous solution [97MI(11)153].

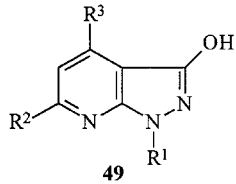
g. *8-Azatheophylline.* The existence of 8-azatheophylline mainly in the N(2)H form **48a** has been concluded from ^{13}C and ^{15}N NMR spectroscopy studies in DMSO-d_6 (87MRC362).



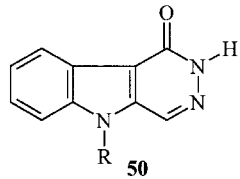
2. *Functional Group Tautomerism*

a. *Azaindoles with One Potential Tautomeric Group.* IR, UV, and ^1H NMR spectral data provided clear evidence for a dominance of the hydroxy form **49** for 3-hydroxypyrazolo[3,4-*b*]pyridines (78BSB309). The preference

of the oxo forms for pyridazino[4,5-*b*]indoles **50** and **51** [93JCR(S)362], for pyrazolo[3,4-*d*]pyridazines **52** (77JHC375), and for the β-oxo acids/esters **53** (83JHC999) has been concluded from analysis of the IR, UV, and NMR spectral data, although the existence of **51** to some extent as a hydroxy form has been proposed from UV spectral observations.



49



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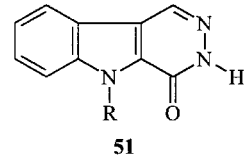

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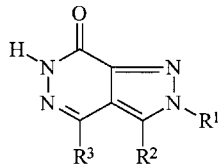

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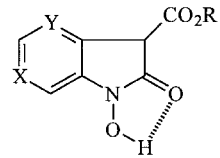
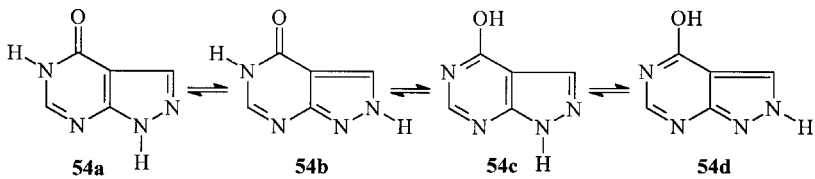


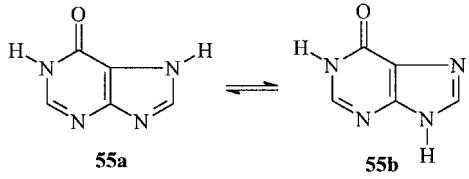
53 (X = N, Y = CH; X = CH, Y = N)

Allopurinol (**54**), which differs from hypoxanthine (**6**) only in the position of the nitrogen atoms in the five-membered ring, has been studied theoretically and experimentally. The crystal structure of neutral allopurinol revealed the 1*H*,9*H* tautomer **54a** as the predominant form [72AX(B)2148]. UV absorption and ^{1}H NMR spectra concluded the presence of 1*H*,9*H* and 1*H*,8*H* forms in solution [75CHE735; 79JCS(P1)2795]. High-level *ab initio* studies [93THE(273)173; 96JOC5964, 96THE(366)185; 99JCC200] suggested a preference for the oxo tautomers **54a** and **54b,** both in the gas phase (**54a** dominates) and in solution (**54b** is stabilized). The lowest energy hydroxy forms **54c** and **54d** are strongly disfavored compared to **54a** and **54b** (compare with hypoxanthine; Section I,A,2,a), and thus only annular tautomerism is exhibited for allopurinol. The X-ray structural analysis of allopurinilium chloride detected the protonation of the predominant tautomer **54a** at N(8) or at N(3) [87MI(137)181].

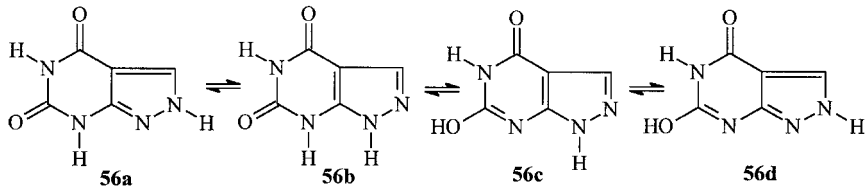


54a **54b** **54c** **54d**

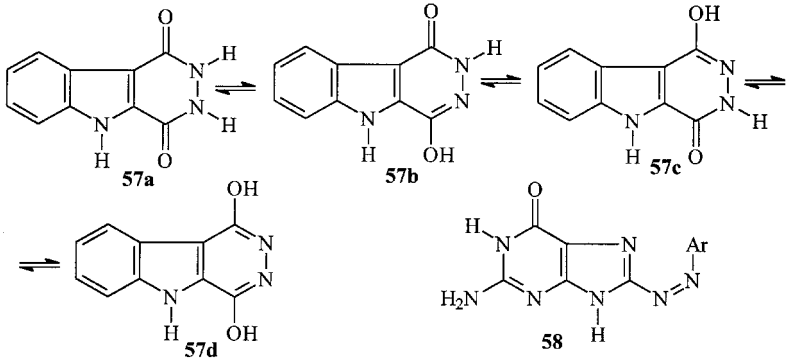
Ab initio calculations at SCF and MP2 levels with the 6-31G+G(d,p) basis [97MI(11)153] predicted a clear preference for the oxo species of 2-azahypoxanthine (**55**) and the predominance of the 7*H* form **55a** both in the gas phase and in aqueous solution.



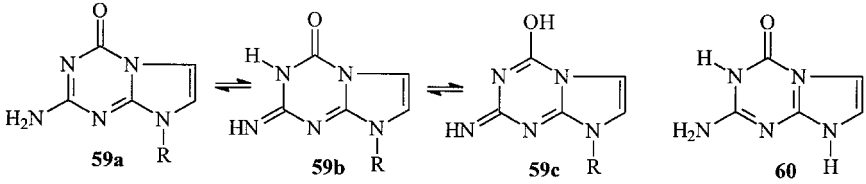
b. *Azaindoles with Two potential Tautomeric Groups.* Alloxanthine (**56**) is the enzymatic oxidation product of allopurinol (**54**), and its structure is isomeric to xanthine (**20**) in the five-membered ring. Structural information about alloxanthine is very limited: X-ray structural studies of some complexes were stated to be planned [93THE(279)173]. Theoretical studies provide some predictions on the tautomerism of alloxanthine. Four tautomeric forms, **56a**–**56d,** were selected by energy considerations. Similarly to xanthine, the 1*H,*3*H,*8*H*-dioxo form **56a** has been found to be the most stable, both in the gas phase and in solution, followed by the dioxo form **56b** [93THE(279)173; 96MI(10)535, 96THE(366)185] (cf. Section I,A,5,a).



All four tautomeric forms have been detected by UV studies in aqueous solution for pyridazino[4,5-*b*]indole system in the relative abundance of $10^5:10^8:10^4:1$ for **57a, 57b, 57c,** and **57d,** respectively (93T11145). The existence of 8-arylazoguanines (**58**) in the 9*H*-oxoamino form in the solid state and in solution has been proved by the detailed IR, and ^{13}C and ^{15}N NMR studies [91AP(324)133].



The 1D and 2D NMR experiments for 5-aza-7-deaza-2′-deoxyguanosine concluded that the oxo–amino tautomer **59a** is preferable in DMSO-d_6; whereas the oxo–imino form **59b** dominates in D_2O (87JOC5136). Evidence for the hydroxy–imino tautomer **59c** was not found. Poor solubility of the parent compound, 5-aza-7-deazaguanine (**60**) did not allow study of its tautomerism, but the pK values of protonation and deprotonation for **60** are identical with those for **59.**

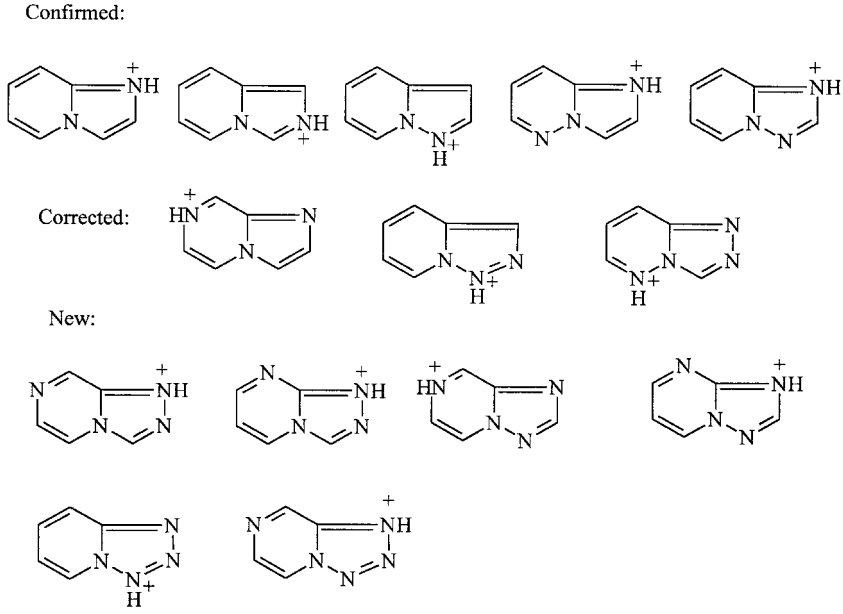


C. Azaindolizines

1. *Annular Tautomerism in Conjugated Acids*

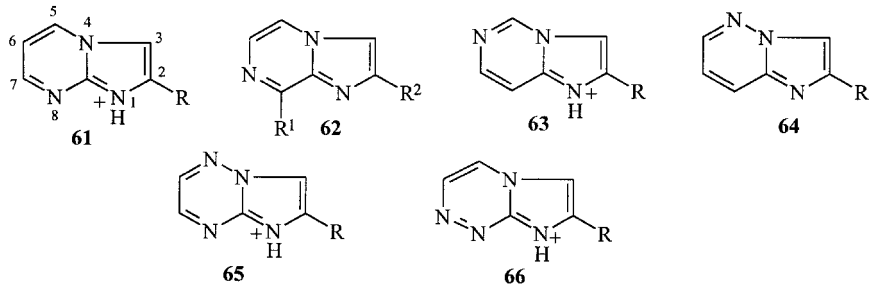
Data on the protonation sites for a variety of azaindolizines have been summarized in the previous survey (76AHCS1, p. 536). The measured magnetic circular dichroism spectra for 14 azaindolizines confirmed with some corrections the protonation sites of polyazaheterocycles previously reported and also established the conjugated acid structures of additional compounds (85JOC302). The data are summarized in Scheme 1.

Several polyazaindolizines (**61–66**) have been studied by ^1H and ^{13}C NMR spectroscopy, and the major protonation sites have been determined



SCHEME 1

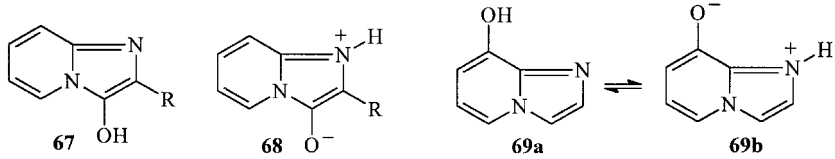
(91MRC468). It was found that **61, 63, 65,** and **66** are all protonated at N(1) (R = H, Ar). Protonation at N(1) occurs also for **62** (R^2 = H) and **64** (R = H), but on introduction of the aryl substituent at position 2, **62** was protonated at N(7) while **64** underwent acid-catalyzed decomposition.



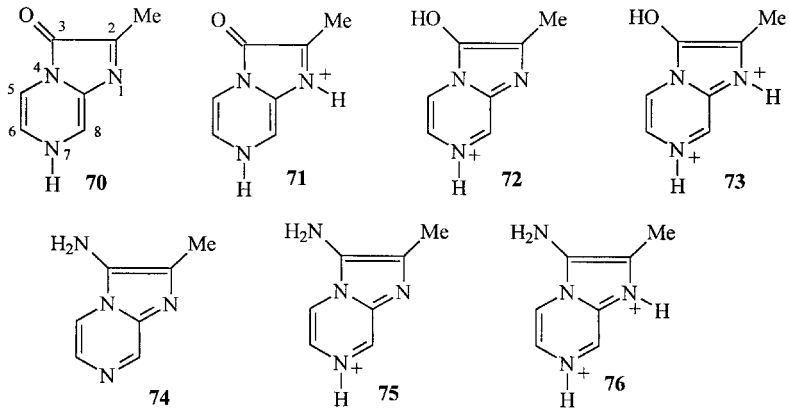
2. *Functional Group Tautomerism*

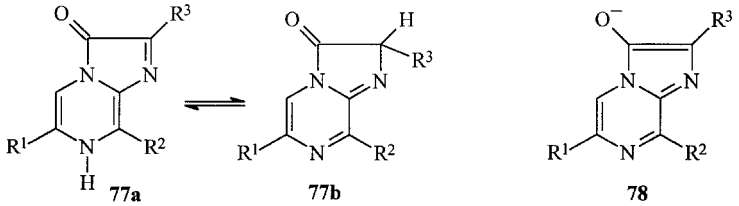
a. *Monoazaindolizines with One Potential Hydroxy Group.* The hydroxy form **67** reported in the previous survey (76AHCS1, p. 537) has been reconsidered, and the alternative betaine structure **68** has been demon-

strated by comparison with the fixed tautomers in UV spectral studies (86TL1627). The presence of the hydroxy form **69a** and the zwitterion **69b** was indicated for neutral solutions of imidazo[1,2-*a*]pyridine system by UV and ^{13}C NMR spectroscopy at different pH [85TL2571; 86JCR(S)50]. A potentiometric study was used in determination of the dissociation constants.



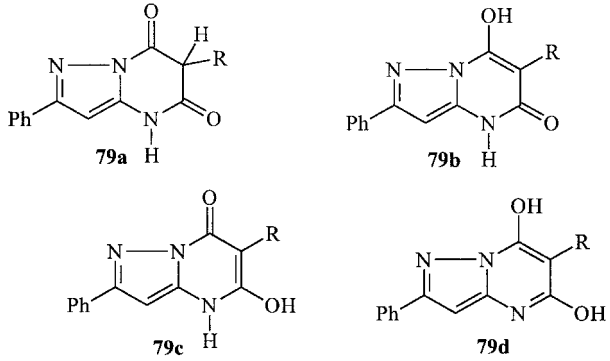
b. *Diazaindolizines with One or Two Potential Tautomeric Groups.* The oxo and amino derivatives of imidazo[1,2-*a*]pyrazines have been studied by UV and NMR spectroscopy at different pH (75T939). In neutral solutions, **70** and **74** exist as the 7*H*-oxo and the amino form, respectively. The oxo monocation **71** is preferred in weakly acidic methanol, whereas in weakly acidic water the hydroxy form **72** is dominant. The amino monocation **75** is formed in weakly acidic solutions irrespective of the solvent; the dications **73** and **76** exist in strongly acidic media. A studies of the effects of pH and protic and aprotic solvents on the visible absorption characteristics of luciferin and its analogs, known for their bioluminescence reaction, made possible the assignment of two tautomers, **77a** and **77b** of *Renilla* luciferin with the predominance of the oxo form [75MI(14)2371; 97RCR187, and references therein]. Deprotonation of **77a** at N(7) was concluded from the UV spectra at pH 11 [75MI(14)2371]; the anion **78** formed will have the charge located largely on oxygen.





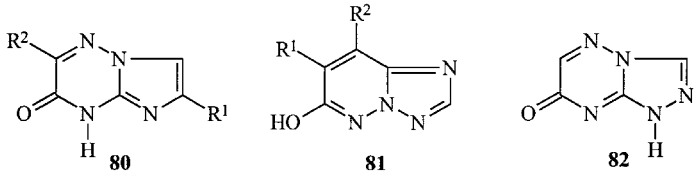
77a **77b** **78**

The existence of all four tautomers of pyrazolo[1,5-*a*]pyrimidine derivatives **79a–79d** was deduced from IR spectroscopy (77ZOR1988). The monohydroxy forms **79b** and **79c** have been ascribed in the solid state; whereas in $CHCl_3$, the absorption bands responsible for all tautomers were claimed to be present. No additional confirmation of these conclusions is available.



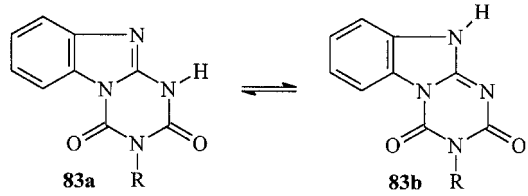
79a **79b** **79c** **79d**

c. *Tri- and Tetra-azaindolizines Containing Potential Tautomeric Groups.* The oxo structure for **80** has been established by UV and IR spectroscopy data (79ZOR1798). The hydroxy tautomer of the species **81** is predominant in solution, as was shown by ^{13}C NMR spectroscopy and by comparison with the corresponding anions and methoxy derivatives (77JHC1403). *s*-Triazolo-*as*-triazinone **82** exists in the oxo form, which was determined by UV spectroscopy in the vapor phase (80OMR330).



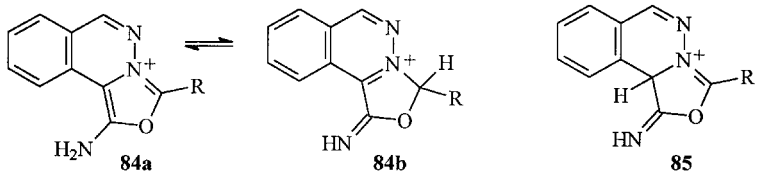
80 **81** **82**

The existence of two annular tautomers in solution has been concluded from ^{1}H NMR spectroscopy for the cyclic *N*-acylbenzazoles **83** [82JPR(324)569]. Enamine and methylene imine tautomers have been described for condensed azolo-quinoxalines [93JHC782, 93JHC1463; 95H2057]; this type of tautomerism is discussed in detail for the [6.6]bicyclic compounds (see Section III,E,2).

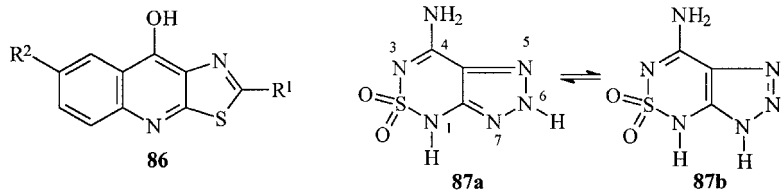


D. [5.6]Bicyclic Compounds Containing O and S in the Five-Membered Ring

The amino form **84a** exists in equilibrium with the imino structure **84b** and not with **85** as concluded from the structure of products of deuterium exchange (87MRC757; 91H329).



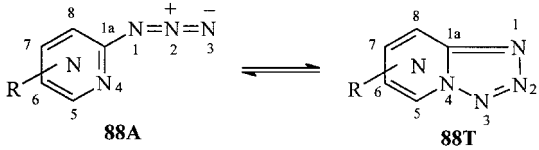
The IR and ^{13}C and ^{15}N NMR spectra for thiazolo[5,4-*b*]quinolines **86** demonstrate their existence in the hydroxy form (96T11929). The preference for 1*H*,6*H* tautomer **87a** in water and in the solid state is supported by ^{13}C and ^{15}N NMR spectroscopy, *ab initio* (STO-3G*) and X-ray crystallographic studies [75AX(B)1427; 92H1399].



E. Azido–Tetrazole Isomerism

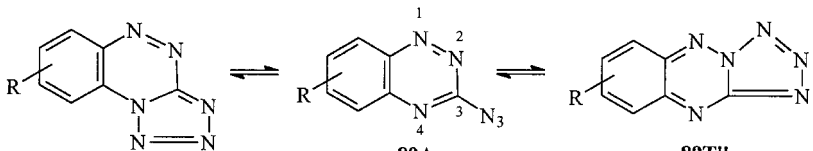
Azide–tetrazole isomerism, or valence tautomerism, was not discussed for [5.6]bicyclic systems in the previous survey (76AHCS1). During recent years, this type of ring-chain tautomerism has been extensively studied for both six- and five-membered heterocyclic azides. The tautomerism of [5.5]bicyclic tetrazole systems is covered in Section II,C. We discuss the tautomerism of the six-membered heterocyclic azides in this section.

A combination of ^{1}H, ^{13}C, and particularly ^{15}N NMR spectroscopy provides a very satisfactory method for obtaining quantitative estimates of the position of equilibrium between the azide (**88A**) and tetrazole (**88T**) forms (97MRC237). The dependence of equilibrium on the solvent and on the position and the nature of the substituent(s) has been reported by multinuclear NMR spectroscopy for substituted azidopyridines (97MRC237) and 2-azidopyrimidines (80AGE924). The tautomerism of azidopyrazine- and azidopyridazine-*N*-oxides is strongly dependent on the structure for π-deficient *N*-oxido azides and on the solvent (70JOC1138; 83H1987).



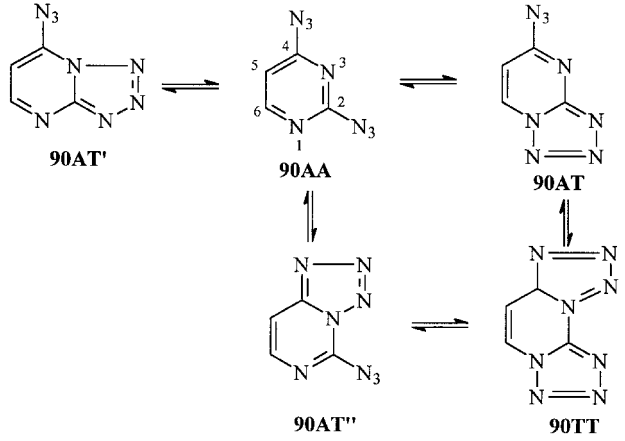
88A **88T**

Azido-pyrimidines and -triazines with substituents in the heterocyclic ring and/or with two azido groups can form structurally isomeric tetrazoles. Thus, 3-azidobenzo-*as*-triazines **89A** cyclize in polar solvents either at N(2) or at N(4), affording ternary equilibrium mixtures in which **89T′** often predominates (82JOC3886). In the naphtho series, cyclization at N(2) largely predominates for naphtho[2,1-*e*]-*as*-triazine and naphtho[1,2-*e*]-*as*-triazine, whereas tetrazole ring-closure at N(4) occurs for naphtho[2,3-*e*]-*as*-triazine (82JOC3168; 84JOC3199). Energies have been estimated by semiempirical and *ab initio* (4-31G) methods for each type of some isomeric tetrazoles (85JOC4894).



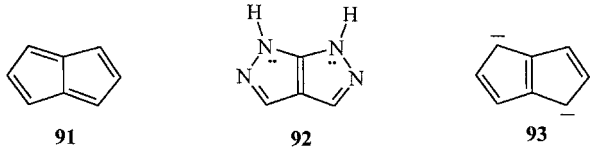
89T' **89A** **89T''**

Krivopalov *et al.* investigated the formation of the ditetrazolo form **90TT** and the dependence of equilibria on the solvent and on the substitution and benzoannelation in the diazides of type **90AA** (86BAU1745; 88MRC42; 89BAU1839).



II. [5.5]Bicyclic Compounds (76AHCS1, p. 544)

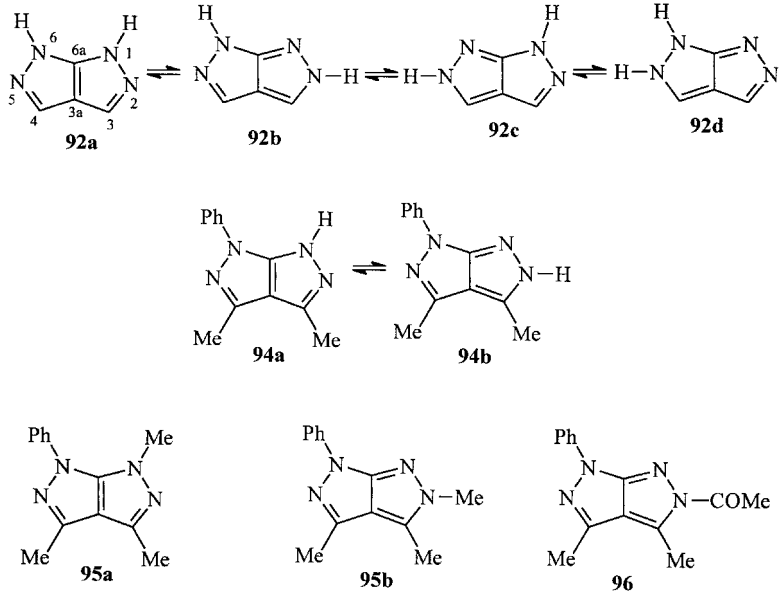
The series of five–five ring systems with nitrogen atoms in both rings can be broadly defined as heterocyclic analogs of pentalene **91** and thus called azapentalenes (for instance, **92**). The 10-π-electron system makes these compounds aromatic, and they are iso-π-electronic with the pentalene dianion **93.** Elguero *et al.* have published a survey on aromatic azapentalenes [78AHC(22)183] where the annular and functional tautomerism and the azide-tetrazole isomerism have been covered comprehensively. No significant data on [5.5]bicyclic compounds with heteroatoms other than nitrogen have been reported since the previous review (76AHCS1, p. 544). New results, which appeared on the subject in addition to the cited reviews, are discussed in this section.



A. Annular Tautomerism

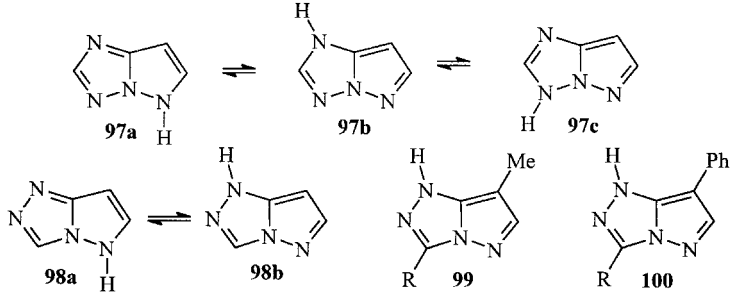
This type of tautomerism can be seen in azapentalenes possessing at least one NH group. The factors, which influence the relative stabilities of NH tautomers, were summarized in four rules [78AHC(22)183].

a. *Pyrazolopyrazoles, -triazoles, and -benzimidazoles and Imidazopyrazole.* Pyrazolo[3,4-*c*]pyrazoles can exist in four tautomeric forms **92a**–**92d** (the first three are the most aromatic). The products of methylation and acetylation of **94,** which exists in just two forms corresponding to **92a** and **92b,** have been studied by ^{13}C NMR spectroscopy (76BSB829). On methylation, **95a** and **95b** were formed in 5:95 ratio, whereas acylation resulted in **96** only. Also, the predominance of **94b** in DMSO-d_6 has been established by analysis of the ^{13}C-chemical shifts in the 6-phenyl substituent.

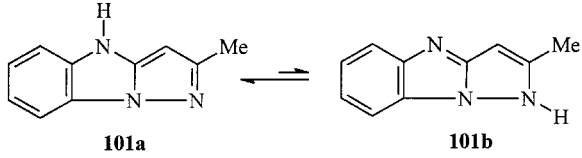


Dipole moments and total energies for pyrazolo[1,5-*b*]-*s*-triazole tautomeric forms **97a**–**97c** were calculated using CNDO/2 and CNDO/S (76T341): the results predict the stability of tautomers in a **97a** > **97b** > **97c** sequence. So far, no *ab initio* calculations or synthesis of **97** have been reported. For pyrazolo[3,2-*c*]-*s*-triazole **98** (76T341), the calculated dipole moments, electronic absorption, and proton chemical shifts are in a good

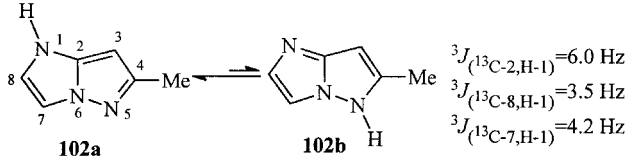
agreement with the experimental data, which indicate that the predominant tautomer is **98a.** The effects of substituents on ^{13}C-chemical shifts in **99** and **100** in DMSO-d_6 have been investigated (77OMR508).



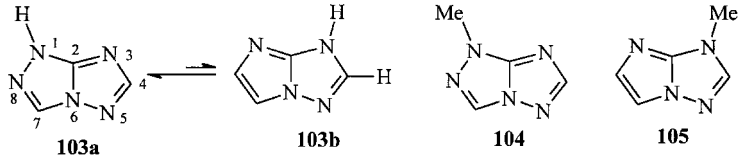
The existence of pyrazolo[1,5-*a*]benzimidazole in form **101a** in DMSO-d_6 has been established by ^{13}C NMR spectroscopy (77ORM508).



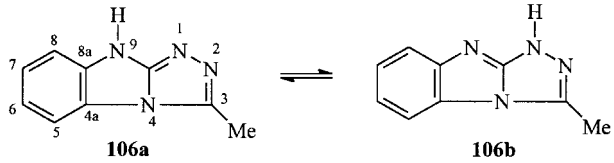
The couplings between the carbon atoms and the proton bonded to the pyrrole nitrogen atom observed for imidazo[1,2-*b*]pyrazole **102** (77OM508) suggest the predominance of **102a.**



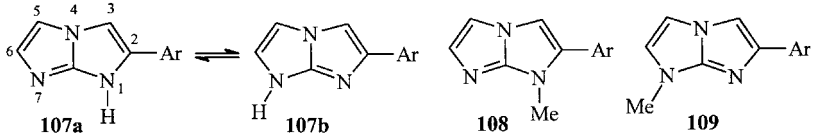
b. *Triazolo-triazoles and -benzimidazoles, and Imidazo-imidazoles and -triazoles.* In the ^{1}H NMR spectrum (in DMSO-d_6) of *s*-triazolo[4,3-*b*]-*s*-triazole **103,** the absence of CH-NH coupling discloses the predominance of **103a** (77OMR508). The ^{13}C NMR spectral chemical shifts and coupling constants for **103, 104,** and **105** support this conclusion.



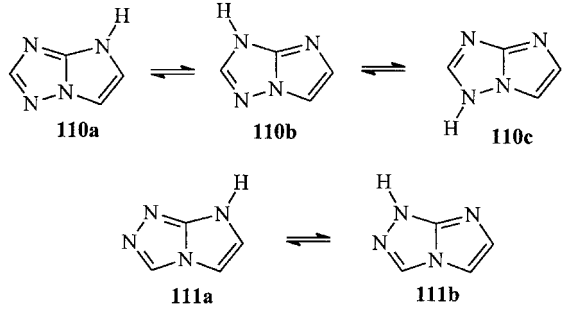
The tautomerism of 3-methyl-*s*-triazolo[4,3-*a*]benzimidazole **106** was established from the ^{13}C-chemical shifts (in DMSO-d_6) of the parent compound and its N-methylated derivatives (78BSF273). Tautomers **106a** and **106b** are both present in DMSO, whereas **106a** is predominant in ethanol and **106b** in dioxane (UV spectroscopy) (75JHC197). The interpolation of ^{13}C-chemical shifts was suggested for calculations of tautomeric equilibrium constants.



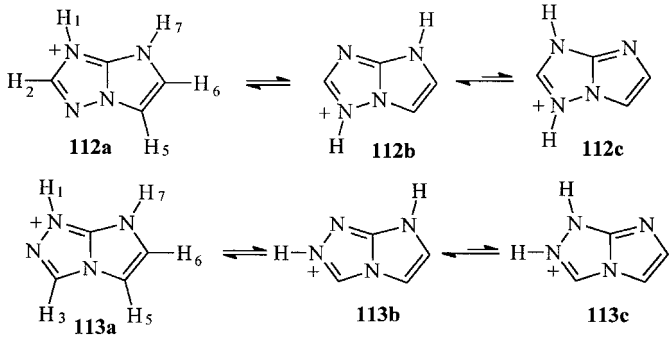
The data on ^{1}H- and ^{13}C-chemical shifts, ^{1}H-relaxation rates, and protonation for 2-arylimidazo[1,2-*a*]imidazoles (**107**) and their methyl derivatives **108** and **109** indicate that **107** exists predominantly as the 1*H* tautomer **107a** in $CDCl_3$ and as the 7*H* tautomer **107b** in DMSO-d_6 or CD_3OD-D_2O (91MRC1147). An X-ray crystallographic study has demonstrated the 1*H* tautomer **107a** in the lattice.



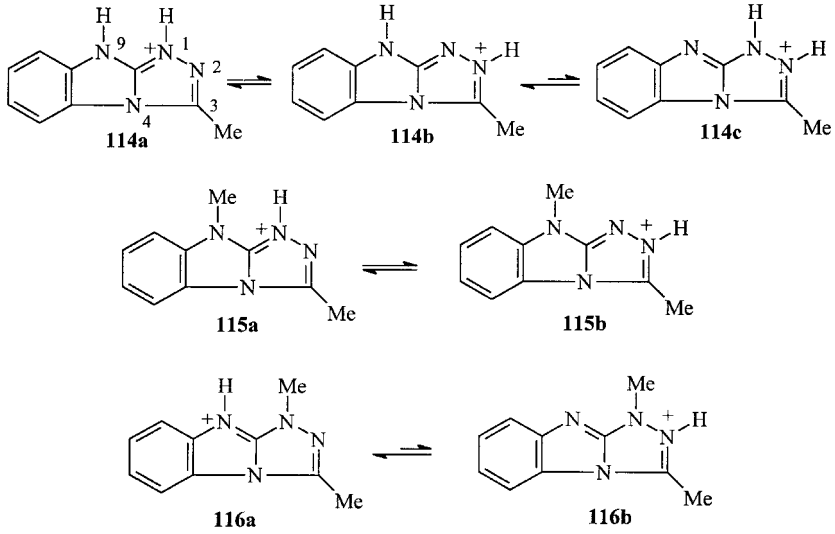
Imidazo[1,2-*b*]-*s*-triazole (**110**) and imidazo[2,1-*c*]-*s*-triazole (**111**) have been studied by ^{1}H NMR and UV spectroscopy, and the calculations (CNDO/2 and CNDO/S) of total energies, dipole moments, and electronic absorption spectra (76T341) have been made. The results demonstrate the existence of tautomeric equilibria in the following stability order: **110a** > **110b** > **110c** and **111a** > **111b.**



c. *Tautomerism in Cations* (76AHCS1, p. 548). The tautomerism of imidazolium cations **112** and **113,** which are protonated forms of **110** and **111** respectively, has been investigated by ^{1}H NMR in 98% H_2SO_4 (for **112***)* and in CF_3COOH (for **113**) (76T341). Based on the chemical shifts and couplings for H-2, H-5, H-6, and H-7, the tautomers **112a** and **112b** are considered to dominate in the mixture. Similarly, the tautomers **113a** and **113b** are implicated. The calculated data on electron absorption (CNDO/S) are in a good agreement with the experimental UV spectra for both **112** and **113.** The calculated total energies and dipole moments (CNDO/2) are also in a good agreement, with the stabilities of the tautomers formed to vary as **112a** > **112b** ≫ **112c** and **113a** > **113b** ≫ **113c.**

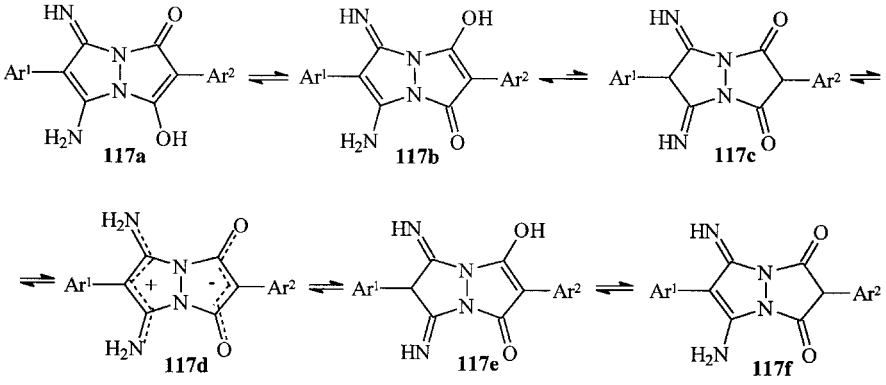


It was shown by UV spectroscopy that the protonation of **106** in EtOH-HCl or in CF_3COOH resulted in a 1 : 1 tautomeric mixture of **114a** and **114b** (78BSF273). For 9- and 1-N-methylated derivatives of **106,** the formation of **115a** and **115b** in a 1 : 3 ratio and the exclusive existence of **116a** has been demonstrated.

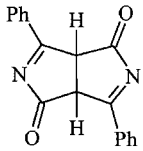


B. Functional Group Tautomerism

Oxo–hydroxy, thione–thiol, and amine–imine tautomerism in the azapentalene series has been previously summarized [76AHCS1, p. 549; 78AHC(22), p. 254]. In addition, the study of the tautomerism of the polyfunctional pyrazolo[1,2-*a*]pyrazole **117** has been reported (86S239). Tautomeric forms **117c, 117e,** and **117f** were excluded by the absence of a methine hydrogen signal in the ^{1}H NMR spectra. The short wavelengths in the UV spectra (λ_{max} = 273–281 nm) excluded the dipolar structure **117d.** Fast tautomerism involving two carbonyl oxygen atoms (^{13}C NMR in DMSO-d_6) provided evidence for **117a** and **117b.** The IR spectra in the solid state indicated a symmetrical structure ($\nu \sim 1600\ cm^{-1}$) with a significant contribution from the hydrogen bonds.



Dioxopyrrolo[3,4-*c*]pyrrole has been reported to prefer the di-oxo form **118** (74TL2549) by analogy to the pyridones, although other forms including **119** and **120** could be also consistent with the given IR and UV spectroscopy data and are more probable.



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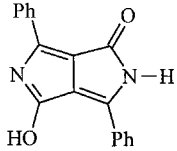

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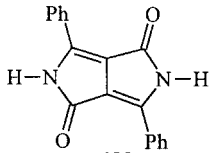
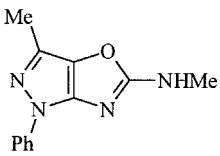


120

The ^{1}H and ^{13}C NMR spectral data demonstrated the existence of **121** in the amino form (in $CDCl_3$) (91H727) and **122** as the thione (in DMSO) (95H497). The structure of **122** (R = NHCOPh) was also confirmed by X-ray structural data (95H497).



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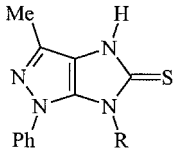
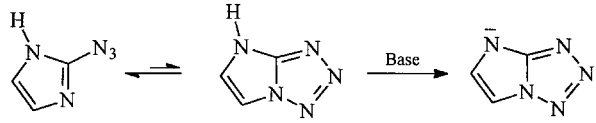


122

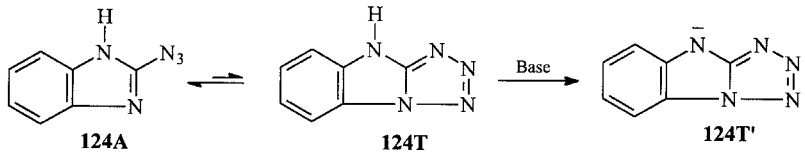
C. Azido–Tetrazole Isomerism

Azido-tetrazole isomerism was briefly mentioned in the previous survey on tautomerism (76AHCS1, p. 547) and systematically dealt with in the reviews on tetrazoles by Butler [77AHC(21)324] and on aromatic azapentalenes by Elguero *et al.* [78AHC(22)183]. We now discuss the data which was not previously surveyed.

The position of equilibrium has been established for imidazo[1,2-*b*]tetrazole (**123T**) and tetrazolo[1,5-*a*]benzimidazole (**124T**) (75TL1523). IR and NMR spectra showed that the neutral molecules exist in the azido forms **123A** and **124A,** whereas the equilibrium is completely shifted to the tetrazole forms in anions **123T′** and **124T′** respectively.

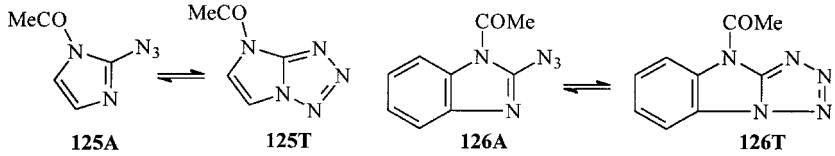


123A **123T** **123T'**



124A **124T** **124T'**

N-Acetyl derivatives **125** and **126** exist as tautomeric mixtures in DMSO-d_6 at room temperature (for both, $K_{[A]/[T]} = 1.5$); at elevated temperature the proportion of the azido form increased. In $CDCl_3$, the azido form only was detected for **125;** for **126,** a **126A** : **126T** ratio was changed to 10 : 1.

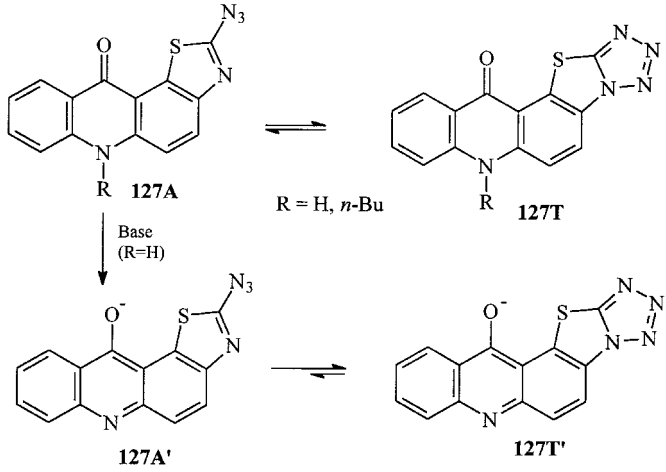


125A **125T** **126A** **126T**

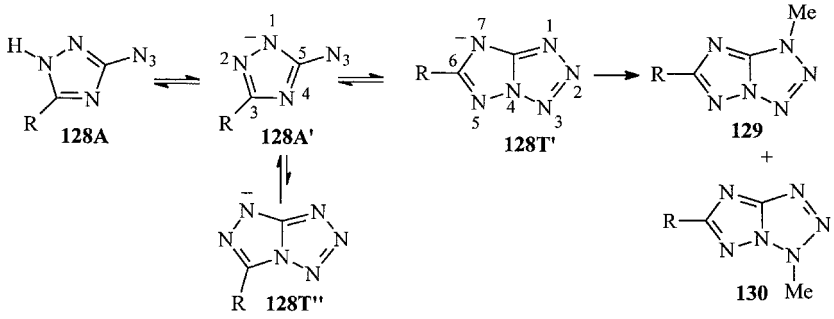
The effects of solvent (polarity), temperature, and substituents (the Hammet σ constants) have been studied in the azide–tetrazole equilibrium for thiazolo[2,3-*e*]tetrazoles (75BSB1189; 77CJC1728, 77JHC1299); oxazolo[2,3-*e*]- and isoxazolo[2,3-*d*]-tetrazoles (77CJC1728); and tetrazolo[4,5-*b*]-1,3,4-thiadiazoles (81CHE721). A rough parallelism has been proposed between the azido-tetrazole isomerism and prototropic tautomerism (75BSB1189).

Azide-tetrazole isomerization has been studied by ^{1}H NMR spectroscopy for 2-azidothiazolo[5,4-*b*]- and 2-azidothiazolo[4,5-*c*]pyridines, and the equilibrium constants were determined at various temperatures (77JHC1045).

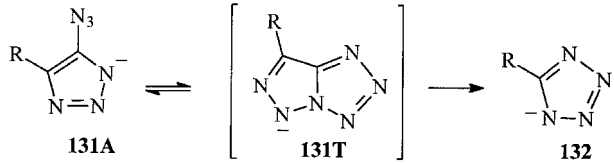
Azide–tetrazole equilibrium data have been recently reported for the thiazoloacridinone series (96JHC747). The $\log K_{[A]/[T]}$ values in various solvents for **127A/T,** 2-azido/tetrazolo-benzothiazole, and 2-azido/tetrazolo-4,5-dimethylthiazole were linearly related, i.e., the solvent effects are independent on the nature of the thiazole. The formation of anion shifted the azide–tetrazole equilibrium to the tetrazole tautomer **127T′,** similarly to **123T′** and **124T′.** This reflects a greater electron release in the anions than in the neutral compounds.



This conclusion is supported by the data on the azide–tetrazole equilibrium for *s*-triazolo[2,3-*d*]tetrazoles (**128**) [79JCS(P1)2886]. Methylation of neutral azide resulted in the 1-methyl derivatives of 3-azidotriazole **128A** only, whereas on methylation of the anion **128A′,** the tetrazoles **129** and **130** were also trapped in 25 and 10% yields, respectively. The predominance of **128T′** over **128T″** was attributed to these two bicyclic anions but no calculations on relative energies have been performed. The azide–tetrazole equilibrium constants were measured for **128A′/T′** in DMSO-d_6: 0.45 at 27°C (R = H), and 0.78 at 23°C and 1.80 at 80°C (R = Ph).

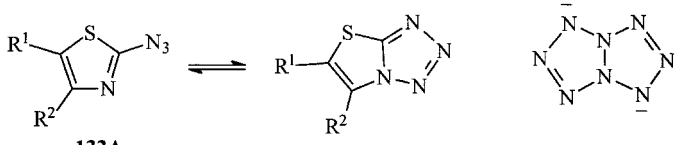


Preu *et al*. have reported that azido-tetrazole isomerism of azido-1,2,3-triazoles **131A** to the intermediate bicycles **131T** is necessary to account for the formation of α-diazoalkylterazolides [98JCS(P2)785].



131A **131T** **132**

Cubero *et al.* have significantly clarified the case of azidothiazole (**133A**) and thiazolo[3,2-*d*]tetrazole (**133T**) isomerism including, for the first time, solvent effects thanks to high-level *ab initio* calculations (98JOC2354, 98JA4723). Nguyen and Ha have reported QCISD(T)/6-31G* and CCSD(T)/DZP calculations on azidopentazole anion **134** and concluded it is probably the lowest energy N8 species (96CB1157).

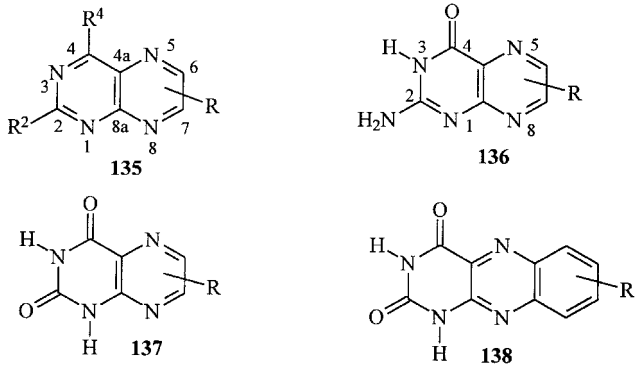


133A **133T** **134**

III. [6.6]Bicyclic Compounds

A. Introduction

Tautomerism of [6.6]biheterocycles was not covered in the previous review (76AHCS1). Since then, several surveys appeared on pyrazino[2,3-*d*]pyrimidines or pteridines (**135**) with some coverage of tautomerism, with the most recent by Pfleiderer [96CHEC(7)679, and references therein]. The results on pteridines not included in the previous surveys, are discussed in this section. Limited data on other heterocycles are also covered.



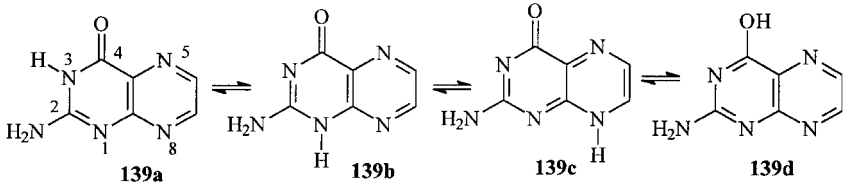
135 **136** **137** **138**

Six–six condensed heterocyclic systems without a tautomeric functional group(s) [for instance, pteridine **135** ($R = R^2 = R^4 = H$)], do not exhibit prototropic tautomerism. The introduction of an oxo(thioxo)- and/or amino group(s) into the pteridine system, and the appearance of at least one NH group in the ring, leads to functional and/or annular tautomerism. Pteridine is formally the parent of three groups of compounds of particular interest because of their biological importance: pterins (**136**), lumazines (**137**), and flavins (**138**).

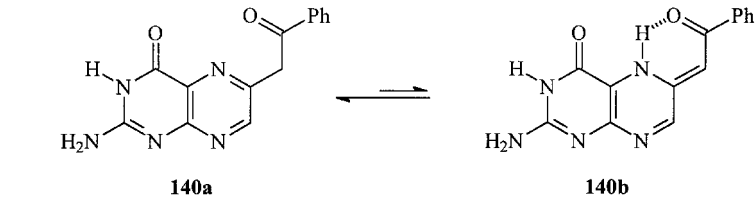
B. Pterins

1. *Annular and Functional Group Tautomerism*

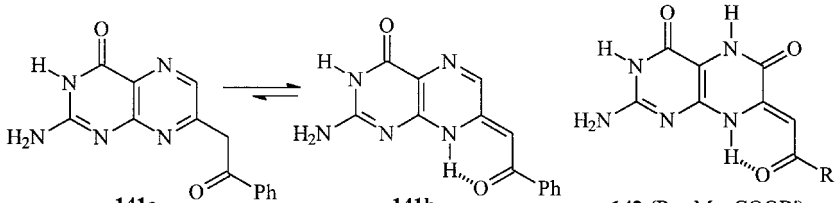
2-Amino-4(3*H*)-pteridinones, or pterins, are the most important naturally occurring derivatives of pteridine. A few *ab initio* studies have been undertaken to calculate the tautomeric forms for pterin. Using STO-3G and 3-21G basis sets, Gready (85JCC377) has shown that 3*H* tautomer **139a** is more stable than 1*H* tautomer **139b** by 6.8 kcal mol^{-1} and more stable than 8*H* tautomer **139c** by 21.6 kcal mol^{-1}. The oxo-form **139a** is favored relative to the hydroxy tautomer **139d** by 9.3 kcal mol^{-1}. Similar results have been reported using the 6-31G* basis [93JCS(CC)1199]. As is generally the case for thermodynamic reasons, the amino and not the imino tautomer is preferred for pterins (85JCC377). Solvation effects have been considered using MP2/6-31G* calculations, yielding $K_{[133b]/[133a]} = 0.162$ at 298K [93JCS(CC)1199]. UV spectroscopy has been used extensively in studies of tautomeric pterins. Early data (60CB2015; 61CB12, 61JCS4413) indicated the existence of pterin as 3*H* tautomer **139a** in aqueous solution. The conclusion was based on comparison of the UV spectra for pterin itself and for the "fixed" compounds 1-, 3-, and 8-methylpterin and the 4-methoxy analog. A recent investigation [94MI(179)55] confirmed the earlier results: the electron absorption spectra for pterin and its methylated derivatives calculated by CNDO/S-CI were in good agreement with the experimental data in pointing to **139a** as the most stable tautomer.



Depending upon the position of a phenacetyl substituent at the pyrazine ring, *ab initio* calculations with full geometry optimizations suggest the oxo form **140a** or the vinylogous amide **141b** predominate [93MI(4)23]. Similar conclusions were reported earlier from ^{1}H NMR and UV spectroscopic studies of **142** (63HCA2592; 63HCA2597).



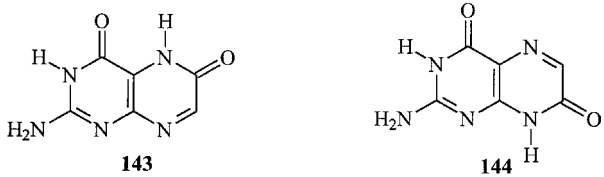
140a **140b**



141a **141b** **142** (R = Me, COOR')

2. *Cation and Anion Structures*

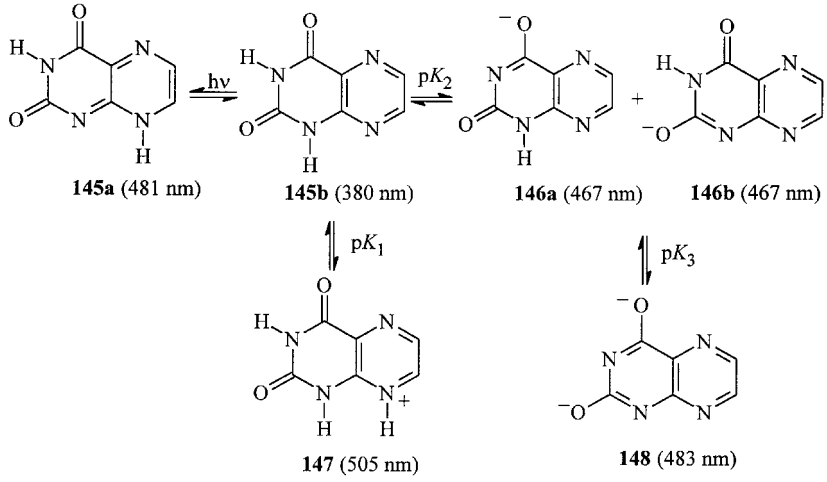
The *ab initio* prediction that pterin is protonated at N(1) (cf. structure **139a**) rather than at N(5) or N(8) (85JCC377) was confirmed by analysis of the electronic spectra of pterins at various pH [94MI(179)55]; the protonation of the hypothetical N(5)-deazapterin at N(1) was based on calculations and needs confirmation. No experimental geometries are available for this series. The amphoteric character of pterins has been studied by ^{1}H and ^{13}C NMR spectroscopy (73HCA2680). It was shown that pterin (**139**) exists as the monoanion in NaOD/D_2O, whereas xanthopterin (**143**) and isoxanthopterin (**144**) form dianions in which the second ionization has occurred in the pyrazine ring. Trifluoroacetic acid effects the monoprotonation of **139a** and **143** at N(1); isoxanthopterin **144** is insufficiently soluble for such studies. In concentrated H_2SO_4, **139, 143,** and **144** exist as dications with N(8) as the second protonation site.



143 **144**

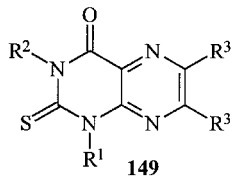
C. Lumazines

2,4-(1*H*,3*H*)-Pteridinone, or lumazine (**145**), has been depicted by two annular tautomeric forms. The formation of 8*H* tautomer **145a** was proposed by a phototautomerization mechanism similar to that suggested for 7-azaindoles and flavins (cf. Sections I,B,1,a and III, D). The dilactam structure of lumazine **145b** has been demonstrated [96CHEC(7)679]. Lumazine is also amphoteric with a possibility of protonation at the nitrogen atom sites and deprotonation at the oxo(hydroxy) sites; the cations and anions may also occur in various tautomeric structures. A few studies have been undertaken to investigate the pH dependence of the tautomerism of lumazines in the excited state. Depending upon pH in aqueous solutions, lumazine can exist as the neutral molecule **145a,** monocation **147,** tautomeric monoanions **146a** and **146b,** and dianion **148.** Early determinations of the pH-dependent equilibrium constants [51JCS474; 57CB2582; 60MI(64)662] produced $pK_1 = -3$, $pK_2 = \sim 8$, and $pK_3 = \sim 12$. Similar results were reported later by Klein and Tatischeff [87MI(45)55]. Based on the fluorescence properties of lumazine and its 1-, 3-, and 6-methyl derivatives (61JCS4413) in aqueous solutions, emission maxima were assigned for the pH-dependent tautomeric forms of lumazine [87MI(45)55]. The ionization constants in the excited state of N-methylated and O-methylated lumazines were reported by Lippert and Prigge [60MI(64)662]. The N(8) protonated form **147** was identified by ^{13}C NMR spectroscopy (73HCA2680). Based on UV spectroscopy, protonation at N(8) was also reported for thiolumazines **149** (R^1 = H) and **150,** but protonation occurs at N(3) for **151** if $R^1 = R^2$ = Me (74CB3377).



145a (481 nm) **145b** (380 nm) **146a** (467 nm) **146b** (467 nm)

147 (505 nm) **148** (483 nm)



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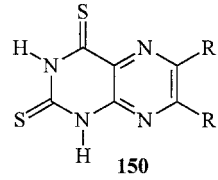

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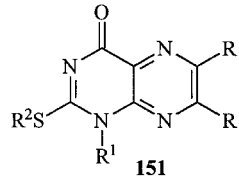
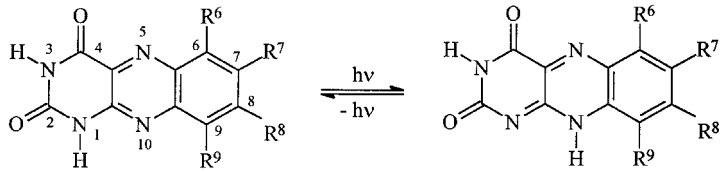


151

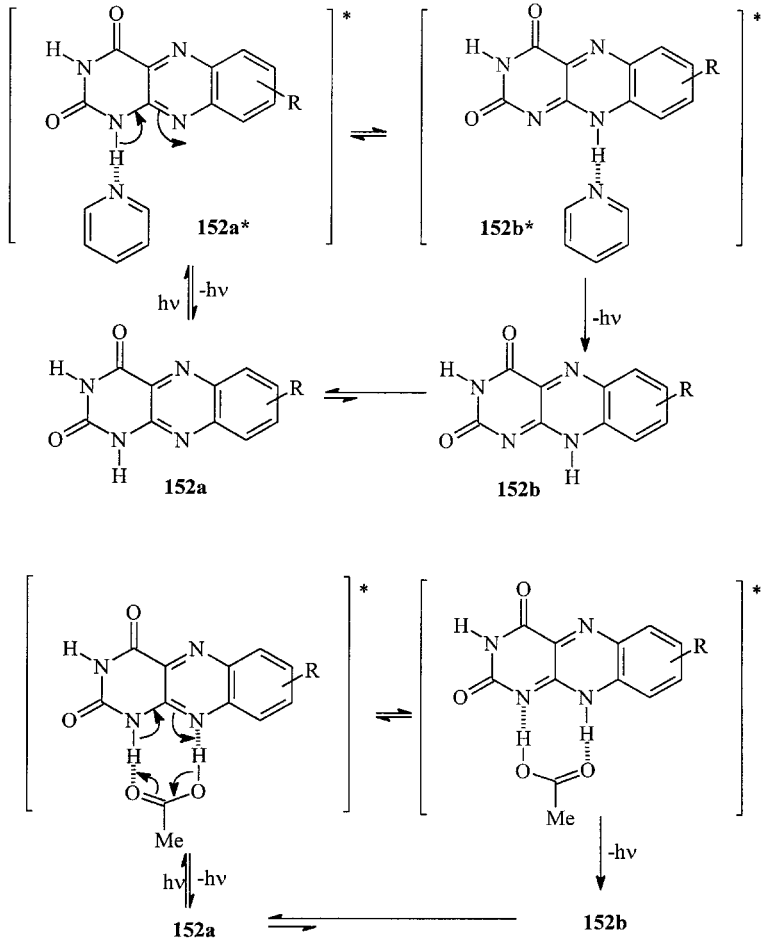
D. Flavins

Flavins (**152**), benzoannelated derivatives of lumazine (**145**), are implicated in a variety of photobiological processes such as photodynamic action, phototropism, phototaxis, and photosynthesis. The biologically active 1*H* form **152a** of alloxazine ($R^6 = R^7 = R^8 = R^9 = H$) is less stable in the ground state than the 10*H* form **152b.** To elucidate the annular tautomerism of flavins in the excited state, comprehensive theoretical and fluorescence and luminescence spectral studies were undertaken by Song *et al.* [68MI(7)311; 69IJQ303; 72JA1730; 74JA4319; 76MI(24)479] and Koziol *et al.* [66MI(5)41; 88MI(48)7, 88THE(170)205; 90MI(52)353; 93PJC1813].



152a (alloxazine) **152b (isoalloxazine)**

It was found that phototautomerism of the flavin system depends on the presence of molecules capable of catalyzing proton transfer from N(1) to N(10) [66MI(5)41; 74JA4319; 76MI(24)479; 79MI(29)459; 88CPL(151)375, 88MI(48)7; 90MI(52)353; 93PJC1813; 96MI(95)215]. This mechanism is similar to the phototautomerism of 7-azaindoles (cf. Section I,B,1,a). Examples of such catalysis with pyridine and acetic acid are shown in Scheme 2. Thus, a double H-bonded complex with acetic acid or water is a part of a concerted biproton mechanism, whereas a noncyclic H-bonded complex with pyridine suggests a dynamic proton-transfer mechanism. A strong temperature dependence was observed for the phototautomerism of 7,8-dimethylalloxazine in various solvents (80JA5293). The formation of flavin covalent hydrates and anions at alkaline p*H* in solution was studied by UV, ^{1}H NMR, and IR spectroscopy [72ZN(B)1027; 76LA1276]. Structure optimization and protonation and deprotonation energies for some flavins have been calculated using both semiempirical and *ab initio* methods [96THE(364)139].

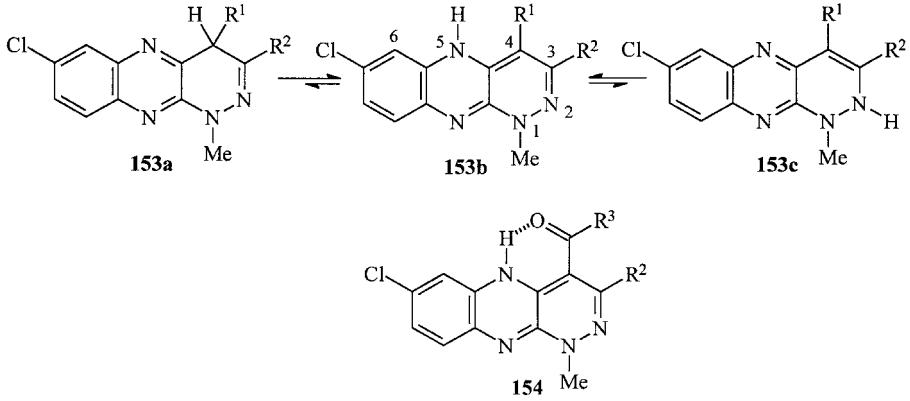


SCHEME 2

E. MISCELLANEOUS [6.6]BICYCLIC COMPOUNDS

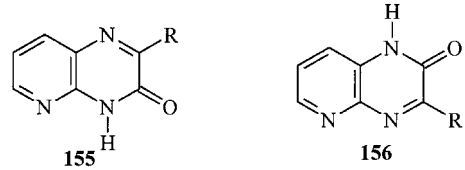
1. *Annular Tautomerism*

The existence of pyridazino[3,4-*b*]quinoxalines as 1,5-dihydro tautomer **153b** in solution and in the solid state has been deduced from NMR spectroscopy studies and from X-ray analysis (93JHC1659; 95CHE1088, 95H1805). Hydrogen bonding in **154** in the solid state was concluded from IR spectroscopy and X-ray cryrallographic data (95CHE1088).

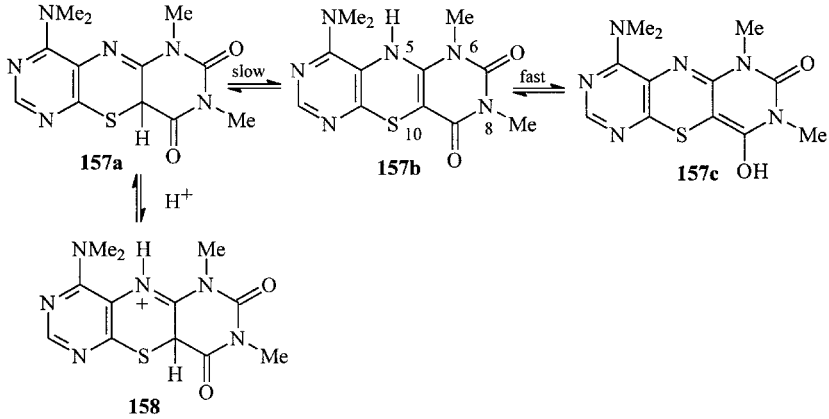


2. *Functional Group Tautomerism*

The expected lactam tautomers **155** and **156** were assigned by UV spectroscopic data for these pyrido[2,3-*b*]pyrazinones (92JHC129).

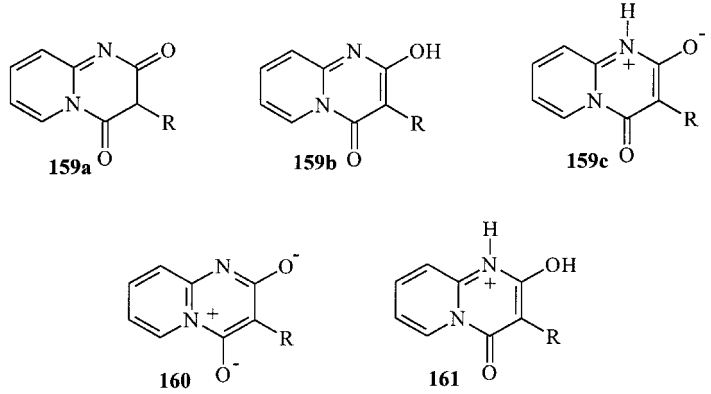


The tautomeric equilibrium of pyrimido[4,5-*b*][4′,5′-*e*]thiazine **157** was studied in DMSO-d_6 by NMR spectroscopy (92CHE1219). Based on ^{1}H and ^{13}C NMR chemical shifts, fast proton exchange was concluded to occur between **157b** and **157c.** Monoprotonation of **157** has been assumed to form



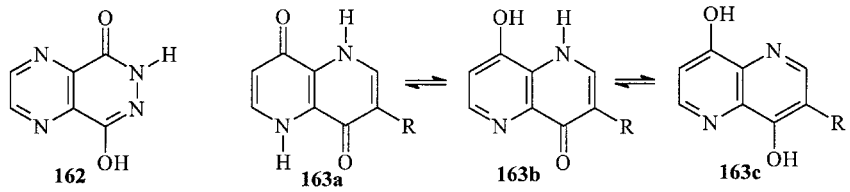
cation **158** since the ^{1}H NMR spectrum in $CDCl_3$ with 1 equivalent of CF_3COOH exhibited a methine hydrogen signal at 4.93 ppm.

Early data suggested the existence of pyrimidazo[2,3-*a*]pyridin-2,4-ones, or "malonyl-α-aminopyridines," as the dioxo form **159a** [24MI(57)1168], hydroxy tautomer **159b** (52JA4910), or betaine **159c** (62JCS1544; 70HCA905). Dvortsák *et al*. confirmed betaine **159c** as the major tautomer in the solid state and in solutions of pH 2–7 and provided evidence for the aromatic anion **160** in an alkaline solution and the protonated hydroxy form **161** in a strongly acidic solution (76T2117). The conclusions were based on ^{1}H NMR, IR, and UV spectroscopic data.

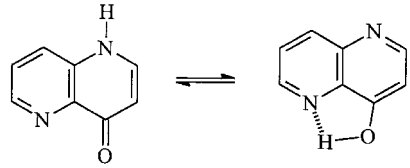


8-Hydroxypyrazino[2,3-*d*]pyridazin-5(6*H*)-one exists predominantly as the lactim–lactam tautomer **162** in aqueous solution (79AJC459). This conclusion was supported by semiempirical calculations (AM1 method) of the relative energies for the dilactam, dilactim, and lactim–lactam tautomers (91JCC17). The UV spectroscopy studies and p*K* values for **162** and its *N*- and *O*-methyl derivatives suggest that monoprotonation occurs in the pyrazine ring.

Tautomerism in 4,8-dioxygenated 1,5-naphthyridines **163** has been studied by UV spectroscopy in aqueous solution. Under these conditions, the compounds exist predominantly as the bis-pyridone tautomers **163a** (78JOC1331).

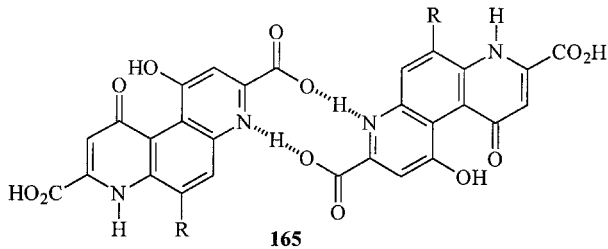


Similar results were reported earlier for **164:** the pyridone **164a** is the major tautomer in polar solvents, while the pyridinol **164b** predominates in nonpolar ones (67AC877). The hydroxy form can be stabilized by intramolecular hydrogen bonding [71JCS(B)2339].



164a **164b**

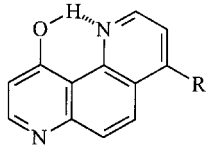
Unexpectedly strong intermolecular hydrogen bonding has been reported by IR spectroscopic studies for tetrahydro-4,7-phenanthroline-1,10-dione-3,8-dicarboxylic acids, which exist in the oxo-hydroxy form **165** in both solid state and in solution [78JCS(CC)369]. The conclusion was based on comparison of B-, C-, and D-type bands for **165** and their dimethyl esters (detection of hydrogen bonding) and on analysis of IR spectra in the 6 μm region (pyridine- and pyridone-like bands).



165

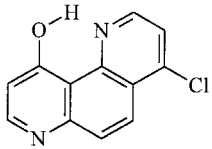
The stabilization of the hydroxy form by intramolecular hydrogen bonding in 10-hydroxy-1,7-phenanthrolines has been studied by Katritzky *et al.* [71JCS(B)2339; 91H329; 96MRC518]. It was shown that **166** are true hydroxy compounds in the solid state and in both polar and nonpolar solvents. IR spectra of **166** in nujol, in CCl_4, or in $CHCl_3$ exhibit broad absorption ca. 2300–3500 cm^{-1}, indicative of strong hydrogen bonding, and display the ring vibrations at ca. 1620–1635 cm^{-1}. The UV spectral data and p*K* measurements also gave a consistent picture for intramolecular hydrogen bonding in the hydroxy form and electron repulsion in the oxo form. No evidence for the presence of the oxo form at equilibrium was found. Recent studies of 4-chloro-1,7-phenanthrolin-10-ol (**167**) by DIS (Deuterium Induced Shifts; cf. 000AHC(76), Ch. 1, Section VI,C) indicated a tautomeric

mixture dominated by the hydroxy form **167a** (96MRC518). In addition, DIS revealed strong intermolecular interaction with the formation of dimers in solution.

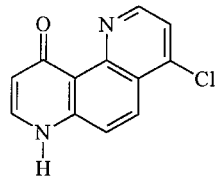


166

R = H, Cl, OEt, NHPh, OH

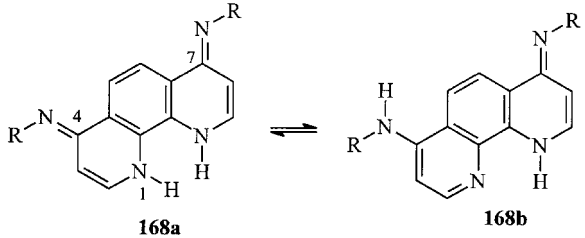


167a

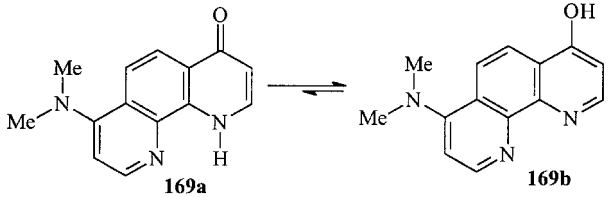


167b

In early work (63AJC833), 4,7-diamino-1,10-phenanthrolines **168** were assumed to exist as the imino tautomers since they showed the negative ferroin test (chelate formation), but this needs reinvestigation. In contrast, a positive ferroin test for **169** led to a claim for the predominance of the hydroxy tautomer **169b.** Again this needs confirmation, especially since the oxo form **169a** can be stabilized by hydrogen bonding [78JCS(P2)1215].

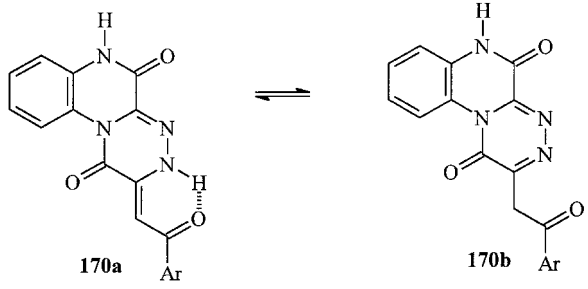


168a **168b**



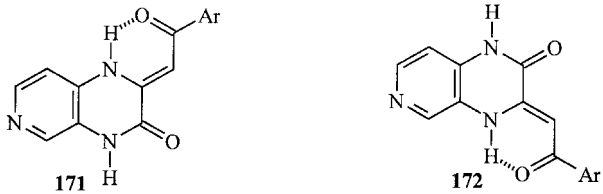
169a **169b**

Tautomeric studies of equilibria between enamino and methylene imino form have been reported for several heterocycles. Tautomerism of 1,2,4-triazino[4,3-*a*]quinoxalin-5-ones was deduced to be solvent dependent: the enamino form **170b** is predominant in DMSO-d_6 (^{1}H NMR), whereas **170a** is the major tautomer in the solid state (IR in nujol) (90JHC691; 95H2057) (cf. Section III,B).



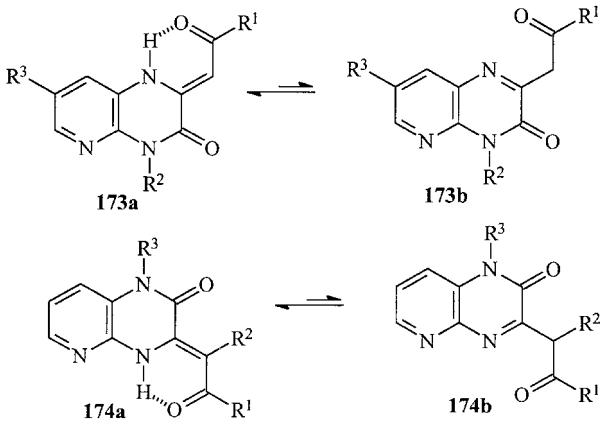
170a **170b**

Pyrido[3,4-*b*]pyrazin-3- and -2-ones exist in the enamino forms **171** and **172** respectively in DMSO-d_6 (^{1}H NMR spectroscopy) and in the solid state (IR spectra in nujol), and temperature appears not to affect these imine–enamine equilibria (97JHC773).



171 **172**

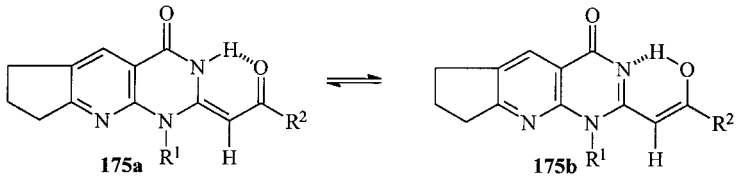
Pyrido[2,3-*b*]pyrazin-3- and -2-ones exhibit temperature-dependent equilibria in DMSO-d_6 solution (^{1}H NMR studies), with gradual increase in the proportion of the imino forms **173b** and **174b** as the temperature increases, although the enamino forms **173a** and **174a** remain predominant (97JHC773).



173a **173b**

174a **174b**

The formation of intramolecular hydrogen bonds in both the enamino **175a** and imino **175b** tautomers of pyrimido[4,5-*b*]pyridin-4-ones was shown by ^{1}H NMR, IR, and UV spectroscopic data (97CHE1199). The chemical shifts at ca. 3–5 ppm in ^{1}H NMR spectra ($CDCl_3$) due to the ethylene hydrogen atom and at ca. 10–15 ppm due to the signals of the chelate ring were assigned to the mixture of **175a** and **175b;** the tautomeric ratio was not reported.



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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Syntheses and Properties of Azafulvalenes

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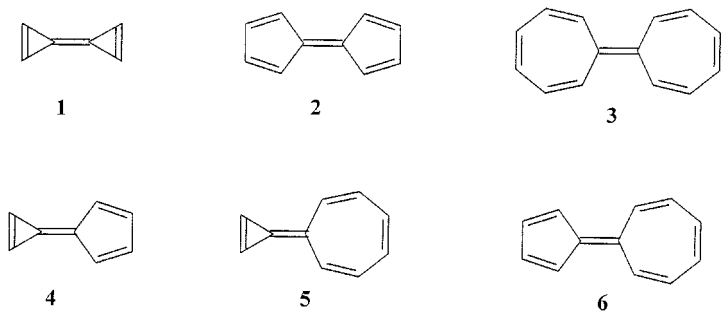
I. Introduction

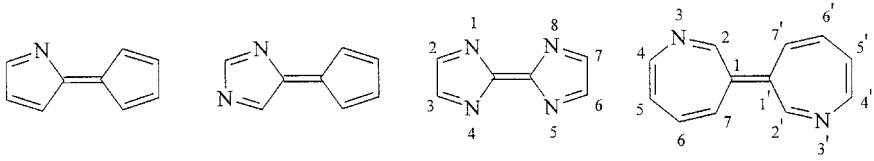
The name "fulvalene" was first mentioned by R. Brown (49TFS296), who expanded the class of fulvenes for those compounds containing two cyclic polyenic systems with a central double bond. Thus, depending on the ring size, cyclopropylidenecyclopropene **1,** fulvalene **2,** heptafulvalene **3** and the unsymmetrical hybrid molecules triapentafulvalene (calicene) **4,** triaheptafulvalene **5,** and pentaheptafulvalene (sesquifulvalene) **6** are members of this class of cyclic cross-conjugated systems (Scheme 1).

Whereas the fulvalenes **1**–**6** are relatively unstable hydrocarbons and therefore largely of theoretical interest, their heteroatom analogs demand considerable attention in synthetic chemistry and material sciences. The general principle of heterocyclic chemistry to relate heterocyclic compounds to carbocyclic ones was the driving force for the synthesis and their application to heterofulvalenes. Numerous heterocyclic derivatives iso-π-electronic with, for example, heptafulvalene **3** were accessible in which pairs of carbon atoms linked by double bonds were replaced by heteroatoms capable of contributing two π-electrons. By this principle, the well-known tetrathiafulvalene and its derivatives have been synthesized successfully (Scheme 2).

To incorporate nitrogen into fulvalenes three principal possibilities are available: (1) Replacement of one or more CH-units leads to derivatives such as **7**–**10,** which contain pyridine-type nitrogen atoms each contributing one π-electron in place of a single carbon atom. (2) Replacement of carbon subunits CH=CH in the seven-membered ring in sesquifulvalene by pyrrole-type nitrogen leads to derivatives of dihydropyridines **11** and **12.** Similarly, when starting from heptafulvalene **3** the result is a group of diazafulvalenes **14,** which are representative of members of the class of electron-rich olefines. All compounds cited previously can be described by classical formulae without formal charges as well as by aromatic ones bearing charges. (3) No uncharged structure can be written for another type of heteroanalogues of fulvalene. Such derivatives are constructed by replacing a pair of carbon atoms joined by a single bond by a pyrrole-type nitrogen with a lone pair of electrons. This gives rise to pyridinium



SCHEME 1



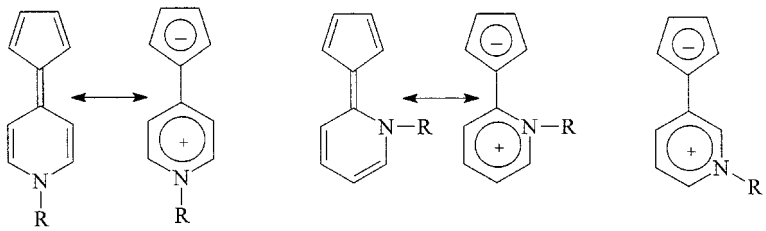
7 **8** **9** **10**

SCHEME 2

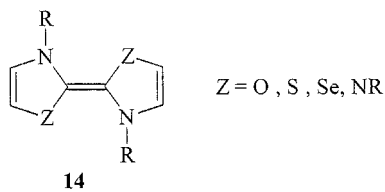
ylide **13,** a typical example of mesoionic heterofulvalenes. Further structural diversity could be effected by heteroatom substitution at the cyclopentadienide substructure as well as at the six-membered ring and by annulation (Scheme 3).

This chapter covers nitrogen-containing fulvalenes that can be obtained by replacement of CH=CH and/or CH, for example, types 1–3 starting from compounds **1–6.** Compounds in which nitrogen atoms are arranged on the periphery of the cross-conjugated system as in **15** or **16,** as well as derivatives in which the central double bond contains heteroatoms as in **17,** are not included. For azoniafulvalenes of type **17** and related heterocyclic betaines see (94AHC197).

Concerning nomenclature, fulvalene **2** and its related systems **1** and **3–6** are the parent structures of this class of heterocyclic cross-conjugated compounds. Both ring systems are numbered as shown in formula **9** (1,4,5,8-tetraazafulvalene) beginning at the heteroatoms. Alternatively, as in the case of heptafulvalene **10** (3,3′-diazaheptafulvalene), the numbers 1–7 and 1′–7′ can be used. The use of the name of the parent heterocycle connected by an olefinic double bond is often favored for the nomenclature of electron-rich olefines, for example, bis[3-(2,6-diisopropylphenyl)-4,5-dimethylthiazol-2-ylidene] for compound **51a** (97LAR365). Similarly, azafulvalenes of type **11** and **12** can be re-



11 **11'** **12** **12'** **13**



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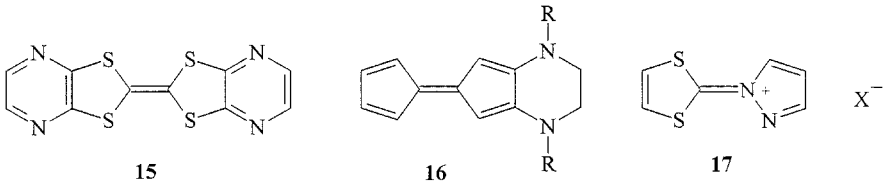
SCHEME 3



15 16 17

SCHEME 4

garded as derivatives of *N*-alkyl-4- or 2-cyclopentadienylidene-1,4- or 1,2-dihydropyridines (65JA2887) (Scheme 4).

Certain abbreviations are used in the article for compounds that are mentioned repeatedly. Thus, TTF is tetrathiafulvalene, TCNQ is tetracyanoquinodimethane, TTDAF is tetrathiadiazafulvalene, DTDAF is dithiadiazafulvalene, and TAF is tetraazafulvalene.

II. Syntheses of Azafulvalenes

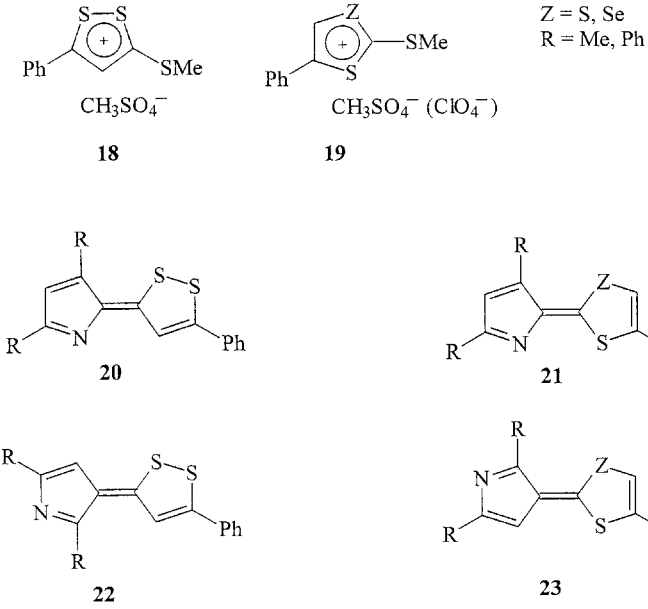
A. Monoazafulvalenes

1. *Reaction of Cyclopentadienides or Their Nitrogen Analogs with Azolium and Dithiolium Salts*

The method of choice for the synthesis of a large number of heterofulvalenes is the condensation of cationic five-membered heterocycles with deprotonated cyclopentadienes or their nitrogen analogs. In 1968 the first synthesis for some azafulvalenes involving this method was described (68AG277). On treatment of 1,2- and 1,3-dithiolium salts **18** and **19** with the corresponding dimethyl-/diphenylpyrroles in acetic acid at room temperature for a few minutes, and upon addition of perchloric acid the azafulvalenes **20**–**23** were precipitated as stable salts. Addition of ethyl-diisopropylamine (Hünigs base) yielded the free azafulvalenes, which in most cases decomposed quickly (Scheme 5).

One decade later, the parent compounds **21** were synthesized (78BCJ1427). For example, the reaction of 2-methylthio-1,3-dithiolium iodide with pyrrole gave 2-(2-pyrrolyl)-1,3-dithiolium iodide in a 92% yield, which on treatment with DBU gave 5-aza-1,4-dithiafulvalene **21** (R = H, Z = S, no Ph at dithiole-ring) as thermally stable orange crystals. Using the same type of reaction, the benzoderivatives of type **24** could be isolated (78BCJ1427).

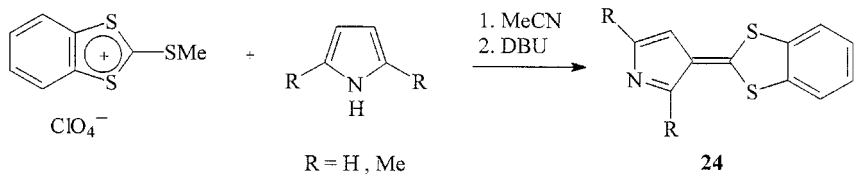
A considerable extension of that method was reached by the condensation of 1,2- and 1,3-dithiolium-; 1,3-thiaselenium-; and 1,2,4-thiadiazolium salts with pyrroles, 2- or 4-phenyl-; 2,4-diphenyl-; and 4,5-diphenyl imidazoles (70TL481). At room temperature and in acetonitrile solution some of



SCHEME 5

these olium salts form with the electron-rich azoles crystalline 1:1 complexes. On heating under reflux for several hours they underwent a condensation reaction to give the perchlorates of the azafulvalenes that were then deprotonated to yield the stable bases (Scheme 6).

The results concerning the highly conductive charge-transfer salts of TTF with TCNQ have created a wide and expanding interest in convenient methods of synthesizing a variety of TTF derivatives containing nitrogen as a further heteroatom. Therefore, some groups developed this heterofulvalene synthesis to involve indoles (78BCJ1427; 80BCJ1661). Instead of benzo-1,3-dithiolium salts, the readily obtainable 2-isopentyloxy-1,3-benzodithiole was used as an electrophilic building block. Subsequent hydride abstraction with trityl tetrafluoroborate gave the precursors for the



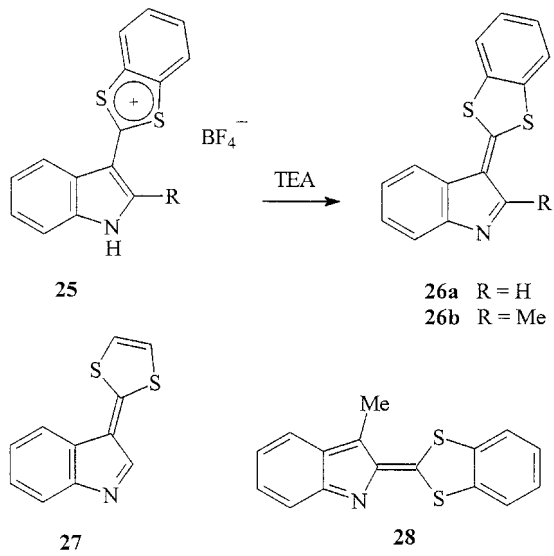
SCHEME 6

desired heterofulvalenes in good yields. Treatment of **25** with triethylamine afforded the azafulvalenes of type **26** in yields up to 92%.

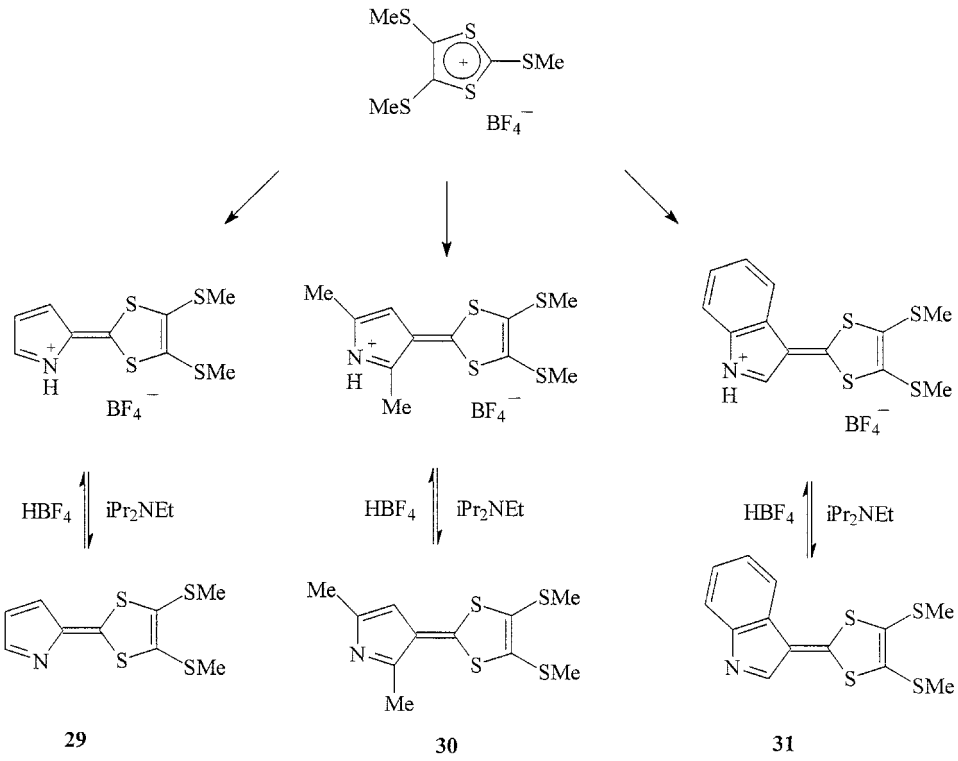
Similarly, indole itself could be converted by 2-methylsulfanyl-1,3-dithiolium iodide to its 3-dithiolium derivative, which gave **27** quantitatively with DBU. However, treatment of indoles, which bear the benzodithiolium moiety in the 2-position with tertiary amines, resulted in a black reaction mixture. All attempts to isolate the *o*-quinoid compound **28** failed (Scheme 7).

With regard to "organic metals," compounds carrying alkylsulfanyl groups appeared to be advantageous. Stimulated by these experimental findings, the bis-(methylsulfanyl)-5-aza-1,4-dithiafulvalenes **29**–**31** were prepared (86TL839). Pyrrole, 2,5-dimethylpyrrole, and indole readily react with tris-(methylsulfanyl)-1,3-dithiolium tetrafluoroborate to afford the fulvalenium salts in high yields. Their deprotonation with Hünigs base allowed the isolation of free bases which can be reprotonated. Whereas **29** and **31** form stable orange solids, **30** could be obtained only in solution (Scheme 8).

Searching for donoracceptor-substituted anions as well as related cations derived from cyclopentadiene, the azafulvalene **32** was synthesized by condensation of the potassium salt of the pushpull-substituted cyclopentadiene with 3-methyl-2-methylsulfanyl-benzothiazolium tetrafluoroborate (85AG996) (Scheme 9).



SCHEME 7

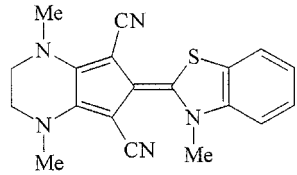


29 **30** **31**

SCHEME 8

2. *Reaction of Cyclopentadienides with Carbonyl Compounds*

The smallest compounds among the azafulvalenes described to date are the azacalicenes, which are formed by combining a cyclopropenylidene moiety with a nitrogen-containing cyclopentadienylidene. Thus, heating di- or triphenylpyrroles with diphenyl-methylsulfanyl-cyclopropenylium perchlorate in acetic acid gives the aza-triafulvalenium salts **33** and **34**



32

SCHEME 9

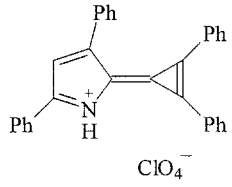
(68AG277). Their deprotonation with strong bases led to free deeply red-colored azapentatriafulvalenes which decomposed quickly (Scheme 10).

Another convenient approach to the azapentatriafulvalene system is given by the *in situ* formation of cyclopropenylium salts from cyclopropenones and dry HCl gas followed by their electrophilic attack on various indoles. The corresponding heterofulvalenium salts of type **35** were isolated as chlorides, which were somewhat photosensitive and thermally labile (68TL5537).

In addition, diphenylcyclopropenone condensed with 3-methylindole in the 2-position to yield **36** and with 2-phenyl-7-methylindolizine to yield **37**. Similarly, cycloheptenocyclopropenone reacted with 2-phenylindole, leading to **38.** Attempts to generate the free bases by treatment of the salts with a variety of bases of low nucleophilicity produced, at best, only fleeting colors attributable to the deprotonated species. The authors suggest that an ionic polymerization takes place due to the dipolar character of the free azapentatriafulvalenes. This hypothesis has been supported by the observation that the azafulvalenium salts were regenerated from the polymeric material by protonation in strongly acidic solution (Scheme 11).

As with diphenylcyclopropenylium salts, tris-(methylsulfanyl)cyclopropenylium tetrafluoroborate reacts with indole or 2,5-dimethylpyrrole to give 2-azacalicenium salts (86TL839). Attempts to prepare the azacalicenes from their salts were in vain. Ring-expanded analogs of the cyclopropenylium system also condense with electron-rich azoles. Thus, treatment of tropylium perchlorate with 2,4-diphenylpyrrole gave a 1 : 2 product for which the structure of an aza-sesquifulvalene **39** has been proposed (68AG277). Its free base was obtained by deprotonation using Hünigs base (Scheme 12).

Especially for the series of nitrogen analogs of sesquifulvalene, the condensation of carbonyl systems with salts of cyclopentadienes became important. Reactions of pyridinium salts with cyclopentadienides, indenides, and fluorenides were widely used to generate a number of azafulvalenes. To our knowledge the first synthesis of nitrogen analogs of sesquifulvalene was described in 1956 (56LA176) and again 1 year later by Russian chemists (57MI191). Substances of this type were prepared by reaction of alkali-



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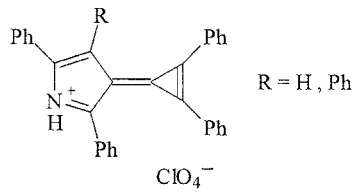

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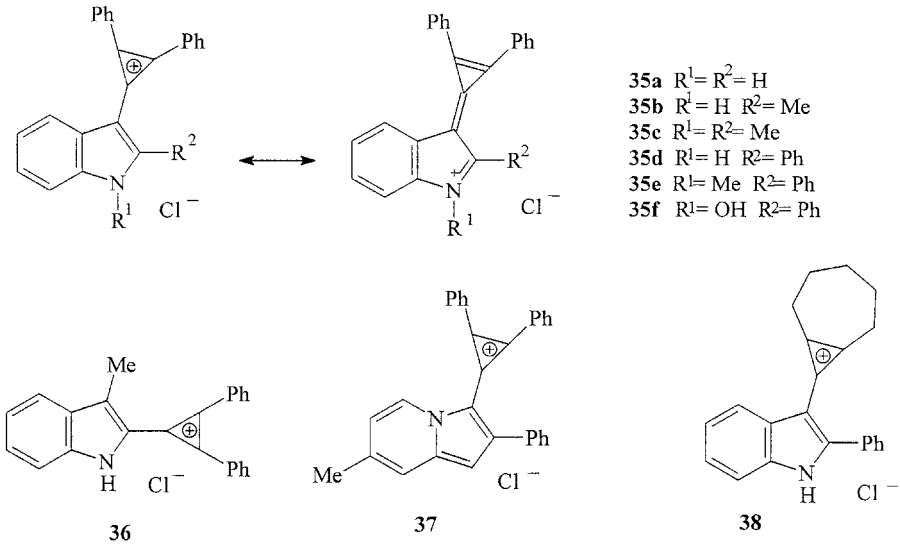
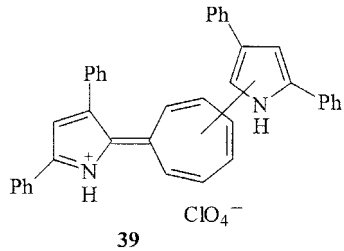
SCHEME 10



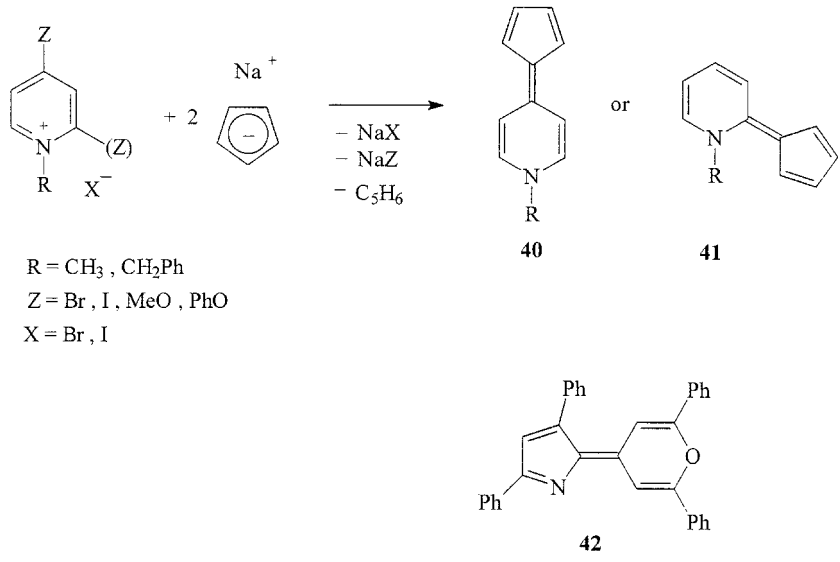
SCHEME 11

cyclopentadienides (indenides/fluorenides) with 2,6-dichlorobenzylpyridinium salts. The final stage of this synthesis involved dehydrogenation of an intermediate addition product, an N-alkylated 1,4-dihydropyridine. The structural assignments for olefination in the 4-position of the pyridine ring require confirmation because other reactions of pyridinium salts with sodium cyclopentadienide carried out under apparently very similar conditions gave intermediates that can be converted to azulenes, presumably by attack at C-2 (58AG419).

Regioselective syntheses of members of the 2- (**41**) and 4-series (**40**) are achieved by nucleophilic substitution of 2- or 4-halo- or -methoxy/phenoxypyridinium salts with sodium cyclopentadienide (60JA3793, 60MI253; 63JCS253; 64TL3087) (Scheme 13).



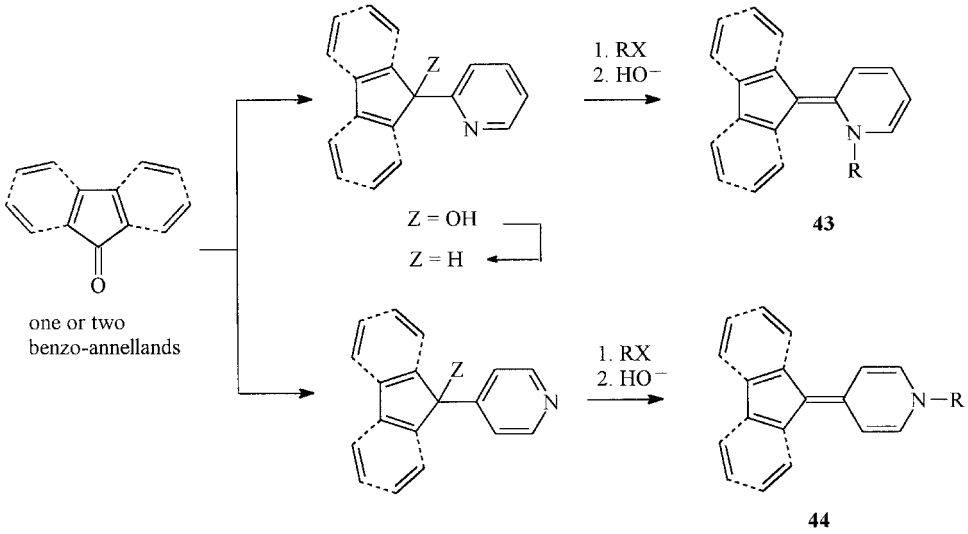
SCHEME 12



SCHEME 13

Another type of leaving group is found in 2,6-diphenyl-4-methylsulfanylpyrylium salts, the methylsulfanyl or methylthio group. This allowed the entry to oxa-aza-sesquifulvalenes of type **42** by reaction with 2,4-diphenylpyrrole in the presence of sodium hydride (67AG277). The initial products of these displacements were the conjugate acids of **40** or **41,** from which the free azafulvalenes were generated by loss of a proton induced by the excess of cyclopentadienide anion. An improved synthesis is given by Berson, who extracted the conjugate acids with dilute aqueous HCl from the organic reaction mixture and then regenerated the free bases with alkali (65JA2887). A similar regioselective attack was described for the preparation of pentadecaazafulvalenes by reaction of substituted tropylium salts with tetraphenylcyclopentadiene (82CB3756). Further synthetic approaches to fluorenylidene and indenylidene derivatives of sesquifulvalenes were given by formally "umpolung" reactions. Thus, 2- and 4-lithio-pyridines first were converted with fluorenone and 1-indanone, respectively, to the corresponding carbinols. Acid-catalyzed dehydration using HI, alkylation at the pyridine nitrogen followed by neutralization of the salts with alkali, afforded the azafulvalenes of type **43** and **44** (65JA2887). Despite the formal possibility of *E*/*Z* isomerism, the indenylidene derivative **43** was obtained as an apparently homogeneous diastereomer (Scheme 14).

In some cases, a simple carbonyl reaction with the CH-acidic cyclopentadienes in the presence of a base gave a convenient entry to special types of azafulvalenes. Starting from the appropriate cyclic carbonylic and thiocarbonylic systems respectively, or their acetals, the following azafulvalenes



SCHEME 14

were synthesized: cyclopentadienylidene-cyclohepta[c]pyrroles (82CB251), pentapseudo-aza-phenafulvalenes [77JCR(S)77; 79AP801; 80AP977; 80LA971; 82M623], and 1-methyl-2-cyclopentadienylidene-dihydroquinoline (61LA1).

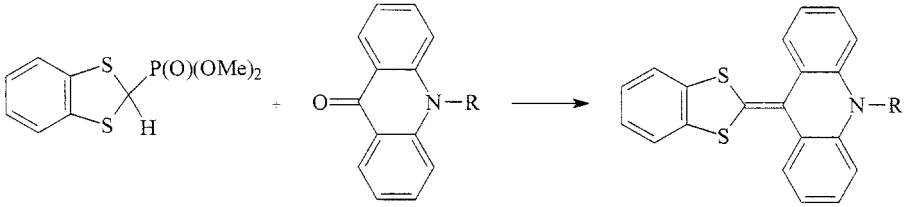
3. *Direct Carbonyl-Olefination*

The interest in the preparation and use of dithiolium salts in connection with the synthesis of TTF derivatives led to the development of a new uses of heteroaromatic cations in organic synthesis. Based on that, a new carbonyl olefination for the synthesis of numerous heterofulvalenes was developed (77S861). For example, 2-dimethoxyphosphinyl-1,3-benzodithiole was deprotonated with butyllithium in THF at −78°C and the resulting phosphonate carbanion reacted with 9-alkyl-acridones to give the dithiaazafulvalenes of type **45** (78BCJ2674) (Scheme 15).

The starting material for this Wittig–Horner-like olefination was easily accessible by reaction of benzo-1,3-dithiolium-tetrafluoroborate with trimethylphosphite in the presence of an equimolar amount of sodium iodide in dry acetonitrile under nitrogen at room temperature (93% yield).

4. *Azafulvalenes by Ring-Transformation Reactions*

In addition to ring-forming reactions, the transformation of preformed heterocycles serves as an efficient alternative route for the synthesis of



45a R = Me
45b R = Et

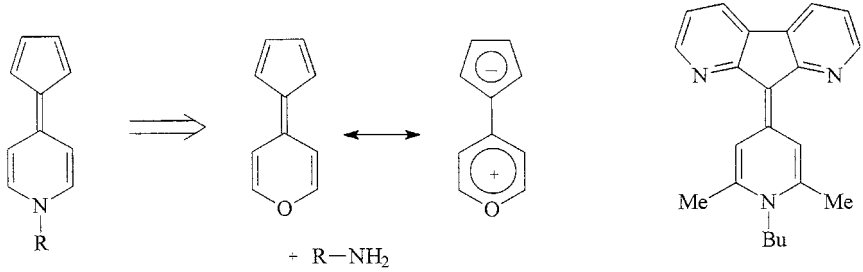
SCHEME 15

highly substituted cyclic compounds in the field of natural products, in material sciences, and in the pharmaceutical industry. In this context, pyrylium salts as well as nitrogen-containing rings (tetrazines, triazines, pyridazines, and others) and their fused systems possess widely demonstrated utility. Thus, heterofulvalenes containing a pyranylidene substructure allow an easy transformation with, for example, primary amines giving aza analogs of sesquifulvalene (67AG96; 69AG518). Using this methodology, azafulvalene **46** of pharmaceutical interest bearing two additional pyridine moieties could be synthesized starting from the corresponding pyranofulvalene and *n*-butylamine (72LA93). This type of reaction, involving a ring-opening/ring-closure mechanism induced by nucleophiles represents a good alternative for the synthesis of azafulvalenes (Scheme 16).

B. DIAZAFULVALENES

1. *Dimerization of Carbenoid Precursors*

A considerable number of dihetero-diazafulvalenes are well-known by the name "electron-rich olefins." They are associated with the problem of

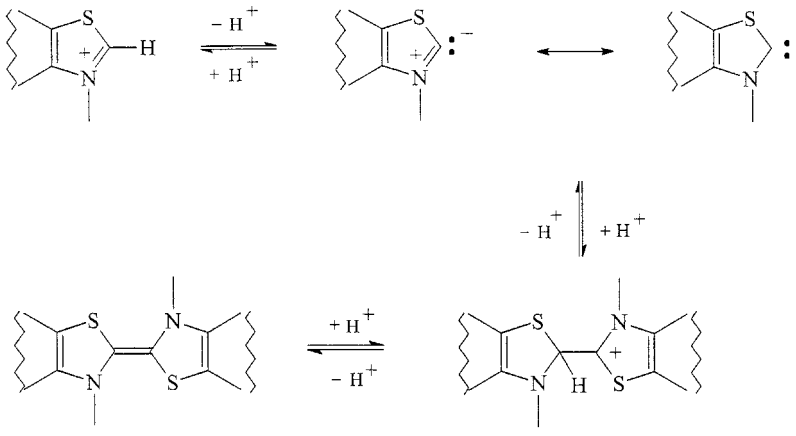


46

SCHEME 16

carbenoid or ylide intermediates and their capacity of dimerization. Dithiadiazafulvalenes and related carbenes have received considerable attention from both the chemical and biological points of view as possible intermediates formed by the deprotonation and subsequent dimerization of thiazolium salts. The conjugate base obtained from the thiazolium cation moiety of thiamin (vitamin B_1) is effective in both enzymatic and nonenzymatic catalysis (Scheme 17).

Breslow first recognized the possible importance of carbene character in ylides, which are formed by deprotonation of thiazolium salts in position 2 (58JA3719). Later work using tetrakis[dialkylamino]ethenes, which were presumed to dissociate readily to carbenes prior to the reaction with electrophiles, led Wanzlick (62AGE75) to the assumption that these ylides were reacting as nucleophilic carbenes with electrophiles. However, further studies ruled out the presence of free nucleophilic carbenes of the thiazolin–ylidene type (64JA2518; 65JA2055), since mixtures of different substituted "electron-rich" ethenes failed to give cross-dimers on heating. In the meantime, other authors (64AGE800; 66CB2017) claimed to have distinguished the reactions of carbenes with azidium salts from those of the corresponding dimer, also formed under these conditions. In 1991 (91JA985) the equilibrium acidity was estimated for the C2-H bond in the 3,4-dimethylthiazolium cation as model for thiamine. It was shown that this and similar dimerizations occur by addition of the conjugate base of a thiazolium salt to the activated CN bond of the thiazolium cation, followed by deprotonation. The same conclusion was obtained independently (91JOC5029) using NMR experiments on ^{13}C-labeled thiazolium salts. On addition of less than one equivalent of base the salt first formed an unsymmetrical dimer in which the C2 atoms of two molecules were bonded to each other and only

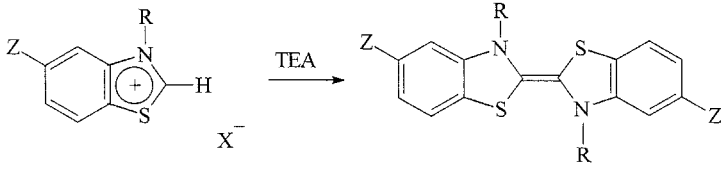


SCHEME 17

one of them still carried a hydrogen. This dimer lost upon addition of excess base the remaining hydrogen at C2 and was converted to a mixture of *E/Z* isomers of the heterofulvalene in nearly equal amounts. Finally, in order to evaluate a kinetically stable model for the thiamin carbene, several thiazol-2-ylidenes and their dimers have been synthesized and structurally characterized by Arduengos group (97LAR365).

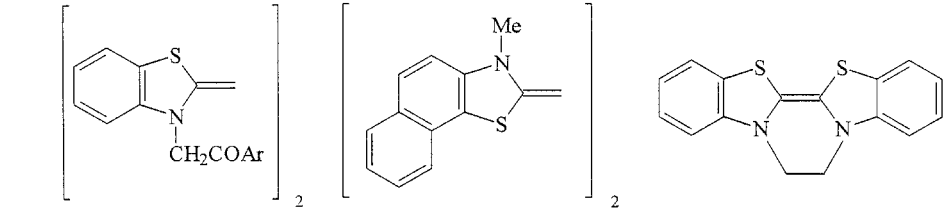
The first attempts to prepare such compounds are attributed to Wanzlick (63AG1204) and, 1 year later, to Vorsanger (64BSF119) and Metzger (64BSF2857). Thus, treatment of benzothiazolium salts with tertiary amines such as triethylamine led to the yellow-colored and well-crystalline dithiadiazafulvalenes of type **47.** This method has been extended to a large number of diazafulvalenes stimulated by interest in the carbene–dimer problem as well as the high degree of nucleophilicity in combination with the electron-donating properties of the intermediate. For example, the phenacyl substituted compounds **48** (65CB3808), the naphtho derivative **49** (67LA155), and the bridged **50** (72LA126) have been prepared (Scheme 18).

Although benzoxazolium salts are more acidic than their benzothiazol analogs in position 2, isolation of the corresponding dioxa-diazafulvalenes was unsuccessful (72LA126). Comparable to the 1,3-dithiolium- and 1,3-thiazolium salts, 1,2,4-dithiazolium salts yielded on treatment with triethylamine in acetonitrile at 0°C mixed geometrical isomers of the TTDAF



R = Me , Et
Z = H , Cl
X = Cl , Br , I , CH_3SO_4

47



Ar = Ph , 4-BrC_6H_4 , 4-$O_2NC_6H_4$

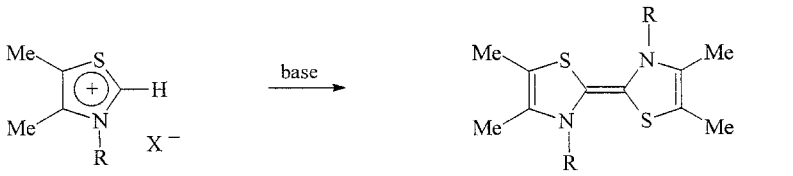
48 **49** **50**

SCHEME 18

65a and **65b** (R = Ph, subst. Ph) (93TL847), although the reaction proceeded less readily. No formation of azafulvalenes by the deprotonation of substituted azolium salts has been noticed in case of 1,3,4,5-tetraphenylimidazolium salts (70LA176); 1,4-diphenyl-3-methylsulfanyl-1,2,4-triazolium salts (75TL1889); 1,3,4-triphenyl-1,2,4-triazolium salts (95AG1119); and a number of related systems.

When 3-(2,6-diisopropylphenyl)-4,5-dimethylthiazolium chloride reacted with potassium hydride in THF at room temperature the stable carbene 3-(2,6-diisopropylphenyl)-4,5-dimethylthiazol-2-ylidene was formed (97LAR365). Whereas in the strict absence of protic acids dimerization on a time scale of weeks was not possible, such dimerization proceeded smoothly in the presence of trace amounts of protic acids. The *E*-arrangement of the sterically congested diazafulvalene **51a** was confirmed by X-ray diffraction studies. The N-mesityl-substituted carbene, also derived from deprotonation, was not stable enough to be isolated at room temperature, but it could be observed in solution by NMR spectroscopy up to 0°C. The corresponding diazafulvalene **51b** was isolated as an orange solid using potassium hydride at room temperature. When the mesityl group in the thiazolium salt was replaced by a methyl group it no longer was easy to detect the corresponding carbene. Instead of generation of the carbene, the deprotonation at room temperature led to the formation of an *E/Z* mixture of the diazafulvalene **51c.** These experimental findings clearly demonstrate that the existence of stable carbenes and their dimers can be influenced by the use of a combination of steric and electronic effects (Scheme 19).

A large number of DTDAFs ("electron-rich olefins") described above are very efficient donors, e.g., for their application in organic conductors; however they are highly sensitive to air. Studies aimed at the preparation of such compounds, especially the aliphatic ones, have so far met with only limited success. For example, a few alkyl-substituted DTDAF derivatives could be detected electrochemically, but an attempt to isolate one of these only led to oxidation products (91JA985). Similarly, an elec-



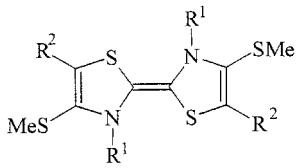
51a R = 2,6 -diisopropylphenyl
51b R = 2,4,6-trimethylphenyl
51c R = Me

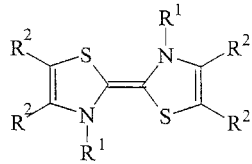
SCHEME 19

trochemical reduction of a bridged 2,2′-bithiazolium salt gave no stable products (90TL1539). Other authors have observed the migration of a benzyl group on attempting to prepare DTDAF from the corresponding thiazolium salt (87BC1) (Section IV,G). The deprotonation of the corresponding thiazolium tetrafluoroborates under mild conditions yielded the desired DTDAF **52a,** which was easily oxidized by simple recrystallization in the preence of air. The synthetic strategy to prepare **52b** allowed the addition of TCNQ during the preparation, giving a stable charge-transfer complex (93CC601) (Section IV,F). The synthesis of the first noncondensed crystalline DTDAF **52d** was reported in 1992 (92JOC1008). With regard to the expected ease of the oxidation of such a compound, a different synthetic approach from that described was chosen. First, the corresponding heterocyclic thione was converted into the 2-(alkylthio)-1,3-thiazolium salt. Second, treatment with sodium hydrogen selenide afforded selones. Finally, the latter was coupled by treatment with triethyl phosphite to give the DTDAF derivative as deeply violet crystals in 85% overall yield. The ^{1}H- NMR data of the fulvalene **52d** obtained in $CDCl_3$ solution showed, in addition to phenyl protons, two methyl singlets for the SMe groups and two others (OMe) in ratios of 1 : 1, testifying to the existence of both *E* and *Z* isomers. A further stabilization was achieved by the introduction of four electron-withdrawing substituents. The DTDAF's of type **53a–53c** were obtained in the same way to give yields of 58–91% (95JA8528) (Scheme 20).

2. *Condensation Reaction of Cyclopentadienides with Azolium Salts*

As described in Section II,A,1, the condensation of azolium salts with aza derivatives of cyclopentadienide (pyrroles, imidazoles, pyrazoles) also plays





52a R^1 = Ph , R^2 = 4-Tol

52b R^1 = Ph , R^2 = 4-ClC_6H_4

52c R^1 = 4-$O_2NC_6H_4$, R^2 = 4-ClC_6H_4

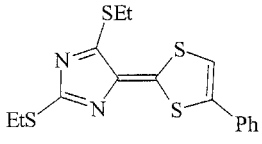
52d R^1 = Ph , R^2 = COOMe

53a R^1 = Me R^2 = COOMe

53b R^1 = Ph R^2 = COOMe

53c R^1 = Me R^2 = CN

SCHEME 20



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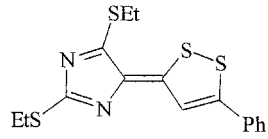

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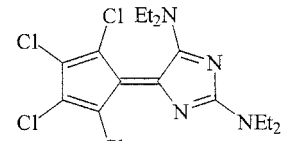


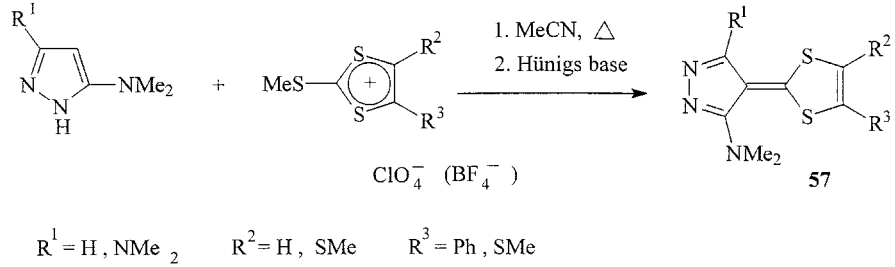
56

SCHEME 21

an important role for the synthesis of diazafulvalenes. Analogous to the formation of monoazafulvalenes, a number of derivatives have been synthesized in low to moderate yields starting from 1,2,4-dithiazolium salts and diphenylpyrroles (68AG277) as well as from the sodium salts of phenylimidazoles (70TL481). Diazafulvalenes possessing two electron-donating groups as in **54** and **55** were prepared by condensation of 2,4,5-tris(ethylsulfanyl)imidazolium chloride with the corresponding dithiolium salts in acetonitrile and in the presence of Hünigs base (86TL839) (Scheme 21).

2,4,5-Tris(dimethylamino)-imidazolium salts, which can be interpreted as antiaromatic cations derived from 1,3-diazacyclopentadiene (88AG1492), are useful building blocks for special kinds of diazafulvalenes. Thus, compound **56** has been isolated starting from this imidazolium salt and tetrachlorocyclopentadiene in the presence of sodium hydride (81TL2973). Derivatives of 6,7-diazafulvalenes having a pyrazole substructure were first synthesized in 1985 (85PS223; 86TL159). 3-Dimethylaminopyrazole and 3,5-bis(dimethylamino)pyrazole belong to electron-rich heteroaromatic five-membered ring systems which react with 1,3-dithiolium salts on heating in solution to give the fulvalenium salts which subsequently can be transformed into the orange 6,7-diaza-1,4-dithiafulvalenes of type **57** (Scheme 22).

Another type of diazafulvalenes was obtained by the condensation of sodium cyclopentadienide with 1,2-dimethyl-3,5-dimethoxy- and -3,5-bis(methylsulfanyl)pyrazolium salts (94AP385). Under mild conditions displacement of MeZ groups in each case led to the diazafulvalenes **58.** A

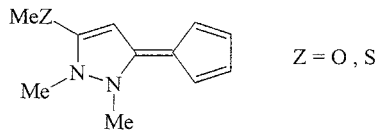


SCHEME 22

twofold substitution by cyclopentadienide was successful after oxidative transformation of both methylsulfanyl residues into methylsulfonyl groups. The anionic heterofulvalene **59,** which forms a yellowish solid, is extremely sensitive toward oxygen and moisture (Scheme 23).

3. Oxidative and Reductive Processes

Due to their relationship to indigoid structures and their use as precursors for phorphyrinoid systems, some oxidative as well as reductive preparations of diazafulvalenes became important. In the case of investigations directed to the behavior of highly substituted pyrroles, the synthesis of the diazafulvalene **60** by oxidation of 2-ethoxy-3,4-dimethylpyrrole with preactivated lead-IV-oxide (67CB1701) has been described. Because of the observation of two different melting points, the interconversion of *E/Z* isomers has been discussed. Similarly, 3-ethoxy-pyrrole-5-carbonic acid could be oxidized by iron-III-chloride to give the deeply colored derivative **61.** The same heterofulvalene can be synthesized in better yields and in higher purity starting from the corresponding 2,2′-dipyrrole by oxidation with air (59%), ferricyanide (45%), or iodine (92%) (68CB1286). It is noteworthy that **61** represents an indigoid dye, which is stable toward bases and acids, giving a leuco compound by treatment with sodium dithionite that can be reoxidized immediately (Section IV,E). In solution, this leuco form displayed an intensive green fluorescence (Scheme 24).



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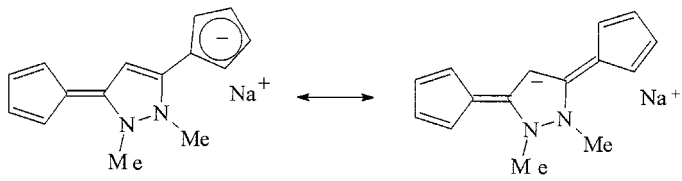
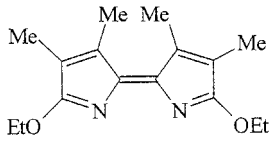
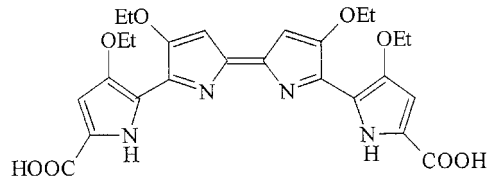


59

SCHEME 23



60



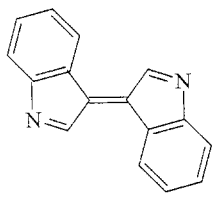
61

SCHEME 24

In addition to pyrroles, their benzo-fused derivatives are easily accessible and useful building blocks for the synthesis of diazafulvalenes. In connection with the two-step redox system of the Weitz-type a series of dicationic benzazafulvalenes **63** have been synthesized by oxidation of the 3,3′-bridged *N*-methyl indoles with lead-IV-acetate (72TL643; 76LA1039). For (aza-)vinylogous compounds derived from 1,2- and 1,3-dimethylindolizine see 76LA317. Despite their high electrophilic character, in most cases the desired derivatives could be precipitated as crystalline perchlorates in an analytical state of purity. 3,3′-Biindole itself was transformed classically to the 3,3′-biindoleninylidene **62** by lead dioxide in ethyl acetate (57CS4141); its structure was investigated by NMR and mass spectroscopy (76LA1039).

Isomeric indigoid compounds were reported in 1966 (66TL3015). 2-Cyanobenzophenones can easily be reduced by hydrogen in the presence of a Raney nickel catalyst to yield the acid-stable 3,3′-diaryl-1,1′-biisoindolylidenes **64** dyes. During a complex intramolecular condensation reaction the formation of dimeric biisoindoleninylidenes has been proposed. The dimers were rapidly dehydrogenated to diazafulvalenes by Raney nickel. Due to their deep color and the high degree of stability they were described in a patent (66BRP1020305); some years later their exact structure (*E* configuration) was determined by X-ray diffraction (71CB3108). Independent from these findings, the diphenyl derivative (R = H) has been isolated by air-mediated oxidation of 1-phenylisoindole (67CS366) (Scheme 25).

The derivatization of TTF, essential for the variation of its electronic properties, has generally been achieved by altering the substituents or by chalcogen exchange. Thus, replacement of one CH group in each of the two rings of TTF by nitrogen should lead to derivatives of tetrathiadiazafulvalene (TTDAF). These compounds would be of interest because, although they are expected to be poorer electron donors, they are sterically less encumbered than their parent TTFs. The synthesis of TTDAFs of type **65a** and **65b** can be realized by reduction of 3-substituted 5-methylsulfanyl-1,4,2-dithiazolium salts with zinc powder and subsequent thermolysis (93CC1226; 94JOC2997). In the first step, the readily available 1,4,2-dithia-



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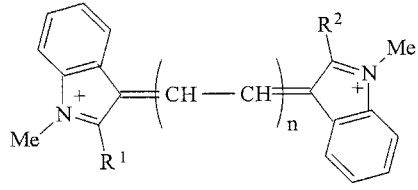
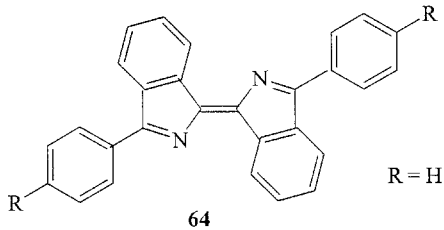


63 n = 0 – 5 , 9 R^1, R^2 = H , Me



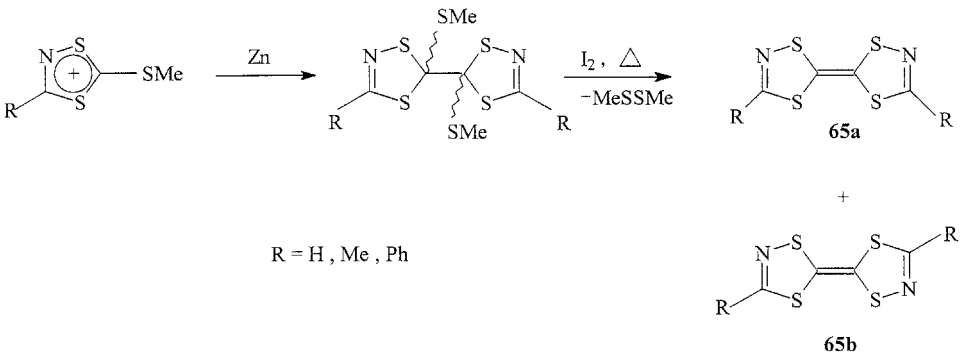
64 R = H , Me , OMe

SCHEME 25

zolium salts were reduced to the corresponding diazahexathiaorthooxalates as 1 : 1 mixtures of the *syn/anti* isomers in quantitative yields. When dilute methylene chloride solutions of the latter were heated in the presence of small amounts of iodine, they slowly turned an orange-red color, indicating formation of heterofulvalenes and dimethyldisulfide. The separation of the *E* and *Z* isomers can be achieved quite easily for the methyl and phenyl derivatives, but cocrystallization occurs for the two isomers of the unsubstituted compound. Attempts to prepare mixed heterocyclic fulvalenes by cross-coupling of 1,4,2-dithiazolium and 1,3-dithiolium salts were unsuccessful (Scheme 26).

4. *Miscellaneous*

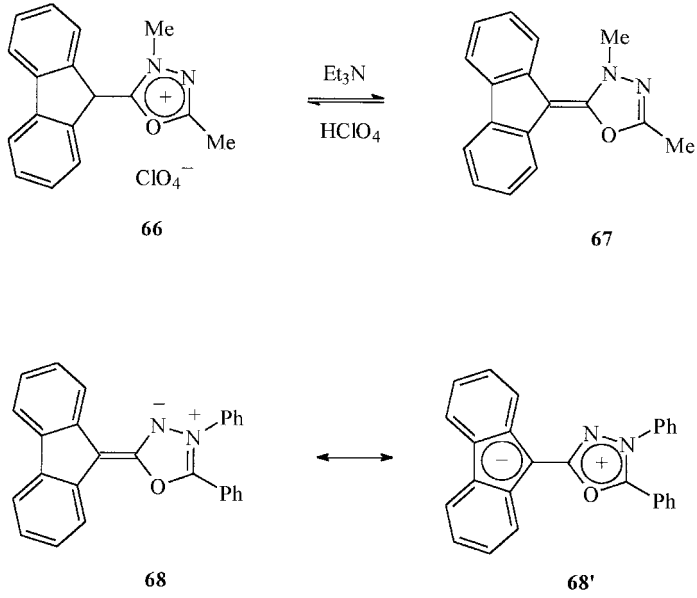
Boyd and coworker found that diacylhydrazines on treatment with acetic anhydride and a strong acid yielded 1,3,4-oxadiazolium salts (67CC954). On applying these cyclization reactions to fluorene-9-carbohydrazides a number of fluorenyl-oxadiazolium salts could be prepared which again were converted to heterocyclic analogs of sesquifulvalene by proton abstraction (70CS807). For example, treatment of salt **66** with triethylamine gave the oxadiazasesquifulvalene **67,** which was reconverted back to the salt by perchloric acid. In the same way, the diphenyl-substituted mesoionic fulvalene **68** was obtained but it was stable only in the solid state. The im-



SCHEME 26

portance of the contribution from the sesquifulvalenoid form in stabilizing the mesoionic molecule is indicated by the failure to isolate a closely related benzhydrylidene derivative (70JCS807) (Scheme 27).

Interest in the mechanism and product distribution of thermal and photochemical transformations of aryl azides led to the isolation of some nitrogen-containing derivatives of heptafulvalene. Based on elemental analysis and spectroscopic data it has been suggested tentatively that the compound isolated following vapor-phase pyrolysis of azidopentafluoro-



SCHEME 27

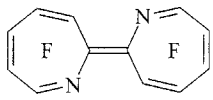
benzene is the *Z* isomer of perfluoro-2,2′-diazaheptafulvalene **69** (73TL99; 74JCS(P1)1365). The authors later reported an arylnitrene 2-azepinylidene ring expansion followed by dimerization to the diazaheptafulvalene confirming the structure of **69** by X-ray crystallography (80CC900).

An intensely colored by-product of the photolysis reaction of methyl-2-azidobenzoate has been identified as the first known derivative of 3,3′-diazaheptafulvalene **70** (94LA1165). Its molecular mass was established by elemental analysis and mass spectroscopy as that of a formal nitrene dimer, whereas ^{1}H and ^{13}C NMR studies demonstrated the twofold symmetry as well as the existence of a cross-conjugated 14 π-electron system in **70.** Involving 1-azido-2,3-dimethoxy-5,6-dimethoxycarbonylbenzene in thermal decomposition reactions, the azaheptafulvalene **71** could be isolated and characterized spectroscopically and by means of X-ray diffraction. This unusual fulvalene can be regarded as a vinylogous derivative of azafulvalenes (96JHC1333) (Scheme 28).

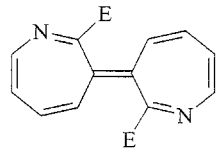
Further synthetic routes to derivatives of diazafulvalenes have been developed; they include the addition of azide ions to azidinium salts followed by decomposition at 0°C, addition of methanol and thermolysis of these alcohol-adducts (64AG995; 81HCA648), or condensation of 2-(formylphenacylamino)thiophenols with orthoformates (65CB3808). The latter two reactions are only marginally attractive, due to their hazardous intermediates, their difficult entry to the starting materials, and their relatively low yields. Finally, the condensation reaction of 2,6-diphenyl-4-methylsulfanyl-pyrylium salts with 4,5-diphenylimidazole in the presence of sodium hydride gave oxa-diaza-sesquifulvalenes (68AG277).

C. Triazafulvalenes

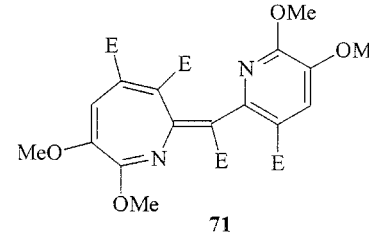
Among the azafulvalenes, those possessing three nitrogen atoms in the cross-conjugated system are the smallest group to date. There are a number



69



70



71

E = COOMe

Scheme 28

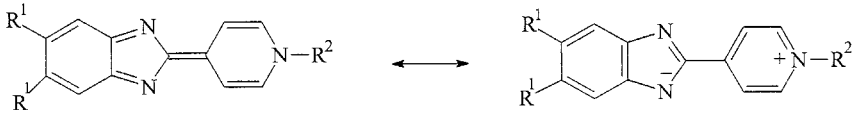
of aza-analogs of sesquifulvalene derived from azolyl-substituted 1,4-dihydropyridines (67JOC3214; 80MI53). Thus, compounds of types **72** and **73** were easily accessible by deprotonation of the 1-alkyl-4-azolylpyridinium salts using an anionic ion-exchange resin such as Amberlit IRA-401 (89CC1086). These heteroanalogs of sesquifulvalene are relatively stable compounds and the dipolar resonance form gives a remarkable contribution to the ground state in contrast to sesquifulvalene itself (Scheme 29).

Recently, a new synthetic route to derivatives of 4H-imidazole was reported (97JPR729). Accordingly, the deeply violet-colored triazafulvalenes **74b** and **74c** have been synthesized starting from the 2-(4-pyridyl)-substituted compound, followed by quaternization with methyl iodide and subsequent reduction with sodium borohydride (97UP1). Finally, the ring transformation of the preformed oxa-diazafulvalenes as well as their protonated species with primary alkylamines offers a further possibility to synthesize triazafulvalenes (70JCS807) (Scheme 30).

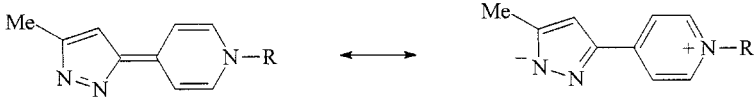
D. Tetraazafulvalenes

1. *Oxidation of 2,2'-Biimidazoles and Their Derivatives*

In contrast to the intensively examined tetrathiafulvalenes (TTFs), which are of interest in the field of material science, the TAFs have been less well

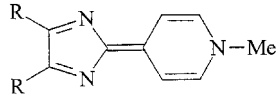


72a R^1= H R^2= Me
72b R^1 = R^2= Me
72c R^1= Me R^2= n-Bu
72d R^1= H R^2= n-$C_{10}H_{21}$



73a R = Me
73b R = n-Bu

Scheme 29



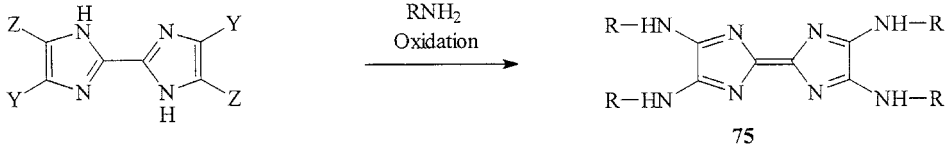
74a R = Ph
74b R = NH-4-tolyl
74c R = NH-3-trifluoromethylphenyl

SCHEME 30

characterized. Probably the first attempt to synthesize TAFs was made in 1943. Tetraamino-substituted derivatives of 1,4,5,8-tetraazafulvalene **75** were isolated, but the lengthy synthetic route, starting from 2,2′-biimidazoles, ended without exact structural assignment (43CB879) (Scheme 31).

Generally, 2,2′-biimidazoles, their benzofused derivatives, as well as vinylogous/phenylogous derivatives constitute useful starting materials for the syntheses of tetraazafulvalenes. Regarding these types of electron-rich heteroaromatic compounds, it becomes clear that two SET processes are necessary for the formation of the typical cross-conjugated system. Therefore, they fit well into the category of Weitz-types of compounds, which are able to act as two-electron transfer reagents starting from the reduced aromatic state (78AG927). This hypothesis has been realized by the oxidation of 2,3,6,7-tetraphenyl-2,2′-biimidazole to **76a** (66TL5221). Using freshly prepared lead dioxide, this symmetrical tetraazafulvalene could be isolated as a stable red-colored and well-crystallized compound. By the same method, the tetrachloro and tetrabromo derivatives (**76b** and **76c**) have been prepared (89KGS1421; 96SM127). Thus, oxidation of the silver salt of 4,4′,5,5′-tetrabromo-2,2′-biimidazole in dichloromethane at −30°C in subdued light afforded **76c** (R = Br) in 53% yield. This perhalofulvalene is stable for months if stored as a solid at low temperatures. However, decomposition takes place at room temperature over several days.

A number of tetraazafulvalenes **77** containing a *p*-quinoid substructure have been synthesized; they include phenylogous biimidazoles such as 1,4-



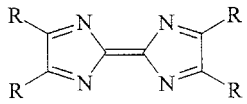
75

Y = Z = Br , Y = Br Z = NO_2 R = Ph , 4-chlorophenyl, 4-tolyl

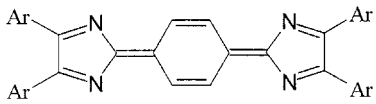
SCHEME 31

bis(4,5-diarylimidazol-2-yl) benzenes. Elemental bromine (66AG303), ferricyanide (72NKK100; 82MI376; 93TL6379), or lead dioxide (79JOC1241) were used as oxidation agents. In order to determine the electronic interactions (quinoid or biradicaloid) in tetraazafulvalenes, compound **78** was prepared by ferricyanide-induced dehydrogenation of 9,10-bis(4,5-diphenylimidazol-2-yl)anthracene (93TL6379). Its X-ray crystallographic analysis revealed a folded molecule whereby the dihydroanthracene moiety adopts a butterflylike conformation in which the dehydroimidazole rings show a syn arrangement. The exocyclic C—C—bond is somewhat longer than the central double bond in bianthronylidene but corresponds to that of the bent quinoid systems. The conjugation between both terminal heterocycles is diminished, leading to the hypsochromic shift of 89 nm (**78:** λ_{max} = 513 nm; **77,** Ar = Ph: λ_{max} = 602 nm) (Scheme 32).

Using ESR spectroscopy, the structural problem of "2,2′-biisobenzimidazolylidene" has been solved. The real structure, described in the earlier literature (63JOC1931; 65JA1651; 67JOC234) as "tetraazafulvalene," is that of the oxidation product of fluoflavine, quinoxalino[2,3-*b*]quinoxaline. Starting from a mixture of 2,2′-bis(benzimidazole) and fluoflavine, only the latter was oxidized under the conditions applied in (63JOC1931) to give this tetracyclic heterocycle. Further proof was given by independent synthesis, comparison of ESR data of the corresponding radical anion, and by spin density calculations (68TL1843).

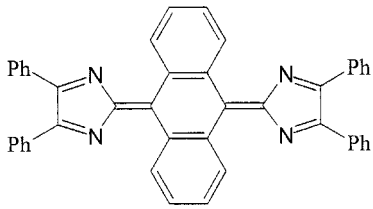


76a R = Ph
76b R = Cl
76c R = Br



77

Ar = Ph , 4-FC_6H_4 , 4-ClC_6H_4 , 4-$MeOC_6H_4$



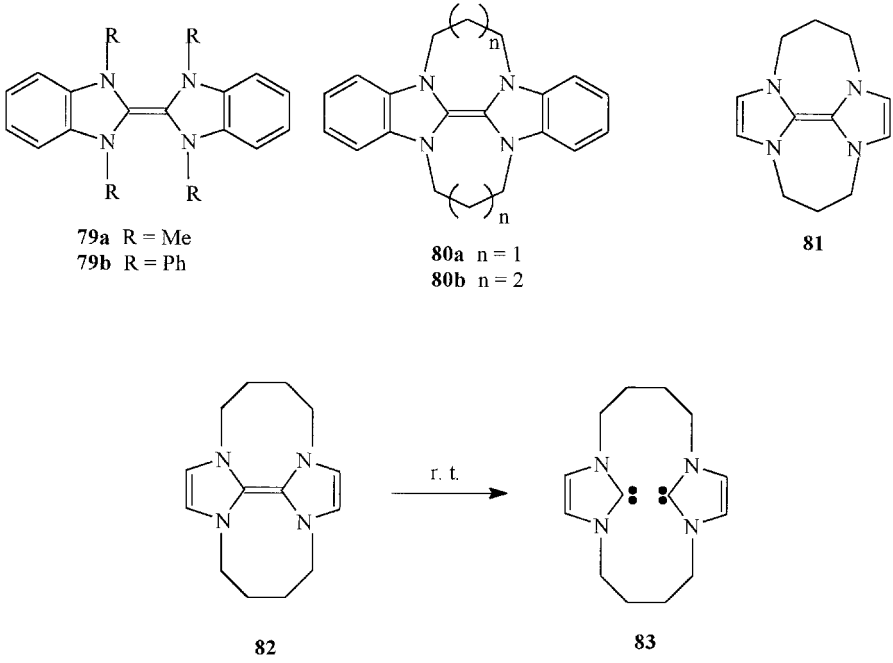
78

SCHEME 32

2. *Dimerization of Carbenoid Precursors*

As in the case of certain diazafulvalenes (Section II,B,1), deprotonation of azolium salts followed by dimerization of carbenoid intermediates can also be used for the synthesis of tetraazafulvalenes. Whereas thiazolium and oxazolium salts readily react with triethylamine, imidazolium salts require stronger bases. On treatment of *N*,*N*′-dimethylbenzimidazolium bromide with sodium hydride the air-sensitive tetramethyl derivative **79a** has been prepared and characterized by NMR spectroscopy (72LA110). Similarly, the tetraphenyl analog **79b** was isolated in nearly quantitative yield by treatment with tetramethylguanidine (71BSF3541). Electrochemical studies on dicationic 2,2′-imidazolium systems indicated extremly high donating properties for the reduced, neutral forms, which made their isolation impossible (89JOC3057). Investigating the chemistry of *N*,*N*′-bis annulated benzimidazolium salts (94TL33), reduction of these diquaternary salts by means of tetrakis(dimethylamino)ethene was tried. However, examination of the products by NMR and by single crystal X-ray analysis showed that ureaphanes (Section IV,E) were isolated as a consequence of an immediate oxidation reaction. Later, the authors were successful while making an effort to generate the corresponding bis-carbene by deprotonation with strong bases. It was necessary to carry out the deprotonation by sodium hydride in acetonitrile with the scrupulous exclusion of oxygen in order to isolate the tetraazafulvalenes **80a** and **80b** (95TL2741). When both compounds were exposed to air intense chemiluminescence could be observed; the yellow color slowly faded to white, and ureaphanes, cited below, were obtained.

Carbenes stabilized by heteroatoms can be isolated (97LAR365). Hence, the question about the magnitude of their dissociation energy to form them is raised. For this reason, the stable tetraazafulvalene **81** was synthesized starting from the bisbridged imidazolium salt by deprotonation by either potassium hydride in dimethyl sulfoxide or by sodium hydride in liquid ammonia (96AG1098). Its X-ray structural analysis and NMR data also clearly indicated the structure to be that of a tetracyclic TAF. Whereas **81** was stable in solution and as a solid for several days, the homologous derivative **82** rapidly underwent a dissociation leading to the bis-carbene **83** on warming to room temperature. Attempts to generate mono- or nonbridged analogs of TAF failed, leading to carbenes. Based on ab initio calculations and various VB models, the authors estimated the value of the bond formation enthalpy to be about 2 kcal/mol. This small energy barrier might explain the failures in synthesizing certain TAFs, which can also be regarded as dimers of singlet carbenes. In agreement with these findings, a stable tris-carbene could be obtained in good yield by the deprotonation method (94TL1365). This tridentate carbene shows neither intramolecular nor intermolecular dimerization reactions when stored under dry nitrogen (Scheme 33).



79a R = Me
79b R = Ph

80a n = 1
80b n = 2

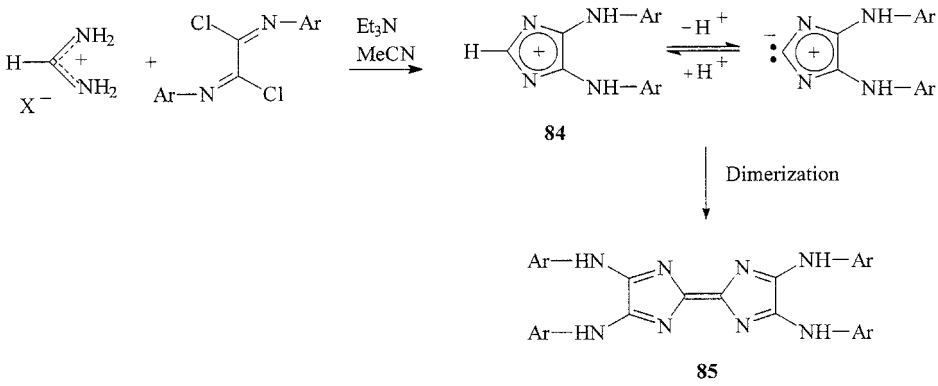
81

82

83

SCHEME 33

In this context, a new one-pot synthesis of aminosubstituted 1,4,5,8-tetraazafulvalenes **85** was reported (97LAR617). Stimulated by the results of investigations about the synthesis of cyclic oxalic amidines, attempts to obtain cycloamidines by reaction of formamidinium salts with bisimidoyl chlorides of oxalic acid were made. However, instead of the desired derivatives of 4H-imidazole, in all cases intensely red-colored products were found; they were identified as 2,3,6,7-tetrakis(arylamino)-1,4,5,8-tetraazafulvalenes **85.** UV/VIS spectra confirmed the dye-character of these heterofulvalenes by their long wavelength absorptions between 528 and 606 nm with extinction coefficients logε >4.5 depending on the nature of the aryl substituents. The formation of these aminosubstituted tetraazafulvalenes may at first sight seem somewhat surprising but can be readily explained. It is likely that cycloacylation between formamidine and bisimidoyl chlorides stops at the stage of the protonated species **84.** On the one hand, this intermediate is a cyclic formamidinium salt, but on the other hand, it is also an antiaromatic, 4,5-di-donor-substituted 1,3-diazacyclopentadienylium cation (88AG1492). As such it is a key intermediate in this dimerization reaction. Subsequent proton abstraction by triethylamine occurs not from the exocyclic position but from the 2-position of 84. Finally, the resulting carbenoid species dimerizes according to the mechanism described in Section II,B,1 (Scheme 34).



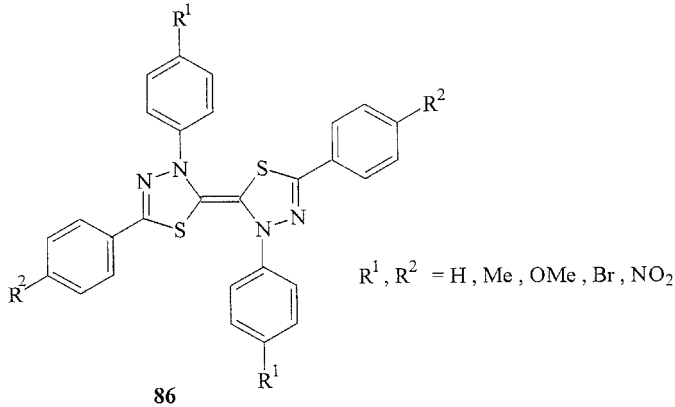
84

85

SCHEME 34

The chemical behavior of 3,5-diaryl-1,3,4-thiadiazolium salts was investigated in order to synthesize strongly acidic olium salts derived from heterocycles which are able to dissociate in suitable solvents (74CB1092; 78LA98). On heating these quaternary salts in trichloromethane or benzene, dissociation under formation of the dimeric form was observed. Treatment with gaseous hydrogen chloride gave back the starting material. Dimers of the type of dithiatetraazafulvalenes **86** were isolated in yields up to 78% by deprotonation using Hünigs base (Scheme 35).

The desulfurization of thiono compounds is another frequently used synthetic approach for the formation of double bonds via carbenoid intermediates. By this methodology, some indigoid 1,3,5,7-tetraazafulvalenes **88** and **90** were synthesized (83BSB781; 90JPR949). This dimerization starting from 2,4,5-tris(dimethylamino)imidazolium chloride via the appropriate thione **87** has been realized in the presence of phosphanes or phosphites to



86

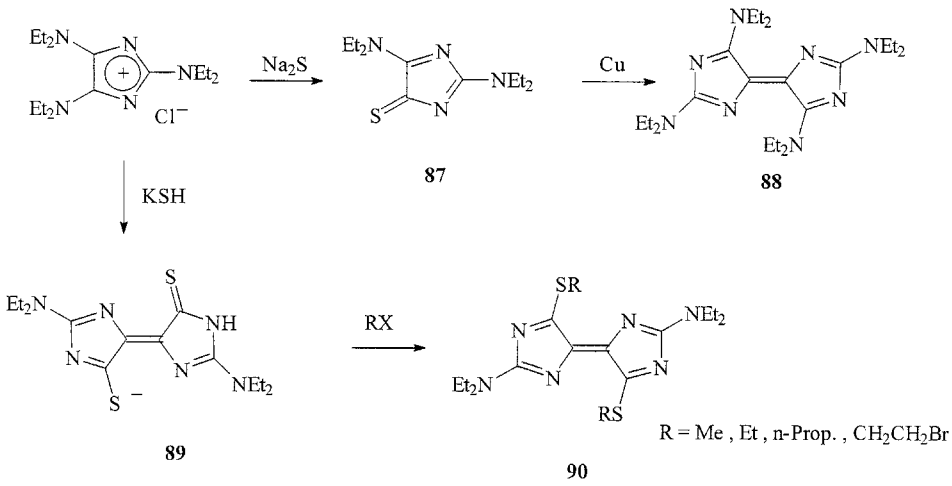
SCHEME 35

give higher yields with preactivated copper powder (90JPR949). The application of potassium hydrogen sulfide instead of sodium sulfide afforded the anionic **89** which in the protonated form was reported to be the first dithiono derivative of an indigoid system (94TL9195; however, compare 91JPR555). Treatment of **89** with several alkyl halides is a convenient approach to 2,6-bis(dimethylamino)-4,8-bis(alkylsulfanyl)-1,3,5,7-tetraazafulvalenes of type **90** (90JPR949) (Scheme 36).

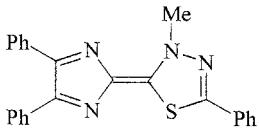
3. Miscellaneous

The condensation method (Section II,A,1) applied for 1,2,4-thiadiazolium salts and phenylsubstituted imidazoles leads to the thia-tetraazafulvalenes **91** and **92** (70TL481). Moreover, 2,4,5-tris(ethylsulfanyl)imidazolium chloride was converted to the unsymmetrical heterofulvalene **93** by a self-condensation reaction in the presence of potassium carbonate and elemental iodine (85PS223) (Scheme 37).

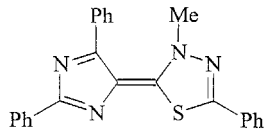
In context with the formation of peraminosubstituted 1,4,5,8-tetraazafulvalenes of type **85** it must be mentioned that the bis-vinylogous compounds **94** can be easily prepared by reaction of acetamidine with bisimidoylchlorides derived from oxalic acid (96S1302). In the course of a complex reaction a cyclic ketene aminal was produced; it immediately underwent an oxidative dimerization to yield deeply colored TAFs. Their high chemical stability can be compared with that of indigoid dyes and manifests itself, for example, by the fact that they are soluble in hot concentrated sulfuric acid without decomposition. The same type of fulvalene is also available by cy-



SCHEME 36



91



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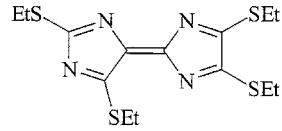
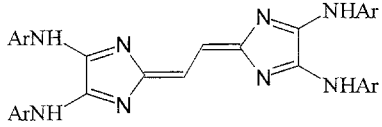


93

SCHEME 37

clization of succinic diamidine with the bisimidoylchlorides followed by spontaneous prototropism. Using this synthetic route, further vinylogous TAFs **95–97** were prepared (98JPR323) (Scheme 38).

Mesoionic compounds in which the positive charge is next to cyclopentadienide substructures are isoelectronic with sesquifulvalene. 1,3-Diphenyl-5-ethoxy-1,2,3,4-tetrazolium tetrafluoroborate was reacted with sodium cyclopentadienide in order to investigate compounds showing such an electronic structure (83CC789). The heterofulvalene **98a** bearing four nitrogen atoms in one ring of the fulvalene is characterized by considerable charge separation resulting from the significant contribution of the dipolar structure to its ground state. Further TAFs were synthesized with three



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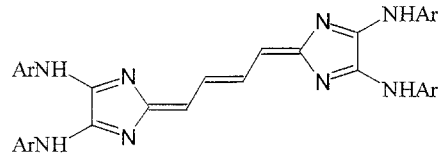

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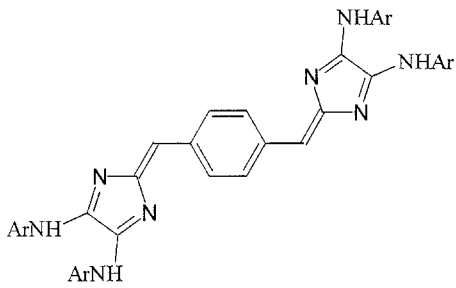

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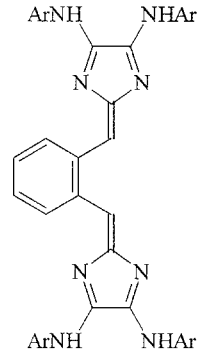


97

SCHEME 38

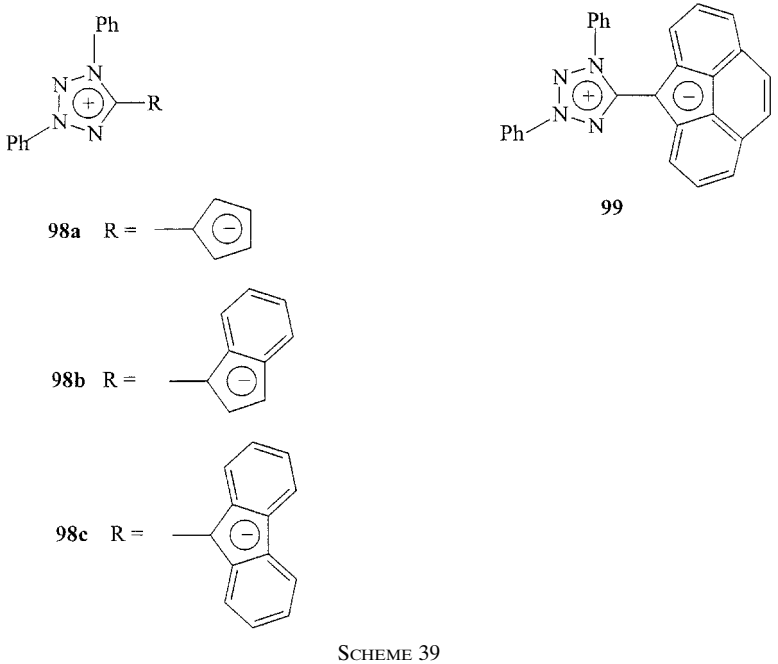
benzannulated derivatives—namely, the indenide **98b,** the fluorenide **98c,** and the cyclopenta [*def*]phenanthrenide **99**—and characterized by means of IR, UV/VIS, NMR, and mass spectroscopy [84JCS(P1)2545] (Scheme 39).

Tetraazafulvalenes bearing two pyrazole subunits could be prepared by an original way. Thus, treatment of benzylidene acetophenone with isopentylnitrite leads to an *N*,*N*′-dihydroxy-bipyrazolyl-*N*,*N*′-oxide, which in turn can be oxidized to TAF of type **100** (72CC961, 79JOC3211). Another type of oxidative dimerization was observed by the reaction of the electron-rich 1-methyl-2,4-bis(dimethylamino)imidazole with silver salts (83TL3563). A bis-cation was isolated in 30% yield in the presence of sodium tetrafluoroborate; an unsymmetrical structure **101** was predicted from its NMR data (Scheme 40).

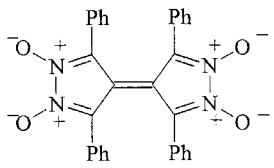
III. Physicochemical Properties of Azafulvalenes

A. Theoretical Calculations

Although azafulvalenes as yet comprise a small class of cyclic cross-conjugated compounds, they have been the subject of a variety of theoretical investigations spanning a range from the Hückel (HMO) theory to the



Scheme 39



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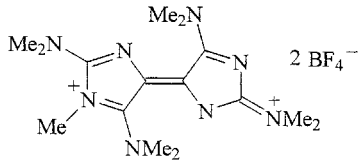


101

SCHEME 40

semiempirical AM1 method. The earliest HMO treatments were carried out for nitrogen analogs of sesquifulvalene (65JA2901, 65JA2908). Using this method calculations were performed on the π-electron energy levels, bond orders, and charge densities for azafulvalenes as well as for a number of related compounds. The dipole moments were calculated by a modified Hückel method, and the agreement with experimental values was quite good. Despite pronounced bond alternation, the azafulvalenes showed substantial charge separation as evidenced by experimental dipole moments. The calculations assigned the negative end of the dipole to the five-membered ring and the positive one to the pyridine ring (65JA2901). The Hückel theory, either in its primary form or in the variant of the ω-calculation, was only partly successful in accounting for the spectroscopic properties of the series of **11** and **12** (65JA2908). Both methods failed to explain the observation of a major difference in the behavior between the members of the 2- and 4-series—namely, the occurrence of two strong, long-wavelength bands in the 2-series but only one of them in the 4-series.

In order to obtain information about the atomic charge densities CNDO/2 calculations on the same heterofulvalenes were performed (75JA2326). The percentages of delocalization were 49% in the azafulvalene **12** (R = Me) with respect to pyridine (100% delocalization) and cyclohexatriene (0% delocalization). Based on the charge distribution, it was concluded that six-ring π-delocalization is larger in the azafulvalene than in 1-methyl-2-pyridone. The five-membered ring bond lengths were correlated with vicinal proton coupling constants and with five-membered ring charge densities. The data obtained by these calculations showed that the large dipole moment of the 4-derivative **11** (R = Me) compared to the 2-derivative is caused by a relatively large dipole separation in the compound and not by a large difference in the charge magnitudes between these heterofulvalenes.

Semiempirical calculations (MNDO//MNDO) have been performed for sesquifulvalene **6** and its aza analogs **11** (R = Me), **12** (R = Me), **72a**/**72b,** and **73a**/**73b** (91JOC4223). In all cases the most stable conformation is the planar one ($\delta\ \Delta H \approx 0$). The calculated barrier of rotation around the cen-

tral C–C– bond decreases in the order **6** ≫ **11** > **73a**/**73b** > **72a** ≈ **72b** ≈ **12.** Assuming a dipolar structure, a positive charge is better stabilized in a pyridinium system than in a tropylium ring and the negative charge is better stabilized in an azolate anion than in a cyclopentadienyl one. For the triazafulvalene **73b,** an excellent agreement was observed between the experimental and calculated values for the dipole moment ($\tau_{min} = 0°$). The dipole moments for derivatives **72a** and **72b** were moderately well predicted and underestimated in MNDO.

For mono- and triaza analogs of sesquifulvalene, molecular orbital calculations were carried out by means of the AM1 method with full optimization of all bond lengths, angles, and torsional angles [94JCS(F)1853]. Then these structures were used to calculate the molecular hyperpolarizability, the dipole moments, and transition energies with CNDOVSB, a sum-over-states procedure which has been specifically parametrized for SHG applications. Calculations at the AM1 level with full optimization of all variables on **11** (R = Me) gave a planar structure which showed a reasonably good correlation with crystallographic data of the closely related 2,6-dichlorobenzyl derivative (75JA2326). The two methods are found to give substantially different values for the ground-state dipole moments. The calculated hyperpolarizability values predicted for heterofulvalenes **11** (R = Me) and **72a** were large and negative and considerably superior to those of conventional donoracceptor aromatics.

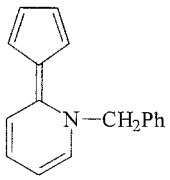
The molecular geometries of four DTDAFs **52d** and **53a**–**53c** were obtained by geometry optimization applying the AM1 semiempirical Hamiltonian of the computer program MOPAC (95JA8528). The ionization potentials of the neutral molecules track well the solution first half-wave oxidation potentials, which were determined by cyclic voltammetry. The optimized geometry was used with an INDO semiempirical Hamiltonian to generate spin densities and calculated hyperfine tensors for the cation radicals of the azafulvalenes. Furthermore, the calculations showed that the *E* isomers of the heterofulvalenes are more stable than the *Z* isomers (typically by 40–60 kJ/mol).

B. X-Ray Structures

Among the variety of nitrogen-containing fulvalenes emerging from types **7**–**14,** X-ray structural determinations have been performed on about 20 representative examples. The first crystal structure determination was carried out by application of the folding-molecule method on 3,3′-diphenyl-1,1′-biisoindolylidene **64** (R = H) (71CB3108). The dimeric isoindolenine system

is approximately planar with a central C=C bond distance of 1.385 Å. The phenyl rings are twisted by 39° with respect to the main molecule plane. Fulvalenes of type **11** and **12** have certain advantages for the investigation of bond length–aromaticity relationships. These pseudoaromatic molecules can formally achieve a Hückel (6π) electron configuration by delocalization of the π-electrons. The five- and six-ring charges can be estimated, for example, from NMR or dipole-moment data. The contribution of structure **b** to the ground state resonance hybrid depends on the ability of both rings to stabilize the positive and negative charges. In order to correlate the structure of heterofulvalenes with their dipolar character the crystal structures of three aza-sesquifulvalenes **102**–**104** have been determined by X-ray diffractometry with MoK_α radiation (75JA2326). The individual rings in all compounds measured were reasonably planar; the relatively large angles between the planes of the *N*-benzyl substituents and the planes of their dihydropyridine rings reflect the steric factors operating between these moieties. The five-membered ring to six-membered ring twist angles were 18.6, 2.6, and 31.2°, respectively, and the interring distances were 1.410, 1.388, and 1.412 Å. All central C—C— distances are long compared to normal values such as the 1.340 Å length in ethene and the 1.347 Å distance for the central C=C bond in 6,6′-dimethylpentafulvalene, indicating that the azafulvalene connections contain appreciable amounts of single bond character (Scheme 41).

In the course of the investigations directed at the structural characterization of another type of aza analog of sesquifulvalene, the X-ray structure of the triaza derivative **72a** was determined (89CC1086). The molecule is effectively planar, the torsion angle between the pyridine and benzimidazole



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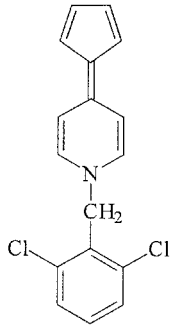

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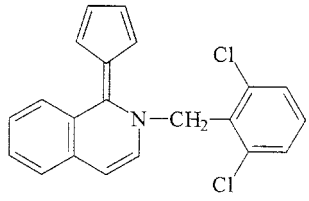


104

SCHEME 41

rings being ≤2.5°. The bond length of the central C—C— bond is 1.448 Å, consistent with a $C(sp^2)$—$C(sp^2)$ single bond. The molecules are stacked in a head-to-tail manner, i.e., the pyridine nitrogen atom of one molecule is located between the centers of the imidazole rings of the two neighboring molecules in the row (stacking distance 3.60 Å). In summary, all these experimental data are fully consistent with the betaine character of compound **72a.**

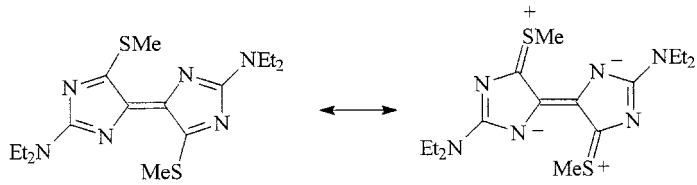
A nonplanar ring conformation was found for nitrogen-containing heptafulvalenes (80CC900; 96JHC1333). For example, in perfluoro-diazaheptafulvalene **69** each seven-membered ring adopts a boatlike conformation; the carbon-carbon lengths alternate in the sense predicted by the classic valence bond structure (80CC900).

With the aim to create new compounds with electron-donating properties, the TTDAFs **65a** and **65b** were synthesized and characterized by X-ray crystallography (93CC1226, 93TL847; 94JOC2997). The results obtained for the *E* isomer of the diphenyl derivative showed that the atoms of the fulvalene ring systems are all coplanar with the two phenyl rings also lying in the same plane (93TL847). Thus, substitution of CH by N causes significant changes in geometry, leading to a flattening of the five-membered ring and also bringing about a shortening of the central C(1)—C(1′) bond: 1.332(2) Å (93TL847) and 1.338(3) Å (93CC1226) vs 1.353 Å in the corresponding diphenyl-TTF (79CSC1009). In contrast, the *Z*-dimethyl compound is markedly nonplanar; the least-squares planes of both five-membered ring units make angles of 24.7 and 19.0°, respectively, with the plane of the central C_2S_4 subunit (93JCSCC1226). In the diphenyl derivative, pairs of molecules are related by a center of symmetry, but are not coplanar, giving rise to intermolecular sulfur–sulfur distances (3.713 to 3.832 Å). The molecules are stacked parallel and above one another in columns along the **b** direction, giving a close perpendicular intrastack distance of 3.56 Å (93TL847). In connection with the synthesis of stable nucleophilic carbenes, an X-ray crystallographic structure of their dimers was determined, constituting DTDAFs of type **51** (97LAR365). Although **51a** is very sterically congested its structural data are those expected for a normal olefin. Both thiazole rings are planar and are twisted by 5° about the central double bond, whereas the 2,6-diisopropylphenyl substituents are approximately perpendicular to the plane of the heterofulvalene. The central double bond is 1.344 Å. The structure of the *E* isomer of **51c** is not as simple as that observed for **51a** because one of the carbon atoms in the central C=C bond adopts a pyramidal geometry and the two thiazole rings are not equivalent. The thiazole ring containing the pyramidal carbon is not planar, and the nitrogen atom in this ring also is

pyramidalized. The nitrogen atom in the distorted thiazole ring is 0.4 Å above the plane of its attached carbon atoms, whereas the nitrogen atom in the planar ring is only 0.01 Å outside the plane of its attached carbon atoms. The central C=C bond length in **51c** is 1.341 Å, similar to that in **51a.** The authors suggested for this unusual structure a dimerization reaction of two singlet carbenes along a non-least-motion pathway. The crystal structure of **81** was determined in order to find out the correlation between singlet carbenes and their dimers, which are electron-rich olefins of the type found in 1,4,5,8-tetraazafulvalenes (96AG1098). The length of the central C=C bond is 1.337(5) Å, typical for an olefinic double bond. Whereas the two imidazole moieties are nearly planar, both trimethylene bridges are strongly folded, which provide a remarkable flexibility in the molecule.

Information obtained by X-ray studies can also serve for a better comprehension of chromophoric systems as in the case of the phenylogous tetraazafulvalene **78** (93TL6379). The X-ray structural parameters revealed that this molecule is a folded one. As a result of the bending of the quinoid system, conjugation between both terminal 2H-imidazoles via the 9,10-dihydroanthracene moiety is diminished and this accounts for the hypsochromic shift of 89 nm in comparison to the parent compound **77** (Ar = Ph). Using X-ray data, comparison of the 1,3,5,7-tetraazafulvalene **90** (R = Me) and indigoid dyes was possible (90JPC949). Thus, the molecule is completely planar; even both methylsulfanyl groups and the methylene groups of the diethylamino moieties lie in the plane of the two imidazole rings. The C–C as well as the C–N distances in the imidazole rings fit well into the picture of a conjugated π-system with localized bonds. The length of the bond between the sulfur and the ring-carbon atom of 1.718 Å is comparable with those in thioacetamide and thioureas and therefore an indigo-like mesomeric structure was formulated for **90** (Scheme 42).

Recently, the structure of the bis-imidazo fused 1,4,5,8-tetraazafulvalene **141a** (anti-isomer) was reported (97LAR617). The ideal planarity of the tetraazafulvalene framework is striking; the exocyclic aryl residues are slightly bent out of the plane. As expected, the central C–C distance



90

SCHEME 42

[1.367(3)] is that of a typical double bond. The vicinal carbon nitrogen bond distances also fit well into the picture of a conjugated system.

C. Spectroscopic Properties

1. Optical Spectra

Due to their cross-conjugated π-system nearly all nitrogen-containing fulvalenes absorb in the visible region. In some cases, the azafulvalenes show the behavior of indigoid dyes. Early studies on the absorption of nitrogen analogs of sesquifulvalenes were carried out by Berson (65JA2908), who extended the theoretical treatment to the electronically excited states and correlated the experimental data on ultraviolet-visible spectra. All compounds of the 2-series (type **43**) exhibited two broad intense maxima in the region 360–550 nm as well as short wavelength absorptions in the form of shoulders and/or maxima. The derivatives of the 4-series (type **44**) show only a single broad maximum in this region. The color of all these fulvalenes is instantaneously discharged by proton acids, a change that is reversed by alkali (65JA2887). The comparable triazafulvalene **74a** (λ_{max} = 501 nm) also behaves like an anhydrobase and was decolorized in acid solution forming its conjugate acid, which has a long wavelength maximum at 394 nm (67JOC3214).

In both heterofulvalenes of type **45,** the longest wave absorption (π-π*-excitation) was observed at a shorter wavelength ($\Delta\lambda = 2 - 5$ nm) than that of the corresponding oxo compound (77S861; 78BCJ2674). The contribution of a polar structure to π* of an oxo compound is significant and thus reduces the excitation energy, whereas the contribution of a polar structure to π* of a fulvalene is less significant due to the electron-donating property of the 1,3-benzodithiolydene moiety and thus enhances the excitation energy relatively.

The fulvalenium salts **35** and **38** react reversibly in aqueous buffer solutions to yield the corresponding triarylcyclopropenols, as evidenced by the well-defined isosbestic points in their UV spectra. The p*K* values derived from spectra are compatible with extensive delocalization of charge in the heterocyclic ring (68TL5541).

A relatively large bathochromic shift was observed on transition from tetraazafulvalene **76a** (66TL5221) (λ_{max} = 494 nm) to phenylogous derivatives of type **77,** which absorb between 602 and 677 nm (66AG303; 72NKK100; 82MI376; 93TL6379). In contrast, the bis-benzofused product **78** absorbs hypsochromically at 513 nm, due to the bent quinoid system (93TL6379).

The basic chromophors of indigo and of some tetraazafulvalenes are very similar and therefore the frontier orbitals are comparable (90JPC949). PPP calculations on the 1,3,5,7-tetraazafulvalene **90** (R = Me) showed a good agreement with its UV/VIS spectrum. The substitution of both methylsulfanyl groups in **90** by diethylamino/piperidino moieties led to a hypsochromic shift of about 45 nm.

Azafulvalenes, especially mesoionic analogs of sesquifulvalene behave solvatochromically [83CC789; 84JCS(P1)2545]. The longest wavelength transition of derivative **98a** shows a large bathochromic shift on changing from polar to less polar solvents; solvent/λ_{max} [nm]: MeOH/464, EtOH/476, acetone/493, Et_2O/548, CCl_4/565 (83CC789). In the case of benzofusion at the cyclopentadienyl substructure, an increase in this shift to 111 nm was observed [84JCS(P1)2545]. These different absorptions can be considered to arise from the intramolecular charge transfer from the cyclopentadienylide ring to the tetrazolium ring. This solvent effect together with the ^1H and ^{13}C NMR data indicate considerable electron delocalization and charge separation resulting from the significant contribution of the dipolar structure to the ground state (Table I).

2. *Nuclear Magnetic Resonance Spectra*

For azapentatriafulvalenium salts of type **35** the charge distribution was made evident by a comparison of the ^1H NMR spectra of these heterofulvalenes and of 3-benzhydrylidene-3H-indolium salts and their common indole precursors (68TL5541). The results suggested that the best description involves extensive delocalization of charge throughout the cyclopropene and indole rings.

The chemical shift values of $\delta = 6.78$ and 6.73 of the dithiole ring proton signals of azafulvalenes **105** and **106** were slightly lower than the reported value ($\delta = 6.60$) for the nitrogen-free fulvalene **107** (65CB2825), thus suggesting that the contribution of a dipolar structure is somewhat larger in **105** and in **106** than in **107** due to the influence of the electronegative nitrogen atom (78BCJ1427). In order to study the influence of the heteroatom in heterofulvalenes of type **108** for the aza derivative (Z = N-nBu) even at −50°C the equivalence of both pyridine protons was revealed by ^1H NMR measurements, and therefore a very fast rotation around the central C—C— bond was predicted (69AG518). In contrast, for the oxa- and the thiaderivative (Z = O, S) the ΔG values for the rotation around the intercyclic bond were determined to be 16.5 and 13.8 kcal/mol, respectively. Moreover, a large solvent effect has been reported (78BCJ1427). The dithiole ring proton signals of **105** and **106** were shifted to lower fields by 0.37–0.50 ppm upon changing the solvent from CCl_4 to acetonitrile, the other proton sig-

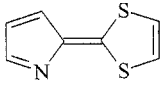
TABLE I

LONG-WAVELENGTH ABSORPTION MAXIMA OF SOME AZAFULVALENES

Compound no.	λ_{max}[nm]	1gε	Solvent	Reference
11 (R=benzyl)	430	4.55	Dioxane	65JA2887
20 (R=Ph)	535	4.46	Acetonitrile	68AG277
20 (R=Ph) $HClO_4$	517	4.59	Acetonitrile	68AG277
21 (R=Ph, Z=S)	480	4.61	Acetonitrile	68AG277
21 (R=Ph,Z=Se)	485	4.53	Acetonitrile	70TL481
22 (R=Me)	580	3.96	Acetonitrile	68AG277
23 (R=Me) $HClO_4$	468	4.23	Acetonitrile	68AG277
23 (R=Me)	412	4.38	Acetonitrile	68AG277
23 (R=Ph,Z=Se)	468	4.30	Acetonitrile	70TL481
26a	417	4.55	CH_2Cl_2	80BCJ1661
32	520	4.58	Acetonitrile	85AG996
33	390	4.70	Acetonitrile	68AG277
35d	367	4.34	EtOH/H_2O(1:1)	68TL5541
36	374	4.59	EtOH/H_2O(1:1)	68TL5541
39	554	4.83	Acetonitrile	68AG277
42	490	4.64	Acetonitrile	68AG277
45a	395	4.30	CH_2Cl_2	77S861
46	455	4.76	CH_2Cl_2	72LA93
47 (R=Me,Z=H)	340	3.79	Cyclohexane	64BSF2857
50	380	3.88	CH_2Cl_2	72LA110
53b	494	3.86	CH_2Cl_2	95JA8528
56	570	4.19	$CHCl_3$	81TL2973
60	350	4.50	MeOH	67CB1701
61	597	—	MeOH/OH^-	68CB1286
61	683	—	MeOH/H^+	68CB1286
65b (R=Ph)	410	3.68	Cyclohexane	93TL847
70	470	3.82	Acetonitrile	94LAR1165
74a	501	4.53	Benzene	67JOC3214
76a	494	4.75	CH_2Cl_2	66TL5221
76c	387	4.62	Acetonitrile	89KGS1421
77 (Ar=Ph)	602	4.95	$CHCl_3$	66AG303
78	513	4.71	$CHCl_3$	93TL6379
81	330	3.90	*n*-Hexane	96AG1098
85 (Ar=4-tolyl)	542	4.78	DMSO	97LAR617
88	587	3.64	Acetonitrile	90JPR949
90 (R=Me)	630	4.16	CH_2Cl_2	90JPR949
91	458	4.57	Acetonitrile	70TL481
91 H^+	418	4.37	Acetonitrile	70TL481
91 $2H^+$	380	4.11	Acetonitrile	70TL481
94 (Ar=4-tolyl)	551	4.31	Dioxane	96S1302
95 (Ar=3-$CF_3C_6H_4$)	561	5.00	DMSO	98JPR323
96 (Ar=3-$CF_3C_6H_4$)	537	4.82	DMSO	98JPR323
97 (Ar=3-$CF_3C_6H_4$)	549	4.80	DMSO	98JPR323
98a	475	3.08	Acetonitrile	84JCS(P1)2545
98b	530	3.08	Acetonitrile	84JCS(P1)2545
98c	589	3.17	Acetonitrile	84JCS(P1)2545
99	568	3.18	Acetonitrile	84JCS(P1)2545
100	502	4.29	—	72CC961

nals also being shifted to lower fields. This behavior was ascribed to the increase of dipolar structures in the polar solvents as well as by charge-transfer interactions with the solvent molecules, the heterofulvalenes serving as electron donors (Scheme 43).

Using ^{1}H (92JOC1008) and ^{13}C NMR data (94JOC2997; 97LAR365), the existence of *E/Z* isomers in dithia- as well as in tetrathiadiazafulvalenes could be detected. For NMR data on ^{13}C-labeled thiazolium salts together with mechanistic interpretations for dimerization reactions see 91JOC5029. A twofold symmetry was predicted for the 3,3′-diazaheptafulvalene **70** by NMR data (94LA1165). The ^{1}H NMR spectrum showed the presence of four consecutive vicinal olefinic protons (5.88, 4.69, 5.03, and 5.79 ppm); the central double bond carbon atoms absorb at unusually high field at δ = 93.6 ppm. In general, the ^{13}C-chemical shift of the central double bonded carbon serves as reliable evidence for the distinction between the monomeric nucleophilic carbene and the dimeric heterofulvalene. For example, in the DTDAF **51a** the resonance of the former carbene center is shifted dramatically upfield from δ = 254.3 to 107.8 ppm (97LAR365). The resonances of the C4- and C5-ring atoms also showed an upfield shift of about 12–32 ppm in comparison to the carbene. Similarly, the ^{15}N NMR signal for derivative **51a** showed a large upfield shift (carbene: δ = −267.6 ppm, dimer: δ = −148.7 ppm). This shift is at sufficiently high field to suggest the presence of a delocalized lone pair of electrons at nitrogen but does not fall in the range for a pyramidal nitrogen. The carbon



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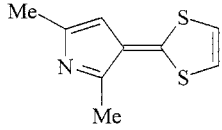

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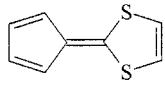

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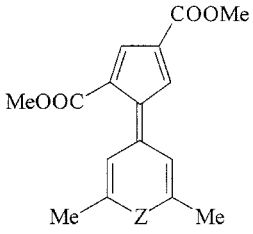


Z = O , S , N-nBu

108

SCHEME 43

atoms in the comparable tetraazafulvalenes absorb at somewhat lower fields: **81:** δ = 127.5 ppm (96AG1098), **80a:** δ = 140.5 ppm (95TL2741), **85** (Ar = 3-$CF_3C_6H_4$): δ = 150.5 ppm (97LAR617).

The ^1H and ^{13}C NMR parameters of some 1-alkyl-4-benzimidazolyl-2-idene- (type **72**) and 1-alkyl-4-(5-methylpyrazolyl-3-idene)-1,4-dihydro pyridines (type **73**) were discussed in 89CC1086 and 91JOC4223. Comparison of the shifts for DMSO-d_6 and $CDCl_3$ solutions with data reported for quaternary pyridinium compounds as well as anionic species in the azole series and data obtained for mesoionic betaines of the azinium azolate class left no doubt that these heterofulvalenes have a betaine character and, therefore, the NMR signals correspond to their dipolar resonance form.

For the mesoionic TAF **98a** the chemical shifts of the cyclopentadienyl protons, a complex multiplet centered at δ = 6.20 ppm, are comparable with that of the cyclopentadienide anion; this indicates the high electron density at the cyclopentadiene ring of **98a** (83CC789). Analogous behavior was reported for the corresponding benzo fused derivatives [84JCS(P1)2545]. The ^{13}C-chemical shifts of the tetrazolium ring carbon for fulvalenes **98** and **99** are almost coincident (158.3–153.6 ppm). However, the pivotal carbon of the cyclopentadienyl ring is shifted to a higher field on successive benzannulation (from 96.9 for **98a** to 83.1 ppm for **99**), indicating the increasing π-electron density on this carbon in the order **98a** < **98b** < **98c** < **99**.

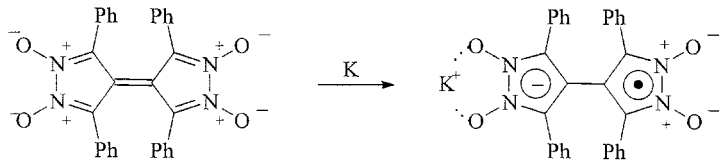
3. Electron Spin Resonance Spectra

By means of ESR spectroscopy (68TL1843), the real structure for the "2,2′-biisobenzimidazolylidene" (63JOC1931; 65AS1651; 69JOC234) could be assigned (Section II,D,1).

The reduction of TAF **100** by metallic potassium resulted in the formation at room temperature of the stable anion radical **109,** which yielded a simple nine-line ESR pattern caused by the two sets of two equivalent nitrogens with A_{N1} = 3.40 and A_{N2} = 0.81 G (79JOC3211). The nonequivalency of the nitrogens was explained by the association of the potassium cation with one of the two diazacylopentadienyl moieties (Scheme 44).

Occasionally, equilibria between a quinoid and a diradicaloid form of tetraazafulvalenes of type **77** have been discussed (66AG303; 72NKK100; 79JOC1241). Based on ESR measurements, only traces of radicals (0.1% at 200°C) could be observed and therefore **77** (Ar = Ph) exists at room temperature predominately in the quinoid structure. Other authors stated that the thermochromism of **77** mainly results from a change in intermolecular interaction, not from biradical formation (84MI1030).

Solutions of the radical cations of **65b** (R = H, Me, Ph) were conveniently generated by the addition of bromine to dichloromethane solutions of the corresponding TTDAF (93CC1226; 94JOC2997). All radical cations exhibit similar spectra with g = 2.0071. In the case of R = H, Me, the signal con-



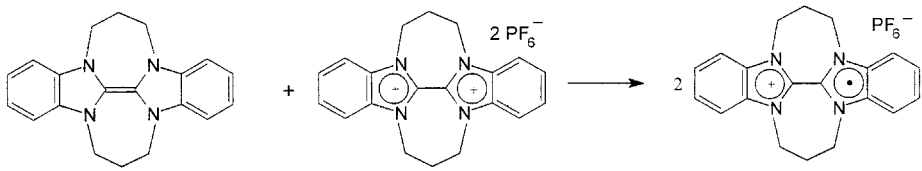
100 **109**

SCHEME 44

sists of a broadened singlet (due to hyperfine coupling to hydrogen), but for R = Ph the absence of close-range hyperfine coupling to H provides better resolution. The spectrum now appears as a broad quintet with a_N = 0.08 mT. The small hyperfine coupling to nitrogen is consistent with the calculated (MNDO) spin distributions obtained, which show a depletion in spin density at the periphery of the molecule relative to that observed in the equivalent positions of the radical cation of TTF.

When equimolar quantities of **80a** and its dication **110** are combined in acetonitrile, single electron transfer occurs and the coproportionation product was obtained (95TL2741). This deeply red-colored, air-sensitive radical cation **111** showed a strong ESR signal (g = 2.0034). On the other hand, the excellent electron donor **80a** could be prepared by electrolytic reduction starting from **110.** It was necessary to carry out the reduction with scrupulous exclusion of oxygen. Thus, the electrolysis of **110** at −1.10 V initially gave rise to an intense red color, which was presumably due to the formation of **111.** Upon further reduction, the red color faded and the tetraazafulvalene **80a** was isolated at a 62% yield (Scheme 45).

Electron transfer also occurred when TTF was treated with the electron-poor tetrabromotetraazafulvalene **76c** (96SM127) in a 3:1 ratio. The ESR spectrum of this donoracceptor complex consists of a single symmetric signal [g = 2.0078, $\Delta H_{p\text{-}p}$ (G) = 13], typical of TTF^+ complexes devoid of heavy elements. Spin on the tetraazafulvalene moiety by reverse-charge transfer could be ruled out since a large linewidth expected from spin-orbit coupling on bromine atoms was not observed. The spectrum of the analogous complex with tetrachlorotetraazafulvalene was very similar. Variable



80a **110** **111**

SCHEME 45

temperature studies (room temperature to −140°C) showed a temperature-independent linewidth and a curie paramagnetic behavior of the signal intensity. This could be taken as indicative of a lack of metallic character in these materials.

4. Mass Spectra

Nitrogen-containing fulvalenes have not been systematically studied by mass spectroscopy. Only isolated data for several examples of compounds have been reported. Most of the data consist of electron impact (EI) mass spectra recorded for analytical purposes. Only a minor fraction dealt with the characterization of ion structures or focused on the effects of substituents, the ring size of fulvalenes, or the number and arrangement of nitrogen atoms and the fragmentation pathways.

For naphtho-fused DTDAF of type **49,** in addition to the parent peak, an intense peak at m/2 was observed. Further fragments were traceable to the loss of one or two methyl groups (67LA155). The mass spectra of all deeply colored 1,4,5,8-tetraazafulvalenes of type **85** exhibit the corresponding molecular ion peaks with strong intensities (base peak), indicating the high stability of these heterofulvalenes (97LAR617). A similar behavior was reported for the mesoionic analogs of sesquifulvalene **98** and **99** [84JCS(P1)2545]. Another type of tetraazafulvalenes, the pyrazole derivative **100,** showed no molecular ion in its mass spectrum, but a prominent peak at m/e = 440, for which the loss of two molecules NO was discussed (72CC961).

D. Dipole Moments

In 1972 it was reported that the resonance contribution of a dipolar form is not significant for sesquifulvalene **6,** fulvene, and heptafulvene, which were shown to have a largely olefinic character from their ^{13}C NMR data and relatively small dipole moments (72C194). The substitution of carbon by nitrogen in the fulvalenes leads to a perturbation of the olefinic character; therefore, in some cases remarkable dipole moments were measured. The first reports on dipole moments of azafulvalenes were given by Russian authors (58MI159), but without experimental details, and 5 years later by Kumler (63JOC1731). For the two nitrogen derivatives of sesquifulvalene **12** (R = Me) and **11** (R = CH_2Ph) values of 5.20 and 8.93 D were found. These values indicate a contribution of about 25 and 27% respectively of forms with a separation of charge.

A detailed structural study of aza analogs of sesquifulvalene as well as other heterocyclic betaines was performed by Alcalde and coworker (89CC1086; 91JOC4223), who also reviewed the pyridinium azolates class

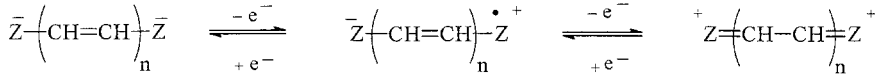
(94AHC197). The experimental dipole moment values of the three 1-alkyl-4-azolylidene-1,4-dihydropyridines **72a** and **72b** and **73b** are high and in the range of 9.0–9.7 D, which implies a substantial charge separation.

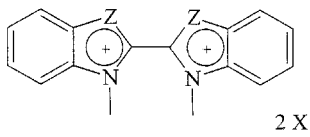
E. Electrochemical Properties

Nitrogen-containing fulvalenes, particularly their di- and tetraazaderivatives, have to be classified in the large group of organic compounds which comprise two-step redox systems (78AG927) (Scheme 46).

Polarographic investigations showed that systems of type **112** display two-step polarograms from which the semiquinone formation constants $k = 10^2 - 10^{14}$ can be derived. In the series of benzoxazoles and benzothiazoles, nearly equal values were measured, whereas the fused imidazoles could be reduced at much more negative potentials due to the donating effect of four nitrogen atoms (twofold amidines) (72LA126, 72LA765). For comparable studies on indole and indolizine derivatives see 76LA317 and 76LA1060.

The deprotonation of thiazolium salts (see Section II) under argon at room temperature allowed the characterization of nonfused DTDAF of types **52** and **53** by cyclic voltammetry. Their very good donor properties were confirmed by two "quasi-reversible" peaks of equal intensity (93CC601). It is noteworthy that upon a second scan the first oxidation peak was shifted from −0.03 to −0.04 V. Upon further scans the voltammogram remains unchanged. This interesting feature has been observed previously with TTF analogs. It was demonstrated that the neutral form





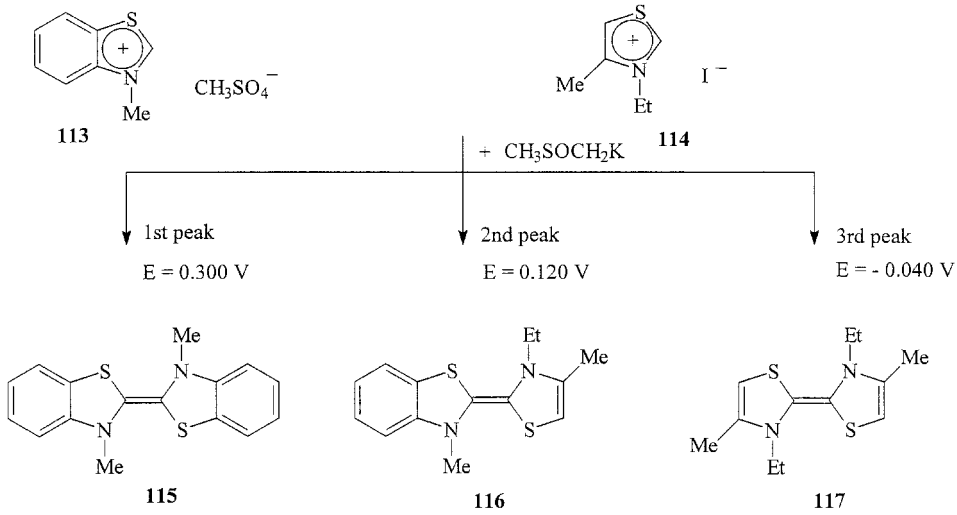
Z = O , S , N - Alkyl

112

Scheme 46

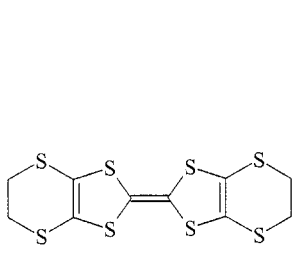
adopted an *E* configuration in the solid state and the corresponding radical cation salt TTF^+ adopted a *Z* configuration. Therefore, the shift of the first oxidation peak between the first and second scans is the result of an *E/Z* interconversion at the $DTDAF^+$ stage. A small increase of the oxidation potentials was observed in the case of DTDAF bearing at least two electron-withdrawing groups at the five-membered ring subunit (92JOC1008; 95JAS8528, 95PMS296). Using cyclovoltammetric measurements, the formation of cross-coupled dimers could be observed (91AS985). When aliquots of CH_3SOCH_2K were added to a mixture of equivalent amounts of the two thiazolium salts **113** and **114, 115** was the initial product, but a cross-coupled material **116** was formed as a secondary product. Finally, the signal derived from **117** appeared (Scheme 47).

As expected, the oxidation potentials of the heterofulvalenes of types **21, 29, 31, 54, 55,** and **57** were found to be somewhat higher than those of the "electron-rich olefins" and were found to be irreversible (86TL849). Thus, **21** (Z = S, R = H), which bears no donor substituents, is most difficult to oxidize. Methylsulfanyl groups lower the oxidation potential only slightly. The 1,4-dithia-6,7-diazafulvalene **57** ($R^1 = NMe_2$, R^2 = Ph, R^3 = H) has the lowest oxidation potential and is comparable in this property to TTF derivative **118.** The tetrathiadiazafulvalenes **65** in which the central C_2S_4 moiety and unsaturated framework of TTF are retained and two peripheral CR-units are replaced by nitrogen atoms also show two reversible oxidation waves corresponding to the formation of a radical cation and a closed-shell dicationic species (93CC1226; 94JOC2997). Measurements on the *Z* deriv-



SCHEME 47

ative (R = Me) gave half-wave potentials identical to those of the *E* derivative within experimental error. Both half-wave potentials of the TTDAF are greater than those observed for TTF and its derivatives. Given the greater electronegativity of nitrogen compared to carbon, this trend is not unexpected. The higher oxidation potentials of these compounds limit their ability to be involved in charge-transfer complexes similar to those observed for TTF and DTDAF (Scheme 48).



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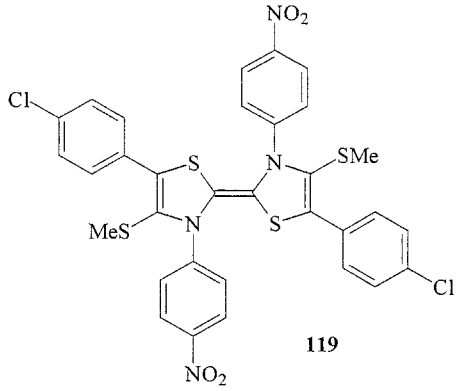

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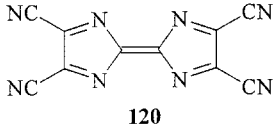

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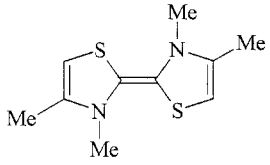

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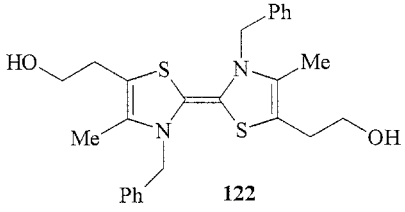

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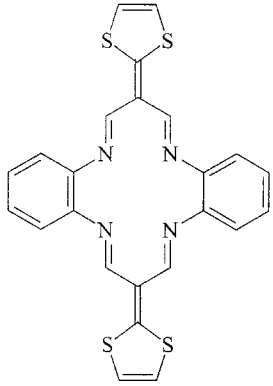


123

SCHEME 48

Cyclovoltammetric studies of the tetrabutylammonium salt of 2,3,6,7-tetracyano-1,4,5,8-tetrazafulvalene indicated two irreversible oxidations at +1.00 and +1.50 V versus SCE. These high potentials support the extreme stability of the dianion under a variety of conditions (96SM127). On the basis of these results, the electrooxidation of TTF could safely be carried out to prepare the corresponding tris-TTF salt. On the other hand, the "quasi-reversible" reduction peak of the tetrabromo-tetraazafulvalene **76c** reported earlier (94KGS1421) indicates that this compound is a strong acceptor (96SM127). A coulometric count at 0.35 V indicates a two-electron reduction, implying that the neutral/monoanion and monoanion/dianion couples occur at very close potentials (Table II).

IV. Reactions

A. Protonation

Depending on the nature of the azafulvalenes, protonation takes place at the nitrogen or at the carbon atoms. Azafulvalenes of types **20–24, 26–31,**

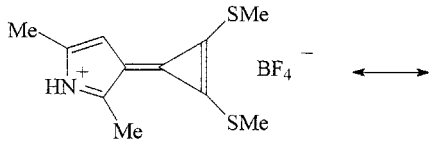
TABLE II
Oxidation Potentials of Azafulvalenes and Related Compounds

Compound no.	Solvent	E_1 [V]	E_2[V]	References
21 (Z=S, R=H)	Acetonitrile	1.00[a]	—	86TL849
29	Acetonitrile	0.90[a]	—	86TL849
31	Acetonitrile	0.98[a]	—	86TL849
47 (R=Me, Z=H)	Acetonitrile	0.323[b]	—	91JA985
52d	$ClCH_2CH_2Cl$	0.00[a]	0.48	95JA8528
53a	$ClCH_2CH_2Cl$	0.10[a]	0.45	95JA8528
53b	$ClCH_2CH_2Cl$	0.15[a]	0.66	95JA8528
53c	Acetonitrile	0.42[a]	0.63	95JA8528
54	Acetonitrile	0.92[a]	—	86TL849
55	Acetonitrile	0.82[a]	—	86TL849
57 (R^1=NMe_2, R^2=Ph, R^3=H)	Acetonitrile	0.57[a]	—	86TL849
TTF	Acetonitrile	0.32[a]	0.70	94SCI64
65b (R=H)	Acetonitrile	0.63[a]	1.00	94JOC2997
65b (R=Me)	Acetonitrile	0.59[a]	0.95	94JOC2997
65b (R=Ph)	Acetonitrile	0.65[a]	1.01	94JOC2997
118	$ClCH_2CH_2Cl$	0.58[a]	1.00	95JA8528
119	Acetonitrile	−0.03[a]	0.17	93CC601
120	CH_2Cl_2	1.00[a]	1.50	96SM127
121	Acetonitrile	−0.028[b]	—	91JA985
122	DMSO	0.019[b]	—	91JA985
123	—	0.75	—	89AG1046

[a] Versus SCE.
[b] Versus Ag/AgI.

39, 42, 54–57, 88, and **90–93** were protonated exclusively at the ring nitrogens (68AG277; 70TL481; 78BCJ1427; 86TL159, 86TL839). Thus, a number of DTDAFs were transformed into the corresponding dications by adding an excess of perchloric acid and could be isolated as stable crystalline salts (68AG277; 70TL481). In many cases, the azafulvalenes are not isolable as free bases or are stable only for a short time, and therefore they were isolated as the stable salts on treatment with strong acids (68TL5537; 86TL839). For example, the only isolable azacalicenes **124** bearing two methylsulfanyl groups are salts, and they predominately exist in the form **124′,** evidenced by the shielded pyrrole protons in their NMR spectra (86TL839). By contrast, in triphenyl-1-aza- and -2-azacalicenes **33** and **34** (68AG277; 70TL481) the pyrrolium resonance structure dominates, demonstrating the strong donor effect of the methylsulfanyl groups (Scheme 49).

Upon treatment with HBF_4 the dithiazafulvalene **125** gave the stable salt **126** possessing two benzodithiole subunits. In the presence of triethylamine the starting material was recovered (78BCJ1427). In contrast, as representative electrophiles neither benzoyl chloride nor methyl iodide reacted with **125** to give N-substituted derivatives. Generally, it is more convenient to purify a large number of azafulvalenes at the stage of their salts which can be stored and then to generate the free bases as needed.



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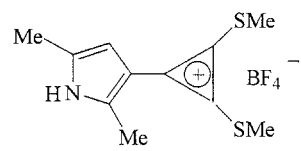
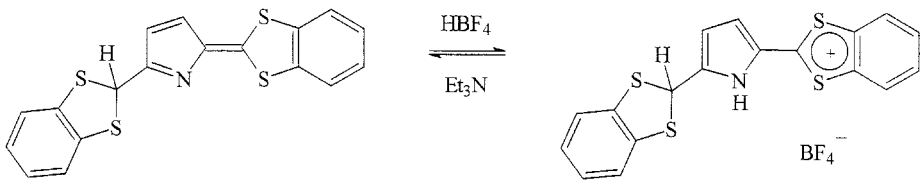


124'

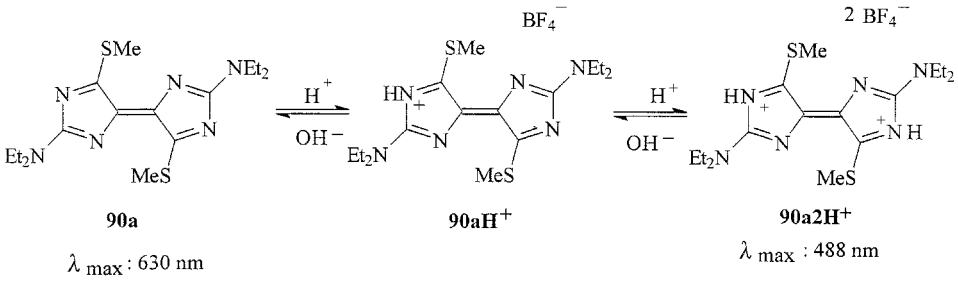


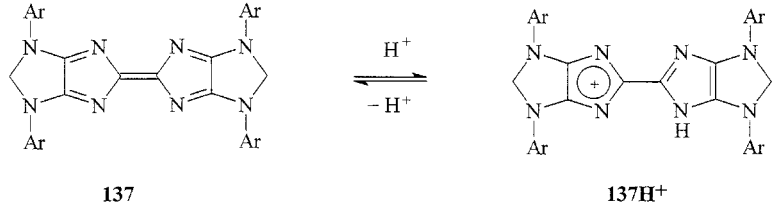
125 **126**

SCHEME 49

In most cases protonation of azafulvalenes leads to a hypsochromic shift in their electronic spectra as exemplified by the blue **90a,** which gives its orange dication (90JPC949). But some derivatives are able to form cyaninelike structures and therefore absorb bathochromically (68CB1287; 82CB3756; 97LAR617). For example, on treatment of imidazo-fused TAFs **137** with acids the color immediately turns from red to deep blue. The protonated species **137H**$^+$ can be considered to be an antiaromatic 1,3-diazacyclopentadienylium cation that is stabilized by three electron-donating groups (Scheme 50).

Nitrogen-containing derivatives of sesquifulvalene are rather strong π-bases and are protonated at the (aza-)cyclopentadiene ring (65JA2887; 67JOC3214; 82CB3756). The aza-sesquifulvalene **41** (R = Me) forms two conjugate acids **127** and **128** on treatment with trifluoroacetic acid resulting from protonation of the five-membered ring. Both species were revealed by their NMR spectra showing two sets of methylene signals but indicating the absence of any significant quantity of the third type of ipso-C protonated species. Analogous results on indenyl and fluorenyl derivatives showed that the corresponding conjugate acids are strong enough to be titrated. Their pK_a values are in the range of 8.5 to 12 (65JA2887). In a similar manner, mesoionic diazafulvalenes can be reconverted to their starting materials (70CS807; 83CC789). Therefore, in some cases, salt formation allowed a





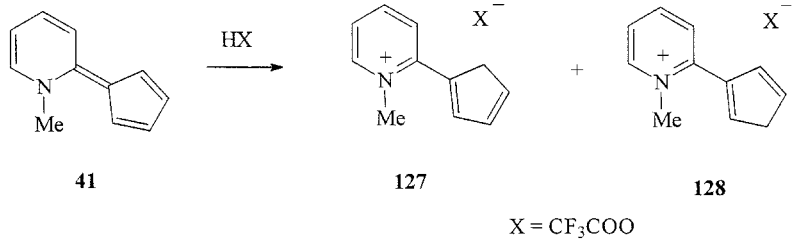
SCHEME 50

simple purification of azafulvalenes from the darkly colored and complex reaction mixture. The fused azafulvalene **46** derived from diazafluorene could be protonated by strong acids to yield the dicationic species **129** (72LA93). The structure was demonstrated by an additional splitting of the pyridine-H_α by a proton on the nitrogen and by the downfield shift of both methyl group signals (Scheme 51).

Strong acids react nearly quantitatively with DTDAFs of type **47** under reformation of their starting material, the *N*-alkylbenzothiazolium salts (64BSF2857). Using the violet-colored derivative **130,** this protonation became visible (81HCA648) (Scheme 52).

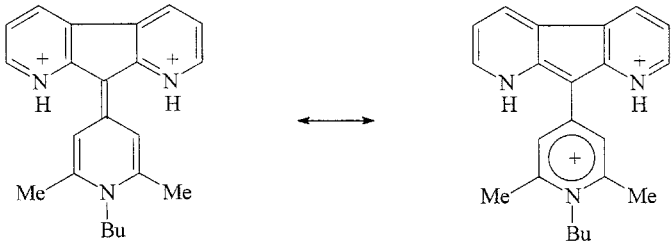
B. Electrophiles

Azafulvalenes of type **7–10** constitute electron-poor compounds; therefore, only a few reactions using electrophilic agents have been described. Thus, heating **26a** with methyl iodide or benzoyl chloride and subsequent treatment of the resulting products with HBF_4 gave the dithiolium salts



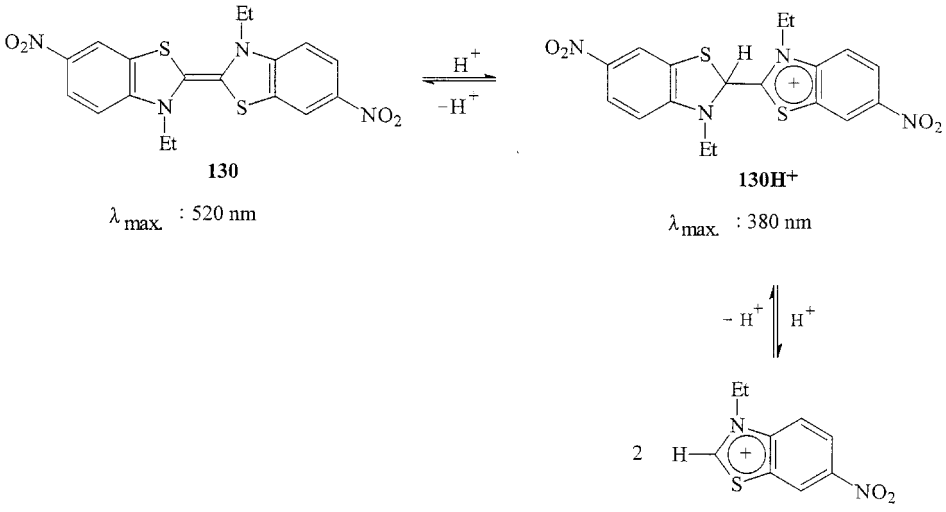
41 **127** **128**

X = CF_3COO



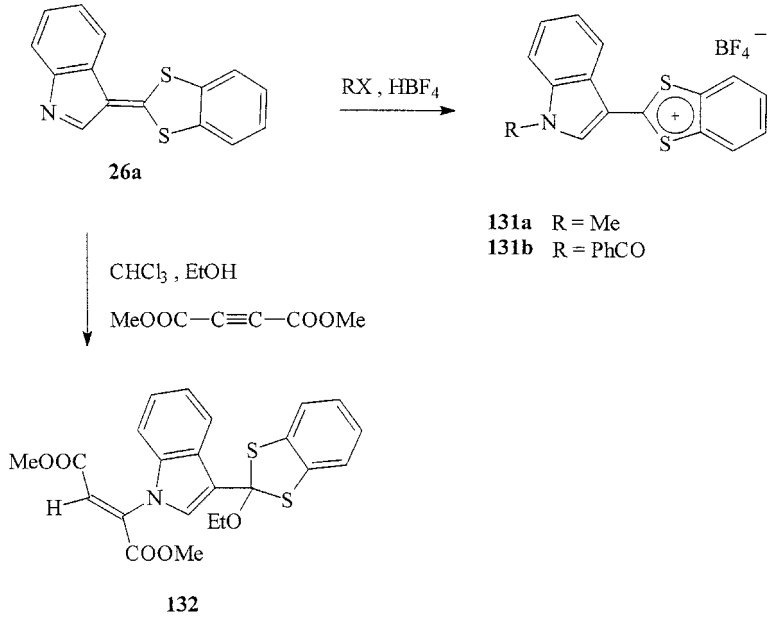
129

Scheme 51



SCHEME 52

131a and **131b** in good yields (80BCJ1661). With the same regioselectivity, the N-substituted compound **132** was produced from dimethyl acetylenedicarboxylate in boiling chloroform/ethanol via a 1,6-dipolar intermediate (80BCJ1661) (Scheme 53).



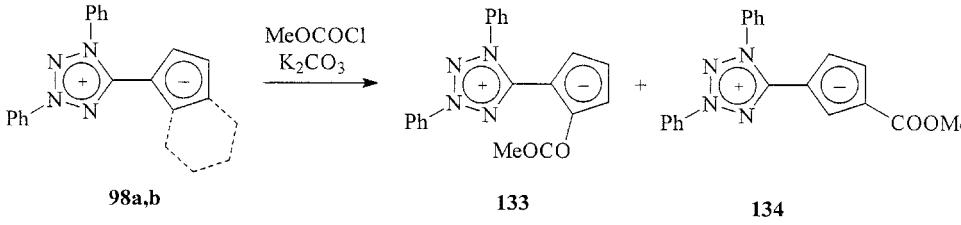
132

SCHEME 53

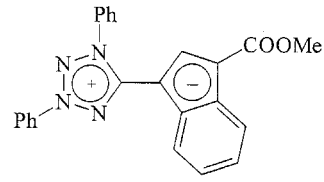
Mesoionic TAFs possessing a cyclopentadienide subunit are nucleophilic enough to be attacked by acyl chlorides. The methoxycarbonylation of **98a** with methyl chloroformate gave a 3:1 mixture of regioisomers **133** and **134.** In contrast, the indenide **98b** formed exclusively the methoxycarbonyl derivative **135** [84JCS(P1)2545]. The position of the ester group of **133** and **134** was deduced from the ^{1}H NMR parameters of the cyclopentadienyl ring protons, while the structure of **135** was unambiguously confirmed by comparison with an authentic sample prepared from corresponding indenide and 5-ethoxy-1,3-diphenyltetrazolium salt. On the other hand, donor substituents lead to an increase of the nucleophilicity of the central fulvalene subunit implying alkylations, acylations, and other derivatization reactions (Scheme 54).

For example, deprotonation of TAF **85** with potassium *tert*-butoxide generated the deeply green-colored TAF anion, which was then methylated to give a mixture of diastereomeric tetramethyl derivatives **136a** and **136b** (97LAR617). It is noteworthy, that methylene iodide as alkylating agent led exclusively to the linear fused product **137,** which showed strong fluorescence in solution. Using the same substrates, a number of acylated and silylated derivatives **138–140** were synthesized (97LAR617; 98JPR323) (Scheme 55).

In all cases investigated, the cycloacylation reaction also occurred at the exocyclic nitrogen atoms. In order to obtain precursors for oligomeric/polymeric heterofulvalenes the TAFs of type **85** were condensed with ortho es-

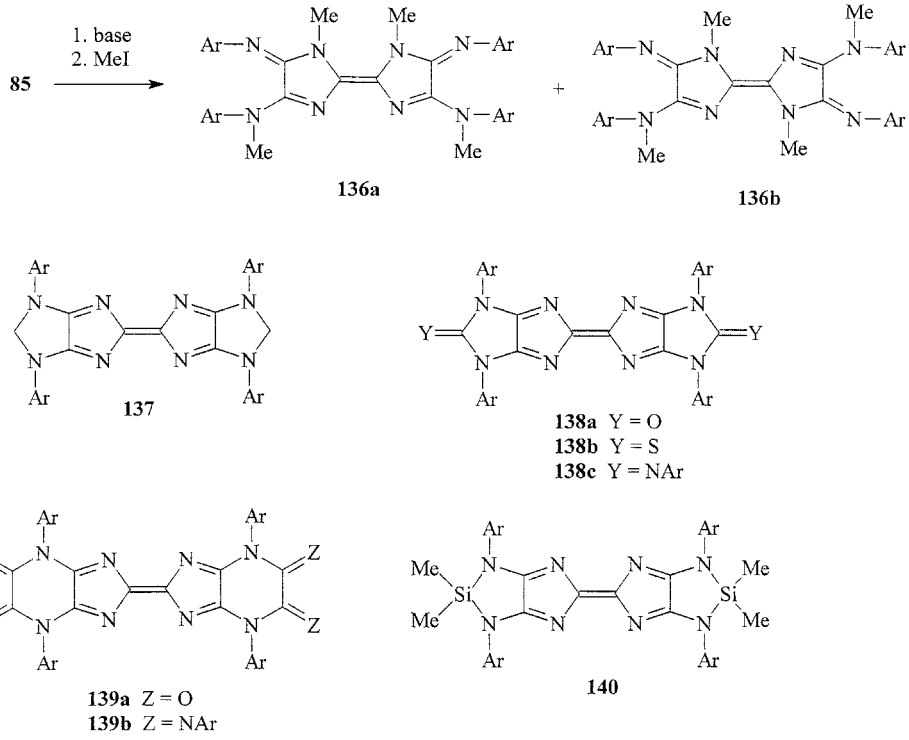


98a,b **133** **134**



135

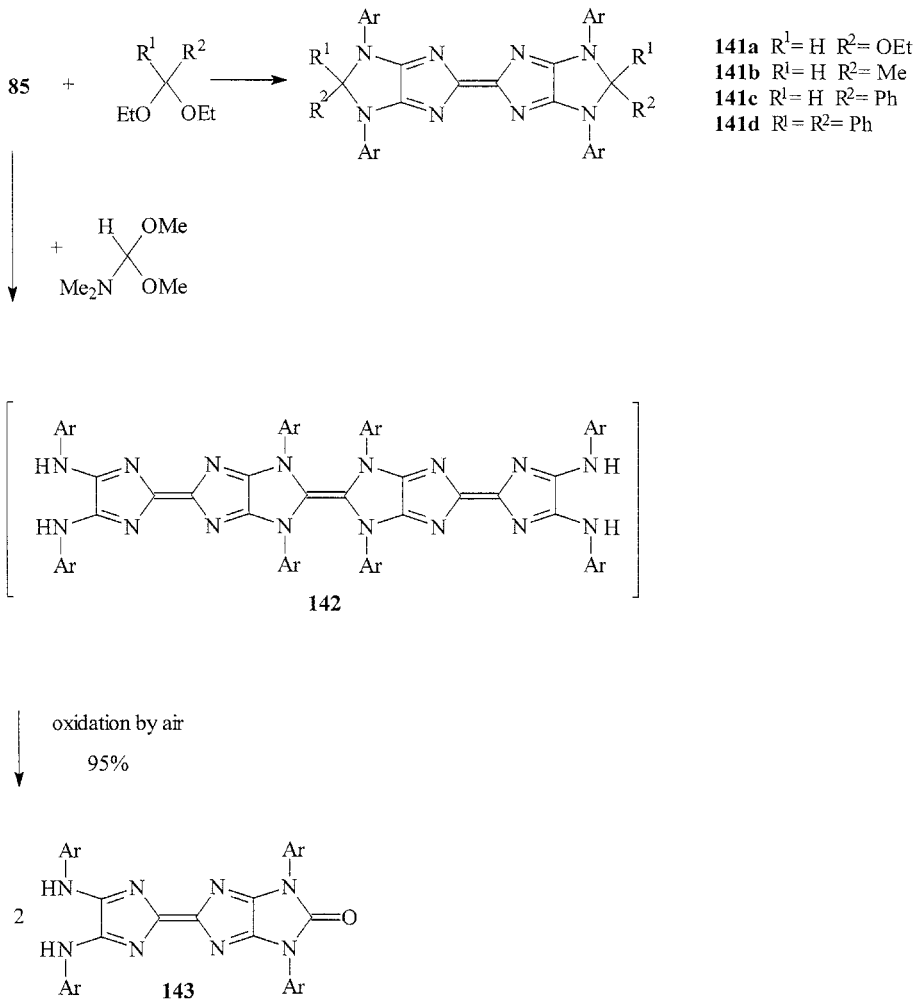
SCHEME 54



SCHEME 55

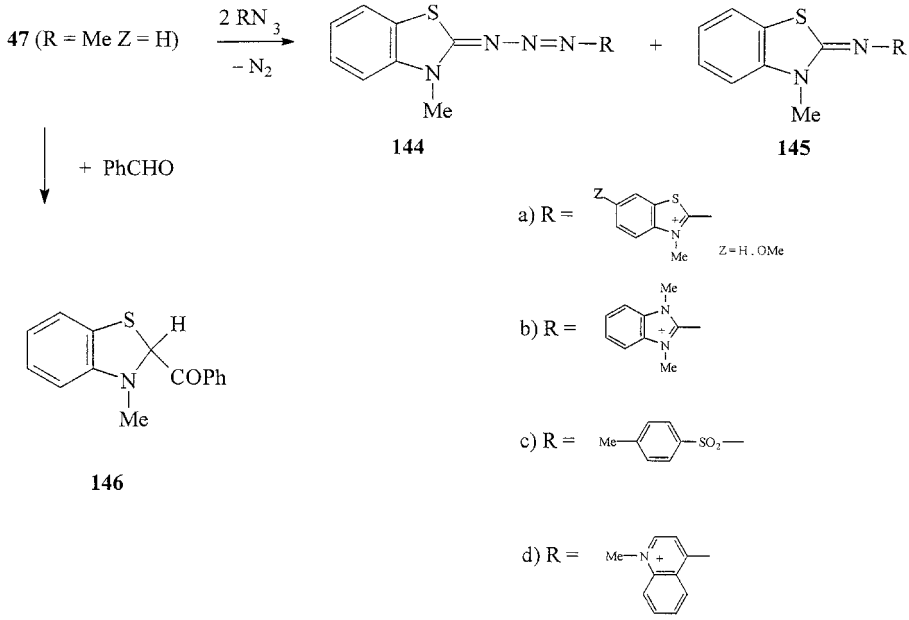
ters and acetals, respectively, to give the imidazo fused compounds **141** (97LAR617; 98JPR323). Somewhat surprisingly, the cyclization reaction with DMF-dimethylacetal led to the oxo derivative **143,** for which a sequence via nucleophilic carbenes, dimerization to **142,** and subsequent oxidative cleavage is assumed (98JPR323) (Scheme 56).

Among the azafulvalenes the subgroup of the electron-rich olefins of type **47** and their nonfused derivatives **52** and **53** shows the highest reactivity toward electrophilic reagents. Reactions with a number of azides were investigated in order to differentiate between DTDAFs **47** (R = Me, Z = H) and their presumed precursor compounds of nucleophilic carbene type (64AG989; 66CB2017). The triazacyanines **144** and the monoazacyanines **145** were isolated in the most cases as main products, whereas the considerably less electrophilic azidinium salt derived from *N*-methylquinoline led solely to product **145.** Analogously, unsymmetric azines could be synthesized starting from DTDAFs and substituted diazocyclopentadienes (67LA155).



SCHEME 56

Active carbonyl compounds such as benzaldehyde attack the electron-rich double bond in DTDAFs to give a dipolar adduct, which immediately undergoes dissociation with formation of two molecules of **146** (64BSF2857; 67LA155). The existence of by-products such as benzoin led to the synthetic application of thiazolium salts in the acyloin condensation. For example, replacement of the "classic" cyanide ion by 3-benzyl-4-methyl-5(β-hydroxyethyl) thiazolium salts allowed the benzoin-type condensation to take place in nonaqueous solvents (76AGE639) (Scheme 57).



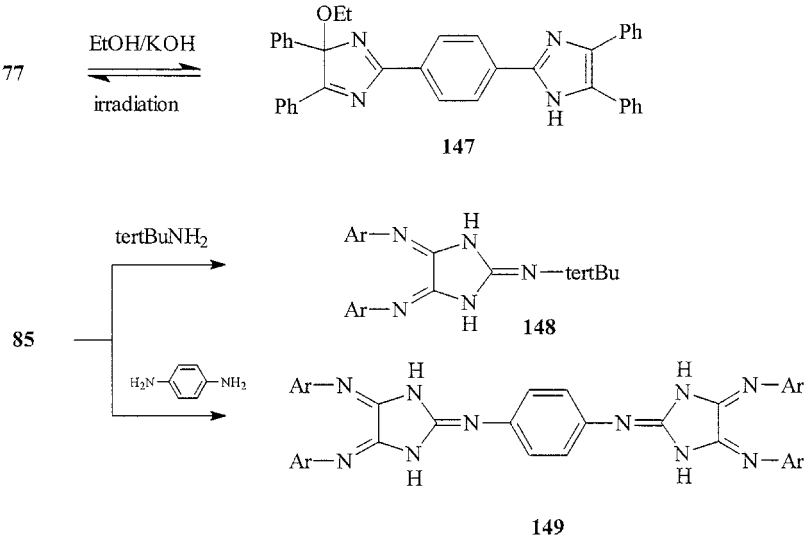
SCHEME 57

C. NUCLEOPHILES

Depending on the electronic state of azafulvalene and the reaction conditions, simple nucleophiles such as amines or alcohols show a different behavior. Upon heating methanol reacted with azafulvalenes as electron-rich olefins by addition to the central double bond (64BSF2857; 67LA155). Using the TAF **77** (Ar = Ph), the addition reaction in a neutral benzene–ethanol solution required several days to obtain a minor amount of **147,** while the reaction proceeded rapidly in the presence of a catalytic amount of potassium hydroxide (79JOC1241). The yellow-colored adduct **147** can be reconverted to the quinoid starting material by irradiation (Scheme 58).

Primary or secondary amines react with different kinds of TAF by cleaving the central double bond (71BSF3541; 97UP1). Thus, *tert*-butylamine is capable of converting TAFs **85** into derivatives of parabanic acid **148** in good yield, whereas *p*-phenylenediamine gives **149** (97UP1). In indigoid derivatives of azafulvalenes, replacement of the methylsulfanyl groups by piperidine allowed a convenient synthesis of further compounds of this series (90JPC949).

To complete this section, we note the cleavage of electron-rich DTDAFs by CH-acidic five-membered heterocycles of the oxazolidine, thiazolidine, and imidazolidine types (64BSF2857).



SCHEME 58

D. DISSOCIATION INTO CARBENES

In 1995 it was suspected that azafulvalenes of the twofold bridged dibenzimidazolinylidene **80a** and type **80b** type might exist in equilibrium with an analogous bis-carbene (95TL2741), but all attempts to detect any carbenoid species were in vain. Instead, these TAFs reacted with rhodium-(1,5-cyclooctadienyl)chloride to give a 1:1 adduct, which was identified by its downfield carbene carbon signal at 195 ppm as well as by X-ray crystallography as a rhodium–carbene complex. One year later, the first experimental data for the existence of nucleophilic carbenes derived from azafulvalenes were published. The yellow crystals decomposed rapidly to a white powder on warming the bisbridged tetraazafulvalene **82** synthesized by reduction of the corresponding biimidazolium salt by metallic sodium in liquid ammonia. Using NMR spectroscopy, it was demonstrated that its structure was that of a twofold bridged biscarbene **83** (96AG1098).

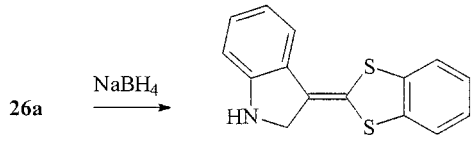
It was observed occasionally that the DTDAF **51a** can revert back to the stable carbene so that the dimerization appears to be reversible (97LAR365). This splitting reaction could not always be clearly reproduced and seems to be influenced by trace contaminants that are as yet unidentified.

E. REDOX REACTIONS

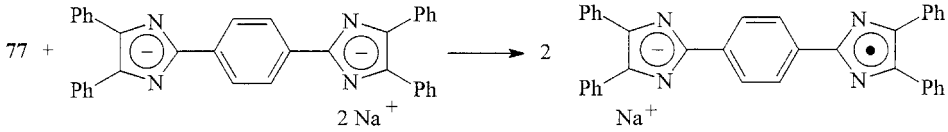
A few reductions using typical hydride reducing agents have been reported for azafulvalenes. Thus, lithium aluminium hydride reduces *N*-methyl-

2-cyclopentadienylidene-1,2-dihydropyridine **41** (R = Me) at first to a dihydro and then to a tetrahydro stage without exact structural assignment (65JA2887). No primary attack at C-2 of the pyridine ring took place, since the dihydro product still contained a fulvalene system. Whereas the azafulvalene **26a** resisted a reaction with strong nucleophiles such as phenylmagnesium bromide, it smoothly reacted with sodium borohydride at room temperature in a mixture of THF and water. Work-up gave the dihydro derivative **150** in an 89% yield; its structure was determined by spectroscopic and elemental analyses (80BCJ1661). The result indicating that hydride ion attacked at the 5-position rather than the dithiole ring carbon is not in harmony with the expected reactivity of **26a.** Single electron transfer was reported during the reaction of the quinoid TAF **77** (Ar = Ph) with its starting material the disodium salt of the diimidazole **151** (66AG303). The paramagnetic properties of the semiquinoid but less stable product **152** could be detected by ESR spectroscopy in a stop-flow apparatus (Scheme 59).

Sometimes the reduced form of azafulvalenes is favored for the preparation of derivatives. For example, the carboxy groups in the indigoid diazafulvalene **61** (Section II,B,3) were transformed into the corresponding methyl ester groups via reduction to the leuco form of **61,** followed by methylation with diazomethane and subsequent reoxidation by air (68CB1286). Finally, a simple synthesis for the unsubstituted 1,4,5,8-tetraazafulvalene **153** was found recently by the present author by reduction of the corresponding tetraarylamino derivatives of type **85** using zinc dust (98JPR323). This parent compound was isolated in good yield as a slightly yellow oil which rapidly decomposed to tarry material. The sequence alkylation–reduction–alkylation allows a convenient approach to



150



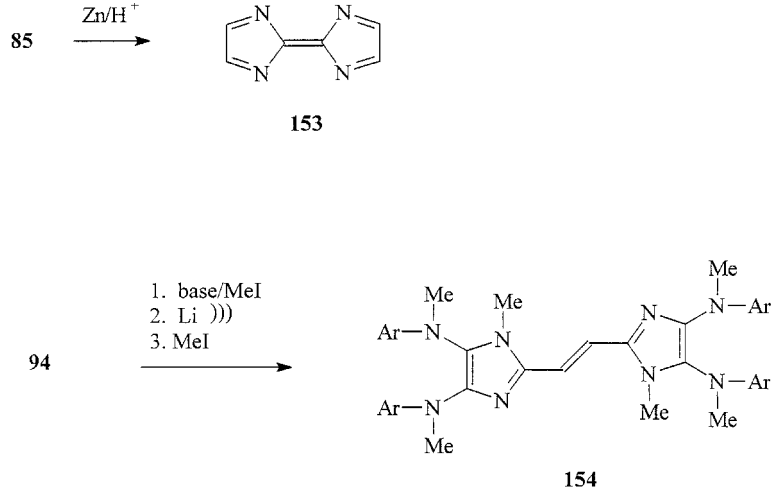
151 **152**

SCHEME 59

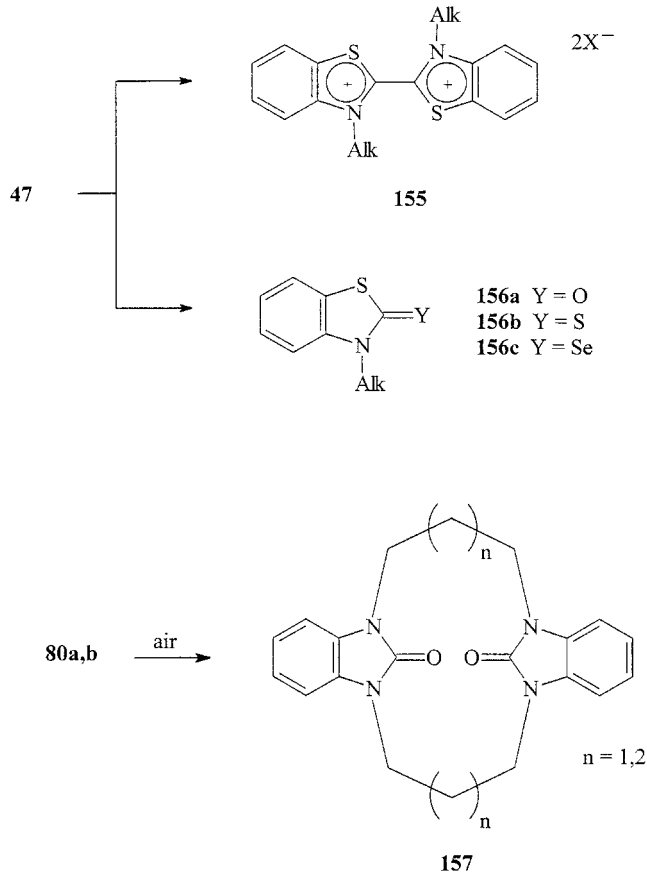
stilbenoids of type **154** derived from imidazole (98JPR323). The reaction conditions were optimized by adopting ultrasonic irradiation and metallic lithium as base as well as reducing agent so that the reaction could be carried out in a "one-pot" fashion (Scheme 60).

There are a number of two-step redox systems which in the oxidized form constitute azafulvalenes or their vinylogous derivatives. For example, polyenes carrying indole residues as terminal groups attached via position 3 can readily be oxidized in two steps to diazafulvalenes of type **63** via the radical cation (76LA1039). On the other hand, this reaction can be carried out reversibly by two single electron reduction steps, realized by treatment with tin-(II)-chloride in dimethylformamide. These kinds of two-step redox systems are of interest in electrooptical systems, in organic conducting systems as organic metals, as redox catalysts in photographic processes, and as redox indicators (78AG927) (Scheme 61).

DTDAFs as well as TAFs of the type of "electron-rich olefins" are extremely sensitive toward oxygen and therefore must be stored under inert conditions at low temperatures (64BSF2857; 67LA155; 92JOC1008; 95AS8528, 95MI296, 95TL2741). They can be oxidized selectively to the corresponding dicationic 2,2′-biheterocycle **155** by chlorine or bromine (72LA110), by Ag^+ (71BSF3541), and by $PhI(OAc)_2$ in the presence of perchloric acid (92JOC1008; 95AS8528, 95MI296); to the radical cation by iodine (85AG996); and to the bisheterocycle by nitrobenzene with dealkylation (65CB3808). Using hydrogen peroxide, cleavage of the central fulvalene double bond takes place to form benzthiazolones **156a**



SCHEME 60



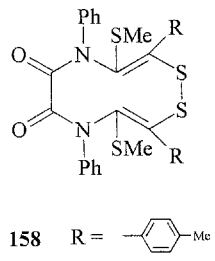
SCHEME 61

(64BSF2857). Similarly, elemental sulfur or selenium are able to oxidize 2,2′-dibenzthiazolinylidenes, leading to the heteroanalogous carbonyl compounds **156b** and **156c** (64BSF2857; 65CB3808; 67LA115). Occasionally, the formation of spiranes have been reported (64BSF119; 67LA155) on treatment with air in different solvents. The bis-bridged TAFs **80a** and **80b** undergo a spontaneous chemiluminescence reaction with dioxygen to afford ureaphanes **157** (95TL2741). Singlet oxygen also led to a selective cleavage of the C–C bond in 1,4,5,8-TAFs of type **85** under formation of derivatives of parabanic acid (97LAR617). Another type of oxidation was observed by preparation of the DTDAFs **52a,** which were easily converted to the macrocycle **158** by simple recrystallization in ethanol in the presence of air (93JCS601). Starting from the DTDAFs **47** and **49,** oxidation with air in xy-

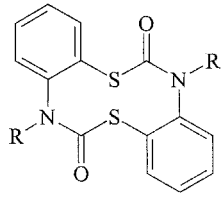
lene led to the fused macrocycles **159** and **160** in which sulfur–sulfur interactions were discussed (67LA155). When equimolar quantities of **80a** and **110** are combined in acetonitrile, single electron transfer occurs and the coproportionation product **111** is obtained as a deeply red-colored, air sensitive cation radical (95TL2741) (Scheme 62).

F. Charge-Transfer Complexes

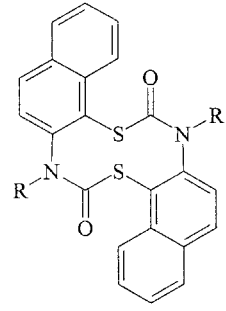
After many years of research on the organic solid state of quasi-one-dimensional metals, there is still a need to discover new classes of systems with high conductivity, capability of superconductivity at higher temperatures, new nonlinear optical properties, or unusual device characteristics. The design and synthesis of electrically conducting organic charge transfer complexes and ion-radical salts, initiated by the landmark discovery of organic semiconductors, continue to be fascinating problems. The majority of the nonpolymeric organic conductors and superconductors known today are based on the tetrathiafulvalene (TTF) donor or its heteroanalogs (Se, Te) and derivatives (91CSR355). The structural similarity of nitrogen-containing fulvalenes, especially dithiadiaza- and tetraazafulvalenes with TTF, led to the examination of this family of potential acceptors. Whereas TTF and its derivatives constitute donors with seven π-electrons in each ring the corresponding aza analogs are acceptors with five π-electrons in each ring. AM1 calculations (96SM127) showed that, for example, halonitro-, and cyanosubstituted TAFs would be very strong acceptors (2,3,6,7-tetracyano-1,4,5,8-tetraazafulvalene, electron affinity 3.82 eV). A brief report on tetrahalo derivatives (89KGS1421) also mentioned formation of dianionic species on reduction. In agreement with these findings, aza-1,2- and 1,4-dithiafulvalenes are more difficult to oxidize than TTF. Depending on the substituents, they react with TCNQ either in a 1:1 or 2:3 ratio to form heterofulvalenium salts whereby the electrical conductivity of these



158 R =



159

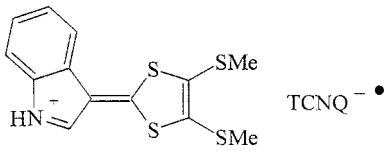


160

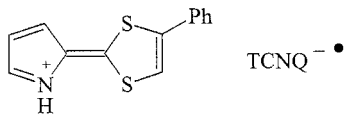
SCHEME 62

salts is strongly influenced by the nature of the substituents (86TL949). Thus, the conductivity of alkylsulfanylfulvalene salts is much higher than that of phenyl-substituted derivatives. TCNQ reacts with azafulvalenes in hot acetonitrile to furnish the salts **161–163,** consisting of protonated fulvalenes and TCNQ radical anions (86TL849). The pellet conductivities of **161** and **163** are remarkably high, whereas the extremely low conductivity of **162** demonstrates that the phenyl group hinders sterically the formation of separate stacks (Scheme 63).

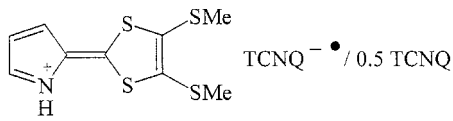
The strong electron-acceptor properties of TAFs in which each nitrogen is π-valent were demonstrated by the synthesis of tetraazafulvalene-diide salts of TTF (96SM127). These fulvalene–fulvalene salts are found to be semiconductors with room-temperature powder-compaction resistivities in the range of $10^2 - 10^3\ \Omega\ \mathrm{cm}^{-1}$ and band gaps of 0.18–0.08 eV. On the other hand, in the past few years such compounds, namely DTDAFs of types **52** and **53,** have attracted attention as possible strong electron donors possessing TTF-like two-wave redox behavior. These properties suggest that these kinds of heterofulvalenes may function as precursors in the synthesis of conducting organic materials. The first compound of this family, the 2,2′-



161 8.3×10^{-3} S/cm



162 5.6×10^{-12} S/cm



163 1×10^{-4} S/cm

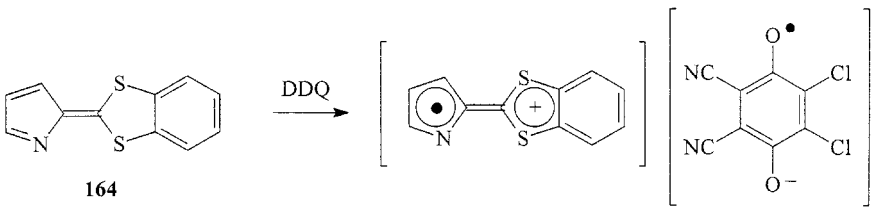
SCHEME 63

bis(*N*-methyl-2,3-dihydro-benzothiazolin)ylidene **47** (R = Me, Z = H), was already reported in 1964 (64BSF119, 64BSF2854). However, caused by their extreme sensitivity toward oxidation processes only a few could be isolated and characterized. About 30 years later, a new synthesis was reported allowing *in situ* generation of complexes with TCNQ (93CC601). When TCNQ is added during the preparation of DTDAF **52b** the complex **52b**/5TCNQ precipitate as a dark powder. In its IR spectrum, the ν_{CN} shifted from 2227 to 2194 cm^{-1}, suggesting a partial charge transfer. Consistent with these results a single crystal conductivity of $6\ 10^{-4}\ \Omega\ cm^{-1}$ was observed. Somewhat surprisingly, tetrathiadiazafulvalenes do not react with TCNQ, but form conducting complexes with iodine (94JOC2997). In the meantime, several dithiadiazafulvalenes have been prepared and their complexes with TCNQ were studied (92JOC1008; 95JA8528). In 1995 the first isolable derivatives of DTDAF **53** were described, which are stabilized by electron acceptor substituents. These strong electron donors form crystalline charge-transfer complexes with TCNQ, which precipitate from acetonitrile solutions at room temperature under nitrogen (95PMS296). The most conductive salts **53a:**TCNQ = 1:4 and **53b:**TCNQ = 2:5 are probably of the segregated-stack type, where stacks of TCNQ-radical anions, mixed with TCNQ neutral molecules, dominate the quasi-one-dimensional conductivity ($\sigma = 8.3\ 10^{-2}, 1.1\ 10^{-2}$ S cm^{-1}).

The relatively high conductivity of the 1:4 complex and of the 2:5 complex seems typical for segregated-stack TCNQ-complexes where the TCNQ species are not formally mixed-valent and the cation functions as a counterion rather than participates in the π-electron conduction. The room temperature compaction conductivity data are disappointing for both TCNQ complexes of **52d**/TCNQ (**52d:** TCNQ = 1:1 and 1:4:2MeCN) and the 1:1 complex of **53b**/TCNQ. The presence of the bulky phenyl groups in **53b** leads to a disturbance of planarity and impedes π-stacking of the donors. The donor **53a** is more likely to be planar. The search for new organic metals has led to the preparation of a new air-stable complex of buckminsterfullerene with the dithiadiazafulvalenes. However, only derivatives with the behavior of an insulator ($\sigma < 10^{-10}$ Scm^{-1}) could be obtained (95SM1435). Using DDQ, another type of acceptor molecule was reported (78BSJ1427); with azafulvalene **164** it formed a dark-violet precipitate consisting of a 1:1 charge-transfer salt **165** (Scheme 64).

G. Miscellaneous Reactions

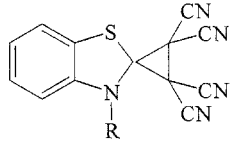
Azafulvalene itself can serve as starting material for the synthesis of further heterofulvalenes. Using the ring-opening/ring-closure methodology



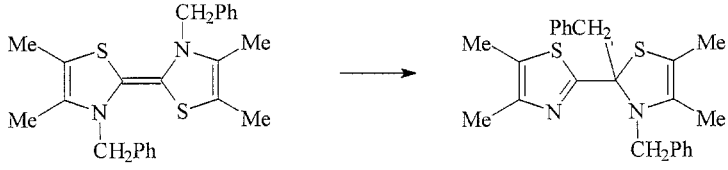
164 **165**

SCHEME 64

oxa-diazafulvalenes can readily be transformed by methylamine into triazafulvalenes (70CS807). Due to their powerful electron-donating properties, the DADTFs **47** (R = Me, Et, Z = H) can react with tetracyanoethene under mild conditions to give the spirocyclopropanes **166** (64BSF2857; 81HCA648). The authors exclude the structure of a ring-opened, zwitterionic compound because of the existence of only one valence vibration band in its IR spectrum at 2190 cm^{-1} (81HCA648). A further feature of electron-rich-ethenes was observed during the deprotonation of several *N*-alkylthiazolium salts. Whereas the lower alkyl (methyl, ethyl) derivatives of dithiadiazafulvalenes were quite stable and had no tendency to rearrange, the benzyl derivative **167** underwent a [1,3]sigmatropic rearrangement of one of the benzyl groups from nitrogen to the central carbon to give **168** in the presence of an excess of base (91AS5029) (Scheme 65).



166



167 **168**

SCHEME 65

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Chemistry of *N*-(1-Haloalkyl)Heteroarylium Salts

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I. Introduction

N-Substituted pyridinium salts are important synthetic reagents in many fields of organic chemistry, as evidenced by several comprehensive reviews that deal with their chemistry and reactions [53AG605; 62AG811; 63AG181;

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76S1; 79AG798; 85H1513, 85H1765; 86H181; 92HOU(E7b,II,2)286; 93MI2, 93ZOR2070; 94AHC(60)197; 95T13365, 95CHE682; 96CHEC(5)]. Many references also cover the syntheses and nucleophilic substitution reactions of a wide variety of functional groups at the Cα position of N-alkyl-substituted pyridines. Examples of such groups that have been successfully employed are OH, OR, OCOR, CN, $OSiR_3$, SiR_3, PR_3, AsR_3, NO_2, NR_2, SR, and SR_2. The chemistry of these derivatives is not covered in the present chapter. They have been included to a minor extent only when a more sophisticated background was needed for the interpretation of the synthetic applications and theoretical reactivity investigations.

Pyridinium salts with an α-halogen atom in the N-substituent were described as early as the 1930s (33CB1386; 36CB2006; 37CB864). Obviously, due to the poor results reported in the first synthetic approaches, they have received little further attention in the literature (71T4209; 86T601; 94MI1).

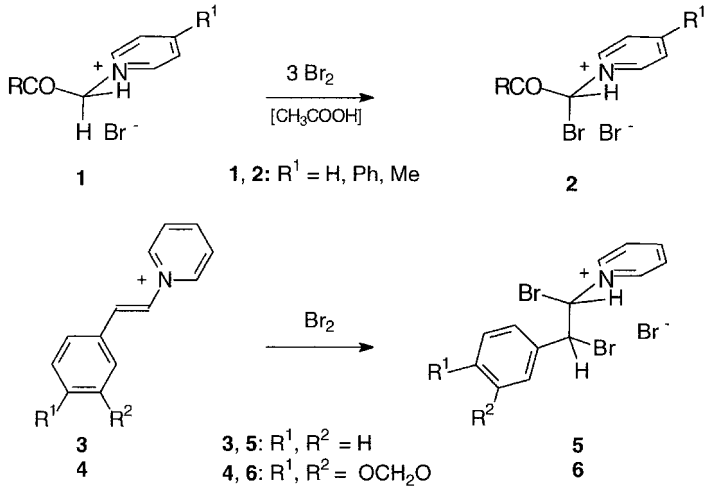
Almost a decade ago, we reported the first preparation of N-(1-bromo- and chloroalkyl)heteroarylium salts using a three-component reaction consisting of an *N*-heteroaromatic compound such as pyridine (or pyridine derivatives, isoquinoline, etc.), an aldehyde, and thionyl chloride or bromide (87BSB719; 89JOC4808; 97LA745). This very convenient method has invoked significant current interest in such compounds and has led to many interesting synthetic applications. These (title) salts have been reacted—in many cases *in situ*—with a variety of nucleophiles. Systematic investigations have yielded many useful products, such as novel C1-sulfonato-pyridinium betaines, C1-phosphonato-pyridinium salts, geminal-substituted bis-onium salts such as phosphonium/pyridinium species, as well as bis-heteroarylium compounds. Furthermore, one can synthesize 5-, 6-, and 7-membered ring systems as well as unusual imines using the title compounds. The most recent applications for these salts are as precursors for the synthesis of novel cationic tricyclic (5/6/5) heterocyclic systems (98EJOC2923).

II. Synthesis

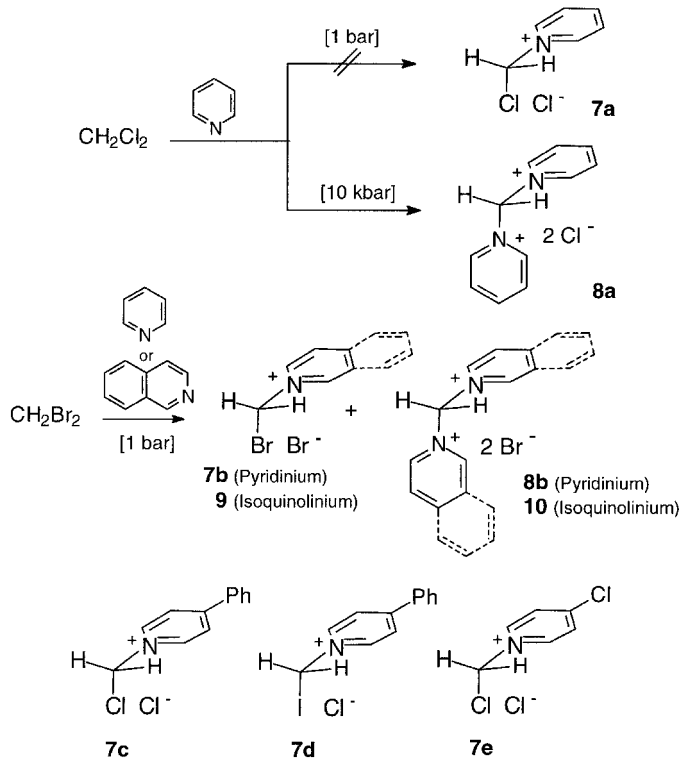
A. Miscellaneous Methods

To the best of our knowledge, the first paper which mentioned an *N*-(1-haloalkyl)pyridinium compound appeared 66 years ago in the *Chemische Berichte* (Kröhnke; 33CB1386). The author described the reaction of phenacyl pyridinium derivatives **1** with bromine in acetic acid to give the halides **2** (36CB2006; 37CB864). The addition of bromine to the double bonds of *N*-vinylpyridinium salts **3** and **4** giving the adducts **5** and **6** has also been reported (51CB399) (Scheme 1).

It is noteworthy that pyridine does not react at atmospheric pressure with dichloromethane to yield salts such as **7a** (Scheme 2). Applying higher pressures resulted in *N,N′*-methylene-bis(pyridinium) dichloride (**8a**) (86T601).



SCHEME 1



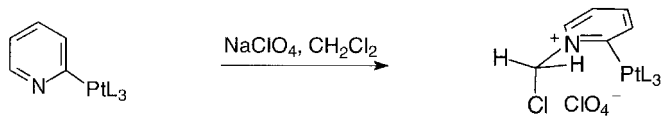
SCHEME 2

The compounds **7a** and **7c** were mentioned in a paper in which the inhibition of mitochondrial respiration by pyridinium cations is discussed. However, no details for the synthesis of **7a** and **7c** were published. Starting from Cl-CH_2-I and pyridine, the iodide Cl-CH_2-Py^+ I^- was synthesized by C. H. Calderon *et al.* (and from this the corresponding chloride could be obtained via an anion exchange reaction) (94MI1). Dibromomethane reacts either with pyridine or isoquinoline, giving exclusively the *N,N′*-methylene-bis(heteroarylium) dibromides **8b** and **10** (86T601). The partial formation of the pyridinium salt **7b** could be induced, however, by selecting a suitable pressure [solvent-free, molar ratio 2(**7b**) : 1(**8b**)]. In this reaction (86T601), **7b** was neither isolated nor characterized by spectroscopic data or other methods. Attempts to use Br-CH_2-I and pyridine or isoquinoline for the synthesis of **7,** although conceivable, have not yet been reported. The 4-phenylpyridinium iodochloride (**7d**) has been employed for the preparation of herbicidal agents (71USP144246); **7e** has been ascribed antibacterial properties (88EP256990). A more convenient method for the preparation of **7** and related compounds is described in Section II,B, "Three Component Syntheses."

Several N-(chloromethyl)pyridinium platinum complexes have been described in the literature [89JOM255; 92JCR(S)296; 92JOM155]. Interestingly, 2-pyridyl platinum(II) complexes **11** and **12,** having been dissolved in dichloromethane, are slowly N-alkylated by the solvent, yielding the *N*-(chloromethyl)pyridinium compounds **13** (76%) and **14** (77%) (Scheme 3).

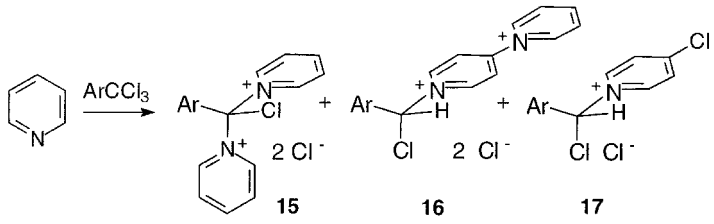
The redox system consisting of a trichloromethylarene and pyridine in trichloromethane is capable of generating *N*-(1-chloroarylmethyl)pyridinium chlorides such as **15, 16,** and **17.** Upon hydrolysis, aromatic aldehydes and 4-chloropyridine or 1,4′-bispyridinium salts are formed. The key step of this reductive condensation is the transfer of a hydride ion from the pyridine ring to the benzylic carbon atom (93MC97; 94KGS686; 95CHE726, 95CHE1346, 95TL5075) (Scheme 4).

The existence of the ylide **19,** which can formally be interpreted as the deprotonation product from the corresponding salt **7a,** has been claimed by trapping chlorocarbene with pyridine during the laser-flash photolysis of *endo*-7-chlorodibenzo[*a,c*]bicyclo[4.1.0]heptane (**18**) (96JPC18426). Bromination of 1-vinyl-2-pyridone (**20**) yields the bicyclic pyridinium bro-



11 (**11**, **13**: L = Cl, 2 PMe_2Ph) **13**
12 (**12**, **14**: L = PPh_3, dimethyldithiocarbamate) **14**

SCHEME 3

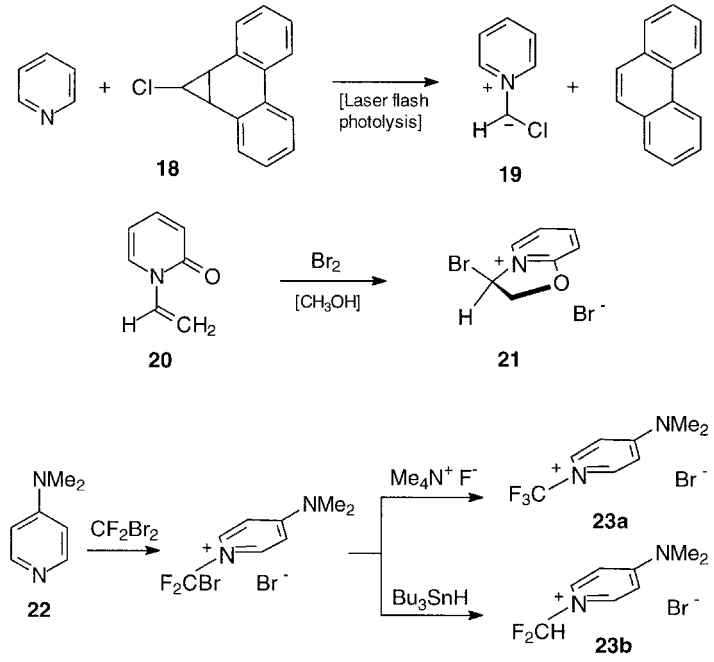


Ar = Ph; 2,4-$Me_2C_6H_3$; 2,4,5-$Me_3C_6H_2$; 2,4,6-$Me_3C_6H_2$

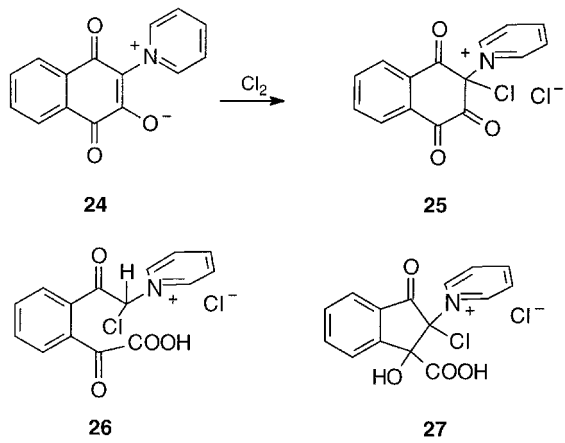
SCHEME 4

mide **21** (91MI1). The *N*-(difluoromethyl)- and *N*-(trifluoromethyl)pyridinium bromides **23a** and **23b** have been synthesized from DMAP **22** and dibromodifluoromethane (Scheme 5). The intermediate N^+-CF_2Br moiety was fluorinated by anhydrous tetramethylammonium fluoride or reductively debrominated by Bu_3SnH (96JCS(CC)335).

The betaine **24,** obtained from the reaction of 2,3-dichloro-1,4-naphthoquinone with a pyridine/water mixture, reacts with Cl_2 to form *N*-(1-



SCHEME 5

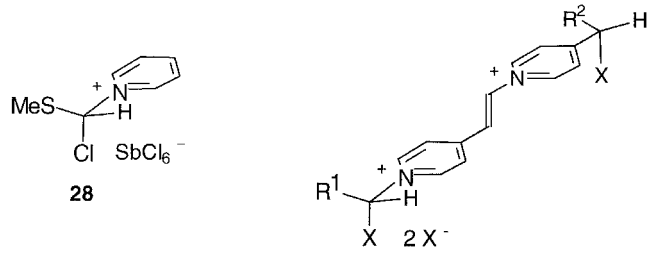


SCHEME 6

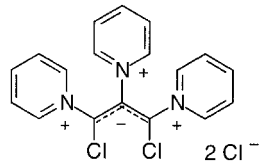
chloroalkyl)pyridinium chloride **25,** which could be easily hydrolyzed to give the chloromethyl pyridinium salts **26** and **27** (51ZOB547) (Scheme 6).

When thiomethoxymethyl hexachloroantimonate was treated with pyridine, a methylthio derivative **28** was isolated in low yield in addition to the expected chlorinated sulfides (71T4209). Several *N*,*N*′-haloalkyl-bis-4,4′-pyridiniumethenes **29** have been reported in a Japanese patent (80JAP75479). These compounds are promising candidates for the construction of electrochromic display devices (Scheme 7).

An interesting intermediate **30** was proposed to result from the sequential addition of pyridine to tetrachlorocyclopropene (**31**). Compound **30** represents an alkyl nitrogen ylide with two 1-chloroalkyl pyridinium moieties in the same molecule. Pyridines with electron-withdrawing groups and heterocycles with an electron-deficient nitrogen, for example, pyridine-3-carbaldehyde or quinoline, react with **31** to yield the corresponding monosubstituted products **32a** and **32b** (83JOC2629) (Scheme 8).



SCHEME 7



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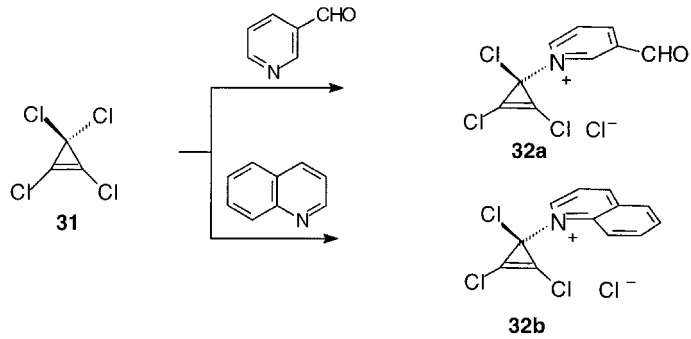


31 **32a** **32b**

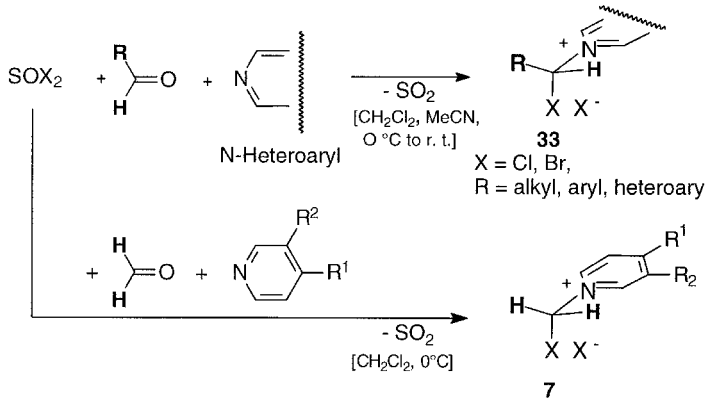
SCHEME 8

B. THREE-COMPONENT SYNTHESES

The procedure described in one of our papers (87BSB719) has the advantage of being more general. Its scope of applicability is the widest among all the methods presented here for the preparation of a large variety of salts **33.** The experimental conditions are very simple. An azine, an aldehyde, and a thionyl halide react with each other in an inert solvent. In the earliest report, the reaction was performed in dichloromethane at −50°C under nitrogen. Such precautions seem to be superfluous and the salts can be obtained by running the synthesis at 0–20°C in the presence of air and in any solvent which does not react with any of the three components. The protocol is characterized by its flexibility since various azines have been successfully involved: pyridine, 3-bromopyridine, 3-methylpyridine, pyridine-3-carbonitrile, 4-*tert*-butylpyridine, pyrimidine, pyrazine, quinoline, isoquinoline, and 1-methylimidazole (87BSB719; 89BSB523, 89JOC4808; 91CB2013). Thionyl chloride has been most often employed in the procedure because it is easy to handle. Aromatic, heteroaromatic, and aliphatic aldehydes (even the highly branched trimethylacetaldehyde) have been found to be suitable for the preparation of **33.** Most of the resulting salts are soluble in dichloromethane. Exceptions to this are *N*-[chloro(3-nitrophenyl)methyl]-pyridinium chloride and *N*-(1-chloro-2,2-diphenylethyl)pyridinium chloride. Some of the salts are hygroscopic. However, all are characterized by an exceptional stability and can be kept unaltered either as the dry salt itself or in solution.

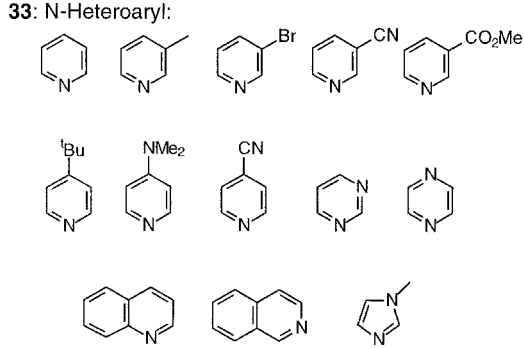
Recently, the "parent" *N*-halomethylpyridinium halides **7a, 7b,** and **7f–7i** (X-CH_2-Py^+X^-, X = Cl, Br) have been synthesized with yields up to 90% by treating a mixture of an equimolar amount of SOX_2 (X = Cl, Br) and the corresponding pyridine with gaseous formaldehyde in CH_2Cl_2 or MeCN at O°C. The formaldehyde was generated externally from paraformaldehyde in a special apparatus (99JOC3113).

The use of trichloroacetaldehyde instead of formaldehyde in this reaction leads to the corresponding Cl_3C-CH(Cl)-Py^+ Cl^- salt (CH_3CN, 0°C, 80%, Scheme 13), in which the one of the CH_2-hydrogens in **7** was replaced by the strongly electron-withdrawing CCl_3 substituent (99JOC3113). The chemistry of that compound is discussed in a separate section (Scheme 9).



7	R^1	R^2	X	[%]
a	H	H	Cl	90
b	H	H	Br	73
f	NMe_2	H	Cl	78
g	CN	H	Cl	30
h	H	CN	Cl	77
i	H	CO_2Me	Cl	86

33: N-Heteroaryl:

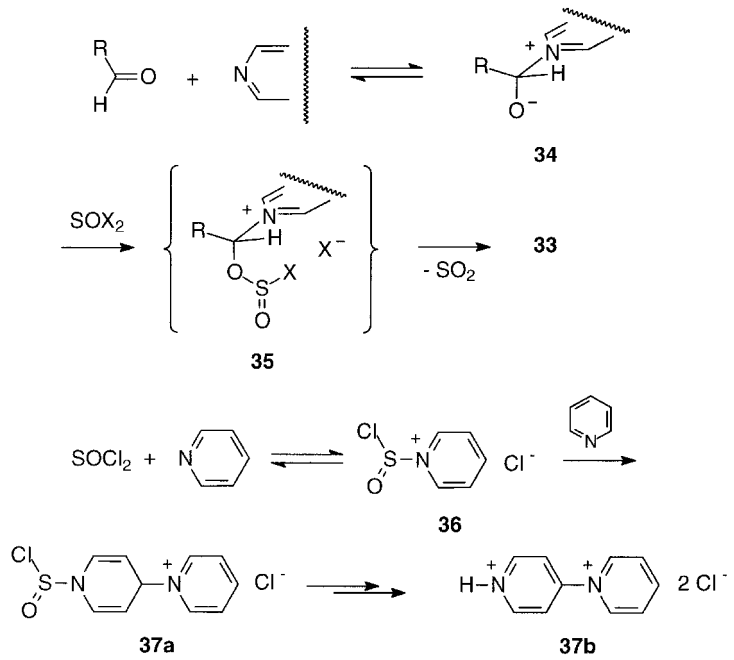


SCHEME 9

To establish a mechanism for the formation of **33,** the reaction has been monitored by ^{1}H-NMR spectroscopy (91CB2013). The basicity of the azine is a rate-determining effect as well as a steric hindrance. Pyridine is more reactive than pyrimidine. 2-Substituted pyridines do not give the corresponding salts.

The kinetic data rule out the presence of a preequilibrium between the thionyl halide and the aldehyde or between the thionyl halide and the heterocycle. It has therefore been suggested that the azine adds to the aldehyde to form the betaine **34** prior to interaction with the thionyl halide. Further O-sulfinylation and elimination of SO_2 via the intermediate formation of **35** affords the salts **33** (73JOC1570; 81S661). This mechanistic proposal is supported by several reports on the existence of adducts between nitrogen bases and carbonyl derivatives (78HCA2783; 80JA4271; 83CB1506; 87CB735).

Thionyl halides and *N*-heteroaromatics are known to be in equilibrium with the corresponding *N*-(halosulfinyl)heteroarylium halides. *N*-(Chlorosulfinyl)pyridinium chloride (**36**), for example, readily reacts with a second molecule of pyridine to give the *N*-[1-chlorosulfinyl-1,4-dihydropyridine-4-yl]pyridinium chloride (**37a**). The intermediate **37a** is probably involved in the preparation of *N*-(pyridine-4-yl)pyridinium chloride hydrochloride (**37b**). However, the authors could not detect either **37a** or **37b** in their experiments (91CB2013) (Scheme 10).



SCHEME 10

III. Experimental Structural Methods

A. ^{1}H and ^{13}C NMR Spectra

Many *N*-(1-haloalkyl)heteroarylium salts **33** have been characterized by their ^{1}H and ^{13}C NMR spectra (Table I) (Scheme 11).

A characteristic feature of these compounds is the relative position of both H and C signals in ^{1}H and ^{13}C NMR spectra, respectively. The signals of the CH protons range between 6.3 and 9.8 ppm, which is a good indicator of their acidic character. The α-halogen atom has only a weak influence on the chemical shift of the CH signal. The other α-substituent has a stronger influence on the chemical shift. The CH signals of compounds with aliphatic chains are observed at a relatively high field, whereas the negative σ-effect of aromatic rings causes a shift to lower fields.

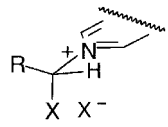
TABLE I

Selected ^{1}H- and ^{13}C-Chemical Shifts (in Parts Per Million) of *N*-(1-Haloalkyl)Hetarylium Halides **7, 33,** and **43**

Compound				^{1}H	^{13}C		
No	R	X	Heteroarene	(H-Cα)	(H-Cα)	Solvent	Reference
7a	H	Cl	C_5H_5N	6.7(s)	64.1	DMSO-d_6	99JOC3113
7f	H	Cl	DMAP	6.3(s)	62.4	DMSO-d_6	99JOC3113
7h	H	Cl	3-CNC_5H_4N	6.8(s)	64.7	DMSO-d_6	99JOC3113
33a	4-MeC_6H_4	Cl	C_5H_5N	9.2(s)	76.8	$CDCl_3$	89JOC4808
33b	4-MeC_6H_4	Cl	4-$tBuC_5H_4N$	9.5(s)	77.6	$CDCl_3$	
33c	4-MeC_6H_4	Cl	3-MeC_5H_4N	9.2(s)	95.1[b]	$CDCl_3$	
33d	Et	Cl	C_5H_5N	7.7(t)	82.9[b]	$CDCl_3$	
33e	4-MeC_6H_4	Cl	1-Me-imidazole	8.4(s)	68.5	$CDCl_3$	
33f	4-MeC_6H_4	Br	C_5H_5N	9.0(s)	67.1	$CDCl_3$	
33g	Pr	Br	C_5H_5N	8.8(t)	67.7	$CDCl_3$	
33h	Ph	Br	C_5H_5N	9.2(s)	66.4	$CDCl_3$	
33i	2,4,6-$Me_3C_6H_2$	Cl	*N*-4-pyridyl-C_5H_4N	8.7(s)	79.4	DMSO-d_6	95CHE726
33j	2,4,6-$Me_3C_6H_2$	Cl	4-ClC_5H_4N	8.3(s)[b]	—	CD_3COCD_3	
33k	Ph	Cl	C_5H_5N	9.0(s)	—	$CDCl_3$	89BSB523
33l	Ph	Cl	Quinoline	9.5(s)	—	CD_2Cl_2	
33m	4-NCC_6H_4	Cl	3-BrC_5H_4	9.3(s)	—	CD_2Cl_2	
33n	Ph	Cl	Isoquinoline	9.1(s)	—	CD_2Cl_2	
33o	2-Thienyl	Cl	C_5H_5N	9.2(s)	—	CD_2Cl_2	92T1263
33p	1-Naphthyl	Cl	C_5H_5N	9.8(s)	76.9	DMSO-d_6	97LA745
33q	Bu	Cl	C_5H_5N	7.3(t)	75.6	DMSO-d_6	
33r	9-Anthryl	Cl	C_5H_5N	9.8(s)	76.0	DMSO-d_6	
33s	4-BrC_6H_4	Cl	C_5H_5N	9.0(s)	77.3	DMSO-d_6	
43	CCl_3	Cl	C_5H_5N	8.8(s)	82.7	DMSO-d_6	99JOC3113

[a] Relative to TMS.

[b] Data of the corresponding hexachloroantimonate.



33

For X, R and the heteroarylium part: cf. Table I

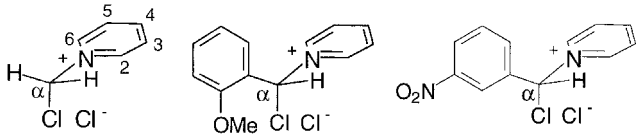
SCHEME 11

The CH carbon shift ranges between δ 62.4 and 95.1 ppm and is typical of carbons carrying two electronegative substituents. This could be a hint for the observed overall ease of substitution reaction at this center. However, electronic and structural properties of these substituents cause no characteristic differences in the δ ^{13}C values.

B. X-RAY DIFFRACTION AND MO CALCULATIONS

The molecular structures of **7a** (99JOC3113), **38,** and **39** (98JST55) have been determined by X-ray single crystal diffraction. The conformations of both **38** and **39** in the crystalline phase are mainly determined by the properties of the C-bonded Cl atoms. These substituents are found in a more or less orthogonal position relative to the pyridinium ring. The acidity of the methylene hydrogens promotes the formation of the intermolecular C-H… Cl hydrogen bonds in **38** and **39.** Further specific properties are exemplified for **7a** (Scheme 12).

The Cα-N^+ bond length in **7a** [146.5(14) pm] appears not to be affected by the electronic influence of the Cl atom. It is almost identical to the corresponding bond length in the *N*-methylpyridinium cation (146.0 pm, 90CB321) and is somewhat shortened as compared with the corresponding bond in *N*-(1-chlorobenzyl)pyridinium chloride (R = Ph, 150.0 pm, 98JST55) or in the *N*-(1-sulfonatoalkyl)pyridinium betaines [Scheme 18, **53,** R-CH(SO_3^-)-Py^+, R = 4-MeC_6H_4: Cα-N: 149.1 pm, 97BSB383]. In contrast to this, the Cα-Cl bond lengths are almost identical (178 pm) with those in the haloalkylpyridinium salts, e. g., **38** and **39.** *Ab initio* calculations on sev-



7a **38** **39**

SCHEME 12

TABLE II

STRUCTURAL DATA OF THE *N*-(CHLOROMETHYL)PYRIDINIUM CATION OF **7a**[a]

Method[b]	Cl-Cα (pm)	Cα-N (pm)	C2-N (pm)	C2-C3 (pm)	C3-C4 (pm)	ClCαNC2 (°)
PM3	177.2	148.9	137.7	139.1	139.6	88.5
AM1	174.6	146.6	137.1	139.9	140.0	89.4
RHF/6-311+G*	176.4	146.9	134.1	137.0	138.8	88.76
RMP2/6-311+G*	175.7	147.9	135.5	138.9	139.8	89.17
RBP86/6-311+G*	178.4	148.6	136.4	138.8	140.2	88.69
RB3LYP/6-311+G	178.1	147.9	135.5	138.0	139.5	88.78
X-Ray[c]	178.2(11)	146.5(14)	135.2(14)	137.7(16)	138.9(18)	86.97

[a] For numbering cf. Scheme 12.

[b] For the semiempirical and *ab initio* calculations (Gaussian 94) cf. (99JOC3113) and references cited therein.

[c] Reference 99JOC3113.

eral levels of theory as well as the inexpensive semiempirical methods (PM3, AM1) show acceptable overall agreement with the X-ray structure (Table II). The dihedral angle Cl-Cα-N-C2 (X-ray: 86.97°) indicates that the cation **7a** exhibits only a small deviation from ideal C_s symmetry.

In order to obtain further insight into the structural properties of such compounds, the calculations were extended to include the cations **40** (R = MeO-CH_2-), **41** (R = Me_3SiO-CH_2-), **42** (R = X = H), and **43** (R = Cl-$CH(CCl_3)$-) (99JOC3113).

The calculated Cα-N^+ bond lengths, Table III, of these pyridinium cations [as well as the bond orders, BO, and the reaction energies, ΔH_R, for a hypothetical dissociation to give the corresponding carbenium ion **44** and pyridine (Scheme 13)] indicate that these bonds are significantly weakened

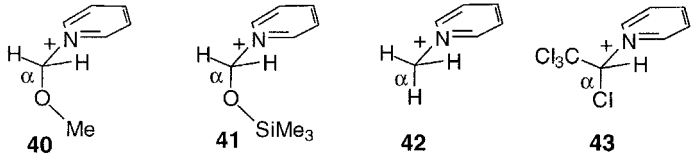
TABLE III

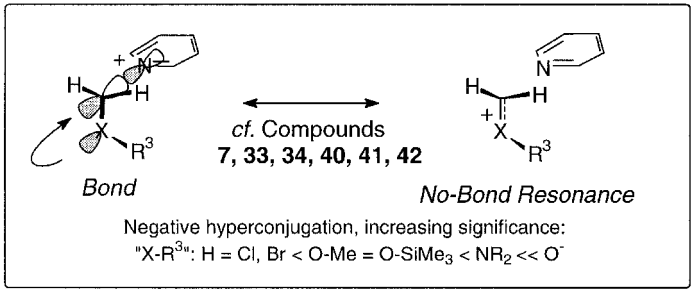
CATIONS OF **7a, 40, 41, 42,** AND **43:** Cα-N^+-BOND LENGTHS (BL), BOND ORDERS (BO), AND DISSOCIATION ENERGIES (ΔH_R) (cf. SCHEME 13[a,b])

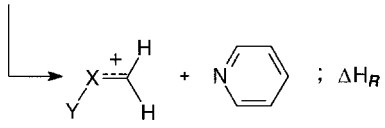
Molecule	BL ($C\alpha$-N^+) (pm)	BO ($C\alpha$-N^+)	ΔH_R (kcal/mol)
7a	148.1	0.91	87.54
40	153.5	0.82	54.16
41	152.3	0.85	44.47
42	148.6	0.91	120.95
43	149.4	0.90	59.58

[a] From Natural Populations Analysis (NPA) (88CRV 899).

[b] RB3LYP/6-31+G*//RB3LYP/6-31+G*, cf. (99JOC 3113); ΔH_R includes the zero-point energy correction; scaling factor, 0.98.







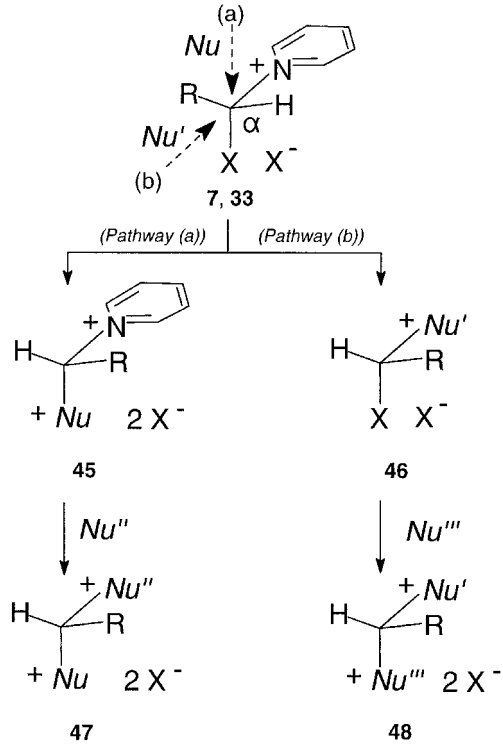
SCHEME 13

in case of **40** (Cα-N$^+$: 153.5 pm, BO 0.82) and **41** (Cα-N$^+$: 152.3 pm, BO 0.85) as compared with **7a** (Cα-N$^+$: 148.6 pm, BO 0.91) and in the methylpyridinium cation **42** (Cα-N$^+$: 148.6 pm, BO 0.91). The electron-withdrawing CCl_3 substituent in **43** (Cα-N$^+$: 149.4 pm, BO 0.90) does not cause such an effect. This bond-lengthening effect can be related to the influence of the negative hyperconjugation or *bond/no-bond resonance,* which depends on the extent of the interaction of the oxygen lone pair (n_O) with the antibonding Cα-N$^+$-sigma bond ($\sigma^*_{C\text{-}N}$) (93HOU(E19d)1).

IV. Reactivity

A. Introduction

In general, all of the title compounds can be classified as either compounds in which the heteroarylium moiety *remains* in the molecule after the nucleophilic substitution (pathway a, formation of **45**) or compounds in which that moiety was *substituted* by a suitable nucleophile to yield **46** (pathway b). Proper selection of the nucleophile *Nu* in **45** (or Nu′ in **46**) should thus allow control of the consecutive substitution reactions, which would lead to a preference of **47** over **48** or vice versa (Scheme 14).



SCHEME 14

Additional control of the nucleophilic substitution pathways a and b should be possible by varying the properties of the heteroarylium moiety in **33** as well as the substituent R and, to a minor extent, by the nature of the C-bonded halogen. The cation of **7a** appeared to be an especially useful model compound and was thus selected in order to systematically study these influences and to define a standard situation. Structure **7a** is easily accessible in excellent yield, and its molecular size allowed high-level MO calculations.

Ab initio calculations suggested that the oxygen-substituted compounds **40** and **41** should be much better candidates for nucleophilic substitution reactions that follow pathway b than the halo salts belonging to the **7a**–**7i** family (Scheme 9). The properties of the CCl_3-substituted cation of **43** should reveal more similarities with those of **7a** than with those of **40** and **41.**

This interpretation is based only upon the structural and electronic properties of the pyridinium cations. The calculation of relative activation barriers for the competing substitution reactions will give more reliable results —especially if solvent effects are included in the calculations. In order to assess the reliability of actual theoretical methods as applied to model sys-

tems in solution, the a and b gas-phase pathways (HF/6-31+G*//6-31+G*) as well as their counterparts in MeCN solution (*vide supra*) have been calculated for the cations of **7a, 40,** and **41.** Ammonia was chosen as a standard nucleophile. The results (Tables IV and V) indicate that all of these cations prefer pathway b via TS(Pyr) in the gas phase (Scheme 15). The activation barrier for the displacement of Cl from **7a** is much smaller [+11.6 kcal/mol, relative to the alternative route (b)], than that for OMe (**40,** +72.8 kcal/mol) or $OSiMe_3$ substitution (**41,** +69.2 kcal/mol). Similar results are found when the activation energies [based on the separated reactants (≡0.0 kcal)] are compared. The pyridine substitution via the TS(Pyr) requires significantly more energy in the case of **7a** (32.8 kcal/mol) than in case of **40** (15.1 kcal/mol) or **41** (14.8 kcal/mol), whereas the activation barrier of

TABLE IV

TRANSITION STRUCTURES AND *AB INITIO*[a] AND SEMIEMPIRICAL GAS-PHASE AND SOLVATION CALCULATIONS[b,c,d]

Structure[e]	Energy, gas-phase[a] (ZPE[e])	Energy, in MeCN solution[a,c] (ZPE[e])	AM1[b]	AM1 in MeCN	PM3[b]	PM3 in MeCN solution[b,c]
TS(Cl)(**7a**)	−801.11928 (107.48)	−801.14475 (106.92)	229.0	142.7	224.7	147.8
TS(Pyr)(**7a**)	−801.13538 (105.82)	−801.14042 (105.64)	209.4	159.5	209.9	159.7
ΔE (**TS**(Cl)−**TS**2(Pyr))[d,e]	+11.58	−1.58	+19.6	−16.8	+14.8	−11.9
TS(40)	−456.04463 (134.54)	−456.06055 (134.29)	217.6	136.7	217.4	142.4
TS(40)	−456.15934 (133.57)	−456.16553 (133.20)	152.9	104.6	165.4	117.0
ΔE (**TS**(OMe)−**TS**(Pyr))[d,e]	+72.84	+66.85	+64.7	+32.1	+52.0	+25.4
TS(41)	−824.29750 (183.64)	−824.33601 (182.77)	167.6	92.8	153.6	81.6
TS(41)	−824.40554 (182.04)	−824.4085 (181.56)	82.1	41.4	72.8	31.9
ΔE (**TS**($OSiMe_3$)-**TS**(Pyr))[d,e]	+69.16	+46.58	+85.5	+51.4	+80.8	+49.7

[a] Energies in a.u., RHF/6-31+G*//RHF/6-31+G*.

[b] Energies in kcal/mol.

[c] *Ab initio:* Simulating MeCN (the Onsager Model), semiempirical: The COSMO Model, MOPAPC 93 keywords: NSPA = 60, EPS = 35.9, TS, PRECISE.

[d] Alternative pathways a *via* **TS**(X) and b via **TS**(Pyr) for nucleophilic substitution reactions, model nucleophile: NH_3, cf. Scheme 15.

[e] All structures: Number of imaginary frequencies = 1. For *ab initio* calculations: Relative energies are ZPE-corrected (scaling factor, 0.89).

TABLE V

ACTIVATION ENERGIES FOR THE NUCLEOPHILIC REACTION OF NH_3 WITH PYRIDINIUM SALTS **7a, 40,** AND **41**[a]

Structure	Activation energy[b] via **TS**(X)	Activation energy[b] via **TS**(Pyr)
7a	+44.42 [+**31.62**]	+32.84 [+**33.20**]
40	+87.89 [+**79.94**]	+15.05 [+**13.09**]
41	+83.94 [+**65.04**]	+14.78 [+**18.47**]

[a] Alternative pathways a and b, gas-phase calculations and [in brackets] simulation of the MeCn solution (cf. Scheme 15 and Table IV).

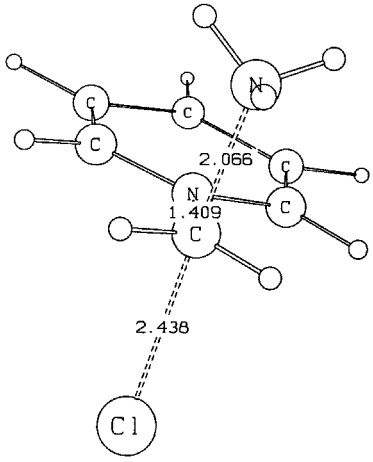
[b] In kcal/mol from RHF/6-31+G*//RHF/6-31+G* optimizations. Separated reactants: ≡0.0 kcal/mol. Relative energies are ZPE corrected; scaling factor, 0.89.

route a to TS(X) is much smaller for **7a** (+44.4 kcal/mol) as compared with the values for **40** (+87.9 kcal/mol) and **41** (+83.9 kcal/mol).

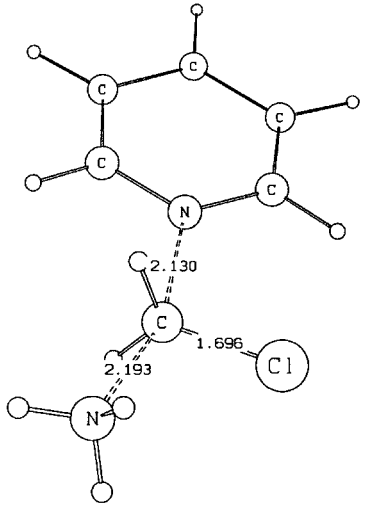
Both of these substitution pathways in MeCN solution have been simulated using the Onsager model (Tables IV and V). Whereas pathway b is favored in the gas phase, inclusion of solvent effects in the calculations causes pathway a to be energetically favored. Substitution of Cl via pathway a is now 1.6 kcal/mol more favorable. In addition, TS(X)/TS(Pyr) calculations (Scheme 15) for the OMe (**40**) and $OSiMe_3$ (**41**) cations have been performed. TS(X) of both **40** and **41** remain significantly disfavored (+66.9 kcal/mol and +46.6 kcal/mol, respectively), thus indicating that pathway b should be preferred in MeCN. These calculations are in complete agreement with experimental observations.

Compound **40** has not yet been synthesized. However, there is a large body of synthetic data for nucleophilic substitution reactions with derivatives of **41** [synthesized from aliphatic and aromatic aldehydes, pyridine, and trimethylsilyl triflate (92S577)]. All of these experimental results reveal that the exclusive preference of pathway b is the most important feature of **41** (and also presumably of **40**).

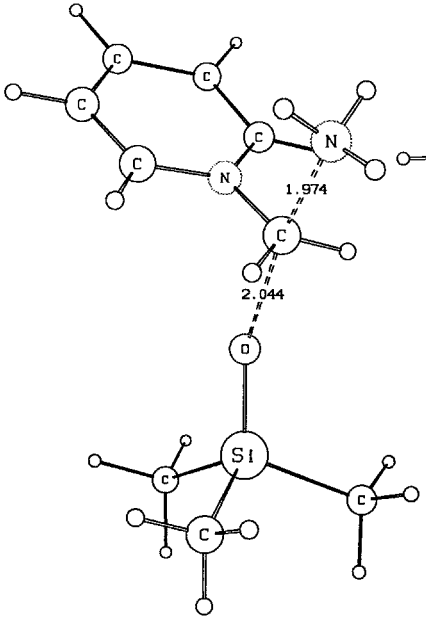
N-(1-Haloalkyl)heteroarylium halides are thus characterized by the presence of two leaving groups on the same carbon atom. Competitive displacement is much more balanced than for the related OR substituted structures. For the model cation **7a,** the energetical difference between both pathways is remarkably small with a slight but significant preference for pathway a in solution. Past and present experimental studies have profited from these properties (87CB735, 87BSB719; 89JOC4808; 93CB1251; 98JST55, 98ECJ2923). Both calculational and experimental evidence indicate that the title compounds react with nucleophiles in the rate-determining step under displacement of the halogen. The bromo derivatives are consumed faster than the chloro compounds. The strength of the carbon–halogen



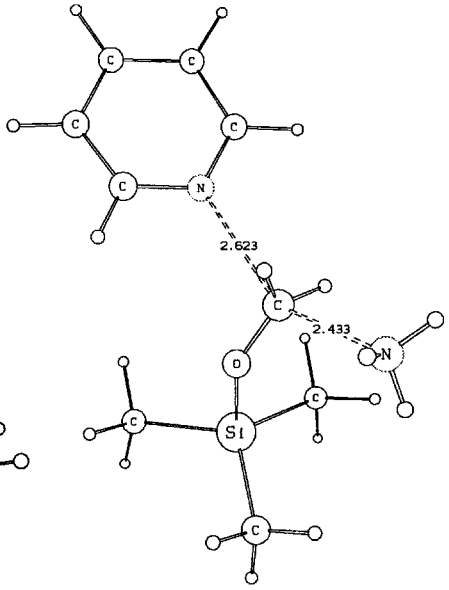
7a → **TS**(Cl)



7a → **TS**(Pyr)



41 → **TS**($OSiMe_3$)



41→ **TS**(Pyr)

SCHEME 15

bond decreases as the electron-withdrawing effect of the heteroarylium moiety increases, so that the pyrimidinium salts appeared to be more reactive than the pyridinium analogs (93CB1251). However, their formation requires longer reaction times (91CB2013).

In addition to the nucleophilic displacement of the halogen atom, subsequent substitution of the heteroarylium moiety has been observed in numerous cases. These substitution reactions benefit from the increasing importance of the negative hyperconjugation (Scheme 13). Such a pathway has been intensively exploited to synthesize (fused) five-, six-, and seven-membered heterocycles.

From a practical point of view, literature data indicate that it is not necessary in most cases to isolate the title salts prior to their reaction. This can be readily understood since their preparation is nearly quantitative and sulfur dioxide is the sole product evolved during their formation. In fact, it is highly advisable to recourse to a two-step procedure during the reactions between *N*-(1-chloroalkyl)pyridinium chlorides and amino acids (Section IV,C,6) (97BSB383).

Trichloro- and dichloromethane, ether, dioxane, benzene, toluene, chlorobenzene, acetonitrile, or even pyridine itself has been employed to carry out the one-pot syntheses. These solvents allow straightforward preparation of the salts. The temperature range between 0° and 20°C is usually employed and the salts formed are sufficiently soluble. In the case of slow reactions, selection of a solvent with a higher boiling point is profitable since thermal instability of the *N*-(1-haloalkyl)heteroarylium halides has not been reported. Addition of water or an aqueous solution of sodium acetate does not cause a rapid decomposition of the salts so that this constitutes a useful step in the optimization of some procedures.

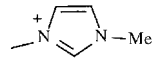
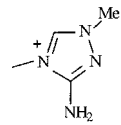
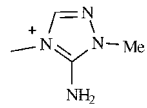
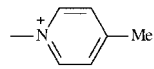
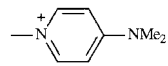
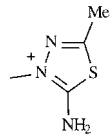
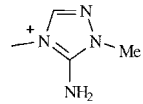
B. Nucleophilic Monosubstitution

1. *Reactions with Uncharged Nucleophiles*

In trichloromethane or acetonitrile, compounds **33** (isolated) react with the uncharged nucleophiles such as triphenylphosphine (87BSB719; 89JOC4808); 1-methylimidazole (87BSB719; 89JOC4808); 3-amino-1-methyl-1*H*-1,2,4-triazole or the isomeric 5-amino-1-methyl-1*H*-1,2,4-triazole (97LA745); 4-methylpyridine; 4-dimethylaminopyridine (DMAP); and 2-amino-5-methyl-1,3,4-thiadiazole (98EJOC2923, 99JOC3113) to afford the salts **45a**–**45h** (Table VI) thus indicating the increased tendency of the halogen atom to be displaced in the presence of a nucleophile. This also applies to the substituted pyridinium derivatives **7g**–**7i,** which reacted with 1-

TABLE VI

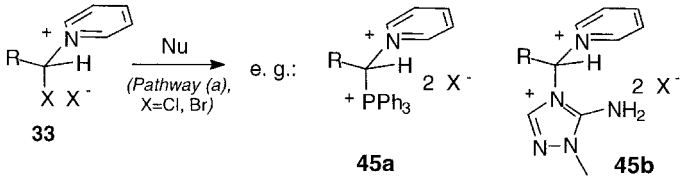
SOME BISONIUM SALTS **45** PREPARED FROM COMPOUNDS **33** AND NUCLEOPHILES (NU)

Compound	Nu^+	Yield (%)	Reference
45a R=Ph, 4-MeC_6H_4		91–95	87BSB719 89JOC4808
45b (R=4-MeC_6H_4,)		93	89JOC4808
45c (R=4-MeC_6H_4, 4-BrC_6H_4)		36–52	97LA745
45d (R=H, alkyl, aryl)		71–86	97LA745
45e (R=H)		77	99JOC3113
45f (R=H)		90	99JOC3113
45g (R=H)		65	99JOC3113
45h (R=H)		92	99JOC3113

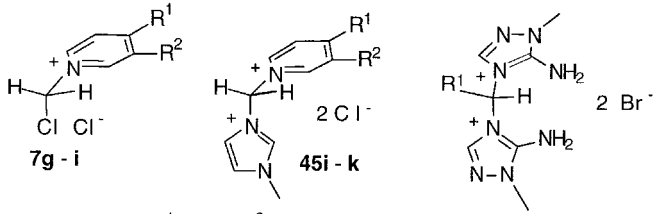
methylimidazole to give the mixed bisonium compounds **45i–45k** (84–93% yields, Scheme 16, 99JOC3113). Only the bromine salt **33f** (Table I) could be transformed to a symmetric bis-triazolium derivative **49** (64%) by using a double molar amount of the respective aminotriazole (98EJOC2923). In notable agreement with *ab initio* and semiempirical calculations (97LA745), the amino function of the triazoles is not involved in the reactions with the salts.

2. *Reactions with Anions*

Not many reactions between *N*-(1-haloalkyl)heteroarylium halides and anionic nucleophiles are reported in the literature. In trichloromethane or

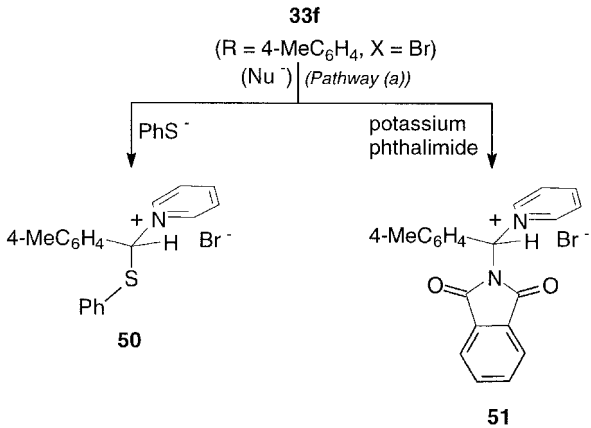


*For R, Nu, and further examples for **45**: Cf. Table VI*



SCHEME 16

acetonitrile, the bromine atom in **33f** (isolated) can be readily displaced either by thiophenolate to give **50** (85%) or by potassium phthalimide (formation of **51,** 86%) (87BSB719; 89JOC4808). Further substitution of the pyridinium moiety is prevented because the negative hyperconjugation

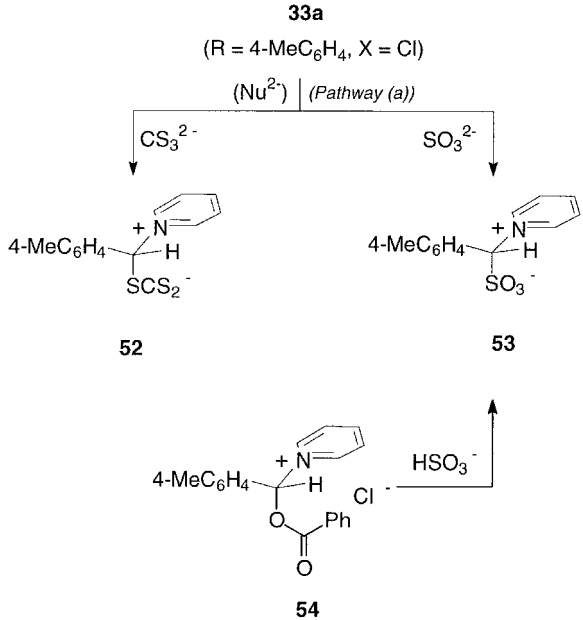


SCHEME 17

n_N/σ^*_{CN+} in **51** is less important (87CB735). The nitrogen lone pair obviously prefers delocalization into the carbonyl groups of the phthalimide residue (Scheme 17).

3. *Reactions with Dianions*

The chloro derivative **33a** yields 37% of the corresponding betaine **52** when treated with an aqueous solution of a trithiocarbonate salt (87BSB719; 89JOC4808). Several analogous *N*-(1-sulfonatoalkyl)pyridinium betaines such as **53** have been obtained (25–45%) in the presence of sulfite dianion (87BSB719; 89JOC4808; 97BSB383). The structure of **53** has been confirmed by X-ray analysis and by an alternate synthesis starting from hydrogen sulfite and *N*[1-acyl-oxy)alkyl]pyridinium chlorides **54** (75%) (97BSB383). Interestingly enough (Section IV,C,6), compound **53** can be isolated from a reaction mixture of **33a** (prepared *in situ*) and an α-amino acid (97BSB383). In such cases **53** is the major reaction product (Scheme 18).

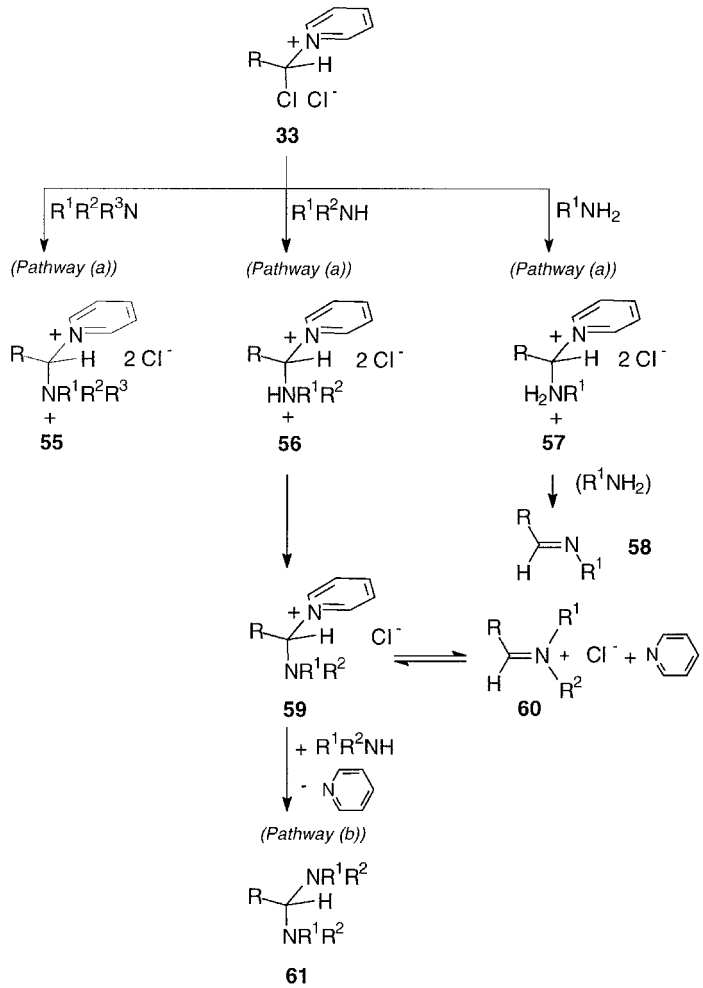


SCHEME 18

C. Nucleophilic Disubstitution

1. *Mechanistic Considerations*

It has been proposed (89JOC4808) that the first step of a reaction between an amine and an *N*-(1-chloroalkyl)pyridinium chloride **33** is a simple substitution of the halogen atom yielding a mixed bisonium salt **55** (pathway a in Scheme 19). This is the final product when various nitrogen het-



Scheme 19

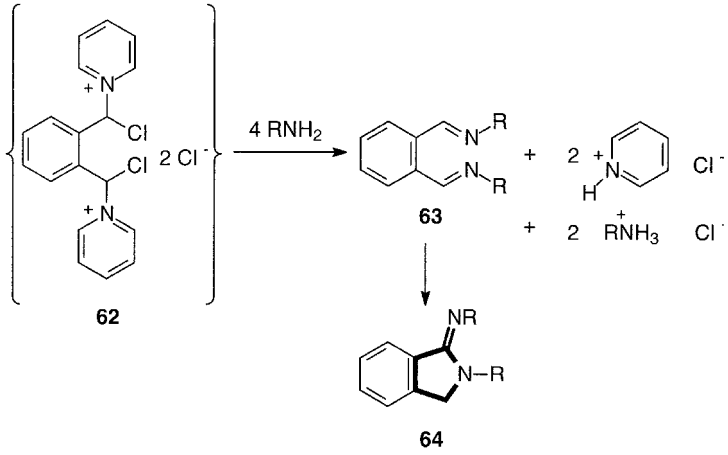
erocycles are employed at room temperature (Section IV,B,1). In the case of secondary amines, the bisonium salt **56** is readily deprotonated by an excess of amine, giving the corresponding *N*-(1-aminoalkyl)pyridinium halide **59.** However, there can be an equilibrium between **59** and the imminium salt **60** (87CB735). Use of a primary amine in the synthesis, as in the case of **57,** promotes further deprotonation and the pyridinium moiety departs, leaving an imine **58** behind. When a secondary amine is employed (**59**), a second substitution could take place to afford 1,1-diamines **61** (pathway b). This is due to the presence of significant n_N/σ^*_{CN+} negative hyperconjugation. The pathways suggested here can be reasonably extrapolated to include other kinds of nucleophiles.

2. *Reactions with Primary Amines*

The reactions of (previously isolated) *N*-(chlorophenylmethyl)pyridinium chloride with primary amines (cyclohexylamine, aniline) (44–66% yields) was studied in one of the earliest papers dedicated to the study of *N*-(1-haloalkyl)heteroarylium halides (89JOC4808). Shortly afterward, it was reported that a one-pot procedure also gives satisfactory yields, and the first use of the corresponding pyrimidinium salt was described (89BSB523). Whereas the preparation of a pyrimidinium salt takes a longer time, it is more sensitive to nucleophiles than the pyridinium analog. This has been illustrated by a comparison of the rates of formation of imines derived from the poor nucleophiles 3-nitroaniline and ethyl 4-aminobenzoate (80–85% yields). This study also showed that *N*-(1-haloalkyl)azinium halides represent an activated form of the starting aldehydes as the former react faster, at least under the conditions described. One disadvantage of an azinium halide is the necessity to work with an excess of amine in order to trap the hydrochloric acid evolved during the reaction. This can be circumvented, however, by using only one equivalent of amine and introducing an aqueous solution of sodium acetate in the reaction medium.

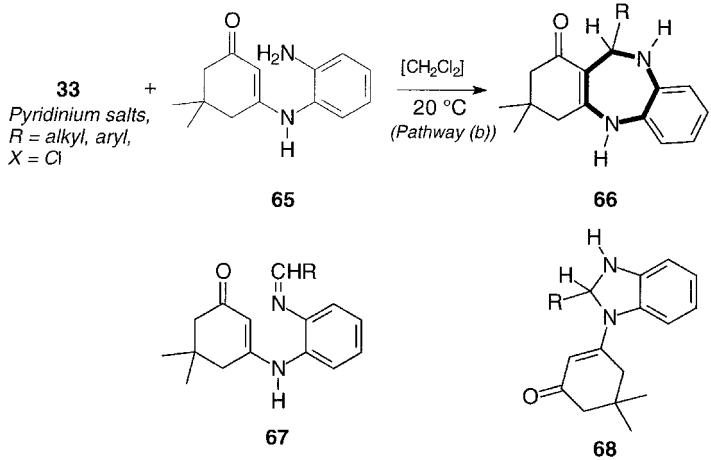
An interesting extrapolation of this synthesis deals with the preparation of the bispyridinium salt **62** from 1,2-phthalic dicarboxaldehyde and its subsequent reaction with primary amines (92BSB509). The expected diimines **63** readily cyclize so that 2-aryl-1-arylimino-2,3-dihydro-1*H*-isoindoles **64** can be isolated in excellent yields (90–95%). Contrary to the reactions performed by employing the dialdehyde and amines directly, the syntheses involving the azinium salts do not produce those typical dark-colored complex mixtures of products (77JOC4217; 85JHC449) (Scheme 20).

A seven-membered fused ring system **66** (85–95%) has been built by variation of the amine component. This example deals with the reaction of **33** with 3-(2-aminophenyl)amino-5,5-dimethylcyclohex-2-enone (**65**)



SCHEME 20

(92BSB801). Formation of the isomeric imines **67** could be readily ruled out on the basis of the spectral data of the final products. The formation of the isomeric dihydrobenzimidazoles **68** is disfavored because the lone electron pair on the nitrogen in the secondary amine function is interacting with the carbonyl and aryl groups and is therefore highly delocalized. The authors assume that the reaction is initiated by nucleophilic attack of the NH_2-group, thus replacing the Cl atom in **33** through substitution. Interestingly enough, the acyl–enamine moiety in **65** functions as a C-nucleophile in the



SCHEME 21

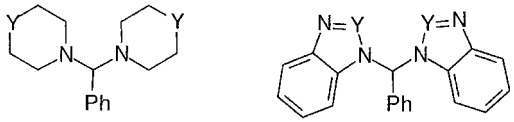
course of the reaction, which finally allows the formation of the seven-membered ring system (Scheme 21).

3. *Reactions with Secondary Amines*

Synthesis of 1,1-diamines from *N*-(1-haloalkyl)pyridinium halides have been performed in one-step reactions (89JOC4808). Bis(morpholino)- and bis(piperidino)-phenylmethanes **69** and **70** have been prepared in this way in moderate yields (40–52%). Reaction of the pyridinium halides with the sodium salt of benzimidazole or benzotriazole provides a new method for the accessibility of *N*,*N*′-(1-alkylidene)bisbenzazoles **71** under mild conditions (37–70% yields). Up to now, very few *N*,*N*′-(1-alkylidene)bisbenzazoles have been successfully synthesized by reaction of the heterocycles with an aldehyde in the presence of either zinc chloride as a catalyst (82JHC1141; 83JHC1245, 83H1787; 84OPP299) or excess thionyl chloride [87JCS(P1)811]. As an alternative, activation of a carbonyl reagent by the preparation of an acetal (83T4133) or a ketal (70JA5118) has been reported, but the procedure has not been widely applied (Scheme 22).

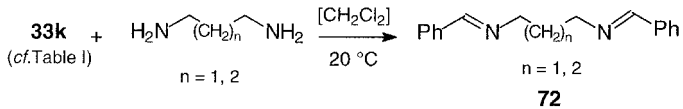
4. *Reactions with Primary Diamines*

There are few examples for the preparation of imines from *N*-(1-haloalkyl)azinium halides and primary diamines. Among those reactions reported, *N*-(chlorophenylmethyl)pyridinium chloride (**33k**), which has not been isolated, reacts with ethane-1,2-diamine and propane-1,3-diamine to afford the corresponding diimines **72** (Scheme 22, 45–80%) (89JOC4808, 92BSB233).



69: Y = O
70: Y = CH_2

71: Y = N or CH

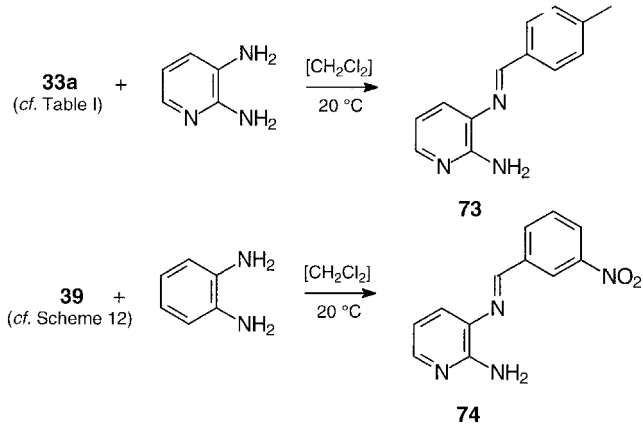


72

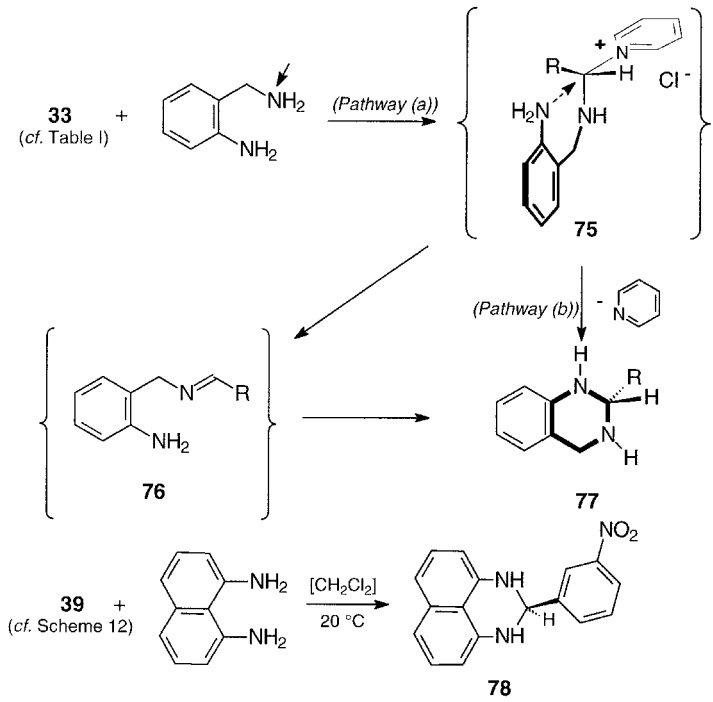
SCHEME 22

The chloro derivative **33a** (not isolated) interacts with pyridine-2,3-diamine in dichloromethane at room temperature to yield **73** (85%) (93BSB357). A further example deals with the reaction between the salt **39** and benzene-1,2-diamine, which gives an imine **74** (80%) under special experimental conditions (93BSB357). In order for the reaction to work, the salt **39** must be isolated prior to its employment (Section IV,C,8). No traces of the diimines were detected for both cases. However, the experimental conditions were not optimized for this purpose since no more than three equivalents of the diamines were used (Scheme 23).

The situation is quite different when one starts with 2-aminobenzylamine. 1,2,3,4-Tetrahydroquinazolines **77** are isolated in this case (93S867). This can readily be rationalized by assuming that again the first step of the reaction is the formation of an *N*-(1-aminoalkyl)pyridinium chloride **75,** which results from the attack of the most nucleophilic aliphatic amino group. Two pathways can then be considered to explain the formation of the bicyclic derivatives. The first pathway involves an intramolecular attack of the primary amino group at the electrophilic carbon atom with substitution of the pyridinium moiety. In the second pathway, a transient imine **76** is formed which readily cyclizes into the more stable six-membered fused system **77.** No experimental evidence has yet been put forward in order to favor one or the other possibility. Nevertheless, the negative hyperconjugation in structure **75** must be significant. The preference of pathway b seems therefore to be a reasonable assumption. It is noteworthy that 300-MHz NMR spectra of the tetrahydroquinazolines **77** in trichloro-



SCHEME 23



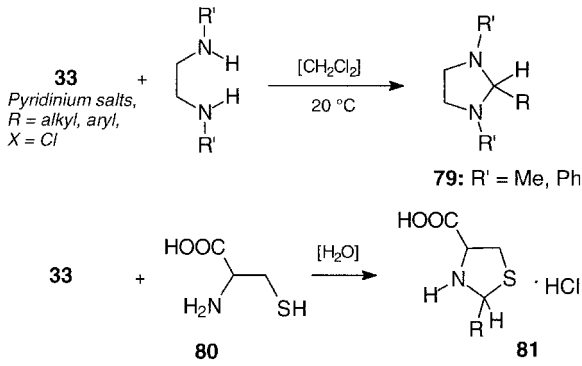
SCHEME 24

methane as well as in DMSO show the coexistence of both the ring and the chain tautomers.

Similarly, the isolated salt **39** reacts with naphthalene-1,8-diamine in dichloromethane at room temperature to afford the 2,3-dihydro-1*H*-perimidine **78** in 85% yield (92SC3141) (Scheme 24).

5. *Reactions with Secondary Diamines*

There is only one report concerning the reaction of *N*-(1-chloroalkyl)-pyridinium chlorides with secondary diamines (92BSB233). 2-Substituted 1,3-dimethyl- and 1,3-diphenyl-imidazolidines **79** have been prepared (75–95% yields) starting from either *N*,*N*′-dimethyl- or *N*,*N*′-diphenylethane-1,2-diamines, respectively (Scheme 25). Reactions are particularly fast for the preparation of the 1,3-dimethylimidazolidines. Reaction times as short as 5 min have been claimed.



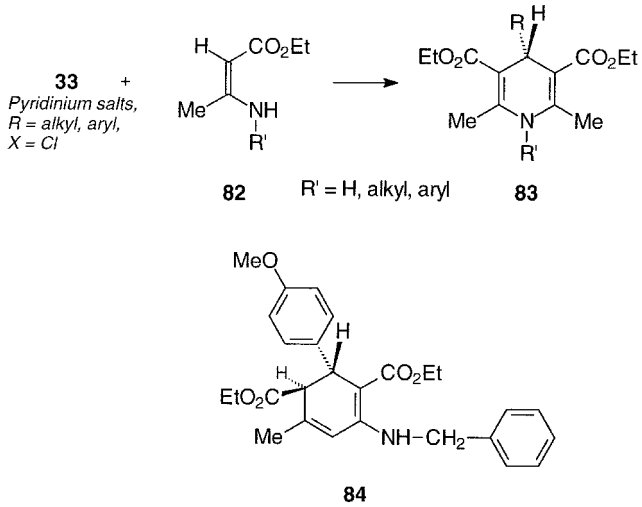
SCHEME 25

6. *Reactions with Amino Acids*

Reactions between *N*-(1-chloroalkyl)pyridinium chlorides **33** and amino acids in organic solvents have a low synthetic value because of the low solubility of the amine partner. A special protocol has been designed and tested in order to circumvent this drawback. Soon after the preparation of the salt, an aqueous solution of the amino acid was introduced in the reaction medium and the two-phase system obtained was heated under reflux for several hours. However, this was not too successful because sulfur dioxide, evolved during the preparation of the salt, was converted into sulfite that acted as an *S*-nucleophile. As a result, *N*-(1-sulfonatoalkyl)pyridinium betaines such as **53** were obtained (Section IV,B,3) (97BSB383). To avoid the formation of such betaines, the salts **33** were isolated and reacted with an aqueous solution of L-cysteine (**80**) to afford thiazolidine-4-carboxylic acids hydrochlorides **81** (60–80% yields).

7. *Multicomponent Ring Syntheses*

N-(1-Haloalkyl)pyridinium halides have been advantageously employed in the Hantzsch multicomponent synthesis, yielding alkyl 1,4-dihydropyridine-3,5-dicarboxylates, which are a well-known class of calcium channel modulators (81AGE762). The halides readily interact with an excess of an ethyl 3-aminobut-2-enoate **82** (R′ = H) in dichloromethane at room temperature to afford the heterocycles **83** (R′ = H) in good to excellent yields (65–95%) (92T1263). This observation has been exploited to perform a quantitative study of the reactivity of the salts (93CB1251). The results have



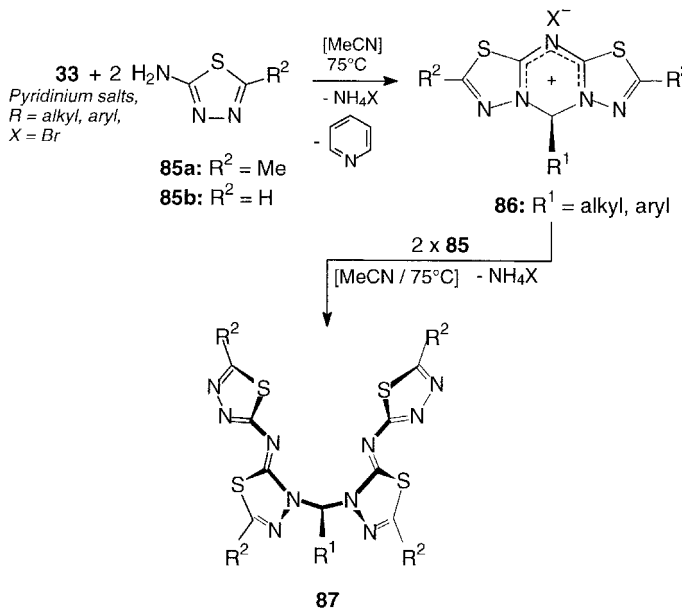
SCHEME 26

clearly established that the reactions involving *N*-(1-chloroalkyl)azinium halides derived from aromatic aldehydes are faster than those involving salts derived from aliphatic aldehydes. It has been also observed that *N*-(chlorophenylmethyl)pyridinium chloride is less reactive than the salts obtained from substituted benzaldehydes independent of the nature of the substituent (electron-withdrawing or electron-donating) present. This parallels the reactivity of benzyl chlorides toward the thiosulfate anion in an S_N2 process (63JA104; 76MI1).

An important extension of this work deals with the preparation of N-substituted 1,4-dihydropyridine-3,5-dicarboxylates. Thirty examples have been described (92SC3291). In most cases the reported yields (10–95%) are higher than those mentioned in the literature. The most significant results concern the synthesis of 1-aryl derivatives, which are hardly accessible by classic methods. One should mention that the aminocyclohexadiene **84** has been isolated as a by-product when starting from ethyl *N*-benzylaminobut-3-enoate (Scheme 26).

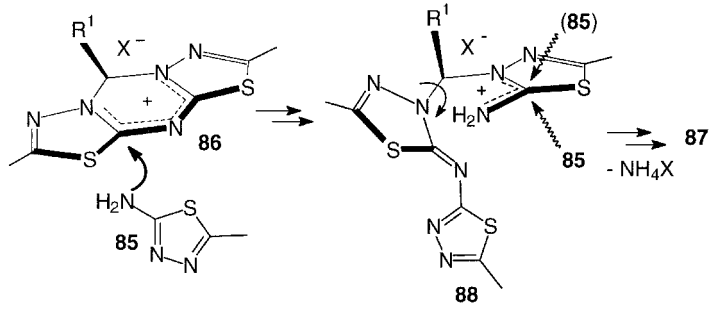
8. *Multistep Cascade Reactions: Synthesis of Bis-1,3,4-thiadiazolo-1,3,5-triazinium Halides*

Some pyridinium halides **33** have been used as a starting material for the synthesis of a novel 5/6/5 heterocyclic system (98EJOC2923). A multistep



SCHEME 27

cascade reaction takes place if a double molar amount of 2-amino-1,3,4-thiadiazoles **85** was reacted with the salts **33** in MeCN at 80°C. The tricyclic 5/6/5-compounds **86,** which contain a central dihydro-1,3,5-triazinium moiety, are formed under extrusion of pyridine and ammonium halide in 55–79% yields (Scheme 27). The selective attack at the N3 atom of thiadiazole parallels both the increasing charge (NPA) at nitrogen in **85** and the decreasing activation barrier for the alkylation of these nitrogen centers. The structures of **86** (R^1 = substituted aryl and alkyl) have been verified by spectral data (^{1}H and ^{13}C NMR, ICMS), X-ray analysis, and *ab initio* calculations. The central structural element prefers a quasi-half-chair conformation. It is worth mentioning that compound **87** is a by-product (12%) of the cyclization reaction to **86.** The authors give a relevant mechanistic explanation for both the formation of **86** and the novel bis-azolyl methanes **87.** Their results reveal an interesting dichotomy of the behavior of the ambident aminothiadiazoles **85.** They function as cyclic (N) nucleophiles in the course of the cyclization reaction which yields **86,** whereas the presence of the amino group determines the formation of **87** (Scheme 28). The authors gave reasonable explanations for both pathways based on *ab initio* and PM3-MO calculations (98EJOC2923).

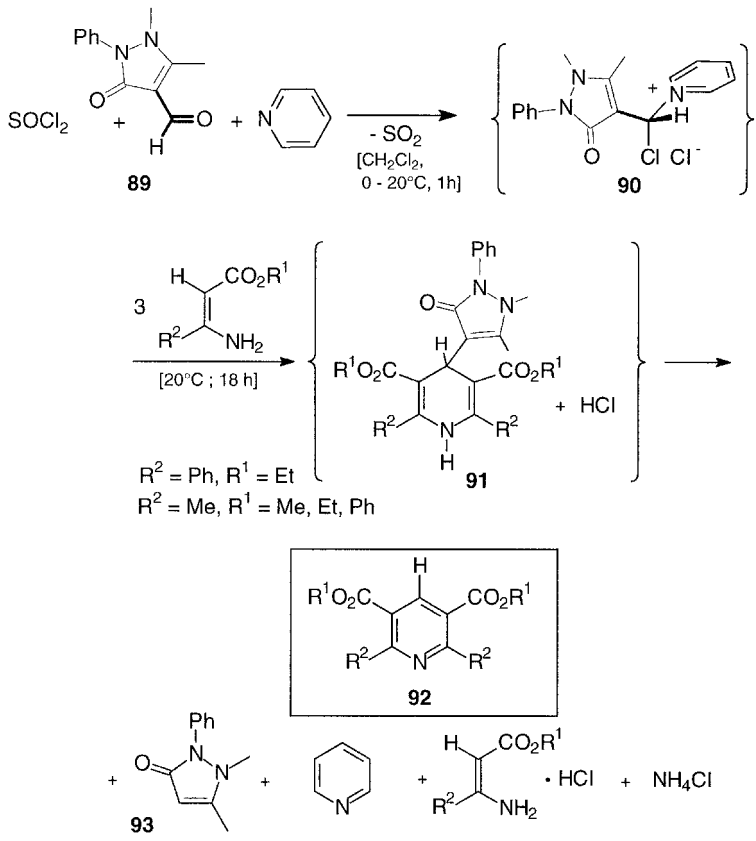


SCHEME 28

9. *Oxidative Ring Syntheses*

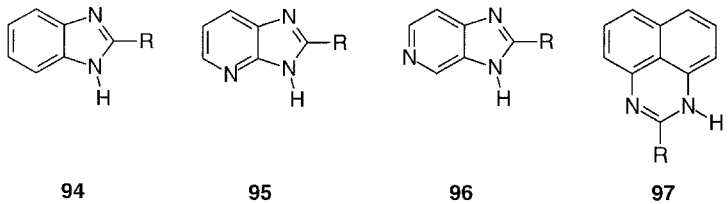
An interesting result has been observed when 4-formylantipyrine **89** was converted into the corresponding pyridinium salt **90** and reacted with alkyl 3-aminobut-2-enoates. The expected 1,4-dihydropyridines **91** are transient species in these syntheses and readily lose the 4-substituent (antipyrine, **93**) so that dialkyl 2,6-dimethylpyridine-3,5-dicarboxylates **92** are obtained (85–95%) (94H815). Protonation of the pyrazole ring by the evolved hydrochloric acid accounts for this particular behavior (Scheme 29).

As mentioned above (Section IV,A), the same final products are obtained in most cases whether or not a salt is isolated prior to the reaction with a nucleophile. However, unexpected results have been obtained in the reactions employing benzene-1,2-diamines, pyridine-2,3- and 3,4-diamines, or naphthalene-1,8-diamine. When the salt is isolated previously, the syntheses yield imines or ring tautomers as in the case of the naphthalene-1,8-diamine (Section IV,C,4). When the salts are not isolated, a further reaction occurs that results in the corresponding oxidized derivatives. Thus, benzimidazoles **94** (93BSB357), imidazo[4,5-*b*]- and -[4,5-*c*]pyridines **95** and **96** (93BSB357), or 1*H*-perimidines **97** (92SC3141) have been directly prepared (70–95%) without the introduction of an external oxidant in the reaction media. The detailed course of these syntheses remains unclear. However, it has been shown that sulfur dioxide plays an essential role at the oxidation step, as the latter does not occur when the salts are previously purified. In addition, the yields of oxidized products dramatically decreased when the whole procedure was performed under a flow of dry nitrogen. Since oxidation by atmospheric oxygen seems unlikely (most imines considered are not air-sensitive), the following has been suggested: sulfur dioxide could form highly hygroscopic addition complexes (44JCS243) with the diamines



SCHEME 29

so that the appreciable amounts of hydrogen sulfite, an oxidative species (65JHC453; 80KGS96; 82MI1; 88FA215; 91SC2171), could be present in the reaction media. The procedure provides an elegant and unexpected method for the preparation of fused systems of commercial importance such as pharmaceuticals, veterinary anthelmintics, and fungicides (74CRV279; 93MI1) (Scheme 30).



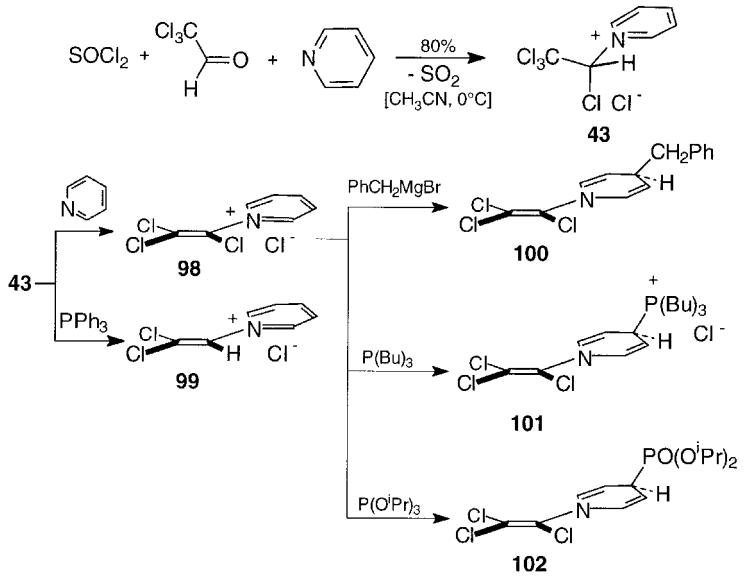
SCHEME 30

D. Elimination Reactions

The Cα substituent effects have been experimentally studied by synthesizing and investigating the *N*-(1,2,2,2-tetrachloroethyl)pyridinium chloride (**43**). The synthesis of **43** follows the standard three-component reaction. Thionyl chloride, trichloroacetaldehyde, and pyridine were reacted at 0°C in MeCN to give this salt in excellent yield (Scheme 31).

As might be expected, the CCl_3 group causes significant downfield shift both in the ^1H and ^{13}C NMR spectra, thus predicting interesting electronic properties for the central αC(H)Cl group.

Compound **43** was then reacted with one equivalent of the ambident nucleophile 5-aminotriazole at room temperature. Interestingly enough, neither substitution pathways a nor b were observed. This salt prefers an alternative route. The triazole derivative functions as a base and, after the elimination of HCl, the *N*-(trichloroethenyl)pyridinium chloride (**98**) was isolated. The synthesis was improved by using pyridine as a base and EtOH as the solvent. Again, the Cl substitution (pathway a) was not observed. Triphenylphosphine (which in case of the reaction of **33a** with R = 4-MeC_6H_4 substitutes the Cl atom to give **45a,** see Scheme 16), initiated an effective dehalogenation with the formation of the *N*-(2,2-dichloroethenyl)-pyridinium chloride (**99**). Both of these novel chloroethenyl-pyridinium compounds **98** and **99** were analyzed by spectroscopic methods (^1H, ^{13}C NMR, IR, MS). The structure of **99** has been further confirmed by X-ray analysis (99JOC3113).



SCHEME 31

Salts **98** and **99** deserve further interest. For example, the reaction of **98** with tri-*n*-butylphosphine allows access to the C4 addition product, i. e., the phosphonium salt **101** (91%). The isomeric C2-product is not observed. The X-ray structure of **101** reveals a remarkably short C(vinyl)-N^+-bond length [139.3(5) pm]. It is noteworthy that nucleophilic reactions at the C atoms of the pyridinium moiety cannot be performed with "normal" N-substituted pyridiniums or the title compounds. Activation of the C4 position requires, in general, very strong electron-withdrawing N-substituents, for example, the CF_3SO_2 group (87TL2675; 89CB113). The trichlorovinyl group fulfills this condition and allows further related reactions, e.g., with Grignard reagents and trialkylphosphites to give the *N*-(trichlorovinyl)-4-benzyl- or 4-phoshonato-1,4-dihydropyridines **100** (74% yield) and **102** (80%), respectively (Scheme 31).

E. Practical Considerations

Practical experience enables us to emphasize the simplicity and the efficiency of the activation of aldehydes by their conversion into *N*-(1-haloalkyl)heteroarylium halides upon treatment with an azine and a thionyl halide. Preparation of these salts requires a minimum of precautions, and a wide variety of solvents can be used. Special glassware and/or the use of an inert gas is not necessary. The salts can be reacted under numerous experimental conditions and, in most cases, it is unnecessary to isolate them. The flexibility of the method represents an interesting feature for the study of the reactivity of *N*-(1-haloalkyl)heteroarylium halides and deserves further investigations in this field. Many elegant compromises can be found in a judicious choice of the precursors and of the experimental conditions, and it is possible to design readily a salt suitable for each individual purpose.

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Chemistry of Dithiiranes, 1,2-Dithietanes, and 1,2-Dithietes

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I. Introduction

The present chapter reviews the chemistry of three- and four-membered ring compounds containing an S–S bond in their ring. Dithiiranes; 1,2-dithietanes; and 1,2-dithietes are the compounds of this type. Although 1,3-dithietanes are four-membered heterocycles which are prepared much more easily and are seemingly more familiar, they have no S–S bond in the ring and hence are not included in this chapter.

The chemistry of dithiiranes and 1,2-dithietanes only recently became of interest in organic chemistry. The first isolable dithiirane and 1,2-dithietane were synthesized in 1993 (93JA4914; 94AGE777) and 1987 (87JA3801), re-

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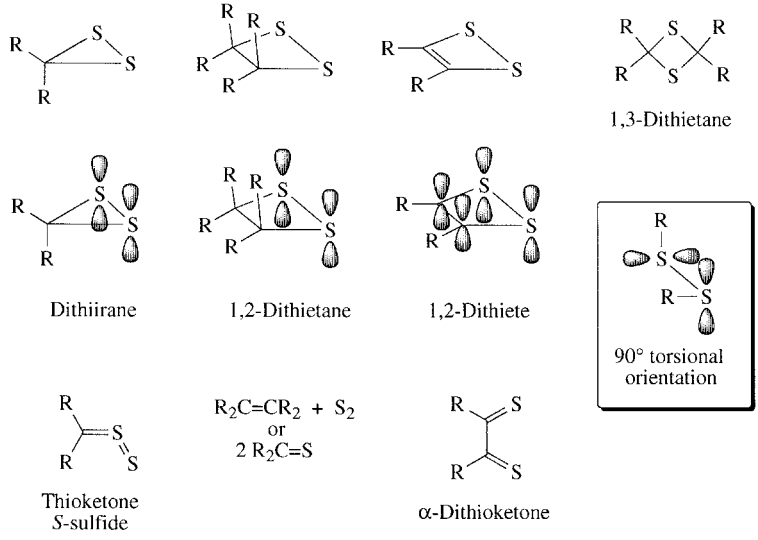
spectively, though they had been often proposed as reactive intermediates prior to these reports; a dithietane 1,1-dioxide derivative was prepared in 1980 (80JA2490). By comparison, the first successful synthesis of an isolable 1,2-dithiete dates back to 1960 (60JA1515).

As is well documented, the S–S bond preferentially adopts a 90° torsional orientation to minimize the S–S lone pair energy interactions. Any deviation from 90° can exert a profound weakening effect on the S–S bond. When an S–S bond is a part of a three- or four-membered ring, it is inevitably forced to adopt a cisoid geometry where repulsive interactions of the lone pair electrons reach a maximum. This, along with the angle strain, renders the S–S bond much weaker and makes the synthesis very difficult. Incidentally, if we consider the two π-electrons of the double bond and four lone pair electrons of the sulfur atoms, the 1,2-dithietes possess a formal six π-electronic structure. Dithiiranes and 1,2-dithietes may isomerize to the corresponding thioketone *S*-sulfides and α-dithioketones, respectively. Correspondingly, decomposition of 1,2-dithietanes is expected to take place in a two-bond scission to give either alkenes + S_2 or two molecules of thioketones. The considerations described previously explain the very reason that makes the synthetic, reactivity, structural, and theoretical chemistry of these heterocycles highly attractive and challenging.

The chemistry of dithiiranes and related species (86T739, 86SUL213; 90SUL83; 94MI1, 94MI2; 96MI1; 97YGK897; 98SR1; 99RHA1); 1,2-dithietanes (94MI1; 96MI2); and 1,2-dithietes (95SR371; 96MI2) has been reviewed previously.

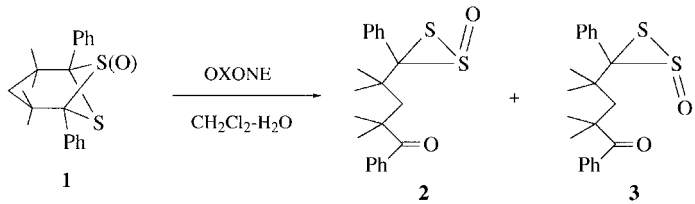


II. Dithiiranes

A. Synthesis of Isolable Dithiiranes

1. *From Bridged 1,3-Dithietanes*

The reaction of the 6,7-dithiabicyclo[3.1.1]heptane *exo*- and *endo*-6-oxides **1** with $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (OXONE) in CH_2Cl_2-H_2O gave the first isolable dithiirane 1-oxides **2** and **3** (93JA4914). The two isomeric dithiirane 1-oxides are colorless, crystalline compounds and stable up to 124° and 110°C, respectively. X-Ray crystallography confirmed their structure unambiguously.



1 **2** **3**

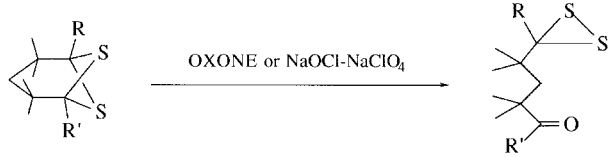
OXONE = $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$

After that, the unoxidized dithiirane **4a** was synthesized from 6,7-dithiabicyclo[3.1.1]heptane **5a** by treatment with OXONE (94AGE777) or with NaOCl in the presence of $NaClO_4$ (95SUL237) (Table I, Entries 1 and 2). The structure of the dithiirane **4a** was determined by X-ray crystallography (Fig. 1). The above synthesis can be regarded as an oxidative hydrolysis of dithioacetals. The same reaction converted 6,7-dithiabicyclo[3.1.1]heptanes **5b**–**5d** to alkylaryldithiiranes **4b** and **4c** (Table I, Entries 3 and 4) (95SUL237) and a dialkyldithiirane **5d** (Entry 5) (97TL1431). The selective formation of the alkylaryldithiirane **4e** from the unsymmetrically substituted 1,3-dithietane **5e** is noteworthy (Entry 6) (97YGK897).

The benzo-fused 1,3-dithietane **6,** from which the formation of two dithiiranes (**7** and **8**) is possible depending on the course of the reaction, only gave the alkylaryldithiirane **7** in 59% yield by treatment with NaOCl-$NaClO_4$ (97BCJ509). This is suggestive of the intermediate formation of the more stable, diaryl-substituted carbocation **9** and not the other counterpart **10.**

TABLE I

SYNTHESIS OF DITHIIRANES **4** FROM 6,7-DITHIABICYCLO[3.1.1]HEPTANES **5**



5a: R = R' = Ph
b: R = R' = 4-$CH_3C_6H_4$
c: R = R' = 4-$CH_3OC_6H_4$
d: R = R' = *t*-Bu
e: R = Ph, R' = *t*-Bu

4 a R = R' = Ph
b: R = R' = 4-$CH_3C_6H_4$
c: R = R' = 4-$CH_3OC_6H_4$
d: R = R' = *t*-Bu
e: R = Ph, R' = *t*-Bu

Entry	R	R′	Conditions[a]	Yield/%	Reference
1	Ph	Ph	A	26	93JA4914
2	Ph	Ph	B	48	95SUL237
3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	B	39	95SUL237
4	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	B	37	95SUL237
5	*t*-Bu	*t*-Bu	A	16	97TL1431
6	Ph	*t*-Bu	B	49	97YGK897

[a]A: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, CH_2Cl_2, H_2O; B: NaOCl, $NaClO_4$, CH_2Cl_2, H_2O.

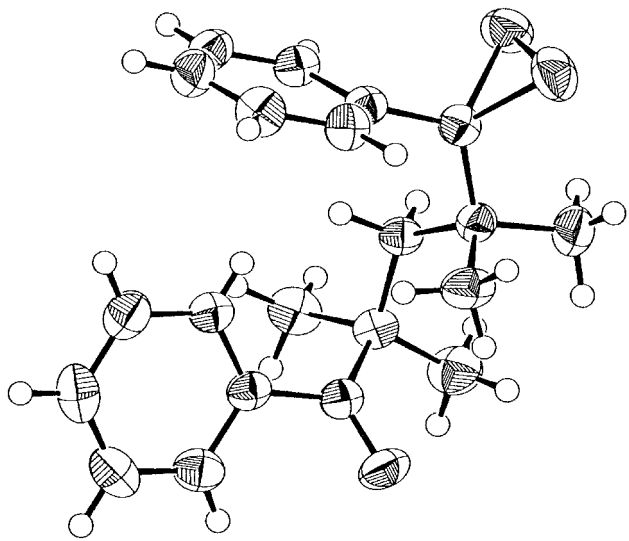
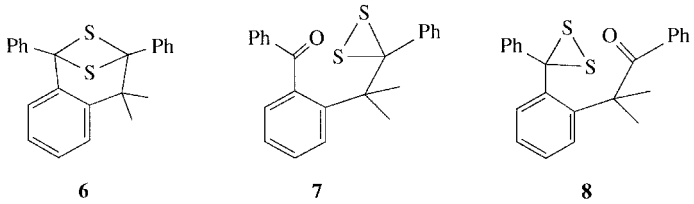
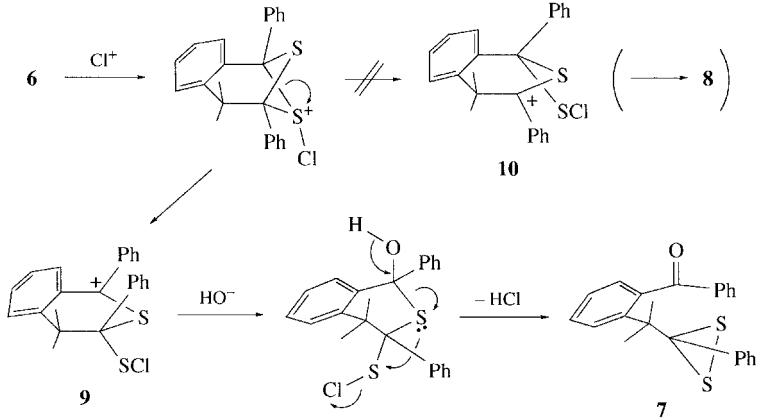


FIG. 1. ORTEP drawing of dithiirane **4a.**

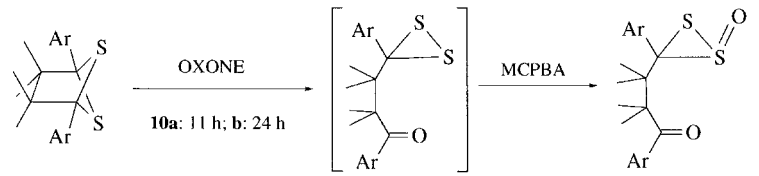


6 **7** **8**



9 **10**

The reaction of 5,6-dithiabicyclo[2.1.1]hexane **11a** with OXONE led to the corresponding dithiirane **12a,** which was, however, stable only in solution (λ_{max} at 442 nm in CH_2Cl_2). Treatment of the reaction mixture containing **12a** with MCPBA gave the dithiirane 1-oxide **13a** (8%) (95TL1867). The introduction of electron-withdrawing substituents on the benzene rings provided the dithiirane oxide **13b** in a better yield (21%).



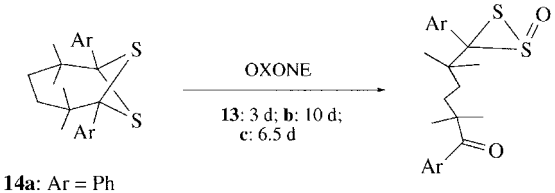
11a: Ar = Ph
b: Ar = *p*-$CF_3C_6H_4$

10a: 11 h; **b**: 24 h

12a: λ_{max} = 442 nm
b: λ_{max} = 438 nm

13a: 8%
b: 21%

The reaction of 1,3-dithietanes **14** with OXONE produced dithiirane 1-oxides **15** directly (95TL1867). Dithiirane 1-oxides **15** would be formed through the initially formed 1,3-dithietane oxides.

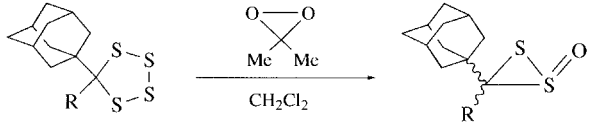


14a: Ar = Ph
b: Ar = *p*-$CF_3C_6H_4$
c: Ar = *m*-FC_6H_4

15a: 9.5%
b: 18%
c: 9%

2. *From Tetrathiolanes*

All the isolable dithiiranes described previously contain a carbonyl group in their structures. The oxidation of tetrathiolanes **16** enabled the preparation of dithiirane oxides **17** that possess no other functional groups (98TL3525).

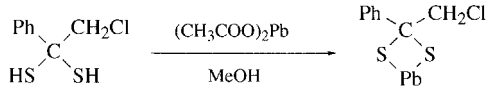


16a: R = 1-adamantyl
b: R = *t*-Bu

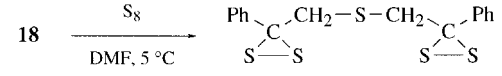
17a: R = 1-adamantyl
b: R = *t*-Bu (two isomers)

3. *Miscellaneous*

The reaction of the lead dithiolate **18** with elemental sulfur was claimed, without unambiguous structure proof, to give a dithiirane **19** in 75% yield (96ZOR1881).



18

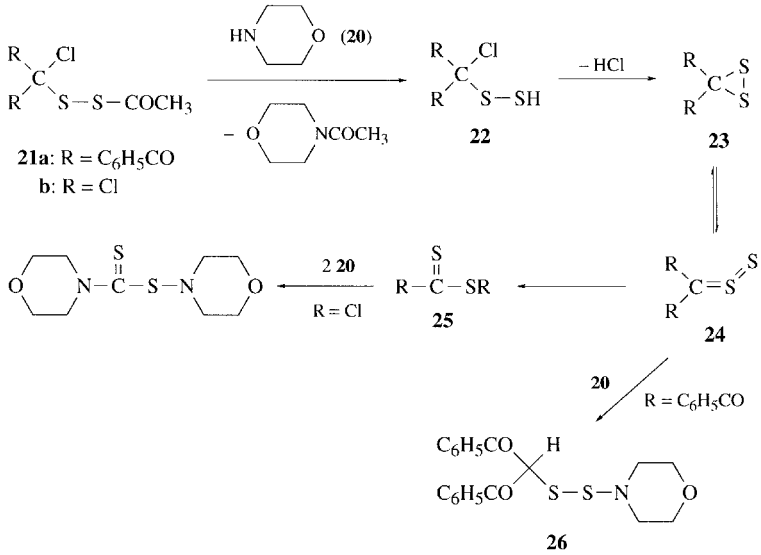


19

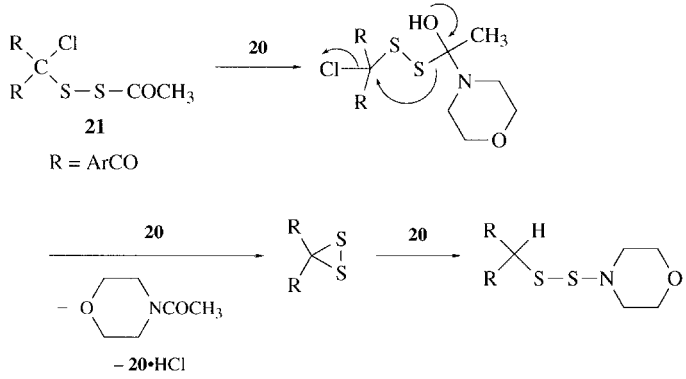
B. Dithiiranes as Intermediates

1. *Dithiirane/Thioketone S-Sulfide Manifold*

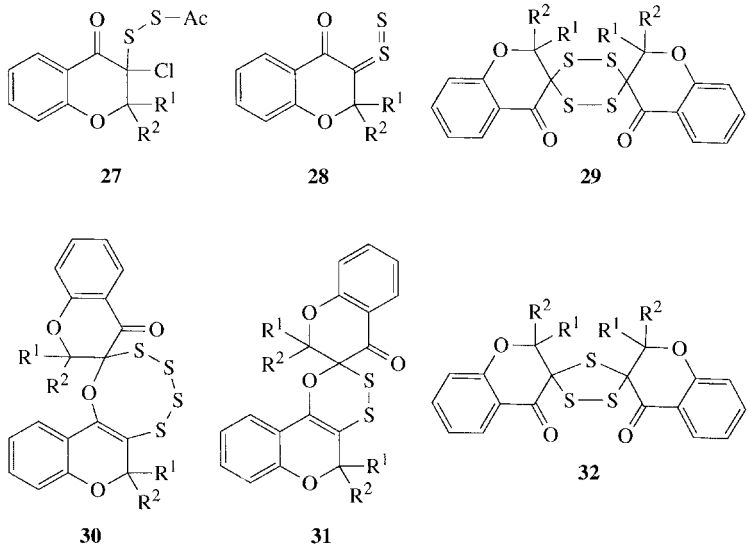
The reaction of acetyl α-chloromethyl disulfides with morpholine (**20**) was investigated with expectation of the formation of dithiiranes and/or thioketone *S*-sulfides (79AGE941; 86T739; 96M909; 98JOC9840). The reaction of acetyl chloromethyl disulfides **21** was proposed to proceed through α-chloroalkyldisulfanes **22** that generate dithiiranes **23** with 1,3-elimination of HCl. Dithiiranes **23** might be in equilibrium with thioketone *S*-sulfides **24** and **23/24** rearrange into the dithioesters **25** (79AGE941; 86T739). In the case of the dibenzoyl derivative **21a,** the thioketone *S*-sulfide **24** was trapped with **20** to give disulfide **26.** Attempted trapping of **23/24** with alkynes or even with strained alkenes, however, failed.

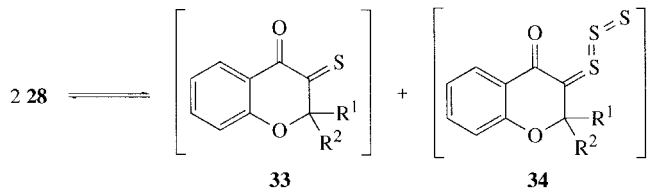


A mechanism, involving dithiiranes as intermediates, was also proposed for similar reactions of **21** with **20** (96M909).



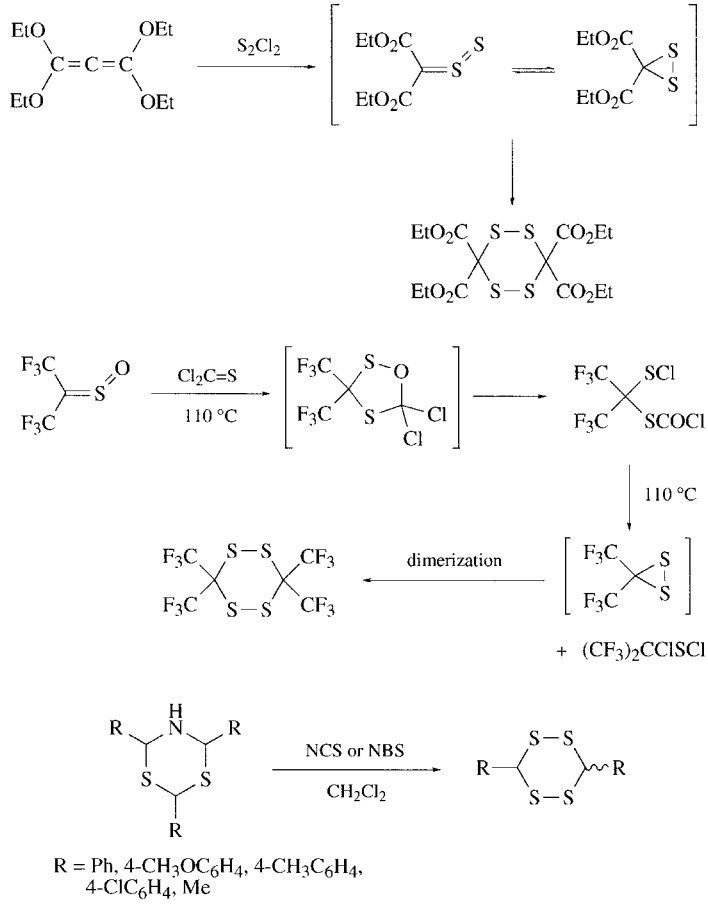
The behavior of β-monooxo derivatives of 4-chlomanones (**27**) toward morpholine was rather complex (98JOC9840). Thus, the proposed thioketone *S*-sulfide intermediates **28** would dimerize into either 1,2,4,5-tetrathianes **29** in a two-step manner or to 1,3,4,5,6-oxatetrathiocins **30** by a [5 + 3] cycloaddition. Meanwhile, the formation of oxadithiins **31** and 1,2,4-trithiolanes **32** is suggestive of the disproportionation of **28** into the thioketones **33** and the thioketone *S*-disulfides **34.** The oxadithiins **31** correspond to a Diels–Alder dimer of **33,** and the 1,2,4-trithiolanes **32** correspond to cycloadducts of **33** and **34.**





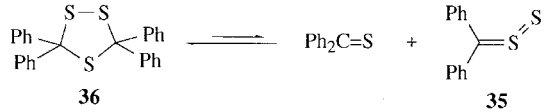
33 **34**

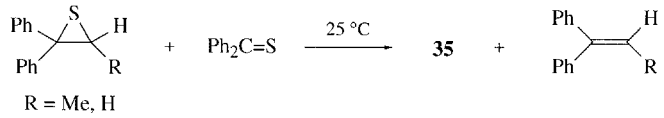
Dimerizations of dithiiranes/thioketone *S*-sulfides to tetrathianes were proposed in some cases (85AGE855, 85CB4553; 88CL1517).

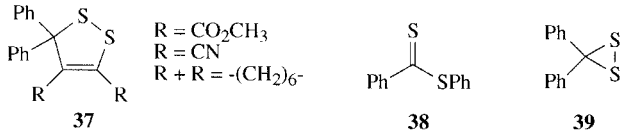


Thiobenzophenone *S*-sulfide (**35**) was successfully generated by a cycloreversion of the 1,2,4-trithiolane **36** at 60°C or by a sulfur transfer from thiiranes to thiobenzophenone (87JA902; 97T939). The thioketone *S*-sulfide

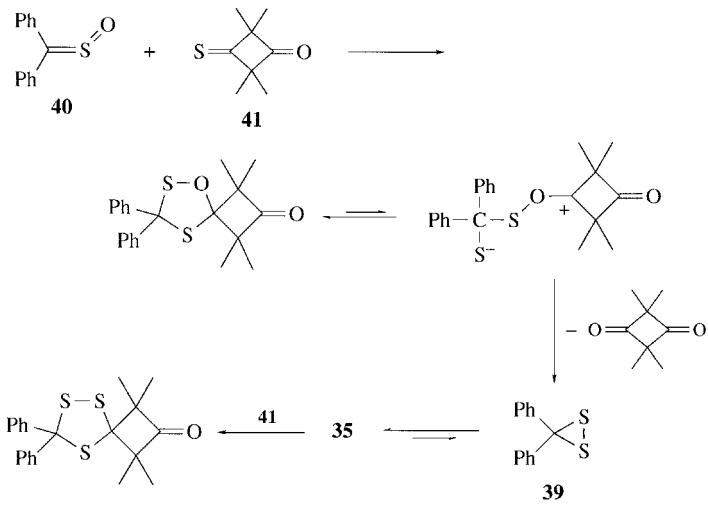
35 yielded 1,2-dithioles **37** or trithiolane **36** by Diels–Alder reactions with activated alkynes or thiobenzophenone, respectively. Dimerization of **35** to the corresponding 1,2,4,5-tetrathiane was not observed (97H507) contrary to previous reports (85AGE855, 85CB4553; 88CL1517). The dithioester **38,** expected to form through a dithiirane **39,** was not found in a pyrolysate of the trithiolane **36,** despite the high migratory aptitude of a phenyl group (87JA902; 97T939).



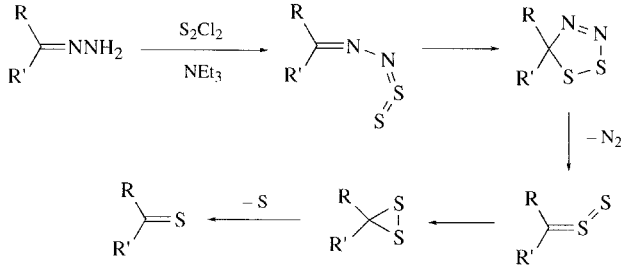




A ring opening of the dithiirane **39** to the thioketone *S*-sulfide **35** was proposed for the reaction of thiobenzophenone *S*-oxide (**40**) with the thioketone **41** (81LA187). The conjugation with the phenyl group would stabilize **35** relative to the dithiirane form.



In a method for the preparation of thioketones, the isomerization of thioketone *S*-sulfides to the corresponding dithiiranes followed by loss of a sulfur atom was presented as a likely mechanism (81BCJ3541).

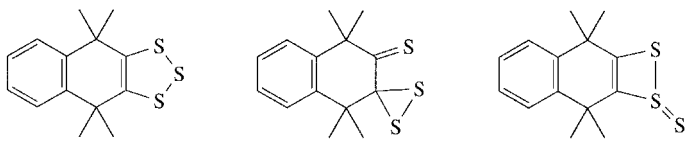


The dithiirane/thioketone *S*-sulfide manifold is also a subject of theoretical chemistry (86JST153; 97JST411; 98SR1). Reaction and activation energies of 1,3-electrocyclic ring closure of thioketone *S*-sulfides to the corresponding dithiiranes were calculated at the DFT B3LYP/6-31+G** and MP2/6-31+G** level of theory (97JST411; 98SR1). The transformation of thioformaldehyde *S*-sulfide to the parent dithiirane is exothermic by 9.9 kcal/mol with an activation energy of 25.6 kcal/mol at the DFT B3LYP/6-31+G** level. Calculations on a substituted dithiirane and its isomeric thioketone *S*-sulfide led to similar results (98SR1).

$R^1 = R^2 = H$	$R^1 = R^2 = H$
$R^1 = R^2 = Me$	$R^1 = R^2 = Me$
$R^1 = R^2 = Cl$	$R^1 = R^2 = Cl$
$R^1 = Me, R^2 = Ph$	$R^1 = Me, R^2 = Ph$

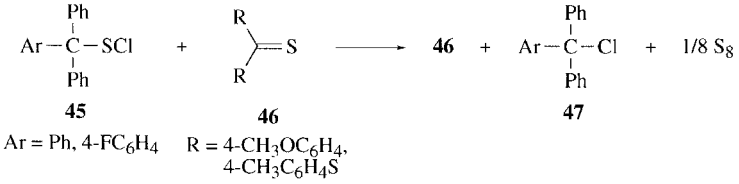
2. *Other Dithiiranes as Intermediates*

Photolysis of the 1,2,3-trithiole **42** in argon matrix (20 K) gave an electronic spectrum exhibiting the absorption maxima at 455 and 340 nm. The spirodithiirane **43** and the thiosulfoxide **44** were believed to be responsible to these absorptions (89TL2955).

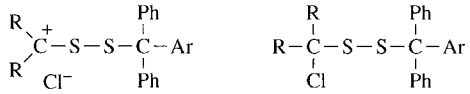


42 **43** **44**

The reaction of sulfenyl chlorides **45** with thioketones **46** led to **47** and elemental sulfur with recovery of **46.** The initial adducts **48** or **49** were believed to decompose to **47** and dithiiranes. Further decomposition of the latter would explain the formation of **46** and sulfur (91TL7633).

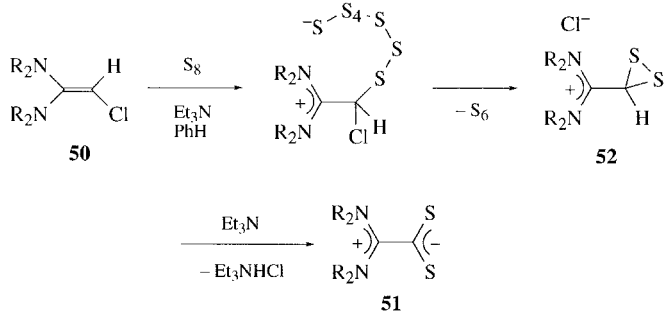


45 **46** **47**



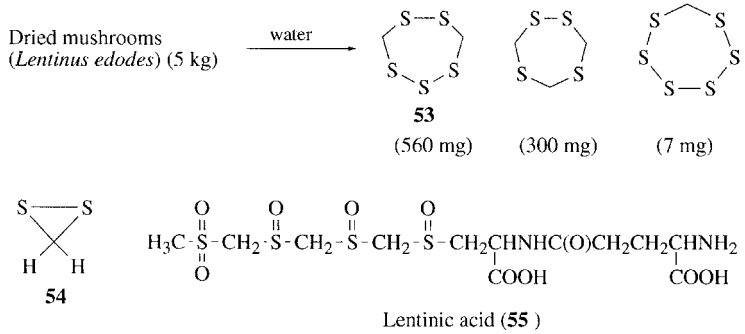
48 **49**

The reaction of 1,1-bis(dialkylamino)-2-chloroethylenes **50** with elemental sulfur in the presence of Et_3N yielded the corresponding inner salts **51** in high yields. It was assumed that the elimination of HCl from the dithiirane intermediates **52** formed the inner salts **51** [92JCS(CC)1522; 97HAC505].

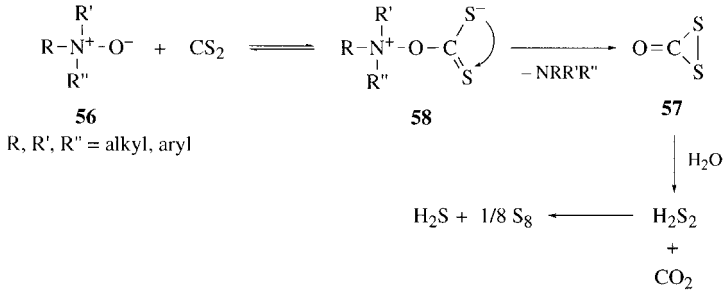


50 **52** **51**

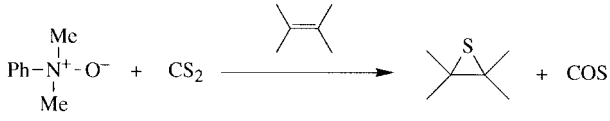
Lenthionine (**53**) is one of flavoring substances in *Lentinus edodes* (Berk.) Sing (67CPB988). It was proposed that **53** is produced by polymerization of the parent dithiirane (**54**), which was formed from lentinic acid (**55**) by enzymatic and then nonenzymatic processes (76TL3129; 77MI1).



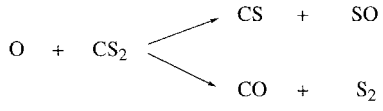
Amine *N*-oxides **56** were reduced to amines by carbon disulfide (62CPB969). The proposed mechanism involved the formation of amines and dithiiranone (**57**) from the initial adducts **58;** the latter is finally hydrolyzed to CO_2 and H_2S_2 (82BCJ3000).



Later, this reaction was applied to thioepoxidation, thereby dithiiranone **57** (or oxathiiranethione) acting as a sulfurization reagent (85JOC3228).

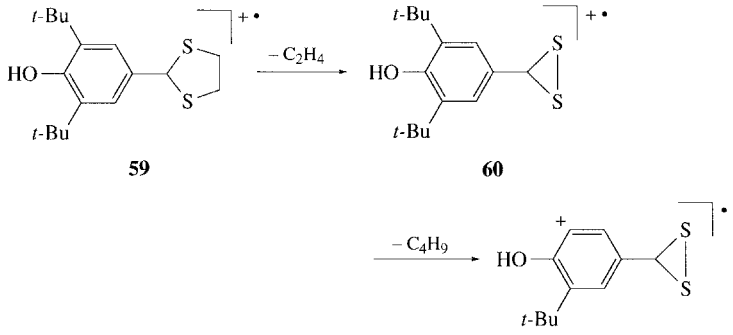


Dithiiranone **57** also accounted for the formation of CO in the reaction of the O(^3P) atom with CS_2 in the gas phase (76JCP2528). The semiempirical CNDO/B calculation on the reaction was reported (82JCC23).



3. *Dithiiranes in Mass Spectroscopy*

The molecular cation radical of 2-(3,5-di-*t*-butyl-4-oxophenyl)-1,3-dithiolane (**59**), which was generated by the electron impact method, split into ethylene and the cation radical of the corresponding dithiirane **60** (79DOK1030).

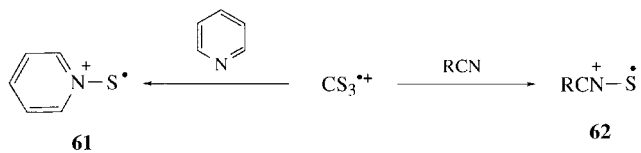


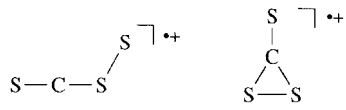
Dithiiranethione is an isomer of CS_3 and its preparation and structure have been drawing much attention [75JCS(P2)559]. In the chemiionization process of $CS_2^* + CS_2$ using the molecular beam photoionization method, the photoionization efficiency curve of $CS_3^{+\cdot}$ was observed (80JCP4242).

$$CS_2 \cdots CS_2 \xrightarrow{h\nu} CS_2^*(n) \cdots CS_2 \longrightarrow CS_3^{+\bullet} + CS + e^-$$

The self-chemical ionization reaction of CS_2 under chemical ionization conditions (approx. 1 Torr) generated $CS_3^{\cdot+}$, which sulfurized pyridine (97MI1) and nitriles (97JPC6970) to give the corresponding cation radicals **61** and **62,** respectively. *Ab initio* calculations on $CS_3^{\cdot+}$ at the G2 (MP2, SVP) level revealed that the ylide radical cation form **63** is more stable than the dithiiranethione radical cation form (**64**) by 42 kJ/mol (97JPC6970).

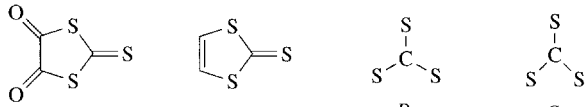
$$CS_2^{\bullet+} + CS_2 \longrightarrow (CS_2)_2^{\bullet+} \longrightarrow CS_3^{\bullet+}$$



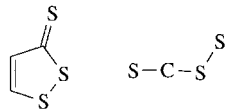


63 **64**

Both $CS_3^{-\cdot}$ and $CS_3^{+\cdot}$ were also successfully generated by the fragmentation of ionized 4,5-dioxo-2-thioxo-1,3-dithione (**65**) and 2-thioxo-1,3-dithiole (**66**) (90JA3750). The three sulfur atoms in the anion and cation radicals were chemically equivalent, suggesting that they take the D_{3h} (or C_{2v}) form (**67** or **68**). On the other hand, under similar conditions, 3-thioxo-1,2-dithiole (**69**) yielded two isomeric cation radicals; the D_{3h} (or C_{2v}) form and the carbon disulfide *S*-sulfide form (**70**). *Ab initio* calculations on three electronic states of CS_3 at the 6-31G*+ZPVE level indicated that the C_{2v} form (**68**) was more stable than the carbon disulfide *S*-sulfide form (**70**) in the neutral (both singlet and triplet states) and the anion radical states, but **68** was less stable than **70** in the radical cation state.



65 **66** D_{3h} **67** C_{2v} **68**



69 **70**

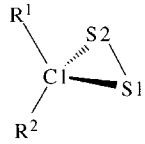
C. Properties of Isolable Dithiiranes

1. *Structure*

Table II summarizes the relevant bond lengths and bond angles of the dithiirane **4a** and three dithiirane 1-oxides, **2, 3,** and **17a.** The dithiirane rings take an almost isosceles triangle geometry and the S–S bond lengths are between 2.07 and 2.11 Å, which are slightly longer than 2.03 Å of the usual S–S bond length (∠C–S–S–C, 75–105°) [87JCS(P2)S1]. The C–S bond lengths (1.81–1.83 Å) in **4a, 2,** and **3** are almost equal to that of the parent thiirane (1.815 Å) (74CPL111). Calculated S–S and C–S bond lengths of the parent dithiirane were 2.123 and 1.811 Å, respectively, at the DFT B3LYP/6-31+G** level (97JST411).

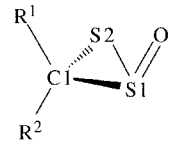
TABLE II

RELEVANT BOND LENGTHS (Å) AND ANGLES (DEG) OF DITHIIRANE AND DITHIIRANE 1-OXIDES



4 a

R^1 = Ph, R^2 = $CMe_2CH_2CMe_2COPh$



2: R^1 = Ph, R^2 = $CMe_2CH_2CMe_2COPh$
3: R^1 = $CMe_2CH_2CMe_2COPh$, R^2 = Ph
17 a: $R^1 = R^2$ = 1-Adamantyl

	4a	**2**	**3**	**17a**
S1—S2	2.073(2)	2.074(2)	2.107(2)	2.098(1)
S1—O1	—	1.442(4)	1.415(5)	1.407(2)
C1—S1	1.821(2)	1.833(4)	1.832(5)	1.860(1)
C1—S2	1.814(3)	1.830(4)	1.832(5)	1.863(1)
C1—C(R^1)	1.515(3)	1.499(5)	1.490(7)	1.606(2)
C1—C(R^2)	1.566(3)	1.568(5)	1.575(7)	1.592(2)
C1—S1—S2	55.07(8)	55.5(1)	54.9(2)	55.8(1)
S1—S2—C1	55.37(8)	55.6(1)	54.9(2)	55.6(1)
S1—C1—S2	69.55(9)	69.0(1)	70.2(2)	68.6(1)
C(R^1)—C1—C(R^2)	117.2(2)	118.3(3)	117.9(4)	123.6(1)
S2—C1—C(R^1)	113.3(2)	113.7(3)	112.6(4)	114.2(1)
S2—C1—C(R^2)	118.0(2)	116.4(3)	117.5(4)	111.6(1)
S1—C1—C(R^1)	113.1(2)	113.8(3)	110.4(4)	113.3(1)
S1—C1—C(R^2)	117.0(2)	116.2(3)	119.4(4)	112.7(1)
S2—S1—O1	—	111.2(2)	115.5(3)	117.5(1)
C1—S1—O1	—	113.9(2)	116.7(3)	118.8(1)

2. *Spectroscopic Properties*

Table III summarizes the longest absorption maxima (λ_{max}) and the molar absorptivities (ϵ) of dithiiranes.

A CNDO/B calculation on the relationship between dihedral angles ($\angle$C—S—S—C) of disulfides and energy levels of the molecular orbitals led to a conclusion that the HOMO (n_π) energy is the highest at 0° and 180° and the lowest at 90°, whereas the LUMO [(S—S, S—C)σ^*] energy is scarcely affected by the change of the angle. Thus, as the dihedral angle approaches 0° or 180°, the HOMO–LUMO gap becomes smaller

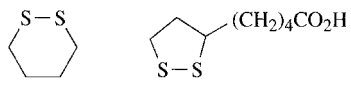
TABLE III

LONGEST ABSORPTION MAXIMA AND MOLAR ABSORPTIVITIES OF DITHIIRANES

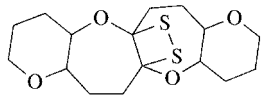
R^1	R^2	λ_{max}/nm[a]	ϵ	Reference
Ph	$CMe_2CH_2CMe_2COPh$ (**4a**)	452	104	94AGE777
4-$CH_3C_6H_4$	$CMe_2CH_2CMe_2CO(C_6H_4$-4-$CH_3)$ (**4b**)	454	106	95SUL237
4-*t*-BuC_6H_4	$CMe_2CH_2CMe_2CO(C_6H_4$-4-*t*-Bu) (**4c**)	460	120	95SUL237
t-Bu	$CMe_2CH_2CMe_2CO$-*t*-Bu (**4d**)	452	55	97TL1431
Ph	CMe_2CMe_2COPh (**12a**)	442	—[b]	95TL1867
4-$CF_3C_6H_4$	$CMe_2CMe_2CO(C_6H_4$-4-$CF_3)$ (**12b**)	438	—[b]	95TL1867
Ph	$CMe_2(C_6H_4$-2-COPh) (**7**)	437	157	97BCJ509

[a] In dichloromethane.
[b] Not determined.

(77JA2931). Figure 2 shows a plot of $1/\lambda_{max}$ of some disulfides against their ∠C–S–S–C angles, where good linear correlation is observed (77JA2931; 97YGK897).



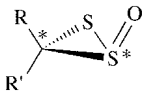
71 **72**



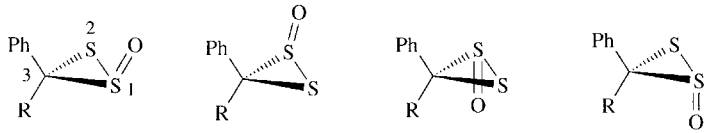
73

3. *Stereochemistry of Dithiirane 1-Oxides*

The presence of two different substituents on the ring carbon atom of dithiirane 1-oxides provides two asymmetric centers, i.e., four stereoisomers.



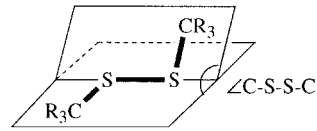
Optical resolution of the dithiirane 1-oxides **2** and **3** was accomplished by HPLC equipped with a chiral column (97T12203). Absolute configurations of **2a** and **2b** were determined by X-ray crystallography. The stereospecific isomerization (epimerization) of **2a** to **3b** and **2b** to **3a** was observed during the resolution study.



(1*R*, 3*S*)-**2a** (1*S*, 3*R*)-**2b** (1*R*, 3*R*)-**3a** (1*S*, 3*S*)-**3b**

R = $CMe_2CH_2CMe_2COPh$

Racemization (1,2-oxygen migration) occurred between **2a** and **2b** (97T12203). The racemization took place slowly in solution at room temperature and obeyed reversible first-order kinetics: $k_{rac} = 4.3 \times 10^{-6}\ s^{-1}$ (25°C, CH_2Cl_2). The $\Delta H^{\neq}$ and $\Delta S^{\neq}$, calculated from rate constants at temperatures between 20° and 40°C, were 24.3 kcal/mol and −2.0 eu, respectively. The rate of the racemization was hardly dependent on either the concentration of the solution or the polarity of the solvent examined. The low activation energy and the analogy of the mechanism to that for the dispro-



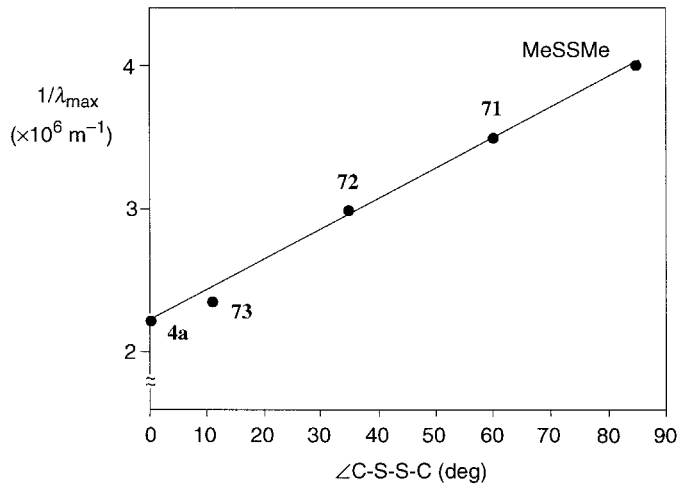
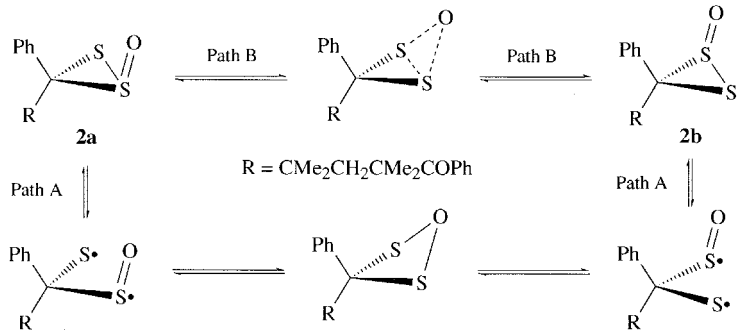


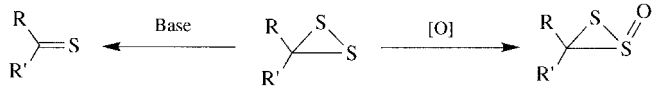
FIG. 2. Plot of $1/\lambda_{max}$ vs ∠C—S—S—C.

portionation of PhS(O)SPh (70JA5971) led to a proposal that a unimolecular radical mechanism (Path A) rather than a concerted mechanism (Path B) is operative.

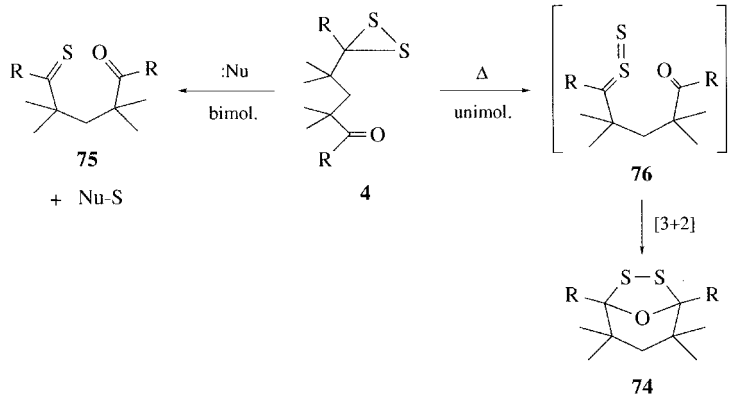


D. Chemical Properties of Isolable Dithiiranes

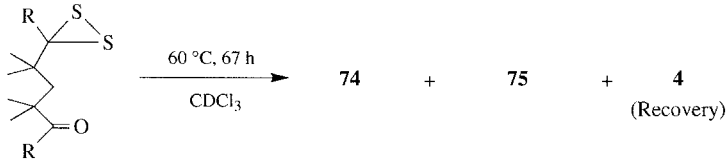
The isolable dithiiranes (**4** and **7**) are fairly stable under acidic conditions but quickly lose a sulfur atom to give the corresponding thioketones under basic conditions (97BCJ509). They are quite sensitive toward amines and phosphines. Oxidation with MCPBA gave the corresponding dithiirane 1-oxides in high yields.



The thermal reaction of dithiiranes is of particular interest in relation with the dithiirane/thioketone *S*-sulfide manifold. Heating δ-oxodithiiranes (**4**) in solution led to both isomerization to 6,7-dithia-8-oxabicyclo[3.2.1]-octanes **74** and desulfurization to δ-oxothiones **75,** the ratio of which was dependent on the reaction conditions employed. The intramolecular [3 + 2] cycloaddition of the thioketone *S*-sulfide **76,** generated by ring-opening, provides a straightforward explanation for the formation of **74.** Meanwhile, **75** is probably formed by a nucleophilic attack on the sulfur atom by another molecule of **4** and/or by elemental sulfur formed during the reaction.



The results of a rate study of the thermal isomerization (decomposition) of alkylaryl- and dialkyldithiiranes indicated that the electron-withdrawing phenyl group stabilizes the dithiirane **4a** by lowering the HOMO level, i.e., the reactivity of the S–S bond, whereas the bulky *t*-butyl group in **4d** effectively hinders the intermolecular reaction, thus giving a high oxadithiolane/thioketone ratio (97TL1431, 97BCJ509).



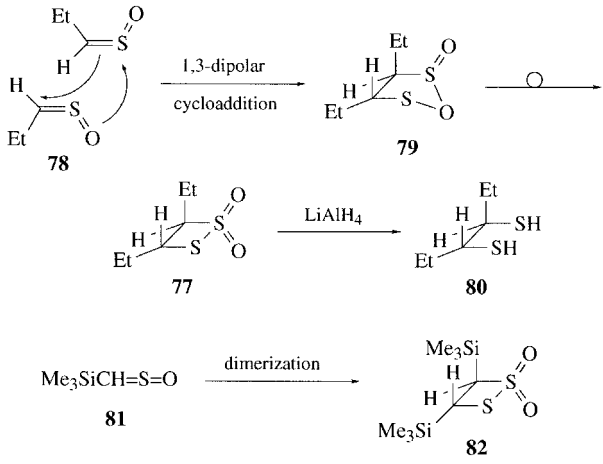
4a: R = Ph	26%	17%	57%
4d: R = *t*-Bu	83%	5%	10%

III. 1,2-Dithietanes

The chemistry of 1,2-dithietanes is still emerging. Isolable and well-characterized 1,2-dithietanes are limited to only two compounds, 3,4-diethyl-1,2-dithietane 1,1-dioxide (**77**) and dithiatopazine (**73**). The synthesis of 1,2-dithietanes has been overshadowed by their thermal instability, which arises most probably from repulsive interactions between the lone-pair electrons on the sulfur atoms, as we have already seen in the chemistry of dithiiranes.

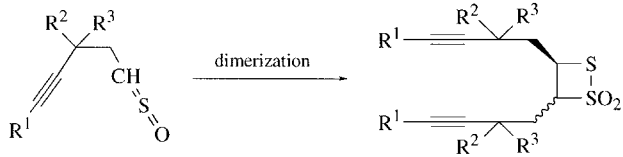
Propanethial *S*-oxide (**78**), the lachrymatory factor of the onion, functions as both a 1,3-dipole and a dipolarophile to give the first isolable 1,2-dithietane **77,** produced by rearrangement of the initially formed unstable

dimer, cyclic sulfenyl sulfinate ester (**79**). In the case of **77,** substitution of the lone pairs on one of the sulfurs with oxygen atoms removes repulsive interactions between the lone-pair electrons, thus allowing **77** to be stable enough to be isolated. The stereochemistry of **77** was established by reduction with $LiAlH_4$, which led to DL-hexane-3,4-dithiol (**80**) (80JA2490). The thial *S*-oxide (**81**) also dimerized on storage at room temperature for several days to afford **82** in 42% yield as a colorless crystalline solid (96JA7492). In the ^{13}C NMR spectrum, the α-sulfenyl and α-sulfonyl carbons of **77** resonate at δ 39.2 and 97.9, respectively (80JA2490, 80JOC4807, 96JA7492).



78 **79** **77** **80** **81** **82**

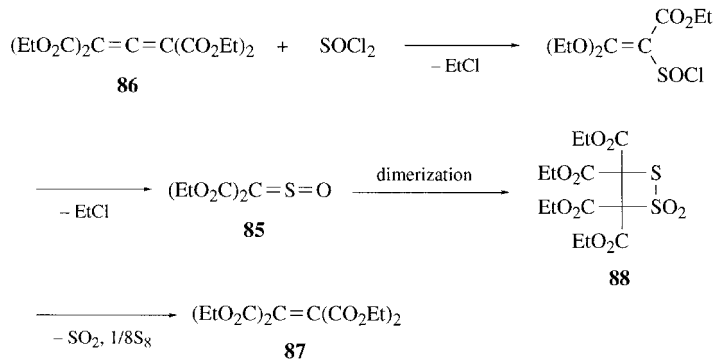
Similarly, a series of thial *S*-oxides **83** dimerized upon standing to give 1,2-dithietane 1,1-dioxides **84,** which were reduced to the corresponding alkenes on treatment with $LiAlH_4$ (93SL839; 96BSF515).



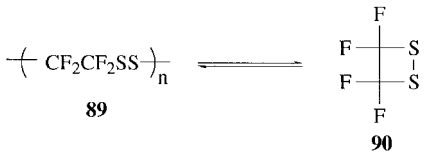
83 R^1 = H, Me, Et, Ph
$R^2 = R^3$ = Me, R^2, R^3 = $(CH_2)_5$

84

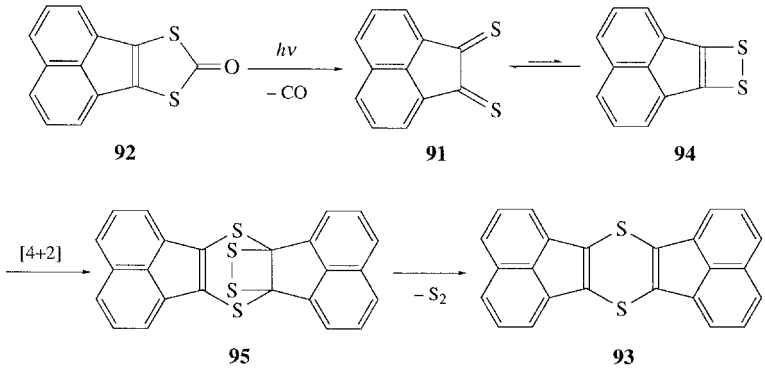
The thioketone *S*-oxide **85,** generated from allene **86** and $SOCl_2$ *in situ*, decomposes to give the alkene **87.** A mechanism, involving the transient formation of the 1,2-dithietane **88** (by dimerization of **85** followed by rearrangement), was proposed (85AGE855).



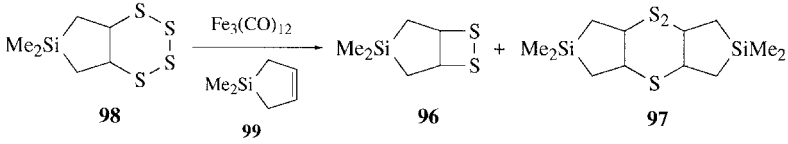
It was claimed that the polymer **89** volatilized by heating as species, indicated by mass spectrometric analysis, to include the 1,2-dithietane **90** (62JOC3995; 65JOC4188).



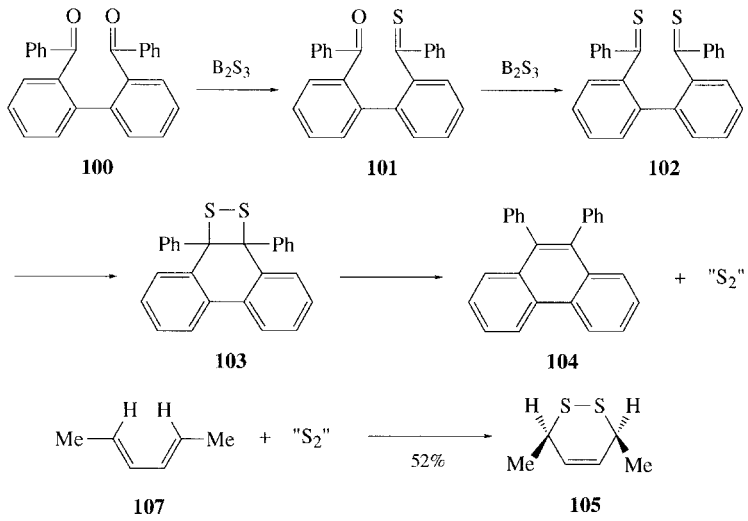
The α-dithione **91,** generated by photolysis of **92,** is transformed into the dithiin **93** (41%) in the absence of a trapping agent. The conversion was proposed to proceed by a [4 + 2] cycloaddition of **91** with its dithiete tautomer **94** leading to the dithietane **95,** which was followed by loss of S_2 (85JOC1550). Such [4 + 2] dimerizations are often encountered in the chemistry of 1,2-dithietes as discussed later.

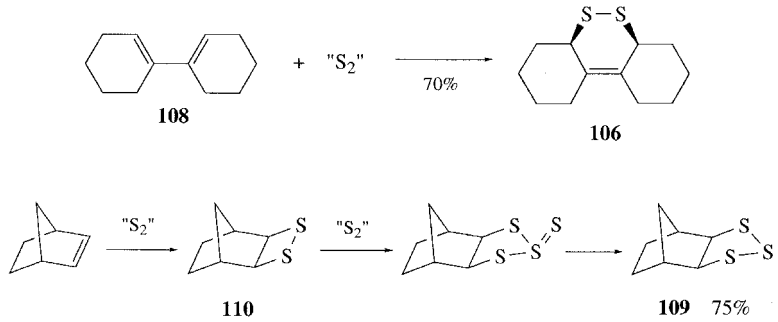


The formation of a dithietane **96** (1%), along with **97** (1%), by treatment of **98** with $Fe_3(CO)_{12}$ in the presence of 1,1-dimethylsilacyclopent-3-ene (**99**) was proposed based solely on a GC/MS analysis (86ZOR1364).

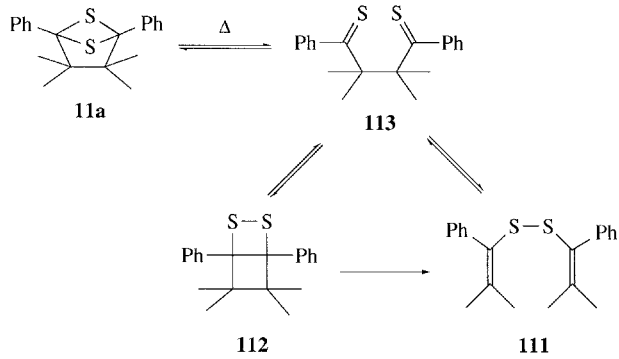


Thionation of the diketone **100** with B_2S_3 produces a quite stable monothione **101** (blue). The dithione **102** (intense blue), produced by further thionation, spontaneously ejects "S_2" to give, through the likely intermediacy of the dithietane **103,** a quantitative yield of the phenanthrene **104.** A free reactive S_2 species, generated here, was efficiently trapped by Diels–Alder reactions with a range of dienes. The reaction is stereospecific, as exemplified by the formation of **105** and **106** from dienes **107** and **108,** respectively. The trapping with norbornene afforded the trithiolane **109** in good yield. A mechanism involving a dithietane intermediate **110** was proposed for this conversion. Although a number of derivatives of **102** were synthesized, the corresponding dithietane intermediates still remained elusive (87JA926; 90JA7819; 91ACR341; 92JA1456).

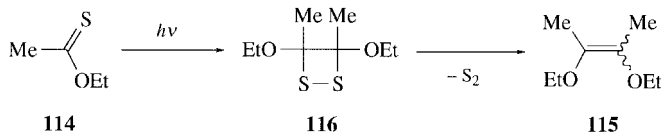




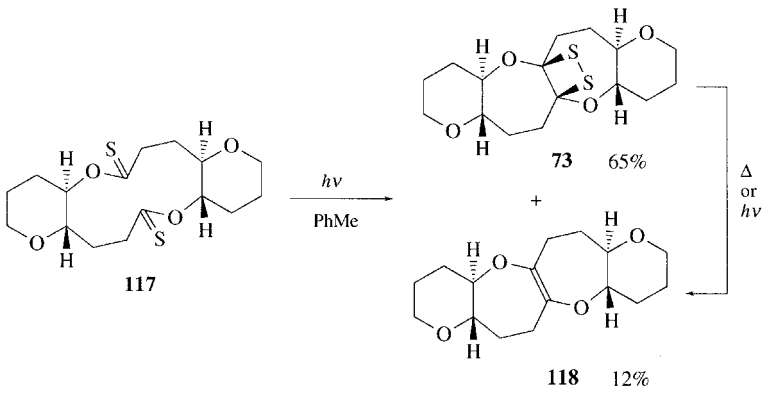
The 1,3-dithietane **11a,** when heated, rearranged quantitatively into a disulfide **111.** The reaction may involve a dithietane **112** as an intermediate, although a [3,3] sigmatropic rearrangement of **113** could equally explain the formation of **111** (90JOC2421).



Photochemical reaction of the ester **114** afforded the alkene **115** and three products derived from **115.** A mechanism, involving dimerization of **114** leading to a dithietane intermediate **116,** was proposed. Trapping of active sulfur species, generated from **116,** with dienes was also described (75CB630).

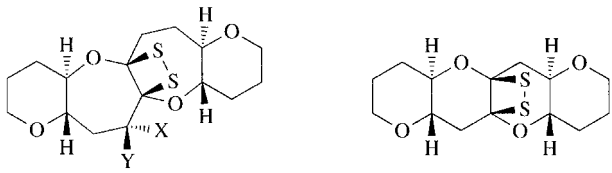


The isolable stable 1,2-dithietane, dithiatopazine (**73**), was prepared in 1988 and fully characterized (the name "dithiatopazine" was coined for its beautifully yellow-orange topazlike crystalline form) (87JA3801; 88JA4856; 90JA3029). Thus, controlled photoirradiation of a dithionolactone (**117**) produced **73** in 65% yield along with an alkene **118** in 12% yield. Photolytic or thermal decomposition of **73** led to the alkene **118,** a conversion that could be also carried out by a variety of reagents [n-Bu_3SnH-AIBN, Raney Ni, MCPBA, $Fe_2(CO)_9$, $Mo(CO)_6$] in excellent yields.



117 **73** 65% **118** 12%

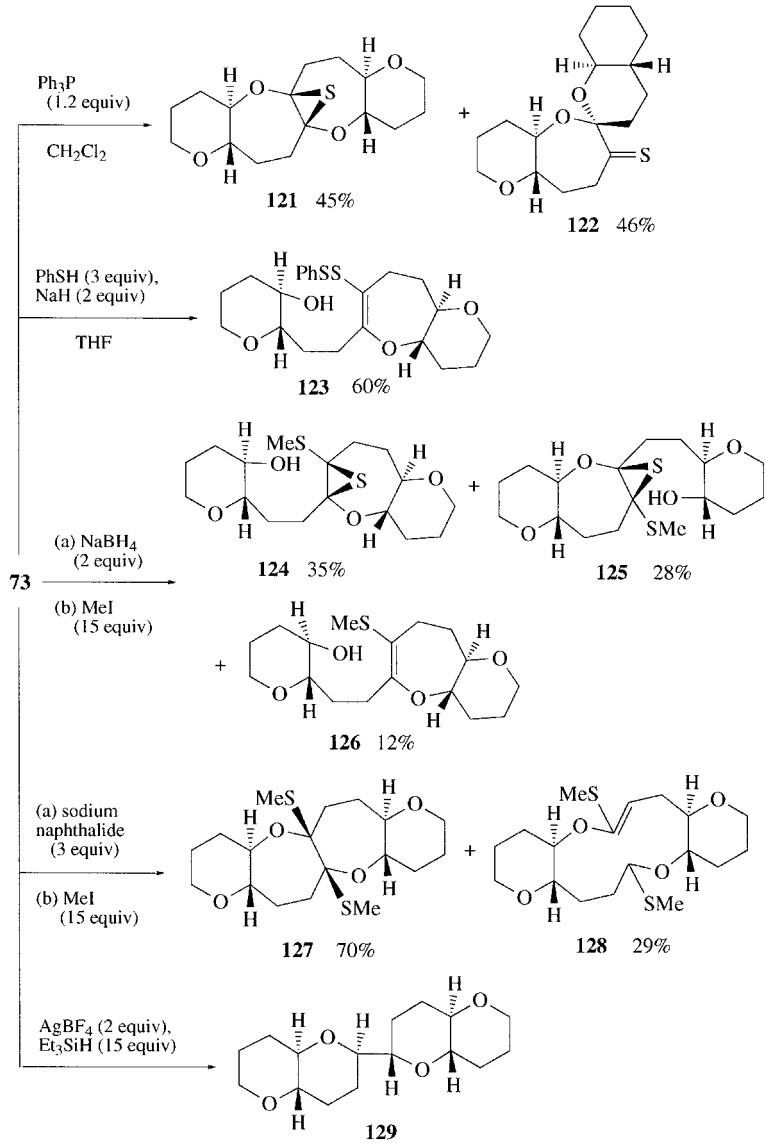
Three related dithietanes **119** (three diastereomers) were obtained by the same photolytic procedure from the corresponding dithionolactones, although attempts to prepare the dithietane **120** failed (90JA3029).



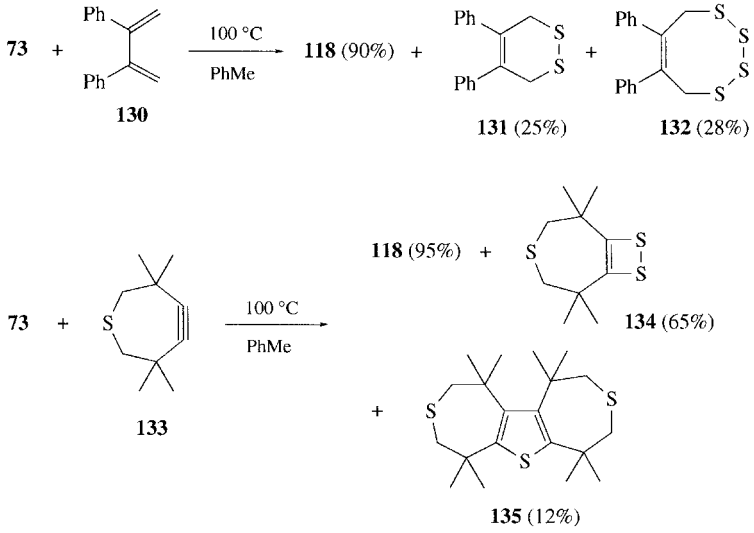
119: X, Y = Me, H **120**

The following are the typical reactions of the dithietane **73.** Treatment of **73** with Ph_3P led to the loss of one sulfur and the formation of the rearrangement products **121** and **122.** Treatment with PhS^- resulted in the formation of **123,** whereas brief exposure to $NaBH_4$ followed by trapping with MeI led to the novel episulfides **124** and **125** and the alkene **126.**

Reduction with sodium naphthalide followed by treatment with MeI gave **127** and **128** in an excellent combined yield. Exposure of **73** to $AgBF_4$-Et_3SiH resulted in a novel skeletal rearrangement leading to compound **129** (90JA3029).



Dithiatopazine **73** serves as a sulfur-transfer reagent under thermal conditions. Thus, heating **73** and diene **130** in toluene at 100°C formed a cyclic disulfide **131** (25%) and a tetrasulfide **132** (28%) with the formation of the alkene **118** (90%). Under similar conditions, the highly strained acetylene **133** was converted to the 1,2-dithiete **134** (65%) and the congested thiophene **135** (12%) (90JA3029).



The half-life of **73** is 1.1 h at 110°C in 0.01 *M* toluene solution. Kinetic studies revealed an activation energy of 26.3 kcal/mol for thermal extrusion of S_2 from **73** leading to **118.** An MM2 parameterization for dithietanes and subsequent molecular mechanics evaluation permitted the conclusion that **73** is a remarkably rigid structure experiencing little conformational mobility. Quantum mechanical (PRDDO) calculations for various dithietane systems suggested the singular stability of **73** to arise from a combination of thermodynamic factors and internal energy redistribution (90JA3029).

The X-ray crystallographic molecular structure of **75** is in good agreement with the MM2-optimized structure as shown in Figure 3 (90JA3029). The observed S-S bond length (2.084 Å) is slightly longer than those of common dialkyl disulfides and elemental sulfur. Figure 4 shows a CNDO/B-optimized geometry of the parent 1,2-dithietane (77JA2931).

Treatment of a series of 1,2-dithiols (**136**) including *cis*-cyclohexane-1,2-dithiol with Al_2Cl_6 in CH_2Cl_2 at 25°C led to persistent ESR signals due to the corresponding 1,2-dithietane radical cations (g = 2.0187 ± 0.0003)

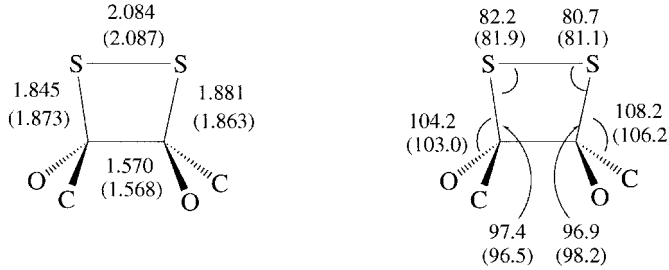
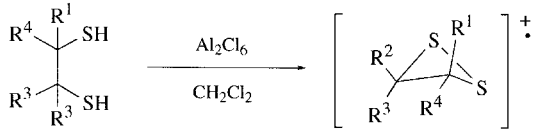


FIG. 3. X-Ray and MM2-optimized structures of **73;** selected bond lengths (Å) (left) and angles (degrees) (right). MM-2 values in parentheses.

(**137**) (86H321). These radical cations exist in a nonplanar conformation. With *trans*-3,4-dimethyl substituents, the barrier to ring flip was estimated to be >5 kcal/mol. In connection with reactions of thiirane with the thiirane radical cation, *ab initio* calculations were reported on the 1,2-dithietane radical cation (93JA12510).



136 **137**

Tetramethyl-1,2-oxathietane (**138**) was prepared by diazotization of **139,** which was prepared from the aziridine (**140**) (86JA3811). The reaction presumably involves the decomposition of the sulfonium ion intermediate (**141**). The dichloromethane solution of **138** at −20°C is sufficiently stable to permit exploration of the chemical reactions. The oxathietane **138** undergoes a formal [σ2s + σ2a] cycloreversion to form acetone and thioacetone. The latter was trapped by tetracyanoethylene and anthracene to give adducts **142** and **143,** respectively.

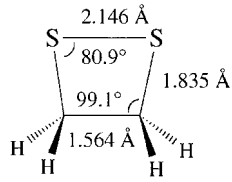
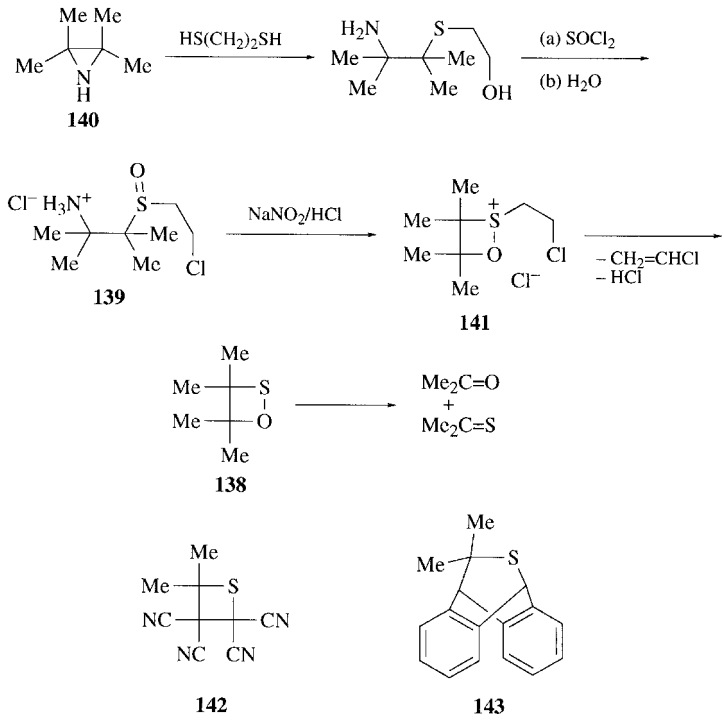


FIG. 4. CNDO/B optimized geometry of the parent 1,2-dithietane (77JA2931).

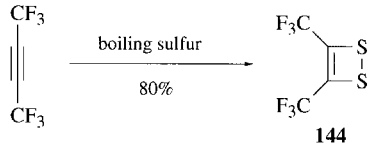


As described above, the chemistry of 1,2-dithietanes is far from being developed. Therefore, development of excellent synthetic methods of 1,2-dithietanes is truly desired in order to understand their intrinsic nature associated with chemical reactivities, structure, and biological activities.

IV. 1,2-Dithietes

A. Synthesis of Isolable 1,2-Dithietes

The first isolable 1,2-dithiete **144** was synthesized in 80% yield by passing hexafluoro-2-butyne through vapors of boiling sulfur under atmospheric pressure (60JA1515; 61JA3434, 61JA3438). This dithiete has been investigated in depth from a variety of points of view and provides a typical example that an electron-withdrawing substituent stabilizes the dithiete form, and not the α-dithione form, by diminishing repulsive interactions between lone-pair electrons on the sulfur atoms. Shortly afterward, the formation of the dithiete **145** by oxidation of sodium mercaptomalenonitrile (**146**) was reported, though **145** is a reactive intermediate and was not isolable (62JA4746, 62JA4756, 62JA4772).



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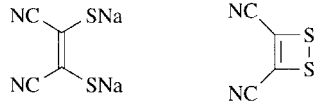
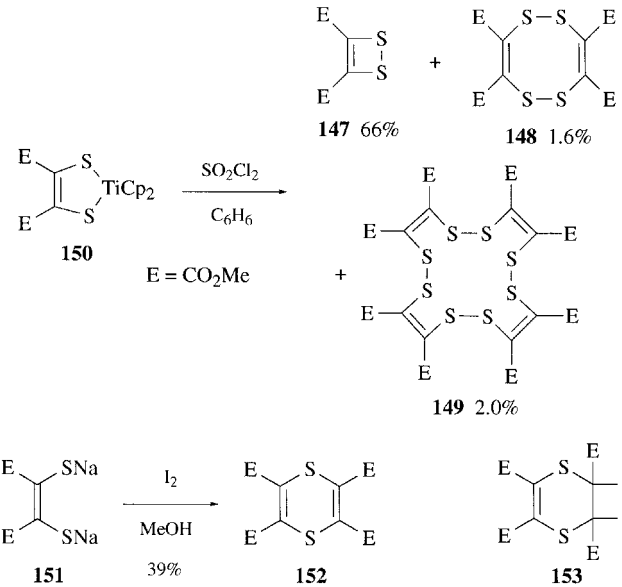
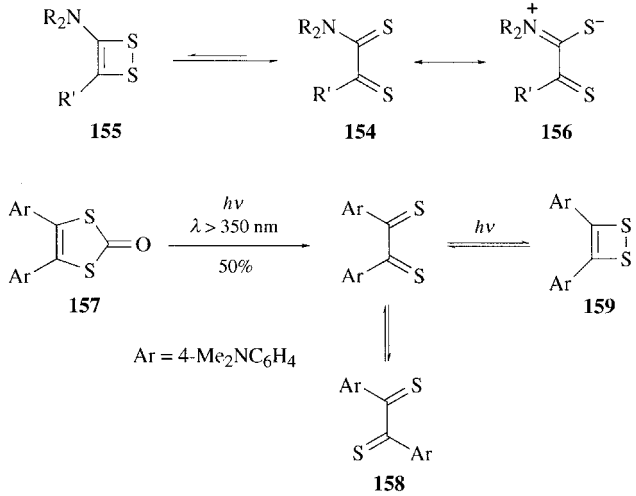


146 145

3,4-Bis(methoxycarbonyl)-1,2-dithiete (**147**) was postulated as an intermediate leading to tetrakis(methoxycarbonyl)thiophene in the reaction of dimethyl acetylenedicarboxylate (DMAD) with elemental sulfur (87H2215; 97NKK424, 90RHA146). Very recently, **147** was isolated in 66% yield, along with **148** and **149** in small amounts, by the oxidation of a titanocene dithiolene complex (**150**) with SO_2Cl_2 (98JOC8192). Iodine oxidation of the dithiolate **151,** obtainable by treatment of **150** with NaOMe in MeOH, formed the 1,4-dithiin **152** in 39% yield. The formation of **152** was explained as the result of dimerization of **147** and loss of S_2 from the dimer **153** (cf. 85JOC1550). Such dimerization is often encountered in dithiete chemistry as described later.

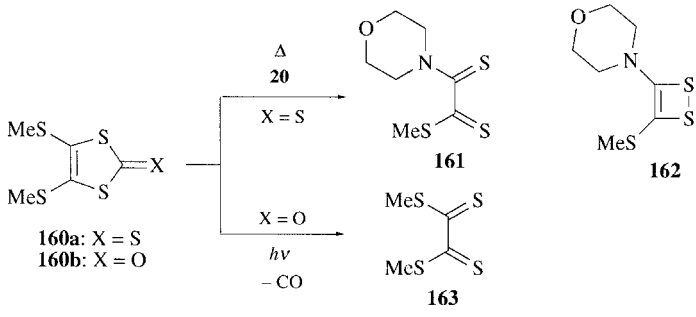


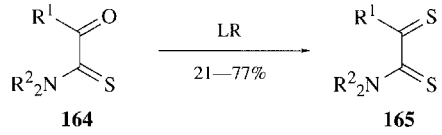
When 1,2-dithietes possess at least one electron-donating substituent such as dialkylamino group, the ring-opened α-dithione form **154** is stabilized, relative to **155,** by contribution of the canonical structure **156.** Irradiation of a benzene solution of **157** under N_2 at room temperature with light of wavelength $\lambda > 350$ nm gave the dithiobenzil **158,** which slowly crystallized from the irradiated solution as dark-red crystals in 50% yield (73JA2383; 74JA3502). In solution, **158** exists as an equilibrium mixture with the valence isomeric dithiete form **159;** the ratio **158:159** is 6:1 in $CDCl_3$ at room temperature. The equilibrium between **158** and **159** is dependent upon (a) the solvent, (b) light, and (c) temperature. The values of the equilibrium at different temperatures yielded the enthalpy change for **159** $\rightarrow$ **158** as $\Delta H° = -4.9$ kcal/mol together with $\Delta S° = -12.5$ eu. This is the only instance that rigid evidence for the presence of an equilibrium between the 1,2-dithiete and α-dithione forms was provided experimentally under ordinary conditions.



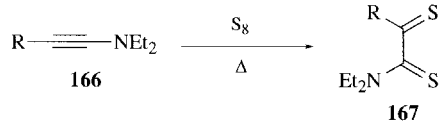
Heating 1,3-dithiole-2-thione **160a** with morpholine (**20**) formed α-dithione **161** in a moderate yield. Although appearance of two different signals due to the SMe group in the ^1H NMR spectrum led the authors to the conclusion that **161** is in an equilibrium with the dithiete **162,** reconsideration might be required (74JOC511). Photolytic extrusion of CO converted dithiole-2-one **160b** into tetrathiooxalate **163** (76ZC318; 80CB1898; 82ZC223). Thionation of thioamides **164** with Lawesson's reagent (LR) produced a series of α-thioxothioamides **165** (80AGE563; 83LA1116).

Reactions of acetylenes **166** with elemental sulfur also gave α-thioxothioamides **167** (93TL115, 93BCJ623; 94CL77). Also known are compounds **168** (74CB3121), **169a** (77CB2506), and **169b** (88MI1). All of these compounds exist in the α-dithione forms. No equilibrium with the corresponding dithietes was observed.

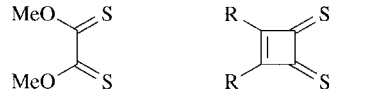




R^1 = *t*-Bu, 4-*t*-BuC_6H_4, 3,5-(*t*-Bu)$_2C_6H_3$
R^2 = Me, Et

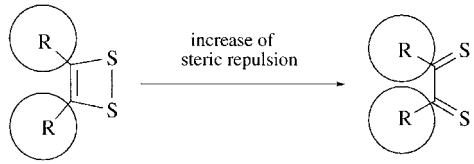


R = PhS, 74%; R = PhSe, 12%; R = Et_2N, 92%



Many stable 1,2-dithietes, which possess at least one bulky substituent, have been isolated. In this system, the strained, reactive double bond of

1,2-dithietes is kinetically stabilized by steric protection. In addition, ring-opening the dithietes to the corresponding cisoid α-dithiones results in the increase of steric repulsion, thus making the dithiete form more favorable relative to the dithione form.

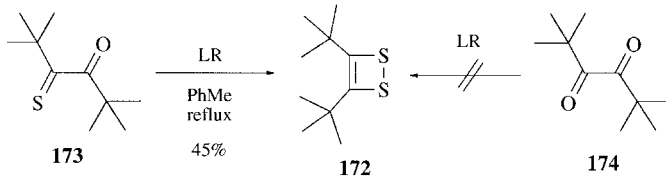


Highly strained, reactive cyclic acetylenes **133** and **170a** and **170b** smoothly reacted with elemental sulfur to form the corresponding dithietes **134** (79H1153), **171a** (79H1153), and **171b** (83TH1). The dithiete **134** was also formed by heating **133** with dithiatopazine **73** as already described (88JA4856; 90JA3029).

133: X = S
170a: X = SO_2
170b: X = CH_2

134: X = S, 77%
171a: X = SO_2, 51%
171b: X = CH_2

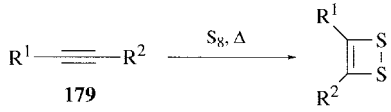
The first synthesis of 3,4-di-*tert*-butyl-1,2-dithiete (**172**) was performed by treatment of **173** with Lawesson's reagent (LR). Direct thionation of the diketone **174** failed to yield **172** [82JCR(S)314].



173 **172** **174**

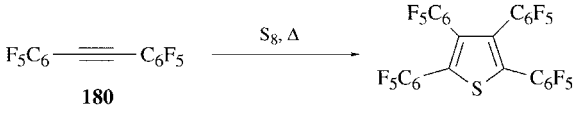
Later a more convenient synthesis of **172** appeared; heating di-*tert*-butylacetylene with elemental sulfur in benzene at 190°C in an autoclave

produced **172** in 58% yield. In a similar way, dithietes **175–178** were synthesized in reasonable yields by heating acetylenes **179** with elemental sulfur in refluxing *o*-dichlorobenzene (93TL115, 93BCJ623). Compounds **176–178** are noticeable in that they exclusively exist as the dithiete form despite the presence of a phenyl group which might conjugate with a thiocarbonyl group in the ring-opened α-dithione form. Sterically more hindered acetylenes failed to react with sulfur, and acetylenes such as **180–182** were converted to the products shown below in moderate to low yields.

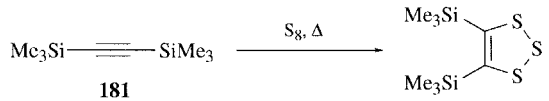


179

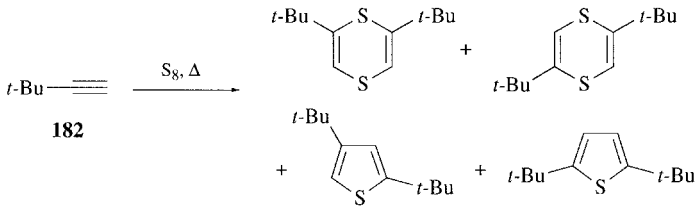
172: $R^1 = R^2 = t$-Bu, 59%
175: $R^1 = R^2$ = 1-adamantyl, 65%
176: $R^1 = t$-Bu, R^2 = Ph, 56%
177: R^1 = 1-adamantyl, R^2 = Ph, 46%
178: $R^1 = C(CO_2Me)Me_2$, R^2 = Ph, 21%



180



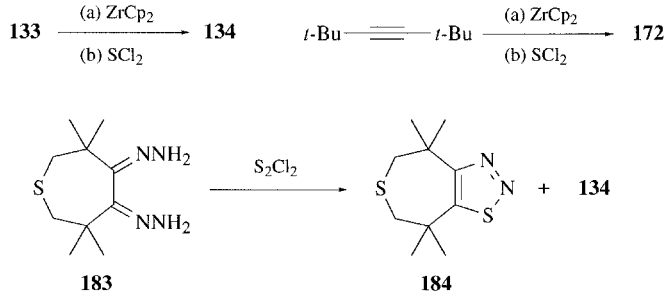
181



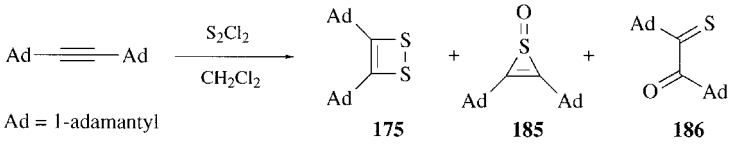
182

Treatment of **133** or di-*tert*-butylacetylene with zirconocene and then with SCl_2 afforded dithietes **134** and **172,** respectively (92TH1). The di-

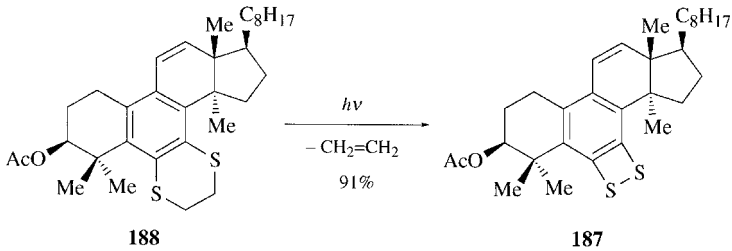
thiete **134** was also formed by the treatment of the hydrazone **183** with S_2Cl_2, though the thiadiazole **184** was the major product (83TH1; 92TH1).



An unexpected reaction is the formation of dithiete **175,** thiirene 1-oxide **185,** and thioketone **186** by the treatment of di-1-adamantylacetylene with S_2Cl_2 (99UP1). The yield of each compound is 30% at most.

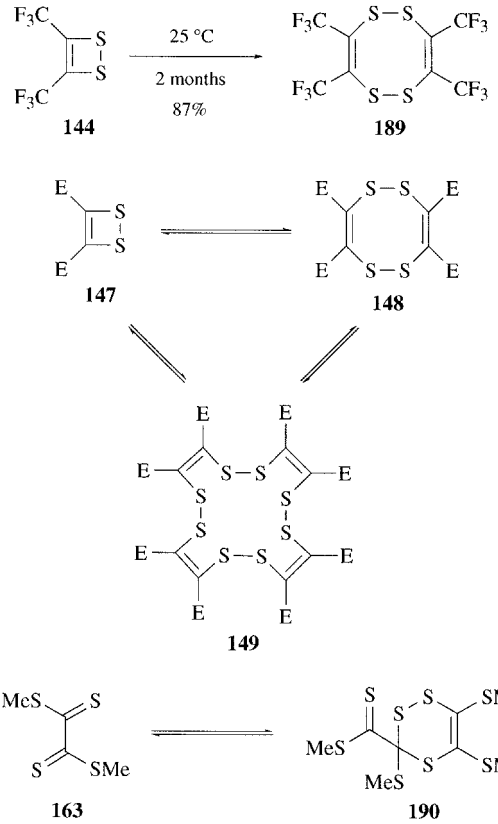


The only instance of isolation of a stable benzo-1,2-dithiete is the yellow crystalline compound **187,** which was obtained by photolysis of **188** in heptane at −20°C using a medium-pressure mercury lamp [75JCS(CC)756; 77JCS(P1)515].

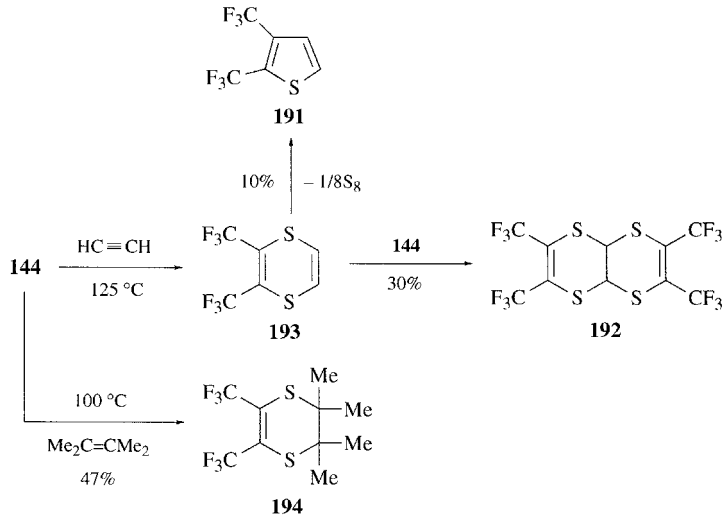


B. Reactions of Isolable 1,2-Dithietes

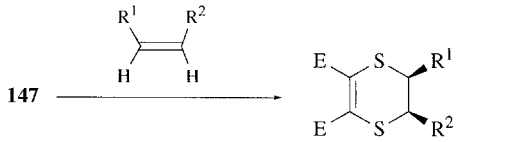
Dithietes as well as their isomeric α-dithiones may undergo dimerization or oligomerization. Thus, dithiete **144** (bp 93°–94°C) crystallized on standing for two months at 25°C to give the dimer **189** (mp 110°–111°C) in 87% yield (61JA3434). A solution of **147** in $CHCl_3$ or C_6H_6, when allowed to stand, afforded a mixture of **147,** dimer **148,** and tetramer **149,** although solutions of **148** and **149** in $CHCl_3$ remained unchanged. However, these three compounds are interchangeable to each other in a mixture of MeCN and $CHCl_3$ or on treatment with silica gel in $CHCl_3$ (98JOC8192). In solution, **163** is in equilibrium with its [4 + 2] dimer **190** (80CB1898). The ratio **163:190** depends upon temperature and solvent: **163:190** = ca. 80:20 at 30°C, 45:55 at −10°C, and 25:75 at −30°C in CD_2Cl_2.



[4 + 2] Cycloadditions in which 1,2-dithietes acted formally as dienes are among the most typical reactions of 1,2-dithietes. The dithiete **144** is highly reactive and capable of reactions even with simple alkenes and alkynes (60JA1515; 61JA3434, 61JA3438). Thus, **144** reacted with acetylene to form **191** and **192** with the initial formation of **193,** and with tetramethylethylene to give **194.** Other [4 + 2] cycloadditions of **144** involved those with ethylene, cyclohexene, *trans*-stilbene, ethyl vinyl ether, butyl vinyl sulfide, 3-hexyne, and DMAD.



The dithiete **147** reacted with a range of dienophiles probably through the ring-opened tautomer. For example, reactions with ethyl vinyl ether and *cis*-1,2-bis(butylthio)ethylene gave **195a** and **195b,** respectively; the reaction with the latter alkene is stereospecific (97MI2). Dithietes **134** and **171a**/**171b** reacted with strained acetylenes **133** and **170a** to form highly congested 1,4-dithiins **196a** (81TH1), **196b** (79TH1), and **196c** (83TH1).



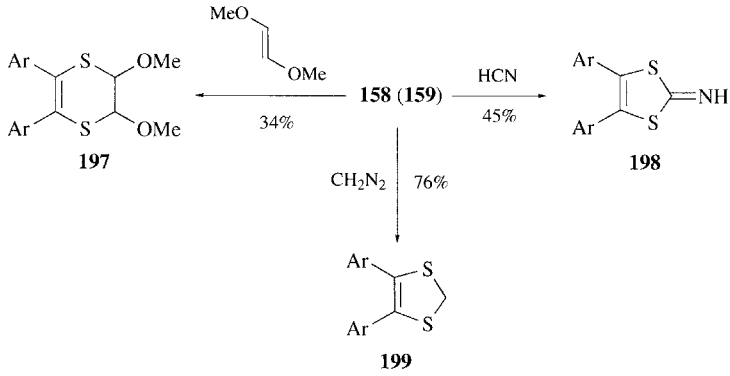
195a: R^1 = H, R^2 = EtO, 65%
195b: R^1 = R^2 = *n*-BuS, 72%

134: X = S
171a: X = SO_2
171b: X = CH_2

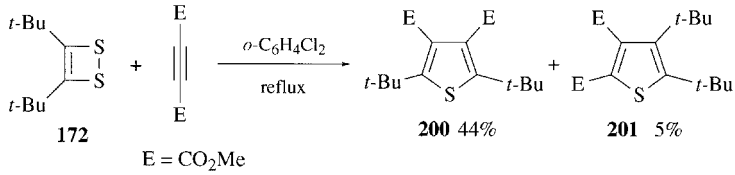
133: Y = S
170a: Y = SO_2

196a: X = Y =S
196b: X = Y = SO_2
196c: X = CH_2, Y = S

The α-dithione **158** (dithiete **159**) underwent a [4 + 2] cycloaddition with *trans*-(1,2-dimethoxy)ethylene to give **197** in addition to reactions with HCN and CH_2N_2, which yielded **198** and **199,** respectively (74JA3502).

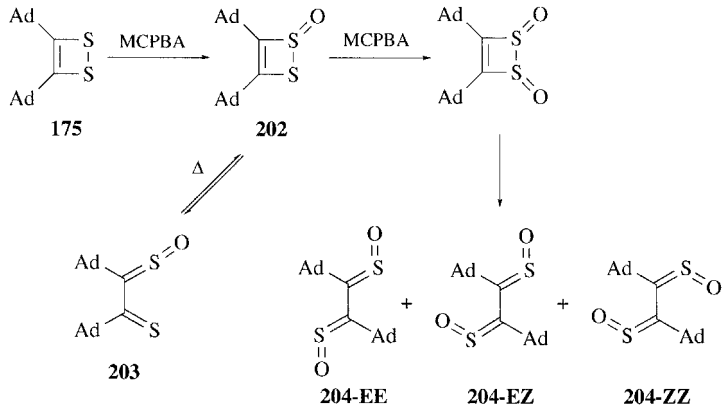


The thermally stable and hence less reactive dithiete **172** reacted with DMAD under forcing conditions to give thiophenes **200** and **201** through an uncertain mechanism (90BCJ1026).

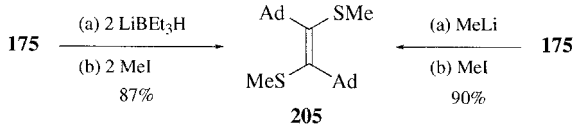


Oxidation of the dithiete **175** with MCPBA (1 equiv.) yielded the dithiete 1-oxide **202** which, when heated in refluxing toluene, formed a mixture of the ring-opened product sulfine **203** (blue, λ_{max} 576 nm) and **202** in the ratio 7 : 1 (95TL8583). Further oxidation of **202** or oxidation of **175** with

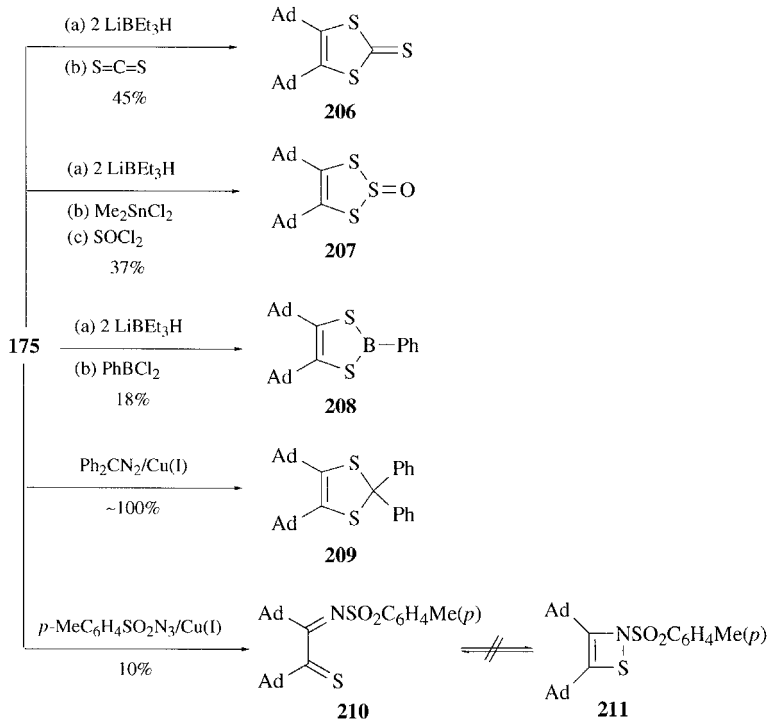
excess MCPBA resulted in the formation of **204,** the first α-disulfine, as a mixture of *E,E,E,Z,* and *Z,Z* isomers in high yield (>90%). The *E,E* isomer **204**–EE was the major product (65–70% isolated yield), whose structure was determined by an X-ray analysis. Minor products *E,Z* and *Z,Z* isomers, formed in the ratio 27 : 2, were not obtained in pure form. Oxidation of **171a** and **172** gave similar results (95TL8583).



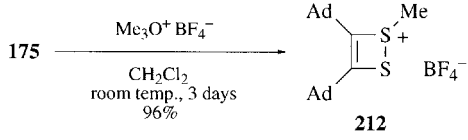
Two methods shown below converted **175** to the *Z* alkene **205** in high yields. No expected *E* alkene with two bulky 1-adamantyl groups in cis positions was formed because of the quick isomerization at the intermediate stage (98BCJ1181).



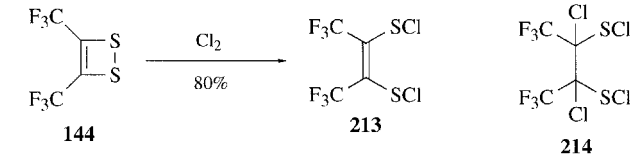
Five-membered heterocycles **206–209,** in which two 1-adamantyl groups occupy cis positions, were synthesized from **175** (98BCJ1181). The reaction of tosyl azide with **175** gave **210,** which has no tendency to cyclize to **211.** These results, together with the fact that compound **173** exists in the ring-opened form, led to the conclusion that, when four-membered rings are constituted by a combination of one S–X (X = N, O, S) and one C–C double bonds, 1,2-dithietes are probably the only species that can adopt a ring-closed structure as the predominant isomeric form.



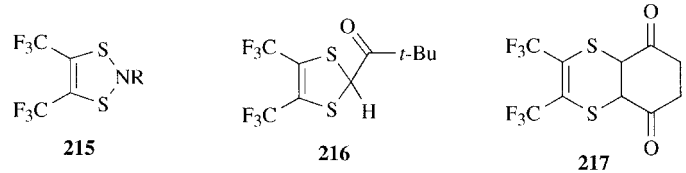
Treatment of the dithiete **175** with Meerwein reagent yielded the sulfonium salt **212** in high yield (99UP1).



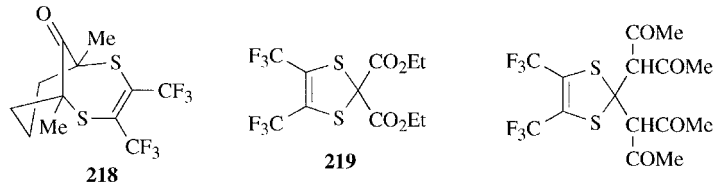
The bifunctional sulfenyl chloride **213** was obtained by chlorination of **144** in good yield, although excessive chlorination led to the saturated compound **214** (94CB533). A series of compounds **215**–**220** were obtained from **213** by reactions with secondary amines; *tert*-butyl methyl ketone; hexane-2,4-dione; 2,6-dimethylcyclohexanone; diethyl malonate; and acetylacetone, respectively.



144 213 214

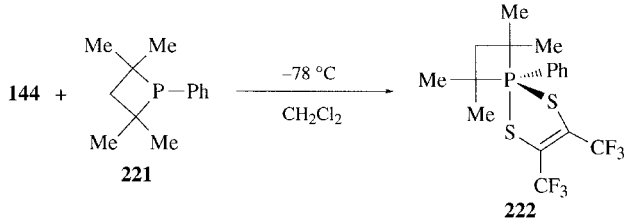


215 216 217

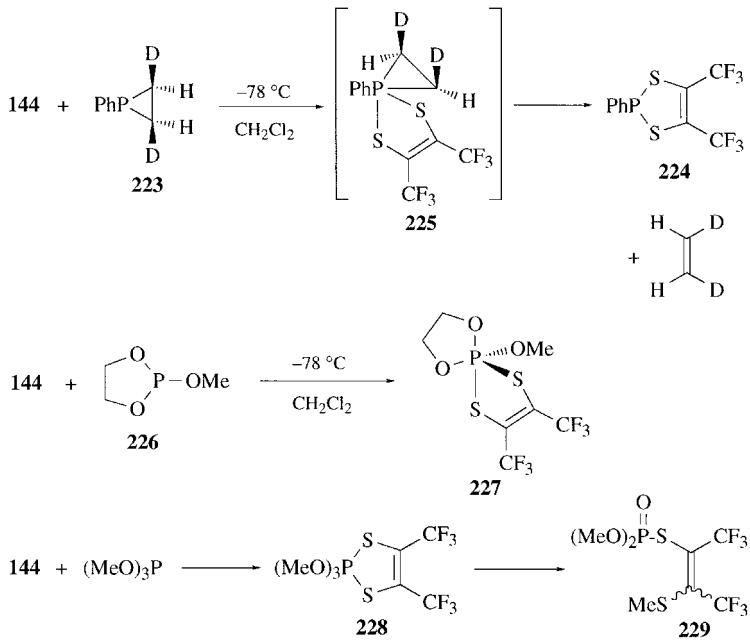


218 219 220

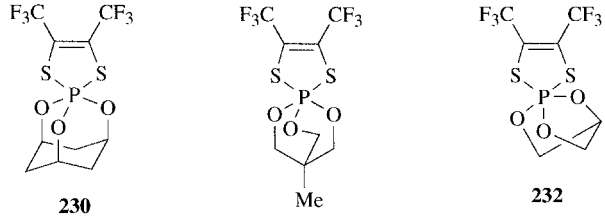
Many papers reported reactions of **144** with phosphorus compounds [72JCS(CC)395; 74MI1, 74JA317; 76JA2924; 77JCS(P1)80; 78JA7300; 80JA5073; 83DOK1264; 84MI1, 84MI2; 85PS71]. Given below are representatives. The reaction of **144** with a four-membered phosphetane **221** yielded the thermally stable phosphorane **222** [72JCS(CC)395, 78JA7300], whereas the reaction with a three-membered phosphirane **223** resulted in the stereospecific formation of *cis*-1,2-deuterioethylene and the phosphine **224** through concerted fragmentation of the probable phosphorane intermediate **225** (74JA317; 78JA7300). Treatment of **144** with methyl ethylene phosphite (**226**) gave the phosphorane **227,** whereas that with trimethyl phosphite produced the thermally unstable phosphetane **228,** which decomposed readily at room temperature to the alkene **229** [72JCS(CC)395, 78JA7300].



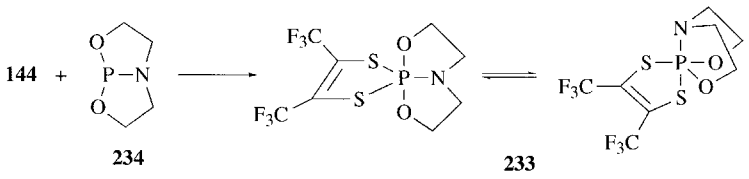
221 222



A series of caged polycyclic thiooxyphosphoranes such as **230–232** were synthesized by allowing **144** to react with bicyclic phosphites (76JA2924). NMR spectra of **230** and **231,** which contain only a six-membered ring in the bicyclic moiety, showed that, over the temperature range investigated, there is a rapid intramolecular motion which renders the nuclei under investigation equivalent. Meanwhile, introduction of five-membered rings led to an inhibition of this intramolecular process, and the activation energy of 12 kcal/mol is found for **232.**

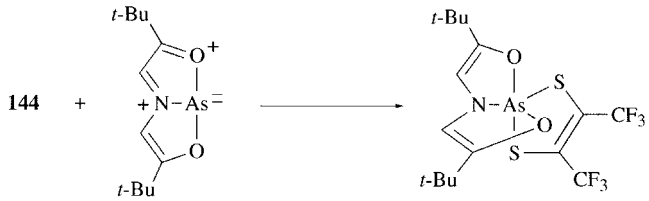


Compound **233** was prepared from **144** and **234,** and its intramolecular ligand reorganization was investigated by variable temperature NMR spectroscopy (80JA5073).



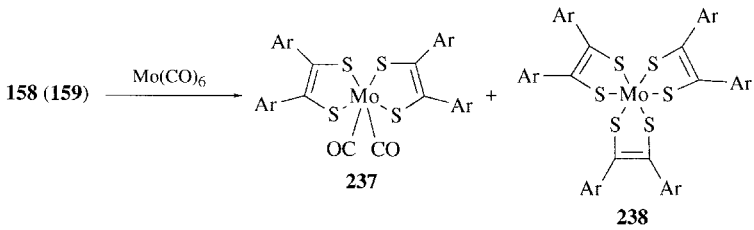
234 233

A stable 10-As-3 species (**235**) underwent a ready reaction with **144** to give adduct **236,** which exhibited a single *tert*-butyl and ring-proton resonance in the ^{1}H NMR at room temperature and showed a single resonance at δ −54.0 in the ^{19}F NMR (85JA1089). The low temperature ^{1}H and ^{19}F NMR showed a split of the room temperature resonances suggestive of the frozen structure of **236.**



235 236

A great number of dithiolene complexes were synthesized from **144** and their properties were investigated in detail [63IC641, 63IC1275, 63JA1584; 64JA2799; 66JCS(CC)771; 67JCS(CC)670), 67IS8; 70IC1820; 71IC1410, 71JOMC19, 71JCS(A)3254; 72JCS(D)1109, 72JA8375; 73IC518, 73JOM113; 75JCS(D)701; 81IC3924; 87OM480]. These are summarized in Table IV. The formulas given in Table IV are simply based on the description provided in the original papers without any criticism. Although a plethora of complexes were derived from these compounds as starting materials, they are not included in Table IV. The α-dithione **158** (dithiete **159**) also formed complexes **237** and **238** on treatment with $Mo(CO)_6$ (74JA3502). Such complexes were also often obtained from reactive dithiete species as described later.



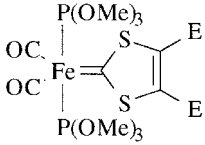
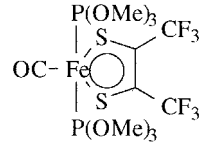
237 238

C. Formation and Reactions of 1,2-Dithietes as Reactive Intermediates

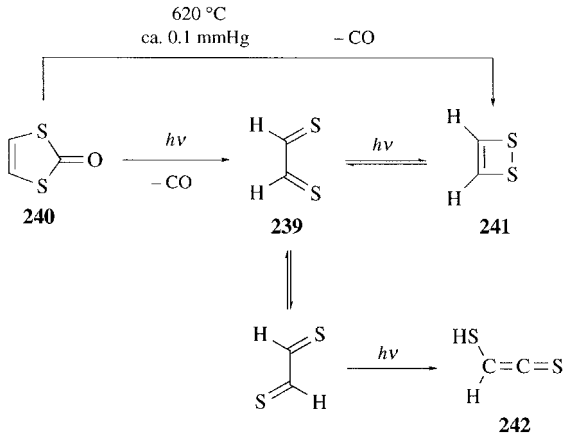
The parent 1,2-dithiete, simple dialkyl or diaryl substituted 1,2-dithietes, and benzo-1,2-dithiete are unstable, highly reactive species and are not isolable under ordinary conditions.

The formation of the parent dithioglyoxal (**239**) was observed by spectroscopic means on photolysis of **240** in methanol glass at 77 K (78NJC331). The reversible interconversion between **239** and its photoinduced tautomerization product 1,2-dithiete (**241**) was also observed on irradiation at selective wavelengths. Meanwhile, photoinduced thione (**239**)–thioenol (**242**) tautomerism was observed by IR spectroscopy after the photolysis of argon-matrix isolated **240** at 10 K (82NJC401). Thermal fragmentation of **240** also results in the formation of the 1,2-dithiete **241** (83JA4519;

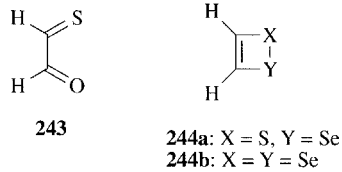
TABLE IV
Complexes Derived from **144**

Starting materials	Metal complexes	References
$Mo(CO)_6$	$Mo(C_4F_6S_2)_3$	63IC641, 67IS8
$Hg[Fe(CO)_3NO]_2$	$C_4F_6S_2FeNO$	63IC1275
$Fe(CO)_5$	$C_4F_6S_2Fe_2(CO)_6$	63JA1584
$M(CO)_6$(M = Cr, W)	$M(C_4F_6S_2)_3$	64JA2799
$Co_2(CO)_8$	$[(CF_3)_2C_2S_2Co(CO)]_3$	66JCS(CC)771
$Ni(CO)_4$	$NiS_4C_4(CF_3)_4$	67IS8
$Fe(CO)_5$	$(CF_3)_2C_2S_2Fe(CO)_3$	71IC1410
$Ru_3(CO)_{12}$	$(CF_3)_2C_2Ru_2(CO)_6$	71IC1410
$Fe_2(CO)_6(XR)_2$ (X = SMe, SEt, SPh, SePh)	$\{Fe(XR)(CO)[S_2C_2(CF_3)_2]\}_n$ (n = 4 in $CHCl_3$, n = 2 in Me_2CO)	71JOMC19
InX(I) (X = Cl, Br, I)	$In(III)[C_2S_2(CF_3)_2]X_n$	71JCS(A)3254
$Fe_2(CO)_9$	$[Fe(CO)_3\{S_2C_2(CF_3)_2\}]_n$	72JCS(D)1109
$Fe(CO)_5 + H_2S$	$Fe_3S_{14}C_{16}F_{24}H_2$	72JA8375
$Fe_2(CO)_6(SMe)_2$	$[Fe_2(\mu\text{-}SMe)_3(CO)_6][Fe_2(S_2C_2(CF_3)_2)_4]$	73IC518
InCp(I) (Cp = C_5H_5)	$In(III)Cp[C_2S_2(CF_3)_2]$	73JOM113
$Fe_2(CO)_6(XR)_2$ (X = SMe, SEt, SPh, SePh)	$[Fe_2(XR)_3(CO)_6]^+[\{Fe\{(CF_3)_2C_2S_2\}_2\}_2]^-$	75JCS(D)701
		81IC3924
$[CpMo(CO)_3]_2$	$Cp(CO)_2Mo[\mu\text{-}S_2C_2(CF_3)_2]_2MoCp$	87OM480

85CPL575). The fragmentation was investigated by variable-temperature photoelectron spectroscopy (83JA4519). The reactive species **241** generated in this way was identified by photoelectron spectral and quantum chemical means. The microwave spectrum (over the range 18–27 GHz), permanent dipole moment [μ_b=1.329(2) D], and molecular structure of **241** were also investigated (85CPL575).

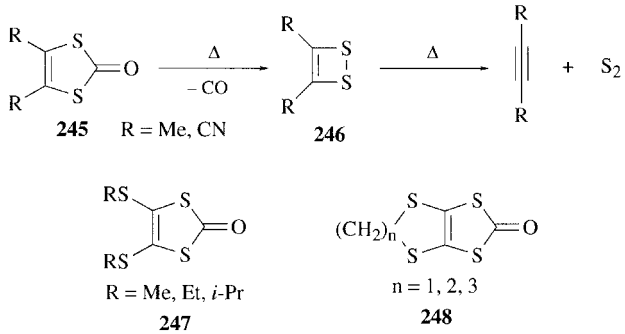


The oxygen analog **243** of **239** (90JOC2596) and selenium analogs **244a**/**244b** of **241** (87AGE343) were generated and their photoelectron spectra were recorded.

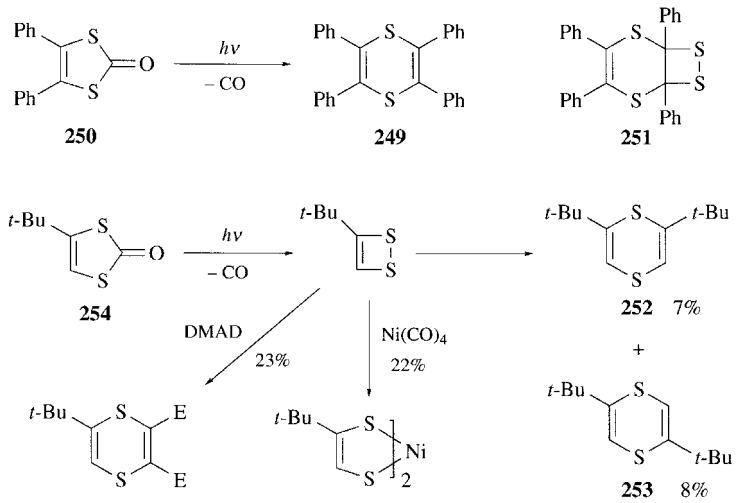


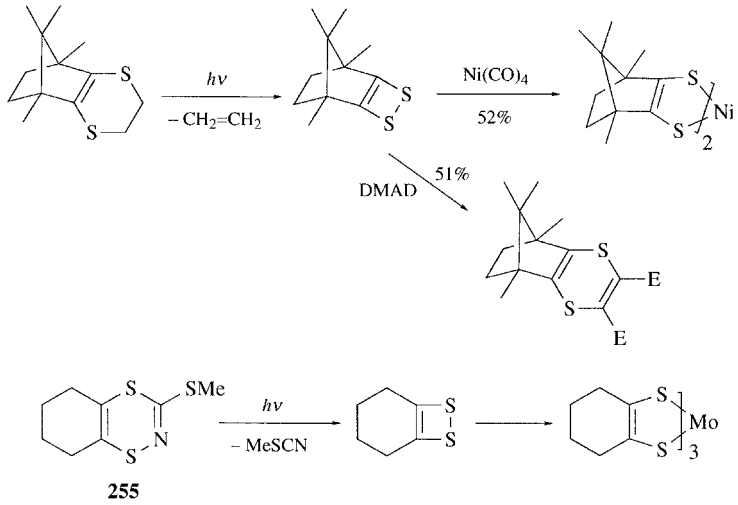
Thermolyses of **245**–**248** were investigated (83JA4519). 1,2-Dithietes **246,** thermodynamically favored products in the equilibrium with their 1,2-dithione counterparts, were satisfactorily generated from **245** and their photoelectron spectra were recorded. At higher temperatures, **246** decomposed to the corresponding alkynes and S_2. Meanwhile, on thermolysis of **247,** the corresponding 1,2-dithiones, and not 1,2-dithietes, were formed in the cases of R = Me and Et, and their photoelectron and IR spectra were

recorded. On thermolyses of cyclic precursors **248,** a smooth reaction took place only when $n = 1$ with the probable formation of the corresponding 1,2-dithione.



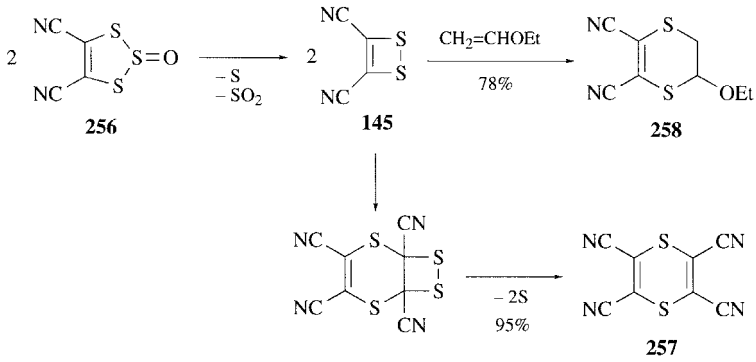
The following photochemical conversions also involve 1,2-dithietes as intermediates whose chemical trapping was reported in most cases. The formation of the dithiin **249** from **250** may best be explained by the formation of the dithiete dimer **251** and the loss of S_2 (73ZC424). The formation of **252** and **253** from **254** (78NJC331) should be compared with the sulfuration of the acetylene **182** with elemental sulfur (93BCJ623). The photolysis of **255** provides a rare example when the ejection of a nitrile was employed for the generation of a 1,2-dithiete (73ZC431).





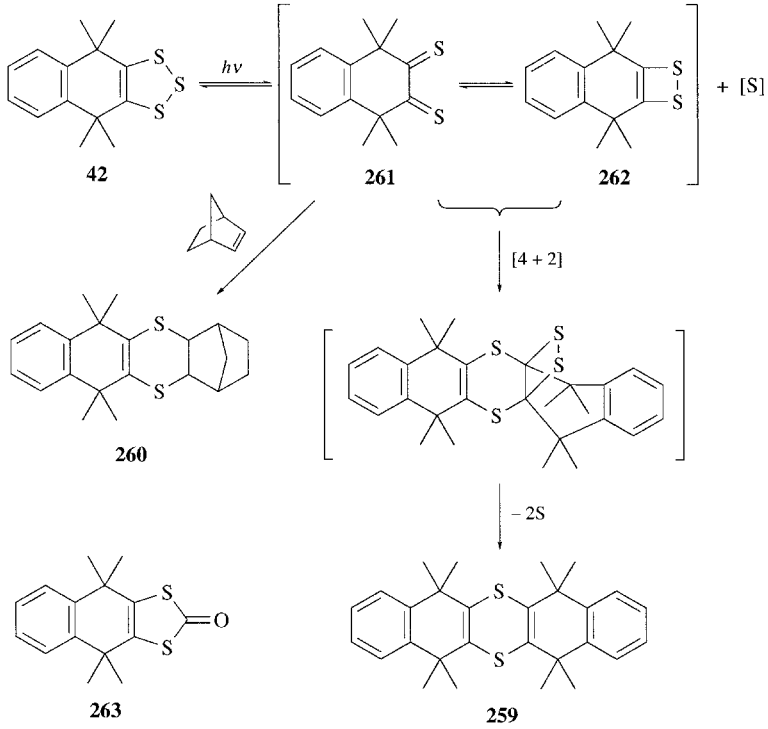
255

As already described, oxidation of sodium mercaptomalenonitrile (**146**) formed the dithiete **145,** though it was not isolable (62JA4746, 62JA4756, 62JA4772). Decomposition of the trithiole **256** in DME at room temperature also produced **145,** which dimerized to yield **257** as the final product or was trapped by ethyl vinyl ether to give **258** (62JA4772).

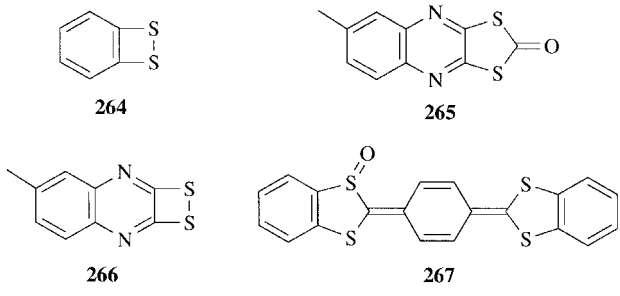


256 **145** **258** **257**

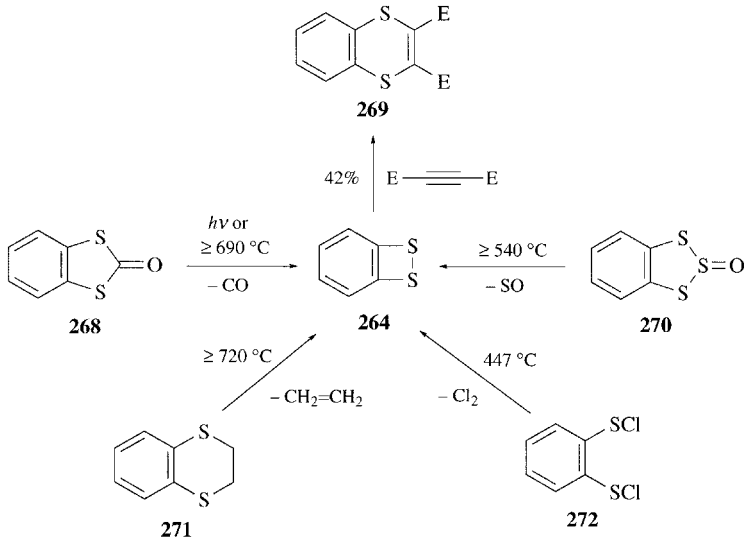
The photolysis (λ = 365 nm) of **42** alone resulted in a very slow conversion to the 1,4-dithiin **259,** whereas the irradiation in the presence of norbornene quickly produced **260** in 95% yield (88CL657). Therefore, the conversion of **42** to **261** (or **262**) and sulfur atom should be reversible. The photolysis of **263** in 3-methylpentane at 77 K yielded a mixture of **261** and **262,** as suggested by the electronic spectrum, which showed two absorption maxima at 580 and 370 nm (89TL2955). Similar results were also obtained for selenium species (88CL657; 89TL2955).

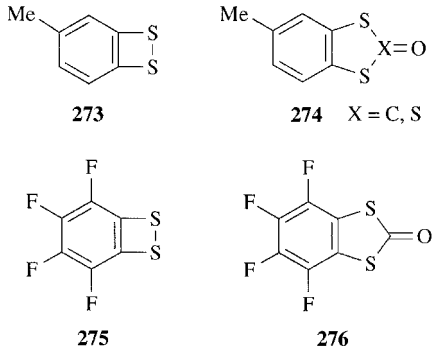


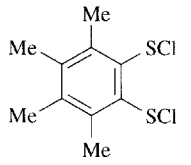
The preparation of benzo-1,2-dithiete (**264**) had been claimed by oxidation of 1,2-benzenedithiol (25JIC318). However, later work has shown that the reaction product was probably a polymeric mixture (61JOC4782). Subsequently, compound **265** was irradiated to give a mixture of CO, sulfur, and dithiin and thiophene derivatives, which could, at least in part, be explained by the formation of **266** (72JHC707). Results of the thermolysis of **267** were also rationalized in terms of the intermediacy of *o*-dithiobenzoquinone (the tautomer of **264**) (78JOC2084).



The photolysis of **268** resulted in the transient formation of the benzodithiete **264,** which exhibited a weak absorption at 370 nm and reacted with DMAD to form the adduct **269** (79JOC1977). Thermolyses of compounds **268, 270,** and **271** all led to the formation of the dithiete **264,** whose structure was proved from the gas-phase UV photoelectron spectrum and the IR spectrum in an argon matrix (82JOC1979). The dithiete **264** was also generated by thermolysis of **272** and subjected to a real-time photoelectron spectroscopic analysis (88PS291). The thermolysis method was applied to the generation of **273** from **274** (82JOC1979) and of **275** from **276** (88PS291). The probable thermolysis product of **277** is **278,** but not the expected dithiete **279** (88PS291). Formation of **280** was claimed as an intermediate upon irradiation of **281** in an argon matrix at 10 K. Depending on the wavelength, the equilibrium lies either on the side of **280** or of **282** (94JPR444).







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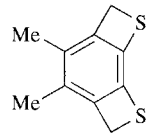

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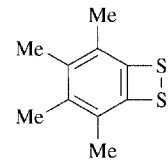

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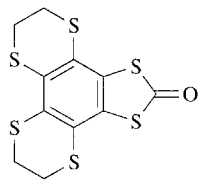
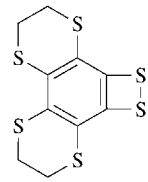


281



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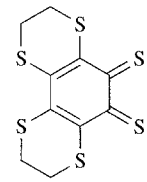
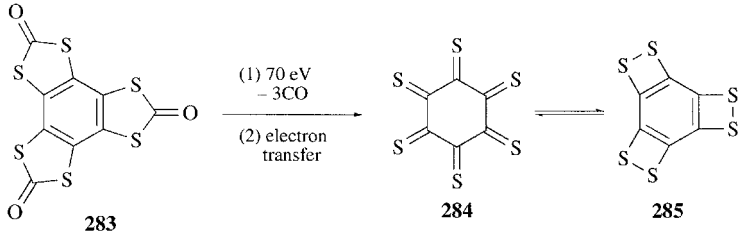
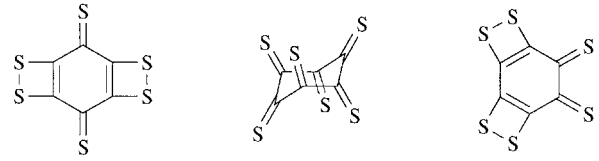


282

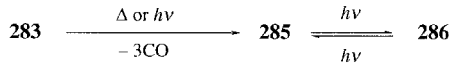
A species that was proposed to be the hexathione **284** or its valence tautomer dithiete **285** was generated from **283** as a stable neutral molecule in beam experiments by subjecting $C_6S_6^{-\cdot}$ to neutralization reionization mass spectrometry (89CB2411). Calculation studies predicted that stability of **284–288** decreases in the order of **285** (D_{3d} dithiete), **286** (D_{2h} quinoid), **287** (D_{3d} chair thione), and **284** (D_{6h} planar thione) (the order of **285** and **286** may depend on the method of calculations) (90AGE1410; 96MI3). A yellow C_6S_6 isomer, which could be interconverted photochemically into a colorless second isomer C_6S_6, was obtained upon matrix photolysis or flash pyrolysis of **283.** The structure of these isomers was most likely **285** and **286,** as shown by comparison of the experimental vs the calculated IR spectra of the five possible cyclic C_6S_6 isomers **284–288** (92CB265).



283 284 285



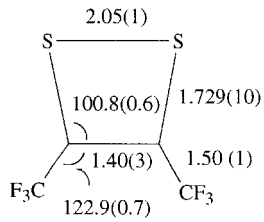
286 287 288



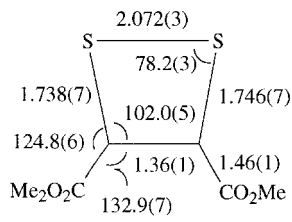
D. Structure and Spectroscopy

Molecular structures of 1,2-dithietes **144** (determined by vapor-phase electron diffraction) (76JA899), **147** (X-ray crystallography) (98JOC8192), **175** (X-ray crystallography), [94UP1; 98AX(C)1175], and **187** (X-ray crystallography) [75JCS(CC)756] are given in Figure 5 with relevant bond lengths and angles. The S–S and C–S bond lengths of **144, 147,** and **175** are in the range of those of normal disulfides, whereas elongation of the S–S bond is observed for **187.** The C=C bond of **147** and **175** is slightly longer than usual C=C bonds and considerably longer for **144.** The four-membered rings are essentially planar for all of the compounds. The torsion angle between two adamantyl groups of **175** is only 7.4° despite the bulkiness of the cis-oriented adamantyl groups, although the exo-adamantyl-C–C bond angle is enlarged to 138.9°.

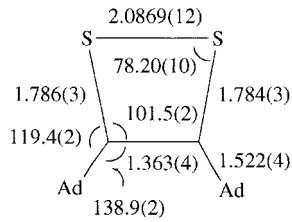
Although ^{1}H NMR chemical shift values of the ring hydrogen of dithietes would provide a criterion on their potential aromaticity associated with a formal 6π-electronic structure, no dithiete, having a ring hydrogen, has ever been obtained under conditions which allow measurement of the NMR spectrum. ^{13}C NMR chemical shift values of the ring carbons of dithietes are summarized in Table V. A remarkable downfield shift (>20 ppm) is observed on going from the dithiete **175** to its *S*-oxide derivative **202** (95TL8583).



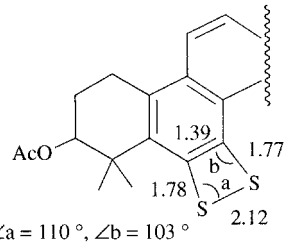
Dithiete **144** (vapor phase electron diffraction)



Dithiete **147** (X-ray crystallography)



Dithiete **175** (X-ray crystallography: values of one of the two independent molecules)



Benzodithiete **187** (X-ray crystallography)

FIG. 5. Molecular structures of dithietes **144, 147, 175,** and **187** (Å for bond lengths and degrees for bond angles).

TABLE V

^{13}C NMR CHEMICAL SHIFT VALUES[a] OF THE RING CARBONS OF REPRESENTATIVE 1,2-DITHIETES

Dithietes	**147**[b]	**134**[c]	**171a**[c]	**172**[d]	**175**[c]	**176**[c]	**177**[c]	**178**[c]	**202**[f]
Chemical shift values (δ)	131.5	139.3	137.7	140.7	141.9	137.1 143.8	137.1 144.3	135.3 135.7	152.8 159.2

[a] $CDCl_3$ as solvent.
[b] 98JOC8192.
[c] 79HI153.
[d] 82JCS(S)314.
[e] 83SCJ623.
[f] 95TL8583.

UV-VIS spectral data of isolable 1,2-dithietes are summarized in Table VI. Most dithietes are colored pale yellow to orange or red. This is due to the tails of weak absorption maxima at about 340–350 nm. Spectra of transient dithietes were also determined at low temperature (78NJC331; 79JOC1977; 82JOC1979; 89TL2955).

Information about the C=C stretching vibration of stable dithietes is limited probably because of a very weak absorption due to this motion (1630 cm^{-1} for **144**) (82NJC401), although identification of the transient dithietes was often based on IR spectroscopy (74JA3502; 82NJC401, 82JOC1979; 83JA4519; 87AGE343; 92CB265; 89JA761). Raman spectral data are not available, though apparently informative. The microwave spectrum of the parent 1,2-dithiete was reported (85CPL575).

No discussion of the fragmentation pattern of dithietes by mass spectroscopy has appeared. Only molecular and major fragmentation peaks

TABLE VI

UV/VIS SPECTRAL DATA OF REPRESENTATIVE 1,2-DITHIETES

Dithietes	λ_{max}/nm (ϵ)	Solvent	Reference
144	340 (80), 238 (7410)	Isooctane	82JCS(S)314
147	287 (13000), 249 (2500), 214 (3400)	Cyclohexane	98JOC8192
134	351 (56), 273 (220), 224 (7690)	Isooctane	82JCS(S)314
172	331 (50), 276 (380)	Isooctane	82JCS(S)314
175	349 (265), 278 (490), 229 (5600)	Hexane	93SCJ623
176	349 (200), 303 (2540), 233 (4490)	Hexane	93SCJ623
177	345 (170), 305 (3130), 233 (5360)	Hexane	93SCJ623
178	*ca*. 345 (sh) (980), 302 (2020), 290 (2060)	Hexane	93SCJ623
187	300 (12100), 253 (24000), 249 (24000)		77JCS(P1)515
202	286 (2350), 275 (2190), 224 (5000)	Hexane	95TL8583

of **147** (98JOC8192), **172** [82JCR(S)314], and **175–178** (93BCJ623) were given.

Photoelectron spectroscopy is among the methods most extensively used for electronic structure consideration of the both transient and stable dithietes (82JOC1979; 83JA4519; 87AGE343; 88PS291; 90JOC2596). Photoelectron spectra of a series of 1,2-dithietes and benzo-1,2-dithietes including the parent compound are in agreement with the ring-closed structure. This conclusion was further supported by quantum chemical calculations. For example, the He(I) photoelectron spectra of a series of stable dithietes were determined and assigned with respect to the orbital consequence derived from an STO-3G model calculations (Figure 6) (83HCA801). In all cases the two highest occupied molecular orbitals are $b_2(\pi)$ = HOMO, $a_2(\pi)$, with exception of the dithiete 144, where the sequence $b_2(\pi)$, $a_2(\pi)$ or $a_2(\pi)$, $b_2(\pi)$ is uncertain.

A large number of dithiete radical cations **289** were generated and studied by electron spin resonance spectroscopy (ESR) (72JA6125; 84PS132; 85JA4175; 86CB3766; 87H321; 88PS121, 88PS291). Many of these radical cations collapse on warming to the corresponding more stable 1,4-dithiin radical cations **290** (72JA6125; 84PS132; 85JA4175; 86CB3766). 1,2-Dithiete radical cations have never been isolated in the crystalline salt form.

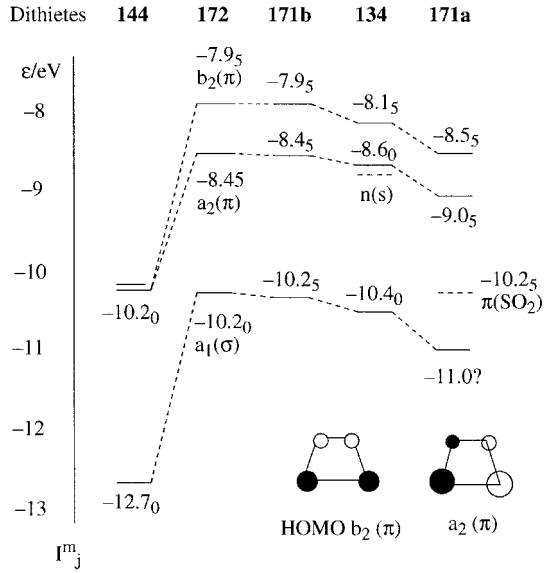
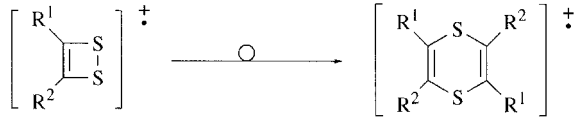
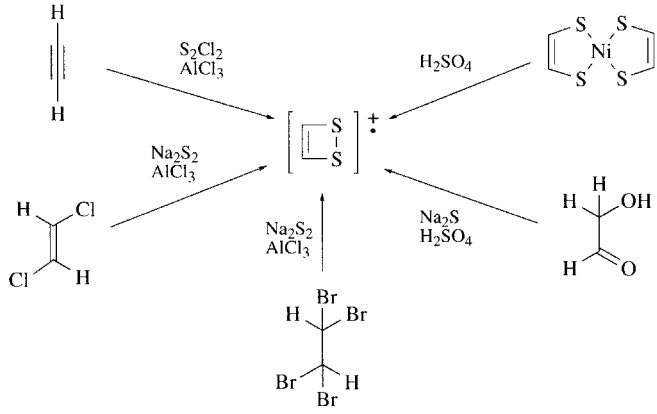


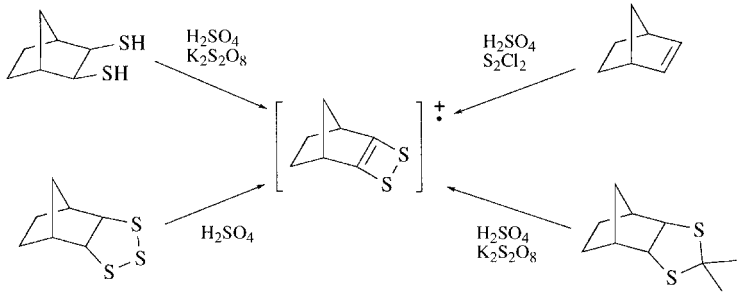
FIG. 6. Orbital correlation diagram for the photoelectron spectra of 1,2-dithietes (the orbital energies given are the negative ionization energies, $-I^m$j in eV).

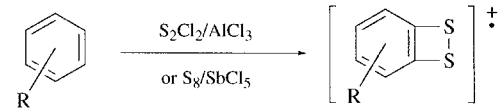


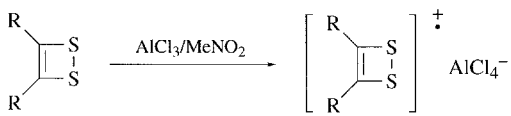
289 290

The following schemes cover those methods which were used for the generation of dithiete radical cations.

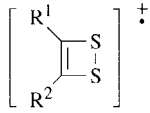




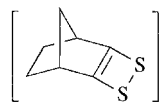




The following summarizes *g*-values and hyperfine splitting values by ^{1}H (a_H) and by ^{33}S (a_{33S}) in natural abundance for the representative 1,2-dithiete radical cations.



$R^1 = R^2 = H$: $g = 2.0153$, $a_H = 0.275(2)$, $a_{33S} = 0.85$ (mT)[a]
$R^1 = t$-Bu, $R^2 = H$: $g = 2.0156$, $a_H = 0.321(1)$, $a_{33S} = 0.88$ (mT)[a]
$R^1 = R^2 = Me$: $g = 2.0148$, $a_H = 0.215(6)$, $a_{33S} = 0.76$ (mT)[a]
$R^1 = R^2 = Me$: $g = 2.0155$, $a_H = 0.219$[b]
$R^1 = R^2 = t$-Bu: $g = 2.0159$, $a_{33S} = 0.81$ (mT)[a,c]
$R^1 = R^2 = CF_3$: $g = 2.0160$, $a_{33S} = 0.86$ (mT)[c]
$R^1 = R^2 = (CH_2)_5$: $g = 2.0157$, $a_{33S} = 0.78$ (mT)[c]
$R^1 = R^2 = Ph$: $g = 2.0148$[a]



$g = 2.0144$[d]
$a_H = 2.75$ (1 H)
$= 0.90$ (4 H)

[a]86CB3766. [b]87H321. [c]84PS132. [d]85JA4175.

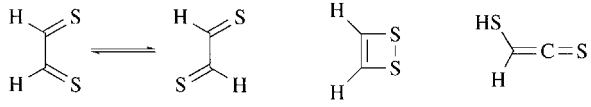
The ESR spectra of the radical anions, generated by one-electron reduction of the α-oxothioketone **173** and the dithiete **172**, were determined, and spin densities were calculated from the coupling constants and, especially, from the anisotropic values (87CB575).

E. Theoretical Study

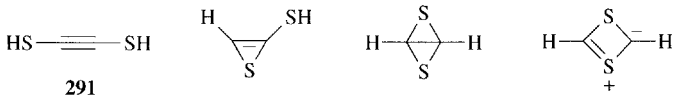
Numerous calculations on 1,2-dithietes and related species have appeared because of their intriguing electronic structure and to collect further supporting evidence for the experimental findings (62AK181, 62AK265; 75JCS(P2)559; 80JA6687; 82JOC1979, 82ZN125; 83HCA801, 83JA4519; 85ZC50; 87JCC389, 87JST149; 88CCC2096, 88PS121, 88PS291; 89JA761; 90AGE1410, 90JA7529, 90ZC176, 90JST247; 91JST287, 91IJQ335, 91CPL175; 92CB265, 92ZN203; 95MI1; 96CPL407, 96IJQ859).

Six species, **239, 242,** and **291–294,** exist as the isomers of the parent dithiete **241.** The relative thermal stability of these species is one of the chief objectives of calculation studies. *Ab initio* calculation at the STO-4G level predicted that stabilities vary in the order **241** > **291** > **242** > **239c** > **239t** > **293** > **292** (82UP1). The most elaborate calculations in 1987 (optimization of molecular structures on the 6-31G* SCF level, addition of 3-21G* SCF zero-point vibrational, and MP4 SDQ) indicated that **241** and *cis*-dithioglyoxal (**239c**) lie close in energy (within 3 kcal/mol) with **239c** more stable (87JCC389). *Trans*-dithioglyoxal (**239t**) is found to be 4.1 kcal/

mol more stable than **239c** and faces a barrier to internal rotation of 5.5 kcal/mol. The results of a combined experimental and theoretical IR spectroscopic approach (89JA761) in 1989, on the contrary, suggested that **241** is more stable than **239** in accordance with the results of photoelectron (83JA4519) and microwave (85CPL575) spectroscopic studies. Calculations in 1991 (91CPL175) suggested the crucial importance of polarization functions for the calculation of molecules with third-row elements. Thus, although, with standard values for the exponents, **241** was predicted at MP2/6-31G (3d) to be 3.40 kcal/mol less stable than **239t;** at MP2/6-31G (3df) **241** is 5.36 kcal/mol more stable than **239t.** A second set of f-functions led to a predicted higher stability of **241** by 8.48 kcal/mol [MP2/6-31G (2d2f)] (91CPL175). The best estimate, which includes zero-point corrections, is that **241** is 6.3 kcal/mol more stable than **239t,** in agreement with the experimental results (91CPL175).



239c **239t** **241** **242**



291 **292** **293** **294**

Cis-dithioglyoxal **239c** was predicted not to be cis and planar (C_{2v}) but to adopt a gauche C_2 conformation (87JCC389; 89JA761). The barrier for **241** to ring open to **239c** (gauche) was calculated to be 32.1 kcal/mol (3-21G* SCF) or 35.5 kcal/mol (6-31G* SCF) (90JA7529). The 3-21G* CASSCF calculation predicted the barrier of 19.9 kcal/mol (90JA7529). The 6-31G* MP4SDTQ method predicted the activation energy of 21.9 kcal/mol (90JA7529). The same study found a transition state geometry (SCCS dihedral angle, 18°; CCS ring angle, 111°) nicely intermediate between **241** and **239c.** The least motion process in the ring-opening **241** to **239c** is a forbidden [$_{\pi}2_{s} + {}_{\pi}2_{s}$] reaction, while a transition state with C_2 symmetry is an allowed [$_{\pi}2_{s} + {}_{\pi}2_{a}$] reaction (75JCS(P2)559).

Molecular structure of the dithiete **241** (C_{2v}) was theoretically predicted by many ways (80JA6687; 85ZC50; 87JCC389; 88CCC2096; 90JA7529, 90ZC176; 91JST287, 91CPL175). Typical results (90ZC176) are given in Table VII together with the experimental values (microwave spectroscopy) (85CPL575).

TABLE VII

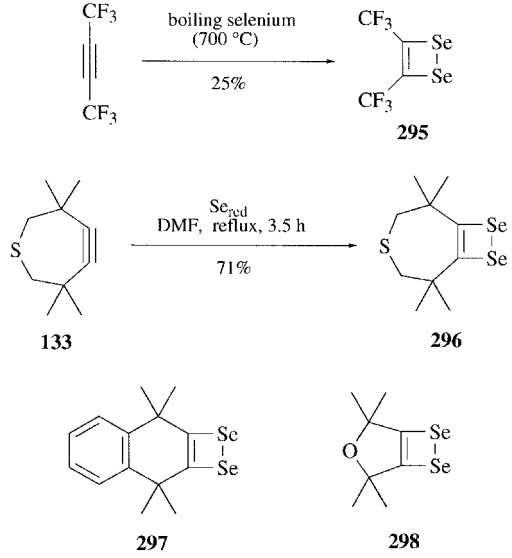
EXPERIMENTAL (MICROWAVE SPECTROSCOPY)[a] AND CALCULATED[b] MOLECULAR STRUCTURES OF THE PARENT 1,2-DITHIETE (**241**)[c]

	r_{CC}	r_{CH}	r_{CS}	r_{SS}	∠HCS	∠CCS
Microwave spectroscopy	1.350	1.080	1.753	2.096	126.7	102.3
SCF/3-21G*	1.326	1.066	1.770	2.105	126.1	102.8
SCF/6-21G*	1.324	1.071	1.765	2.096	125.5	102.6
MP2/6-21G*	1.352	1.083	1.755	2.112	125.2	102.5

[a] 85CPL575.
[b] 90ZC176.
[c] Bond length (r), Å; bond angle (∠), deg.

F. 1,2-DISELENETES

Few stable 1,2-diselenetes are known. The 1,2-diselenete **295** was obtained as a dark-red liquid by passing hexafluoro-2-butyne through vapors of boiling selenium [66JCS(CC)771, 70IC1820]. The strained acetylene **133** reacted with red selenium in refluxing DMF to yield the 1,2-diselenete **296** [mp 109°C, λ_{max} 425 nm (log ϵ, 2.0)] (92TH1). The same 1,2-diselenete **296** was also formed by other reactions (92TH1). Sterically congested 1,2-diselenetes **297** and **298** (or their ring-opened tautomers) were generated and trapped with alkenes (87TL5699; 89TL2955).



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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Chemistry of Nitronaphthyridines

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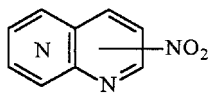
I. Introduction

The chemistry of naphthyridines has developed significantly since the late 1970s. Many compounds containing the naphthyridine ring system show interesting and useful chemical and biological properties and are applied in medical treatment (84MI1; 97MI1).

Naphthyridines are (just as pyridines) characterized as π-deficient systems. Introduction of an electron-withdrawing group such as the nitro group further depletes the ring of its π-electrons and lowers its electron density. On account of this low electron density, nitronaphthyridines show a high reactivity to nucleophilic reagents and low reactivity to electrophiles; several characterictic examples of this behavior are shown in this chapter.

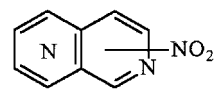
The chemistry of nitronaphthyridines has not been previously reviewed. In a number of reviews, concerning the chemistry of naphthyridines [82H382; 84MI2; 83AHC114, 83AHC154; 85KPZ794; 97MI2] or other related subject a eas [85KGS158; 86CCA38; 87KGS1016; 90AHC376; 91MI1; 93ACS100; 94MI1], only a few references to the chemistry of nitronaphthyridines are mentioned.

The purpose of this chapter is to review the chemistry of the nitro-1,5-, -1,6-, -1,7-, and -1,8-naphthyridines (**1**) [nitro-2,6- and nitro-2,7-naphthyridines (**2**) are unknown], with special attention to the results obtained in the laboratories of both authors. This article mainly refers to the synthesis and reactivity of the nitronaphthyridines; their physical and spectroscopic properties and biological activity are only covered briefly. For the convenience of the reader a table listing melting points of (di-)nitronaphthyridines and some derivatives is included (Table III). The literature to about 1998 has been covered.



(1)

N = 5,6,7,8



(2)

N = 6, 7

II. Methods of Preparation

Several approaches to the synthesis of nitronaphthyridines and their derivatives are reported. Very common ones are those in which the construction of the nitronaphthyridine system was achieved by using nitro synthons (see Section II,A) or by nitration of the naphthyridine ring, although a successful nitration requires the presence of electron-donating substituents (see Section II,B). Furthermore, the oxidation of the amino group in aminonaphthyridines

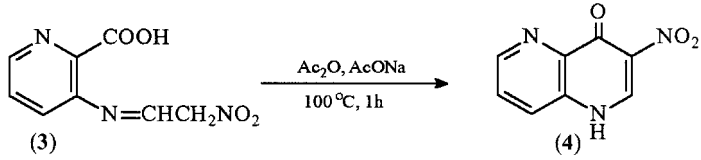
(see Section II,C) and hydro-dehalogenation of halonitronaphthyridine derivatives (see Section II,D) are less common methods for preparing nitronaphthyridines, but certainly of interest for more specific purposes.

A. Syntheses Using Nitro Synthons

The use of nitro synthons for the preparation of nitronaphthyridines and their derivatives has been extensively studied and has found widespread application. Most known nitro compounds have been synthesized using these methods and nearly all of them use an aminopyridine or (substituted amino)pyridine as starting material for the construction of the nitronaphthyridine ring. These synthetic methods can be divided into four categories.

1. *Use of a Starting Material in Which the Nitro Group is Present in the Side Chain*

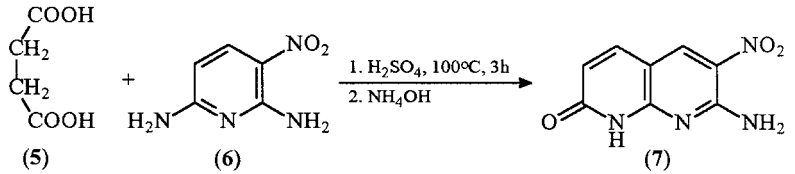
An example of this type of cyclization is the formation of 3-nitro-1,5-naphthyridin-4(1H)-one (**4**) from 3-(β-nitroethylideneamino)pyridine 2-carboxylic acid (**3**) by heating in acetic anhydride [56JCS(I)212]. No yields are given.

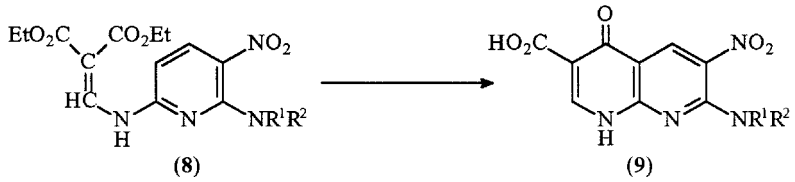


(3) (4)

2. *Use of a (Substituted) Aminopyridine Derivative in Which the Nitro Group is Already Present in the Pyridine Ring as Starting Material*

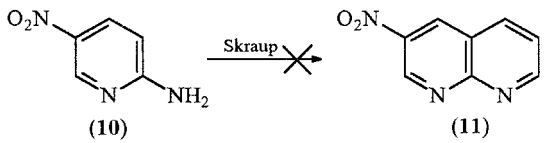
By this method a cyclization occurs between the amino group in a 2-(4)-aminopyridine derivative and the carbon atom in position 3(5), using as reagent a three-carbon atom fragment. This method has been succesfully applied for the preparation of 3-nitro-1,8-naphthyridines and 8-nitro-1,6-napthyridines. Examples of the preparation of 3-nitro-1,8-naphthyridines illustrating these principles follow. Heating of 2,6-diamino-3-nitropyridine (**6**) with malic acid (**5**) in sulfuric acid gives cyclization to 2-amino-3-nitro-1,8-naphthyridin-7(8H)-one (**7**) (69GCI 823). It was also reported that diethyl *N*-[(2-acetylamino-3-nitropyridin-6-yl)]-aminomethylene malonate (**8a**), when heated in boiling Dowtherm A, yields after hydrolysis 2-amino-6-carboxy-3-nitro-1,8-naphthyridin-5(8H)-one (**9,** $R^1 = R^2 = H$) (72GCI253). This cyclization also takes place with the 2-diethylamino and 2-pyrrolidino derivative (**8b** and **8c**) (79YZ155).



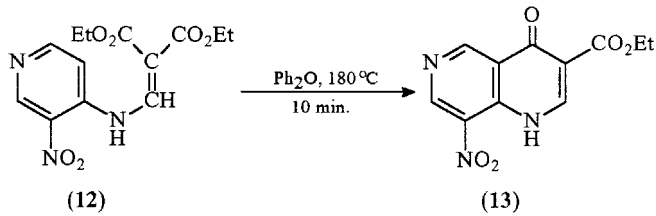


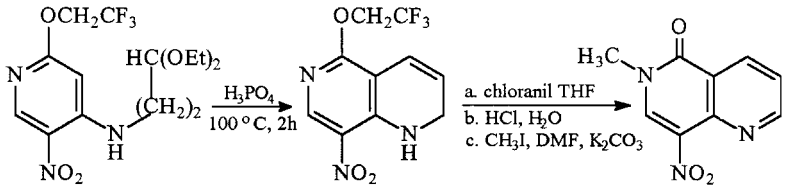
	R^1	R^2
a.	H	$COCH_3$.
b.	C_2H_5	C_2H_5
c.	$-(CH_2)_4-$	

However, attempts to prepare 3-nitro-1,8-naphthyridine (**11**) by the Skraup reaction—heating of 2-amino-5-nitropyridine with glycerol in the presence of an oxidant—were not successful (74YZ1328).



The same methodology as mentioned for the preparation of (**9**) was applied for the synthesis of 8-nitro-1,6-naphthyridines. Heating diethyl *N*-(3-nitropyridin-4-yl)aminomethylenemalonate (**12**) in diphenyl ether yields ethyl 8-nitro-1,6-naphthyridin-4(1H)-one 3-carboxylate (**13**) (63JCS4237, 30%) and acid treatment of 4-(γ,γ-diethoxypropylamino)-5-nitro-2-(β,β,β-trifluoroethoxy)-pyridine (**14**) gives in a similar way 8-nitro-5-(β,β,β-trifluoroethoxy)-1,2-dihydro-1,6-naphthyridine (**15,** 76%). Subsequent oxidation with chloranil, acid hydrolysis, and methylation with methyl iodide gives 8-nitro-6-methyl-1,6-naphthyridin-5(6H)-one (**16,** 63%) (81JHC941).

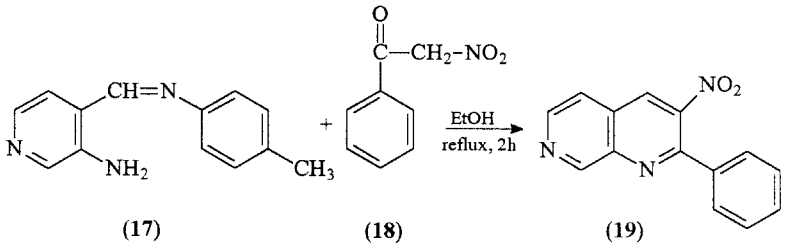




(14) (15) (16)

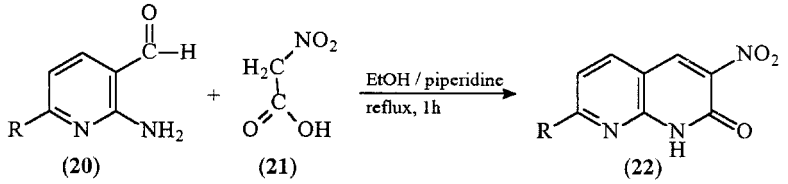
3. *Reaction of an Aminopyridine with an Aliphatic Nitro Compound*

In this method the nitro group in the aliphatic nitro compound is usually present on a carbon atom, which is also activated by CO-functionality (aldehyde, ester, arylketone). A successful application of this method is the Borsche modification of the Friedlander synthesis, involving condensation of *N*-(3-amino-4-picolylidene)-*p*-toluidine (**17**) with *ω*-nitroacetophenone (**18**) and leading to 3-nitro-2-phenyl-1,7-naphthyridine (**19**) (57JOC138). The preparation of (**17**) is, however, tedious and requires several steps; the yield in the transformation of (**17**) to (**19**) is very low (10%).



(17) (18) (19)

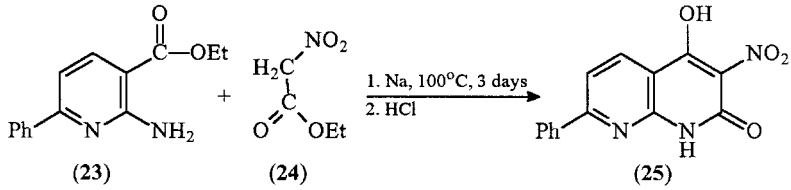
According to the Friedlander method, the condensation of the readily available 2-aminonicotinic aldehyde (**20a**) (74JOC726) or its 6-phenyl derivative (**20b**) [66JCS(C)315] with nitroacetic acid (**21**) in boiling ethanol with piperidine as catalyst is another example of this method, which affords in fair yields the corresponding 3-nitro-1,8-naphthyridin-2(1H)-ones (**22a,** 74%) and (**22b,** 47%), respectively [66JCS(C)315].



(20) (21) (22)

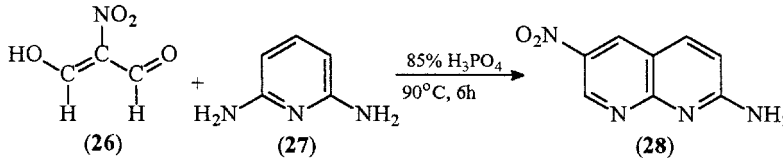
a. R = H ; **b.** R = C_6H_5

It was reported that the Niementowski synthesis of 4-hydroxy-3-nitro-7-phenyl-1,8-naphthyridin-2(1H)-one (**25**) from ethyl 2-amino-6-phenylnicotinate (**23**) and ethyl nitroacetate (**24**) in the presence of sodium was unsuccessful, producing only traces of (**25**), while condensation of ethyl 2-amino-6-phenylnicotinate (**23**) with the less reactive ethyl acetate resulted in the formation of 4-hydroxy-7-phenyl-1,8-naphthyridin-2(1H)-one in good yield [66JCS(C)315]. It seems that the more reactive nitroacetate tends to precipitate rapidly from the reaction mixture as its sodio derivative, which explains the low yield of (**25**).



(**23**) (**24**) (**25**)

The condensation of nitromalonic aldehyde (**26**) with 2,6-diaminopyridine (**27**) in the presence of phosphoric acid, affording 2-amino-6-nitro-1,8-naphthyridine (**28,** 37%) (77TL2087), is another example of a successful application of a nitro aliphatic compound in the synthesis of nitronaphthyridines.

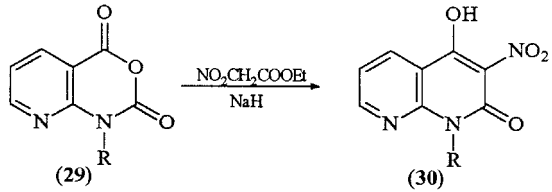


(**26**) (**27**) (**28**)

4. *Formation of Nitronaphthyridines by Ring Transformation*

A great number of N-substituted 4-hydroxy-3-nitro-1,8-naphthyridin-2 (1H)-ones are obtained by reaction of N-substituted azaisatoic anhydrides with ethyl nitroacetate carbanion (Section II,A,4,a). A very specific method, more recently developed, is that of the inverse Diels–Alder method, involving the reactions of enamines with 5-nitropyrimidine (Section II,A,4,b).

a. *Ring Transformations of Azaisatoic Anhydrides.* *N*-Phenyl-3-azaisatoic anhydride (**29a**) is reported to react with ethyl nitroacetate in the presence of sodium hydride to give 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (**30a**) (91JHC2029). This method gives a good approach to the preparation of a number of 1-substituted (alkyl, aryl) derivatives (**30b**–**30k**) (85JHC193; 91MI2; 92JMC4866).



(29) (30)

a. R = Ph (77%); **b.** R = Me (22%)

c. R = $CH_2CH{=}CH_2$ (29%); **d.** R = *n*-C_4H_9 (44%)

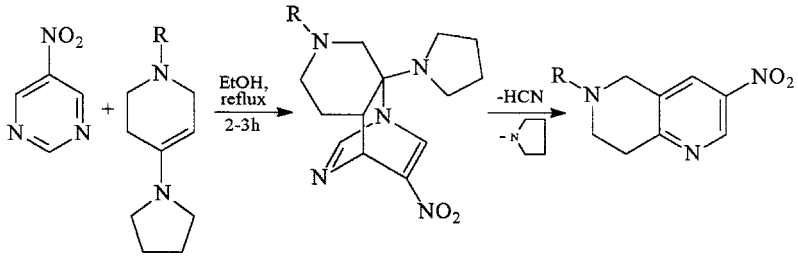
e. R = 4-$CH_3OC_6H_4$ (55%); **f.** R = 3-$CH_3OC_6H_4$ (66%);

g. R = 4-$CH_3C_6H_4$ (78%); **h.** R = 3-$CH_3C_6H_4$ (69%)

i. R = 3-Cl-C_6H_4 (74%); **j.** R = C_6H_4-4-$COOC_2H_5$ (38%)

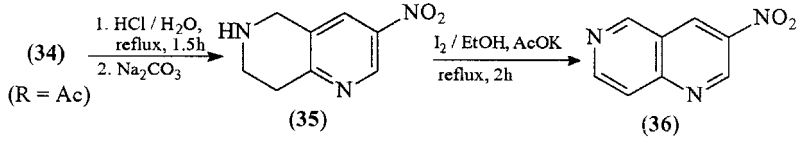
k. R = C_6H_4-3-$COOC_2H_5$ (41%)

b. *Inverse Diels–Alder Reaction of Electron-Rich Enamines Using 5-Nitropyrimidines as Nitrosynthons.* The inverse Diels–Alder method was successfully applied for the synthesis of the not readily available 3-nitro-1,6-naphthyridine. The synthesis involves a reaction between 5-nitropyrimidine (**31**) and the enamine of 4-piperidone (**32a, 32b**); in moderate yield the corresponding 3-nitrotetrahydro-1,6-naphthyridines (**34a,** 16%; **34b,** 48%) are obtained. The *N*-acetyl derivative (**34b**) could be hydrolyzed with hydrochloric acid to 3-nitrotetrahydro-1,6-naphthyridine (**35,** 89%), which, after oxidation with iodine, gave 3-nitro-1,6-naphthyridine (**36,** 24%) (89T2693). The first step involves as intermediate the cycloadduct **33,** obtained by a $4\pi + 2\pi$ cycloaddition of the enamine across N-1 and C-4 of the pyrimidine ring; loss of hydrogen cyanide and pyrrolidine from the cycloadduct **33** gives **34.** For review on this subject, see reference (91THC111). Untill now this method for preparing nitronaphthyridines has not been fully explored, and it certainly deserves attention.



(31) (32) (33) (34)

a. R = CH_3; **b.** R = $COCH_3$

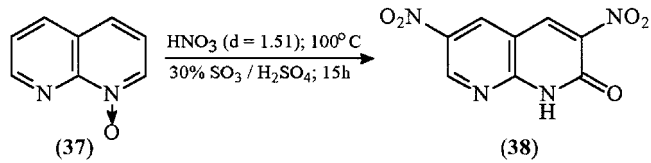


B. Electrophilic Nitration

1. *Parent Naphthyridines*

Due to its high π-electron deficiency the naphthyridine ring is very reluctant to react with electrophiles. Therefore, it can be expected that the preparation of nitronaphthyridines by an electrophilic nitration of the parent naphthyridines is hardly possible. Indeed unsuccessful attempts have been reported about the nitration of 1,5-naphthyridine using a whole range of concentrated nitric and sulfuric acids (54JCS1879). 1,8-Naphthyridine was found to undergo nitration under only very drastic conditions (fuming HNO_3/65% oleum, 110°C, 20 h). The yield of 3-nitro-1,8-naphthyridine is, however, very poor (1%!)(97LAR2601).

The best method to obtain the parent 3-nitronaphthyridines is the reductive removal of the chloro atom from chloronitronaphthyridines (see Section II,D). It is interesting to note that, whereas pyridine *N*-oxide can be converted easily into its 4-nitro derivative (51RTC581; 67MI1) 1,5-naphthyridine 1-oxide and also 1,5-naphthyridine 1,5-di-*N*-oxide could not be nitrated (60MI1). This different behavior was ascribed to the deactivating influence of the nitrogen at position 5 on the attack of the electrophilic nitrating species at position 4. Under severe conditions using fuming nitric acid/oleum, nitration of 1,8-naphthyridine 1-oxide (**37**) gives in low yield 3,6-dinitro-1,8-naphthyridin-2(1H)-one (**38,** 14%) (97LAR2601). Apparently the 1,8-naphthyridine 1-oxide is first transformed into 1,8-naphthyridin-2(1H)-one, which is subsequently nitrated to the 3,6-dinitro derivative.

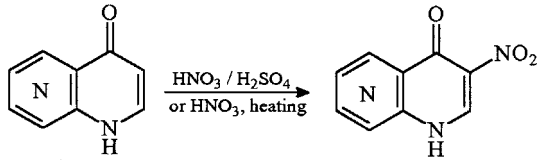


2. *Hydroxynaphthyridines (Naphthyridones)*

The presence of one or more electron-donating groups, such as the hydroxy substituent, is required to make easy nitration of the naphthyridines

possible. Since hydroxynaphthyridines containing the hydroxy group in positions 2 or 4 to the ring nitrogen atom mainly exist in the tautomeric oxo form, in this chapter we use the naphthyridone nomenclature to describe the structure of these compounds.

The 1,5-, 1,6-, 1,7-, and 1,8-naphthyridin-4(1H)-ones (**39a–39d**) easily undergo nitration to afford the corresponding 3-nitro derivatives (**40a–40d**) in fair yields.



(39) (40)

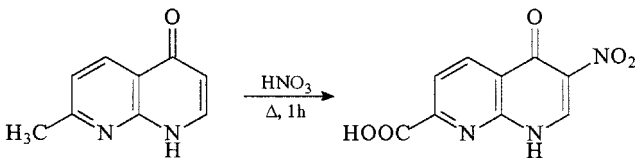
a. N = 5 **a.** N = 5 [? %, 56JCS(I)212]
[46%, 55LA91]
[71%, 63JCS4237]

b. N = 6 **b.** N = 6 [71 %, 58LA153,
63JCS4237]

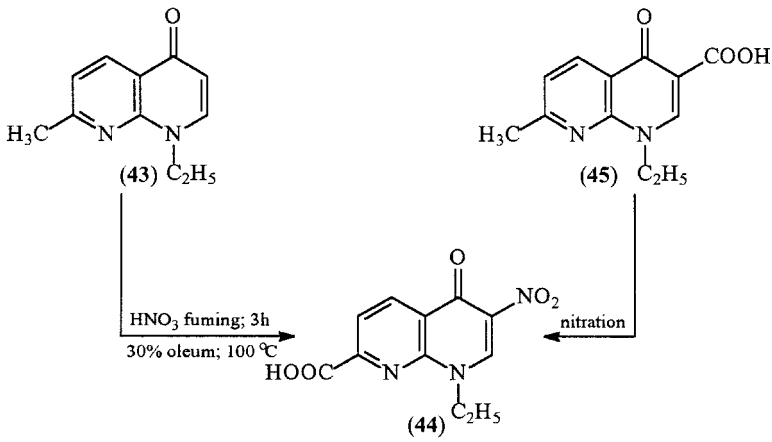
c. N = 7 **c.** N = 7 [21 %, 56LA233]
[74%, 60JCS1794]

d. N = 8 **d.** N = 8 [69 %, 79PJC1665]

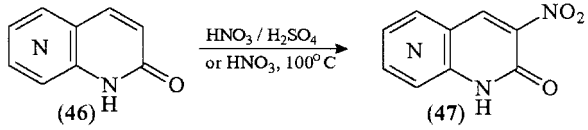
In some cases during nitration of naphthyridones containing a C-methyl group, oxidation of the methyl group into a carboxyl group takes place. So nitration of 7-methyl-1,8-naphthyridin-4(1H)-one (**41**) gives the 7-carboxy compound (**42,** 44%) (58LA153), and nitration of 1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one (**43**) with fuming nitric acid and oleum leads to 7-carboxy-1-ethyl-3-nitro-1,8-naphthyridin-4(1H)-one (**44,** 75%) (79YZ155). The same compound was also obtained by nitration of nalidixic acid (**45,** 74%) (79YZ155). In the last case, besides oxidation of the methyl group, a nitro decarboxylation at C-3 took place.



(41) (42)



In a similar way the 1,5-, 1,6-, and 1,8-naphthyridin-2(1H)-ones (**46,** N = 5, 6, 8) undergo nitration to the corresponding 3-nitro derivatives (**47a**–**47c**).



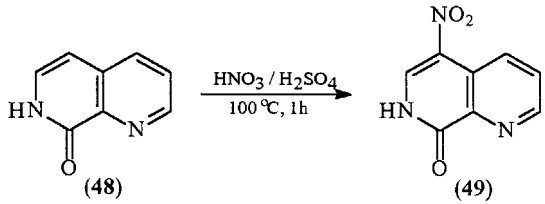
a. N = 5 [64 %, 56JCS(I)212]

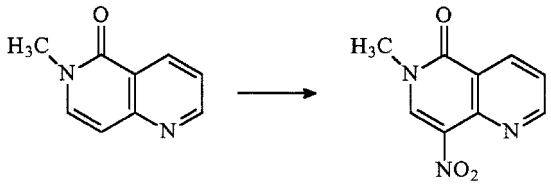
b. N = 6 [83 %, 83RTC359]

c. N = 8 [40 %, 76S691]

1,8-Naphthyridin-2(1H)-one (**46,** N = 8) was found to be nitrated under more severe conditions (HNO_3 fuming/20% oleum, 100°C, 30 h) to give 3,6-dinitro-1,8-naphthyridin-2(1H)-one (**38,** 56%) (85JHC761).

1,7-Naphthyridin-8(7H)-one (**48**) was nitrated to the 5-nitro derivative (**49,** 42%) (78JHC731) and analogously 6-methyl-1,6-naphthyridin-5(6H)-one (**50**) gave the corresponding 8-nitro derivative (**16,** 85%) (86ZOR1793). Interestingly, attempts to nitrate the isomeric 1,7-naphthyridin-2(1H)-one (**46,** N = 7) under various conditions were unsuccesful (98MI2).

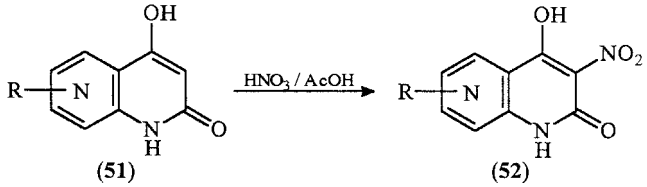




(50) (16)

3. *Hydroxynaphthyridones and Naphthyridinediones*

Many reports deal with the preparation of numerous hydroxynitronaphthyridones and nitronaphthyridinediones. By the nitration of 4-hydroxy-1,X-naphthyridin-2(1H)-ones (X = 5, 6, 7, and 8) (**51a–51d**) using nitric acid in acetic acid, the corresponding 3-nitro substituted compounds (**52a–52d**) were obtained in reasonable-to-good yield (75JMC726; 77MI1; 96MI1).



(51) (52)

a. N = 5, R = H — **a.** N = 5, R = H (30 %)

b. N = 6, R = H — **b.** N = 6, R = H (44%)

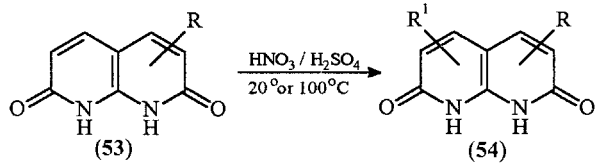
c. N = 7, R = H — **c.** N = 7, R = H (78%)

d. N = 8, R = H — **d.** N = 8, R = H (99%)

e. N = 8, R = 7-Ph — **e.** N = 8, R = 7-Ph (57%)

f. N = 5, R = 7-Cl — **f.** N = 5. R = 7-Cl (38%)

Nitration of the 7-phenyl derivative (**51e**) with nitric acid (d = 1.42, 100°C, 1 h) also leads to nitration at positions 3, yielding the corresponding 3-nitro derivative (**52e**) [66JCS(C)315]. In the patent literature nitrations of *N*-oxides and many other derivatives of 4-hydroxy-1,X-naphthyridin-2(1H)-ones (X = 5, 6, 7, 8) to the corresponding 3-nitro derivatives are reported (96MI2). For example, a detailed description is given of the nitration of 7-chloro-4-hydroxy-1,5-naphthyridin-2(1H)-one (**51f**) to the 3-nitro compound (**52f**) (96MI3). 1,8-Naphthyridin-2,7(1H, 8H)-diones (**53a–53c**) were successfully nitrated at room temperature: from (**53a**/**53b**) the *mono* nitro products (**54a**/**54b**) could be obtained respectively, and **53c** gave the 3,6-dinitro derivative **54c** (69GCI823). Dinitro compound **54c** was also formed during the nitration of **53a** at 100°C. The position of the nitro group in the mono nitration product **54b** was not established (40MI2).



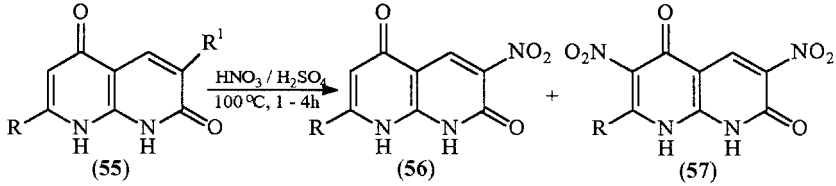
(53) (54)

a. R = H — **a**. R = 3-NO_2 , R^1 = H (33 %)

b. R = 4-CH_3 — **b.** R = 4-CH_3 , R^1 = ?-NO_2

c. R = 3-NO_2 — **c.** R = 3-NO_2, R^1 = 6-NO_2 (>70%)

Nitration of 1,8-naphthyridin-2,5(1H,8H)-dione (**55a**) and some of its derivatives (**55b–55d**) was studied by Carboni and coworkers (72GCI253). They observed the formation of the 3-nitro derivatives (**56a/56b**) from (**55a/55d**); under more severe conditions from (**55b/55c**) the 3,6-dinitro derivatives (**57a/55b**) are obtained. In the case when a carboxyl group is present, decarboxylation is observed.



(55) (56) (57)

a. R = R^1 = H — **a.** R = H — **a.** R = H

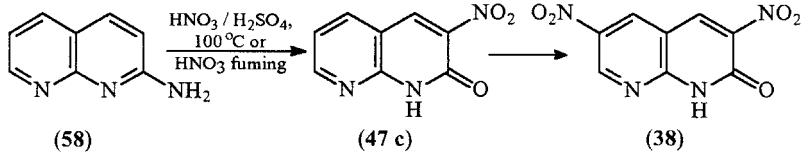
b. R = H, R^1 = NO_2 — **b.** R = CO_2 H — **b.** R = CO_2H

c. R = CO_2H, R^1 = NO_2

d. R = CO_2H, R^1 = H

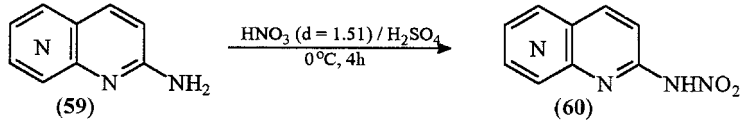
4. *Aminonaphthyridines*

Nitration of aminonaphthyridines into aminonitronaphthyridines is usually not successful, since under the usual nitration conditions the amino group is very easily hydrolyzed. Thus, attempts to nitrate 2-amino-1,8-naphthyridine (**58**) do not lead to the desired 2-amino-3-nitro-1,8-naphthyridine but give 3-nitro-1,8-naphthyridin-2(1H)-one (**47c**). Using a prolonged heating time and fuming nitric acid the 3,6-dinitro-1,8-naphthyridin-2(1H)-one (**38**) was obtained (98 MI3). The hydrolysis of the amino group has also been observed during nitration of the 6- and 7-carboxy derivative (**67b**) and (**67c**) (see Section II,B,5).



(58) (47 c) (38)

A low-temperature nitration of 2-amino-1,8-naphthyridine (**59a**) and 2-amino-1,5-naphthyridine (**59b**) yielded the 2-nitramino-1,8-naphthyridine (**60a,** 65%) (98MI3) and 2-nitramino-1,5-naphthyridine (**60b,** 70%) (63RTC988) respectively. Attempts to rearrange (**60a**) and (**60b**) to 2-amino-3- (or 6-) nitro-1,8-(or -1,5-) naphthyridines failed.

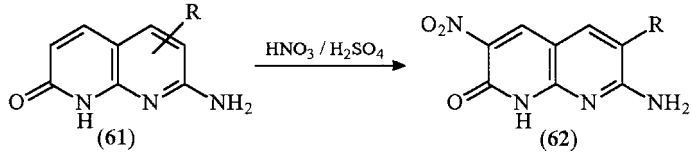


(59) (60)

a. N = 8 ; **b.** N = 5

5. *Aminonaphthyridones*

2-Amino-1,8-naphthyridin-7(8H)-one (**61a**) and their 3-nitro and 6-nitro derivatives (**61b**) and (**61c**) respectively can be nitrated successfully. The nitro substituent enters preferentially at position 6, i.e., formation of **62a** from **61a;** when position 6 is already occupied by a nitro group, the second nitro group is introduced at position 3, i.e., formation of **62b** from **61c** (69GCI823). It has been mentioned that diazotation of **61** (R=Ph) with sodium nitrite/sulfuric acid also gives the 3-nitro derivative [97JHC1501]. This reaction proceeds via nitrozation, in which the NO+ is the attacking electrophile.



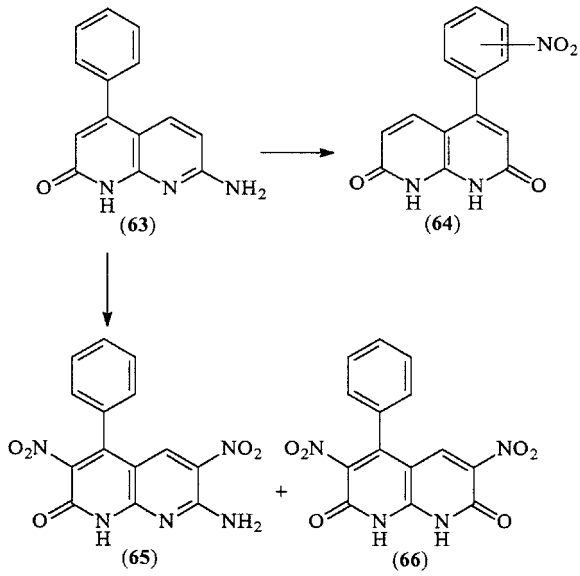
(61) (62)

(61) (62)

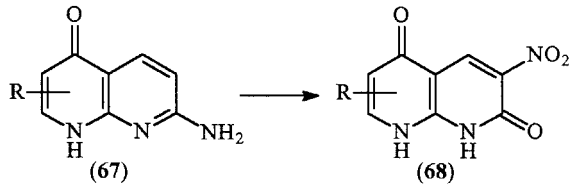
a. R = H ; **b.** R = 3-NO_2 ; **c.** R = 6-NO_2

The products of nitration of 2-amino-5-phenyl-1,8-naphthyridin-7(8H)-one (**63**) vary depending on whether the reaction is carried out with nitric acid in sulfuric acid or in acetic anhydride (74GCI499). In sulfuric acid the phenyl ring was found to be nitrated more easily than the naphthyridine ring, yielding a mixture of 3- and 4-nitrophenyl derivatives (**64**); in acetic

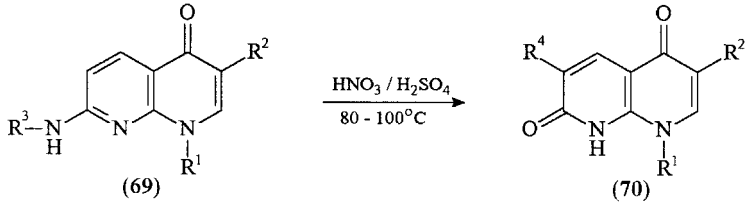
acid the nitro group is introduced into the heterocyclic ring, yielding 2-amino-5-phenyl-3,6-dinitro-1,8-naphthyridin-7(8H)-one (**65**) and 5-phenyl-3,6-dinitro-1,8-naphthyridin-2,7 (1H,8H)-dione (**66**) together with a small amount of 2-amino-3-nitro-5-phenyl-1,8-naphthyridin-7(8H)-one (4.3%). These results seem to suggest that in the sulfuric acid medium protonation of the naphthyridine ring occurs, resulting in deactivation of the heterocyclic ring toward an electrophilic reagent.



Nitration of 2-amino-1,8-naphthyridin-5(8H)-one (**67a**) in acetic acid or in acetic anhydride does not occur; in HNO_3/H_2SO_4 the products obtained were difficult to separate (72GCI253). Hydrolysis of the amino group under nitration conditions has also been observed with 6- and 7-carboxy-2-aminonaphthyridin-5(8H)-ones (**67b**/**67c**), yielding the corresponding (**68b**/**68c**) (72GCI253).



a. R = H ; **b.** R = 6-CO_2H ; **c.** R = 7-CO_2H

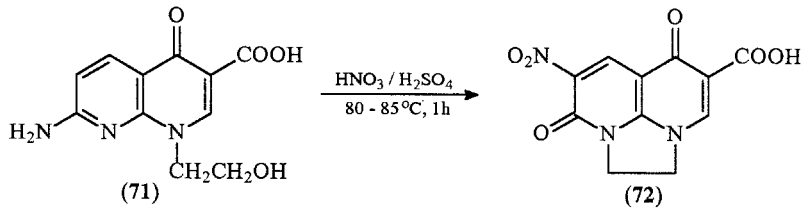


(69) (70)

	R^1	R^2	R^3		R^1	R^2	R^4
a.	C_2H_5	CO_2H	H	**a.**	C_2H_5	CO_2H	NO_2 (96%)
b.	C_2H_5	CO_2Et	Ac	**b.**	C_2H_5	CO_2Et	NO_2 (80%)
c.	$(CH_2)_2$ Cl	CO_2Et	Ac	**c.**	$(CH_2)_2Cl$	CO_2 Et	NO_2 (65%)
d.	$CH{=}CH_2$,	CO_2H	H	**d.**	H	CO_2H	H (63%)

Derivatives of nalidixic acid (**69a–69d**), containing an amino or acetylamino substituent at position 7 and an alkyl group at N-1, were successfully nitrated to give (**70a–70d**). However, in all cases hydrolysis of the amino and acetylamino group was observed (79YZ155; 80CPB235).

Whereas nitration of compound (**69a**) under rather mild conditions (100°C, 1 h) gave the 6-nitro derivative (**70a,** 96%), nitration for a prolonged period of time (4 h) led to partial nitro-decarboxylation, giving a mixture of **70a** and the 3,6-dinitro derivative (**70**, $R^1 = Et$, $R^2 = R^4 = NO_2$). It is of interest that the 1-vinyl derivative (**69d**) did not undergo nitration, but hydrolysis of the amino group with devinylation, yielding product **70d.** Treatment of 7-amino-1-hydroxyethyl-1,8-naphthyridin-4(1H)-one 3-carboxylic acid (**71**) with a nitrating agent causes nitration at position 6, the formation of an oxo group at position 7, and imidazolidine cyclization between N-1 and N-8, yielding (**72,** 77%) (80CPB235).

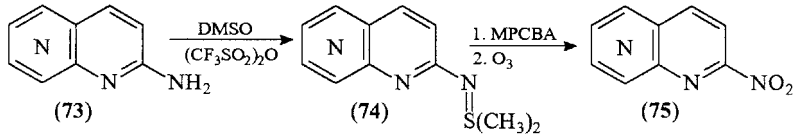


(71) (72)

C. Oxidation

Oxidation of the 2-(S,S-dimethyl)sulfinylimine derivatives (**74**) of 2-amino-1,X-naphthyridines (**73a–73c**) (X = 5,6,8) with *m*-chloroperbenzoic

acid (MCPBA) and ozone was successful for preparing 2-nitro-1,5-, -1,6-, and -1,8-naphthyridines (**75a**–**75c**) [93LA471]. The oxidation proceeds in two steps: in the first step the sulfinylimines (**74a**–**74c**) are oxidized by MCPBA to the nonisolable 2-nitroso compounds which then are converted by ozone into the 2-nitro products (**75a**–**75c**).

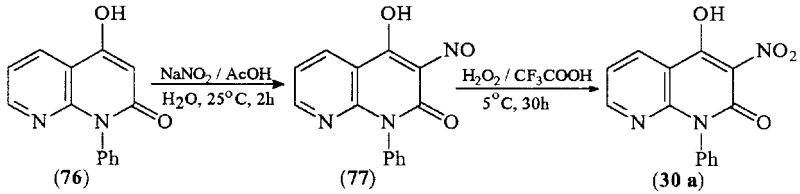


a. N = 5 **a.** N = 5 (68 %) **a**. N = 5 (27%)

b. N = 6 **b.** N = 6 (48 %) **b.** N = 6 (26 %)

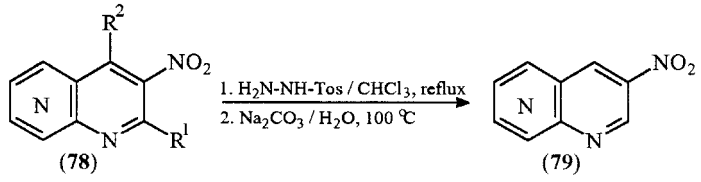
c. N = 8 **c.** N = 8 (33 %) **c.** N = 8 (47 %)

Treatment of 4-hydroxy-1-phenyl-1,8-naphthyridin-2-(1H)-one (**76**) with sodium nitrite gave the 3-nitroso derivative (**77**), which could be oxidized to 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one (**30a**) (94SC3289). According to the authors, this method of preparing (**30a**) is more convenient for large-scale preparation than the one using *N*-phenyl-3-azaisatoic anhydride as starting material (see Section II,A,4,a) [(**29a**) → (**30a**)].



D. Hydrodehalogenation

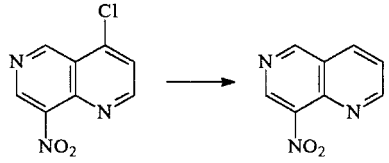
The easy availability of (di)nitronaphthyridones, in which the lactam part can easily be converted into an iminochloride, has successfully led to preparation of the parent (di)nitronaphthyridines by removal of the chloro atom. For that purpose the chloro atom in the 2- and 4-chloro derivative of the 3-nitro-1,5-, -1,6-, and -1,8-naphthyridines (**78a**–**78e**) was first substituted with tosylhydrazine to give the corresponding tosylhydrazide, which then was hydrolyzed in alkaline solution into the corresponding 3-nitro-1,5-, -1,6-, and -1,8-naphthyridines (**79a, 79b,** and **79c**).



(78) (79)

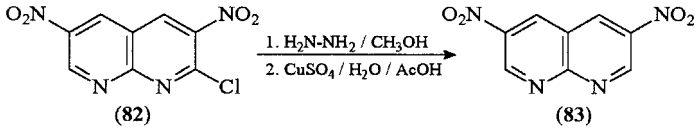
	R^1	R^2	
a. N = 5	H	Cl	**a.** N = 5 [33%, 63JCS4237]
b. N = 6	H	Cl	**b.** N = 6 [11 %, 63JCS4237]
c. N = 6	Cl	H	**b.** N = 6 [15%, 83RTC359]
d. N = 8	Cl	H	**c.** N = 8 [24 %, 76S691]
e. N = 8	H	Cl	**c.** N = 8 [17 %, 79PJC1665]

By the same procedure 8-nitro-1,6-naphthyridine (**81,** 23%) was synthesized from 4-chloro-8-nitro-1,6-naphthyridine (**80**) (63JCS4237).



(80) (81)

Attempts to obtain 5-nitro-1,7-naphthyridine and 3,6-dinitro-1,8-naphthyridine (**83**) from the corresponding 8-chloro-5-nitro-1,7-naphthyridine and 2-chloro-3,6-dinitro-1,8-naphthyridine using the similar reaction failed (85JHC761; 98MI2). However, 3,6-dinitro-1,8-naphthyridine (**83**) could be prepared in 21% yield by hydrazino-dechlorination of 2-chloro-3,6-dinitro-1,8-naphthyridine (**82**) and subsequent cupric sulfate oxidation of the intermediate 2-hydrazino-3,6-dinitro-1,8-naphthyridine (93LA471).



(82) (83)

III. Reactions

A. General Considerations

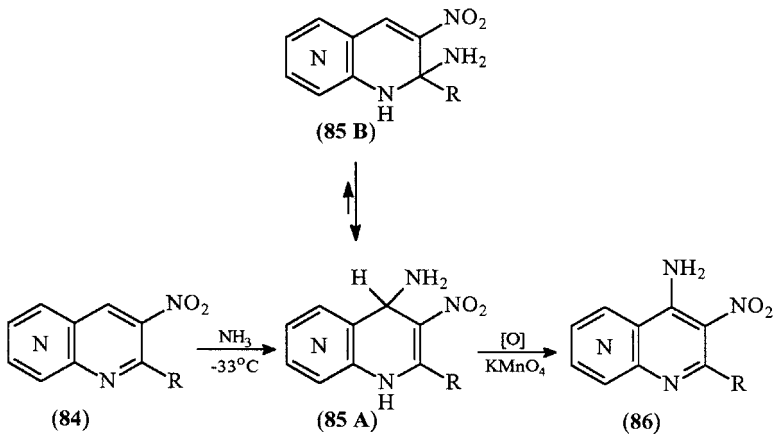
In the naphthyridine ring with its 10 delocalized π-electrons located on five distorted molecular orbitals, due to an electron drift toward the nitro-

gen atoms, the positions α and γ to the nitrogen atom have lower π-electron densities than the β-position. The experimentally observed covalent σ-adduct formation at position 2, when 1,5-, 1,6-, or 1,8-naphthyridine is dissolved in potassium amide/liquid ammonia at -40^{o}C, illustrates this behavior (78JOC1673). Also, calculations of π-electron densities at the different positions in naphthyridines unambiguously show the lowest electron density at the positions adjacent to the ring nitrogens (66JMS25; 69JOC1384; 79BCJ1448; 91PJC1449).

The presence of a nitro group with its strongly π-electron-withdrawing properties at the naphthyridine ring further increases the π-electron deficiency of the naphthyridine ring. Therefore, nitronaphthyridines undergo reactions with nucleophiles rather easily but, as could be expected, are extremely difficult to react with electrophilic reagents. It has been observed that nucleophilic attack occurs at the positions *ortho* and *para* to the nitro group and preferentially para to the ring-nitrogen atom. Calculations on the relative distribution of electron density between the ring carbon atoms, delocalization energy of intermediary anionic σ-complexes, energy of frontal molecular orbitals interactions between nitronaphthyridines, and nucleophilic reagents and other parameters have been successfully applied to predict the site of substitution (see Section IV).

B. Nucleophilic Substitution of the Ring Hydrogen

The replacement of a ring hydrogen in azines by a nucleophilic reagent (S_NH substitutions) has been an area of great interest (94MI1, 99PJC151). Also, the amination of a number of 3-nitro-1,5-, -1,6-, and -1,8-naphthyridines in a solution of potassium permanganate in liquid ammonia (LA/PP system) has been extensively studied. Using this method the 2-R-3-nitro-1,X-naphthyridines (X = 5, 6, and 8) (**84a–84m**) were successfully aminated to the 4-amino-3-nitro-1,X-naphthyridines (**86a–86m**) (83RTC359, 83RTC511, 83JHC9). These aminations involve as intermediates the covalent 4-amino-σ-adducts (**85A**), which are obtained on dissolving the 3-nitronaphthyridines in liquid ammonia; they could be detected by ^{1}H NMR spectroscopy (83RTC359, 83RTC511, 83JHC9; 87MI1, 87MI3) (see Section V). Potassium permanganate has been found to be an effective oxiding reagent for these σ-adducts. It is important to note that when in the 3-nitronaphthyridines a nucleophugal group, such as chloro or ethoxy, is present, the S_NH substitution is still preferred to the S_N(AE) process, even when this group is in the activated 2-position. Apparently, in the presence of an oxidant, the oxidation of (**85A**) is faster that an equilibrium shift from **85A** into the thermodynamically more stable 1 : 1 2-amino-σ-adduct (**85B**), which is involved in the S_N(AE) process as an intermediate.



a. N = 5, R = H

b. N = 5, R = NH_2

c. N = 5, R = Cl

d. N = 5, R = OH

e. N = 5, R = OEt

f. N = 6, R = H

g. N = 6, R = NH_2

h. N = 6, R = Cl

i. N = 6, R = OEt

j. N = 8, R = H

k. N = 8, R = NH_2

l. N = 8, R = Cl

m. N = 8, R = OEt

a. N = 5, R = H (74 %)

b. N = 5, R = NH_2 (33 %)

c. N = 5, R = Cl (32 %)

d. N = 5, R = OH (51 %)

e. N = 5, R = OEt (70 %)

f. N = 6, R = H (55 %)

g. N = 6, R = NH_2 (61 %)

h. N = 6, R = Cl (33 %)

i. N = 6, R = OEt (70 %)

j. N = 8, R = H (45 %)

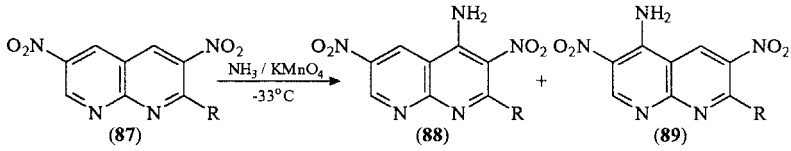
k. N = 8, R = NH_2 (25 %)

l. N = 8, R = Cl (22 %)

m. N = 8, R = OEt (40 %)

In all 3-nitronaphthyridines with an unsubstituted C-2 position (**84a, 84f,** and **84j**) no traces of the corresponding 2-amino-3-nitro-1,X-naphthyridines (X = 5, 6, and 8) were obtained. As already mentioned, in the aminations of 2-R-3-nitronaphthyridines where R is a chloro or ethoxy group, no amino-dechlorination or amino-deethoxylation was observed.

Amino-dehydrogenation (S_NH) using the LA/PP system was also studied with the 3,6-dinitro-1,8-naphthyridines (**87a–87d**) (86JHC473; 93LA471). Besides *mono* amino products, diamino products are also obtained; the yields are, however, moderate.



(87) (88) (89)

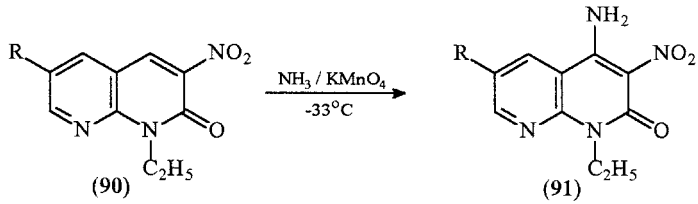
a. R = H **a.** R = H **a.** R = OEt

b. R = NH_2 **b.** R = NH_2 **b.** R = Cl

c. R = OEt **c.** R = OEt **c.** R = NH_2

d. R = Cl

The compounds **87a** and **87b** are aminated at position 4, yielding the 4-amino compound (**88a,** 40%) and the 2,4-diamino compound (**88b,** 11%) respectively; the 2-ethoxy compound (**87c**), however, undergoes amination at position 4 as well at position 5, giving a mixture of the 4-amino compound (**88c,** 20%) and the 5-amino compound (**89a,** 14%). The 2-chloro compound (**87d**) yields a highly complex reaction mixture from which the 5-amino compound (**89b**), the 2,4-diamino derivative (**88b**), and 2,5-diamino-1,8-naphthyridine (**89c**) could be isolated. 1-Ethyl-3-nitro-1,8-naphthyridin-2(1H)-one (**90a**) and 3,6-dinitro-1-ethyl-1,8-naphthyridin-2(1H)-one (**90b**) were aminated exclusively in the 4-position to give compounds **91a** (62%) and **91b** (45%), respectively (93LA471).



(90) (91)

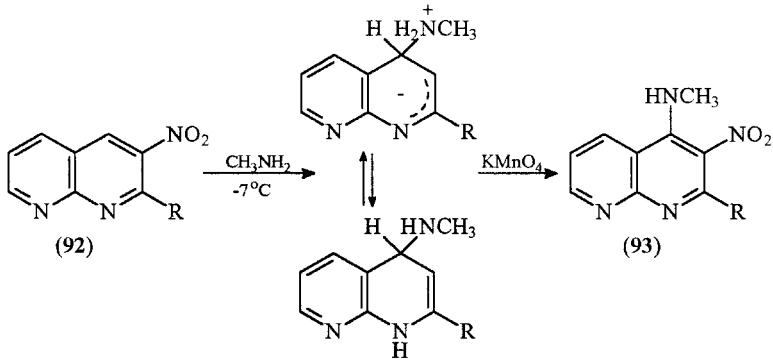
a. R = H ; **b.** R = NO_2

There is ample ^{1}H NMR evidence for the existence of the covalent 4-amino-σ-adduct, formed by the reaction of the 3,6-dinitro compounds (**87a**/**87b**) and (**90b**) with liquid ammonia (see Chapter 5). In the cases of **87c** or **87d,** besides the covalent 4-amino-σ-adducts, the 5-amino-σ-adducts also were detected. The ratio between these adducts was found to be temperature dependent (85JHC761). For example, when **87c** was dissolved in liquid ammonia at −45°C the ratio of 4-amino-σ-adduct to 5-amino-σ-adduct was 60 : 40, while after standing for 1 h at room temperature it changed to 40 : 60. However, **87d,** when dissolved in liquid ammonia at −45°C, gave a mixture of 4- and 5-amino-σ-adducts in the ratio 50 : 50, which changed to about 85 : 15 when the solution was kept for 30 min at room temperature.

2-Nitro-1,5-, -1,6-, and -1,8-naphthyridines (**75a**–**75c**) are very reluctant to undergo S_NH substitution when treated with liquid ammonia/potassium

permanganate. Only amino-denitration, to a very small extent, was observed (93LA471).

This methodology has also been extended to the use of liquid methylamine/potassium permanganate (LMA/PP system). When this system is applied to a number of 3-nitro-1,8-naphthyridines (**92a–92g**), the C-4 position could be successfully substituted by methylamino group yielding **93a–93f.** The intermediary 4-methylamino-σ-adducts could be detected by measuring ^{1}H NMR spectra of solutions of **92** in liquid methylamine (96KGS1652; 97LAR2601).

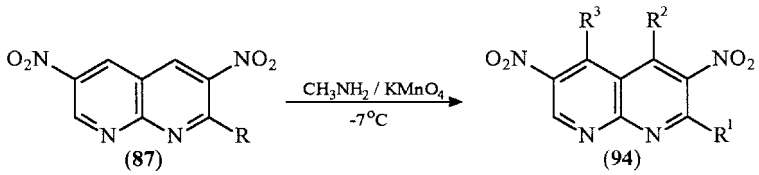


a. R = H
b. R = NH_2
c. R = Cl
d. R = $NHCH_3$
e. R = OCH_3
f. R = NHPh
g. R = OH

a. R = H (90 %)
b. R = NH_2 (86 %)
c. R = $NHCH_3$ (82 %)
c. R = $NHCH_3$ (85 %)
d. R = OCH_3 (78 %)
e. R = NHPh (68%)
f. R = OH (50 %)

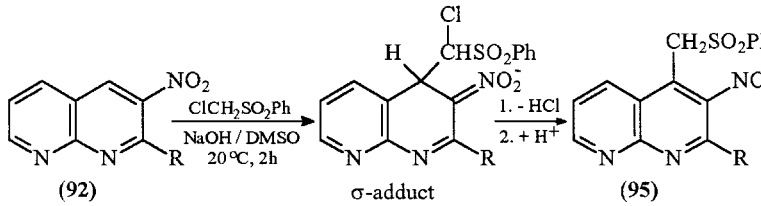
As discussed before, in liquid ammonia/potassium permanganate nucleophugal substituents at C-2, such as ones present in the naphthyridines (**84c, 84e, 84h, 84i, 84l,** and **84m**), could not be replaced by the amino group; only S_NH substitution takes place. However, it has been observed that in the reaction of the 2-chloro-3-nitro-1,8-naphthyridine (**92c**) with liquid methylamine/potassium permanganate S_NH substitution *as well as* methylamino-dechlorination takes place, yielding 2,4-bis-(methylamino)-3-nitro-1,8-naphthyridine (**93c**).

Using the same methodology, a number of 3,6-dinitro-1,8-naphthyridines (**87a–87g**) were converted with the LMA/PP system into the methylamino products (**94**). The methylamino group usually enters at position 4, but in cases where a chloro or methoxy substituent is present at C-2, 2,4-bis(methylamino) derivatives were isolated (97MI3).



		R^1	R^2	R^3	Yield (%)
a. R = H	→	**a.** $NHCH_3$	$NHCH_3$	H	44
a. R = H	→	**b.** H	$NHCH_3$	$NHCH_3$	12
a. R = H	→	**c.** $NHCH_3$	H	H	9
b. R = NH_2	→	**d.** NH_2	$NHCH_3$	H	50
c. R = $NHCH_3$	→	**a.** $NHCH_3$	$NHCH_3$	H	62
d. R = Cl	→	**a.** $NHCH_3$	$NHCH_3$	H	50
e. R = NHC_6H_5	→	**e.** NHC_6H_5	$NHCH_3$	H	46
f. R = OCH_3	→	**f.** OCH_3	$NHCH_3$	$NHCH_3$	22
f. R = OCH_3	→	**a.** $NHCH_3$	$NHCH_3$	H	40
g. R = OH	→	**g.** OH	$NHCH_3$	H	27
g. R = OH	→	**h.** OH	H	$NHCH_3$	14

S_NH substitutions were also studied with carbanions containing a leaving group at the carbon center. This so-called vicarious nucleophilic substitution of hydrogen (VNS) (97LAR1805; 99PJC151) leading to the introduction of carbon substituents in the heterocycles was studied with the 3-nitro-1,8-naphthyridine (**92a**) and some of its 2-substituted derivatives (**92b, 92c, 92e, 92g**) using as vicarious reagent chloromethyl phenyl sulfone in the presence of a base. The reaction can be described to first involve the addition of the carbanion to the nitroarene, which results in the formation of a σ-adduct. A base-induced β-elimination of HCl from the σ-adduct and subsequent protonation during the work-up procedure gives the corresponding 3-nitro-4-phenylsulfonylmethyl-1,8-naphthyridines (**95**) in high yields (80–90%; 91JHC1075).

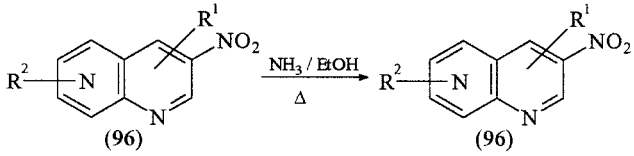


a. R = H ; **b.** R = NH_2 ; **c.** R = Cl ; **e.** R = OEt ; **g.** R = OH

In conclusion, all results obtained thus far on this reaction show that it is especially the 4-position in the 3-nitro-1,8-naphthyridines which is strongly favored toward the attack of the carbanion of chloromethyl phenyl sulfone. When position 4 is occupied by a substituent no reaction occurs. This behavior is in accordance with the behavior observed in reactions with liquid ammonia and liquid methylamine.

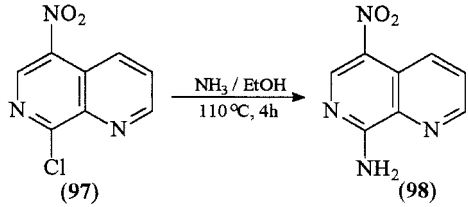
C. Amino(alkoxy)-Dehalogenation

As already indicated in Section III,A, nucleophilic attack easily occurs at positions *ortho* and *para* to the ring nitrogen and/or the nitro group. Amino-dehalogenation in halogeno-3-nitronaphthyridines has been extensively studied and a number of amino-3-nitronaphthyridines (**96l–96v**) were obtained by the action of ethanolic ammonia on the 2- and 4-chloro-3-nitronaphthyridines (**96a–96k**).



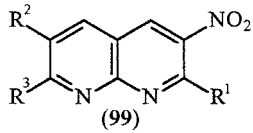
	R^1	R^2		R^1	R^2	
a. N = 5,	2-Cl	H	**l.** N = 5,	2-NH_2	H	[74%, 83RTC511]
b. N = 5,	4-Cl	H	**m.** N = 5,	4-NH_2	H	[75%, 83RTC511, 82MI1]
c. N = 5,	2-Cl	4-NH_2	**n.** N = 5,	2-NH_2	4-NH_2	[66%, 83RTC511]
d. N = 6,	2-Cl	H	**o.** N = 6,	2-NH_2	H	[75 %, 83TC359]
e. N= 6,	4-Cl	H	**p.** N = 6,	4-NH_2	H	[74 %, 83RTC359, 82MI1]
f. N = 6,	2-Cl	4-NH_2	**q.** N = 6,	2-NH_2	4-NH_2	[56 %, 83RTC359]
g. N = 8,	2-Cl	H	**r.** N = 8,	2-NH_2	H	[70 %, 83JHC9,82MI1]
h. N = 8,	4-Cl	H	**s.** N = 8,	4-NH_2	H	[56 %, 79PJC1655]
i. N= 8,	2-Cl	4-NH_2	**t.** N = 8,	2-NH_2	4-NH_2	[56 %, 83JHC9]
j. N = 8,	2-Cl	6-NO_2	**u.** N = 8,	2-NH_2	6-NO_2	[66 %, 85JHC761]
k. N = 8,	2-OH	7-Cl	**v.** N = 8,	2-OH	7-NH_2	[55 %, 94EJMC735]

In a similar manner 8-amino-5-nitro-1,7-naphthyridine (**98,** 61%) was obtained from 8-chloro-5-nitro-1,7-naphthyridine (**97**) (82MI1).



(97) (98)

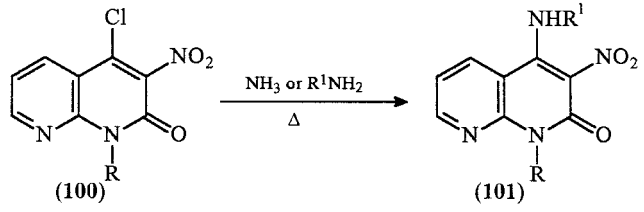
Taking into account the high reactivity of the chloro atoms in 2-chloro-3-nitro- (**99a, 99d,** and **99f**), 7-chloro-3-nitro- (**99e** and **99g**), 2,7-dichloro-3-nitro- (**99c**), and 2-chloro-3,6-dinitro-1,8-naphthyridines (**99b**), a great variety of 2- (or 7-) substituted amino products [**99,** R^1 = $NHCH_3$, $N(CH_3)Ph$, $NHPh$, $N(CH_2)_5$, $NHCH_2Ph$, $N(CH_2)_4O$, $N(C_2H_4OH)_2$; R^3 = $N(C_2H_4OH)_2$, $N(CH_2)_5$] were obtained in reactions with a number of alkyl(aryl) amines; the yields vary but usually are above 50% (94EJMC735; 95MI1; 97LAR2601, 97MI3; 98MI3).



(99)

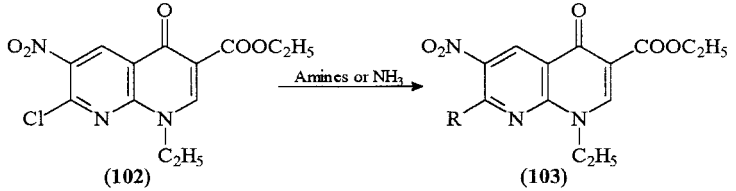
	R^1	R^2	R^3
a.	Cl	H	H
b.	Cl	NO_2	H
c.	Cl	H	Cl
d.	Cl	H	OH
e.	OH	H	Cl
f.	Cl	H	$N(CH_2)_5$
g.	$N(CH_2)_5$	H	Cl

Similarly, a number of 1-alkyl(aryl)-4-chloro-3-nitro-1,8-naphthyridin-2 (1H)-ones (**100**) have been reported to react with ammonia or alkylamines to afford the corresponding 4-amino compounds [**101,** R^1 = H, CH_3, C_2H_5, $CH(CH_3)_2$, CH_2 C_6H_5] (91JHC2029, 91MI2; 92JMC4866).



R = C_6H_5 ,4-CH_3 OC_6 H_4 , 3-CH_3 OC_6H_4 , 4-CH_3C_6 H_4 , 3-$CH_3C_6H_4$,
3-ClC_6H_4 , 4-$C_2H_5O_2CC_6H_4$, 3-$C_2H_5O_2CC_6H_4$, n-C_4H_9

In a very similar way the corresponding 7-amino-substituted compounds (**103a**–**103p**) were obtained from ethyl 7-chloro-1-ethyl-1,4-dihydro-6-nitro-4-oxo-1,8-naphthyridin-4(1H)-one 3-carboxylate (**102**) (77MI2; 79YZ155; 80CPB235).



a. R = NH_2 (68%); **b.** R = NHC_6H_4-*p*-Cl (85 %),

c. R = NH-C_6H_4-*p*-OMe (84 %); **d.** R = NHPh (82 %);

e. R = $NHCH_2CH_2(Et)_2$ (99%); **f.** R = $NHCH_2CH_2CH_2OH$ (92 %);

g. R = $N(Me)_2$ (87 %); **h.** R = $N(Et)_2$ (94 %);

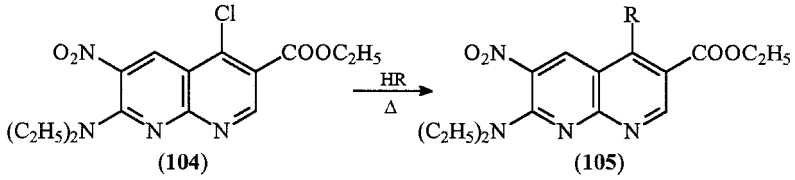
i. R = NMePh (99 %); **j.** R = $N(Et)(CH_2CH_2OH)$ (97 %)

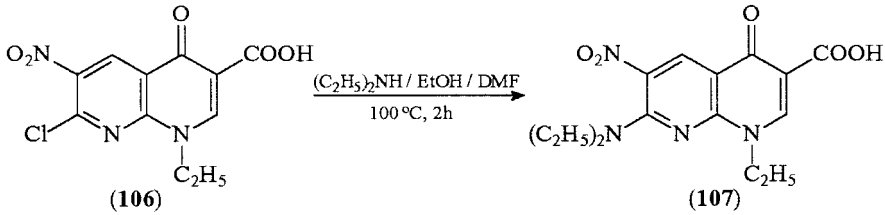
k. R = $N(CH_2CH_2CH_2OH)_2$ (83 %); **l.** R = $N(CH_2)_4$ (98 %)

m. R = $N(CH_2)_5$ (57 %); **n.** R = $N(CH_2)_4O$ (92 %);

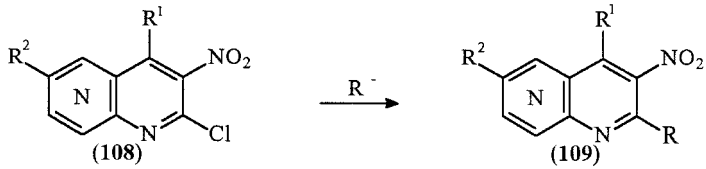
o. R = $N(CH_2)_4NH$ (36 %); **p.** R = $N(CH_2)_4NCH_4$ (49 %)

Treatment of ethyl 4-chloro-7-diethylamino-6-nitro-1,8-naphthyridine 3-carboxylate (**104**) with the amines RH [R = $N(CH_2)_5$; $NH(CH_2)N(C_2H_5)_2$] gives the corresponding 4-amino derivatives [**105,** R = $N(CH_2)_5$, 74% and **105**, R = $NH(CH_2)N(C_2H_5)_2$, 50%]. With diethylamine the 7-chloro-6-nitro derivative of nalidixic acid (i.e., **106**) yields the 7-diethylamino compound **107** (62%) (79YZ155).





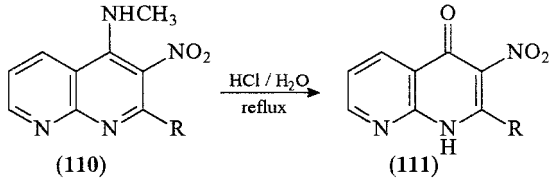
2-Chloro-3-nitro-1,5-(**108a**/**108b**), 2-chloro-3-nitro-1,6-(**108c**/**108d**), 2-chloro-3-nitro-1,8- (**108e**), and 2-chloro-3,6-dinitro- 1,8- (**108f**) naphthyridines easily undergo nucleophilic substitution with alkoxy anions, giving **109,** (R = OCH_3, OC_2H_5) in moderate yield; with mercapto ions the corresponding 2-mercapto derivatives (**109,** R = SH, SPh) are produced (80RTC83; 83RTC511, 83RTC359, 83JHC9; 85JHC761; 95MI1; 97MI3; 98MI3).



	R^1	R^2
a. N = 5	H	H
b. N = 5	NH_2	H
c. N = 6	H	H
d. N = 6	NH_2	H
e. N = 8	H	H
f. N = 8	H	NO_2

The 4-methylamino-3-nitro-1,8-naphthyridines (**110,** R = H, $NHCH_3$) undergo hydrolysis when heated with aqueous hydrochloric acid to give in

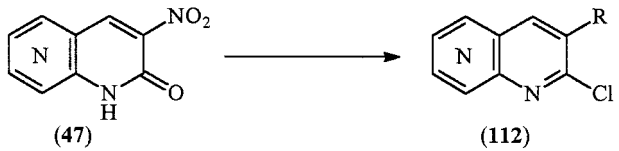
high yield the 1,8-naphthyridin-4(1H)-ones (**111**). In the case of **110** (R = OCH_3), 4-hydroxy-3-nitro-1,8-naphthyridin-2(1H)-one (**52d**) was obtained. Under these conditions 2-methylamino-3-nitro-1,8-naphthyridine remains unchanged (97LAR2601).



(110) (111)

D. Replacement of Hydroxy and Nitro Groups by Halogen

Hydroxy (oxo) groups in 3-nitronaphthyridines, especially those in positions *ortho* or *para* to the ring nitrogen, are easily replaced by halogen in reactions with phosphorus pentachlorides, phosphorus oxychloride (bromide), or mixtures of both reagents. Depending on the reactions conditions, replacement of the 3-nitro group can occur as well. Thus, from 3-nitro-1,X-naphthyridin-2(1H)ones (X = 5, 6, 8) (**47a**–**47c**) the 2-halogeno compounds (**112a**–**112d**) were obtained, and, similarly, from

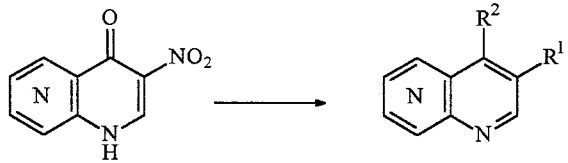


(47) (112)

Reagent, conditions

a. N = 5 $PCl_5/POCl_3$, 130° C ,	**a.** N = 5, R = NO_2 [65 %, 40MI1]
a. N = 5 $PCl_5/POCl_3$, 135° C , 2.5h	**a.** N = 5, R = NO_2 (2 parts) + **b.** N = 5, R = Cl (3parts) [83RTC511]
a. N = 5 $POCl_3$, reflux, 15h	**a.** N = 5, R = NO_2 [60%, 83RTC511]
b. N = 6 $POCl_3$, reflux, 8h	**c.** N = 6, R = NO_2 [44 %, 83RTC359]
c. N = 8 $POCl_3$, reflux, 0.5h	**d.** N = 8, R = NO_2 [57 %, 76S691]

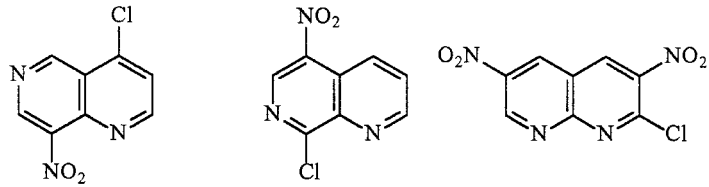
the 3-nitro-1,X-naphthyridin-4(1H)-ones (X = 5, 6, 7, 8) (**40a**–**40d**) the corresponding 4-halogeno-1,X-naphthyridines (**113a**–**113e**) are easily afforded.



(40) (113)

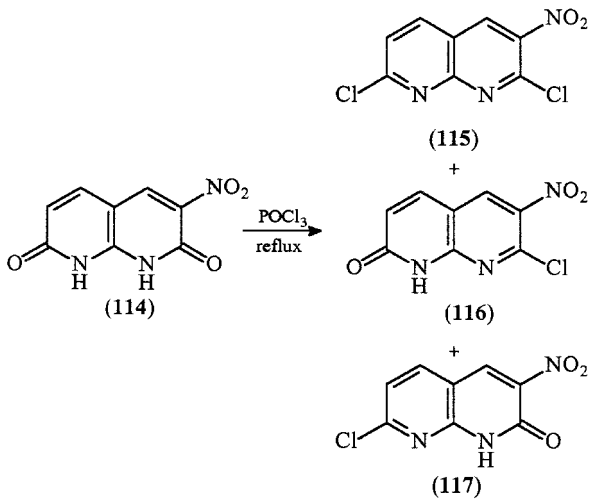
	Reagent, conditions	R^1	R^2	
a. N = 5	$PCl_5/POCl_3$,reflux, 1.15h	**a.** N = 5, NO_2	Cl	[53 %, 63JCS4237]
b. N = 6	$POCl_3$, reflux, 2h	**b.** N = 6, NO_2	Cl	[78 %, 63JCS4237, 50 %, 83RTC359]
c. N = 7	$POCl_3$, reflux, 3h	**c.** N = 7, Cl	Cl	[29 %, 74RTC144]
c. N = 7	$POBr_3$,170° C, 4h	**d.** N = 7, Br	Br	[55 %, 83PJC587]
d. N = 8	$POCl_3$, reflux, 3h	**e.** N = 8, NO_2	Cl	[58 %, 79PJC1665]

Analogously, 4-chloro-8-nitro-1,6-naphthyridine (**80,** 68%) (63JCS4237), 8-chloro-5-nitro-1,7-naphthyridine (**97,** 51%) (78JHC731), and 2-chloro-3,6-dinitro-1,8-naphthyridine (**82,** 66%) (85JHC761) were obtained from 8-nitro-1,6-naphthyridine-4(1H)-one, 5-nitro-1,7-naphthyridin-8(7H)-one, and 3,6-dinitro-1,8-naphthyridin-2(1H)-one, respectively.

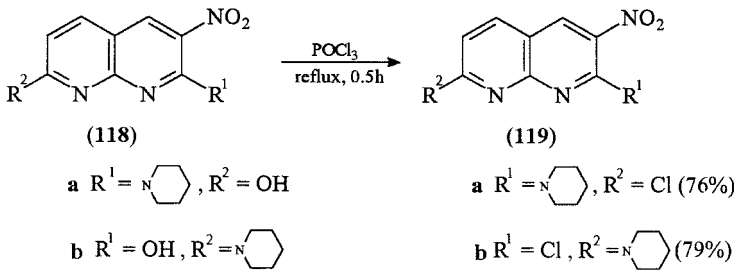


(80) (97) (82)

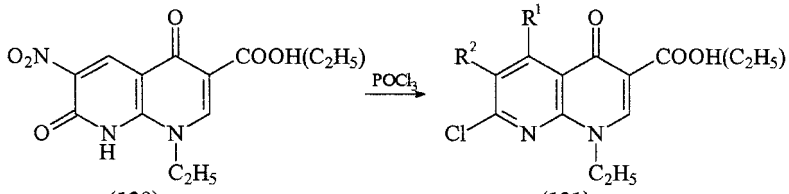
When more than one oxo (hydroxy) group is present, a mixture of chloro-hydroxy- and dichloro-naphthyridines is usually formed. Thus, reflux of 3-nitro-1,8-naphthyridin-2,7(1H,8H)-dione (**114**) with phosphorus oxychloride gives the three halogeno compounds (**115, 116,** and **117**), the ratio being dependent on the reaction time (94EJMC735).



Hydroxypiperidino-3-nitro-1,8-naphthyridines (**118a/118b**) were converted into the corresponding chloropiperidino derivatives (**119a/119b**) (94EJMC735).



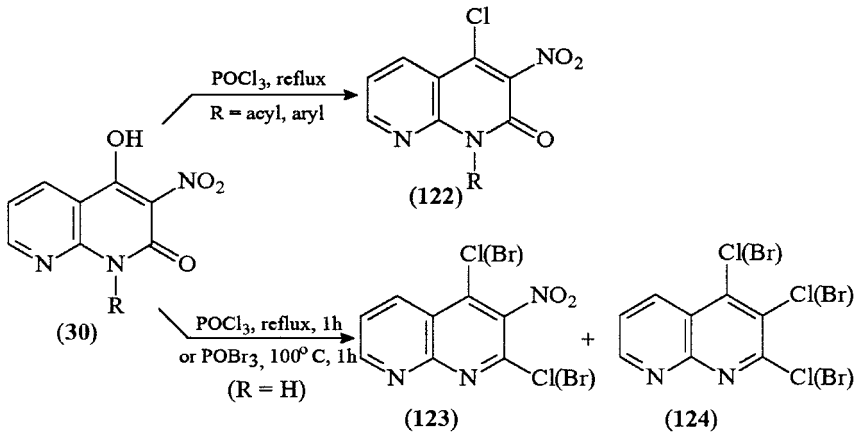
1-Ethyl-6-nitro-1,8-naphthyridin-4,7(1H,8H)dione-3-carboxylic acid (or its ethyl ester) (**120**) is converted into the 7-chloro derivatives (**121a**–**121e**). Under somewhat more drastic conditions, the replacement of the nitro group as well as the ring hydrogen in position 5 by a chloro atom has been observed (79YZ155; 80CPB235).



(120) (121)

Reaction conditions	R^1	R^2
$POCl_3$, 80-90C°, 2h	**a.** H	NO_2 (80 %)
$POCl_3$, 100°C, 5h	**b.** Cl	Cl (1.6 %)
	c. H	Cl (not given)
$POCl_3$, 80°C,4h	**d.** Cl	NO_2 (43 %)
PCl_5, $POCl_3$, 110 - 120°C , 5h	**e.** H	Cl (53 %)

A number of 1-substituted 4-chloro-3-nitro-1,8-naphthyridin-2(1H)-ones (**122**) (R are the same substituents as in the scheme in Section II,A,4,a) were obtained from the corresponding 4-hydroxy-1,8-naphthyridin-2(1H)-ones (**30**) (91JHC2029, 91MI2; 92JMC4866).



Reaction of (**30,** R = H) with phosphorus oxychloride or phosphorus oxybromide leads to a mixture of 2,4-dihalogeno-3-nitro- (**123**) and 2,3,4-trihalogeno compounds (**124**) in a ratio of about 2 : 1 (98MI3).

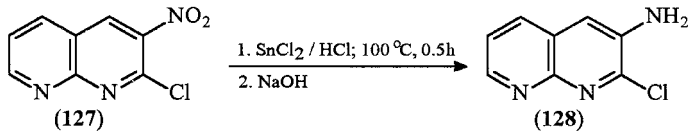
E. Reduction

The reduction of the nitro group in nitronaphthyridines to aminonaphthyridines has been described mostly for compounds in which the nitro group is located at the β-position to the ring nitrogen. As reducing agents, Raney-nickel, tin(II) chloride in hydrochloric acid, hydrogen and palladium on carbon, and sodium hydrogen sulfite were used. The method of choice strongly depends on the substrates used. The process has very little application for obtaining aminonaphthyridines, since the alternative way to synthesize aminonaphthyridines, i.e., removal of the halogeno atom from the readily available aminohalogenonaphthyridines is easy, especially when the halogeno atom is present in the α- and/or γ-positions.

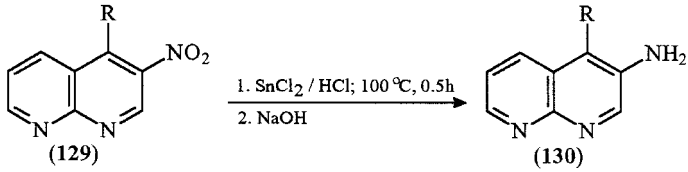
Catalytic hydrogenation (Pd/C) of 2-chloro-3-nitro-1,5-naphthyridine (**125,** R = Cl) in methanolic solution afforded 3-amino-1,5-naphthyridine (**126,** R = H, 74%) isolated in the form of its trihydrochloride (40MI1). Similar Pd/C hydrogenation of 2-ethoxy-3-nitro-1,5-naphthyridine (**125,** R = OEt) gave 3-amino-2-ethoxy-1,5-naphthyridine (**126,** R = OEt, 47%) (80RTC83). Reduction with tin(II) chloride in hydrochloric acid also leads to **126,** (R = OEt, 73%) (63RTC997).

R = Cl, OEt

Interestingly, no dehalogenation occurs when 2-chloro-3-nitro-1,8-naphthyridine (**127**) is treated with tin(II) chloride in hydrochloric acid; 3-amino-2-chloro-1,8-naphthyridine (**128,** 33%) is the sole product (76S691).

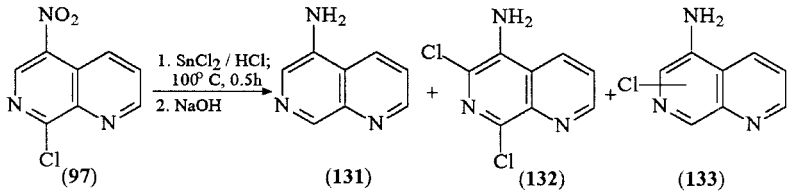


Tin(II) chloride reduction of both 4-chloro-3-nitro-1,8-naphthyridine (**129,** R = Cl) (79PJC1665) and 3-nitro-1,8-naphthyridine (**129,** R = H) (76S691) gave in 30–35% yield 3-amino-1,8-naphthyridine (**130,** R = H); reduction of the 4-amino-3-nitro compound (**129,** R = NH_2) yielded 3,4-diamino-1,8-naphthyridine (**130,** R = NH_2, 37%) (79PJC1665).

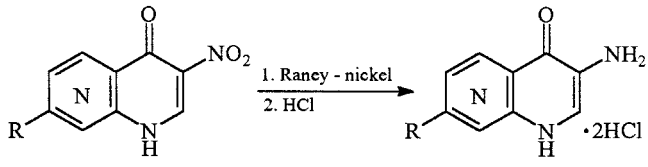


R = Cl, H, NH_2

Subjecting 8-chloro-5-nitro-1,7-naphthyridine (**97**) to reduction with tin(II) chloride leads, besides loss of the chloro atom and reduction of the nitro group, i.e., formation of 5-amino-1,7-naphthyridine (**131,** 22%), to the formation of small amounts of 5-amino-6,8-dichloro- (**132,** 1.5%) and 5-amino-6-(or 8-)chloro-1,7-naphthyridine (**133,** 2.5%) (88PJC305).



Raney-nickel nitro reductions were reported for 3-nitro-1,X-naphthyridin-4(1H)-ones (X = 5, 6, 7, and 8) (**134a–134d**), yielding 3-amino-4(1H)-ones, isolated as their hydrochlorides (**135a–135d**).



a. N = 5, R = H — **a.** N = 5, R = H [57%, 55LA91]

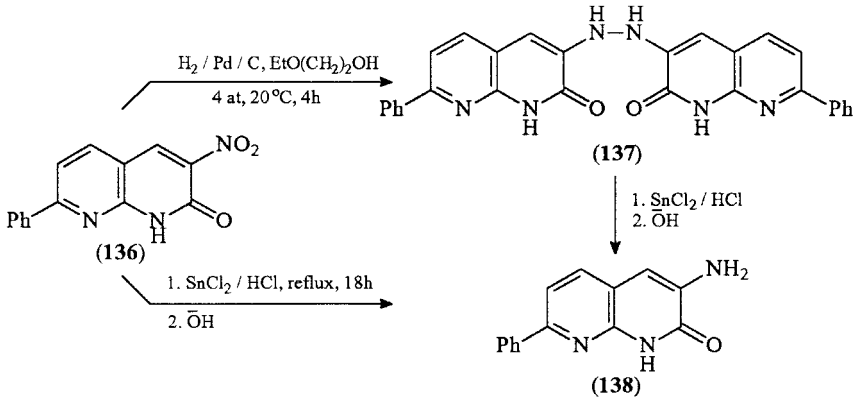
b. N = 6, R = H — **b.** N = 6, R = H [48 %, 58LA153; 60JCS1794]

c. N = 7, R = H — **c.** N = 7, R = H [69 %, 56LA233; 75%, 60JCS1794]

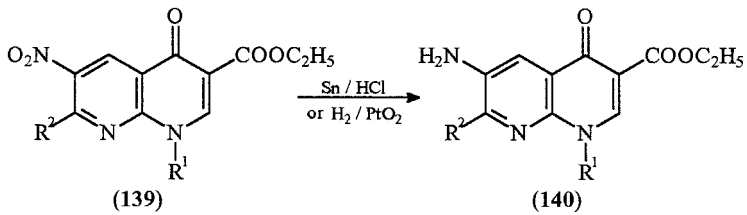
d. N = 8, R = 7-CO_2H — **d.** N = 8, R = 7-CO_2H[42%, 58LA153]

Catalytic reduction of 3-nitro-7-phenyl-1,8-naphthyridin-2(1H)-one (**136**) with palladium on carbon in 2-ethoxyethanol gave the 1,2-di(1,8-

naphthyrid-3-yl)hydrazine derivative (**137,** 97%), while treatment of (**136**) with tin(II) chloride in hydrochloric acid gave 3-amino-7-phenyl-1,8-naphthyridin-2(1H)-one (**138,** 36%). Hydrazino compound (**137**) could be further reduced to the amino compound (**138,** 32%) with tin(II) chloride [66JCS(C)315].

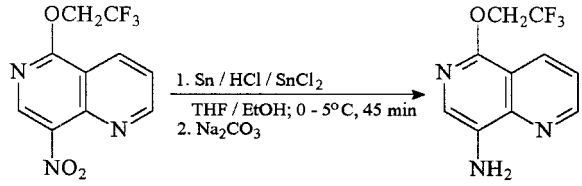


The 1,7-disubstituted derivatives of ethyl 6-nitro-1,8-naphthyridin-4(1H)-one 3-carboxylate (i.e. **139a**–**139d**) were reduced to the 6-amino compounds (**140a**–**140d**) (79YZ155; 80CPB235) using tin/hydrochloric acid or hydrogen/platinum oxide.



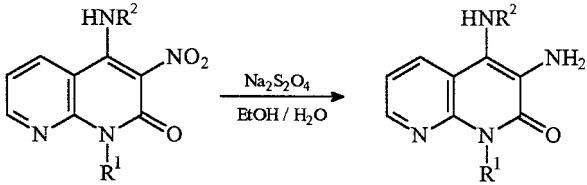
	R^1	R^2
a.	C_2H_5	Cl
b.	C_2H_5	C_6H_4-*p*-Cl
c.	CH_2CH_2 Cl	Cl
d.	CH_2CH_2Cl	$NHCH_3$

Reduction of 8-nitro-5-(*β*,*β*,*β*-trifluoroethoxy)-1,6-naphthyridine (**141**) afforded the corresponding 8-amino compound (**142,** 45%) (81JHC941).



(141) (142)

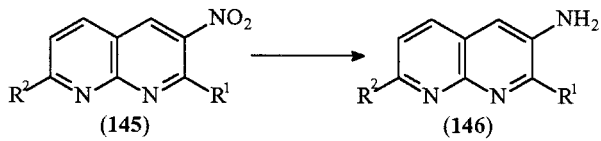
Sodium hydrosulfite successfully reduced the nitro group in a number of 1-*N*-alkyl(aryl) 4-(substituted) amino-3-nitro-1,8-naphthyridin-2(1H)-ones (**143**) to give the corresponding 3-amino derivatives (**144**) (91JHC2029, 91MI2; 92JMC4866). These products could not be purified but were used in their crude form for further annelation into imidazonaphthyridin-4(5H)-ones (see Section III,G).



(143) (144)

R^1 = aryl, alkyl ; R^2 = H, alkyl

Palladium on carbon was successfully applied for hydrogenation of 3-nitro-2,7-disubstituted 1,8-naphthyridines (**145a**–**145c**), affording the corresponding 3-amino compounds (**146a**–**146c**) in 83–85% yield (94EJMC735).



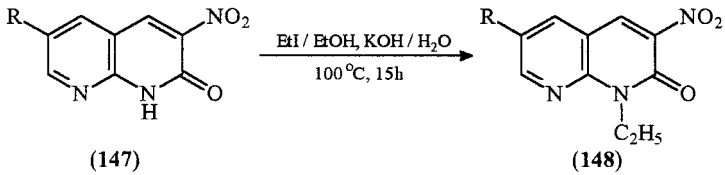
(145) (146)

	R^1	R^2
a.	$N(CH_2)_5$	$N(CH_2)_5$
b.	OH	$N(CH_2CH_2OH)_2$
c.	OH	$N(CH_2)_5$

F. Reactions on Ring Nitrogen

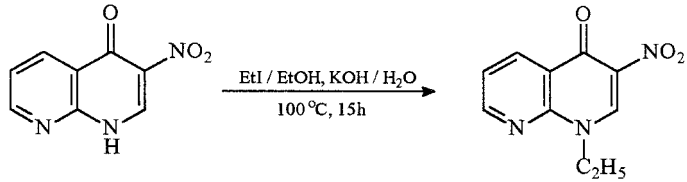
The parent 1,X-naphthyridines (X = 5, 6, 7, and 8) give with methyl iodide *N*-methyl naphthyridinium iodides. In 1,6- and 1,7-naphthyridine the

site of methylation is the "isoquinolinic" nitrogens N-6 and N-7 respectively. This was convincingly proved by oxidation to the corresponding 6-methylnaphthyridin5(6H)-one and 7-methylnaphthyridin-8(7H)-one respectively (84MI3) and by ^{13}C NMR spectroscopy (77OMR165). It is interesting that the rate constant for methylation of 1,8-naphthyridine is much greater than that of 1,5-naphthyridine; the ratio being 4.25 : 0.232. This is probably due to the interaction in the transition state of the methyl group with the peri lone pair of electrons on the ring-nitrogen. Diquaternary salts of the parent 1,X-naphthyridines have been prepared by reaction with dimethyl sulfate or with methyl fluorosulfonate (84MI3). 3-Nitro- (**147a**) and 3,6-dinitro- (**147b**) 1,8-naphthyridin-2(1H)-ones and 3-nitro-1,8-naphthyridin-4(1H)-one (**149**) undergo 1-N-ethylation with ethyl iodide in alkaline solution, affording the derivatives **148a** (70%), **148b** (32%), and **150** (25%) respectively (93LA471). Compound (**150**) was also obtained by decarboxylation of 7-carboxy-1-ethyl-3-nitro-1,8-naphthyridin-4(1H)-one (**44**) in 34% yield (79YZ155).



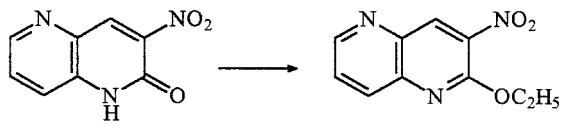
(147) (148)

a. R=H ; **b.** R=NO_2



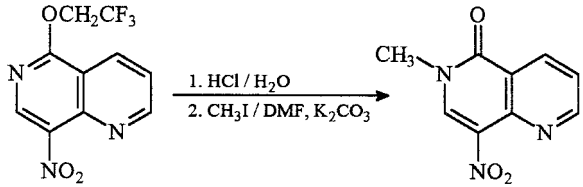
(149) (150)

It is interesting that the silver salt of 3-nitro-1,5-naphthyridin-2(1H)-one (**151**) reacts with ethyl iodide to give 2-ethoxy-3-nitro-1,5-naphthyridine (**152**). 1-*N*-Ethyl-3-nitro-1,5-naphthyridin-2(1H)-one has not been isolated, indicating that in the silver salt the nucleophicity of the oxygen is higher than that of the ring-nitrogen (63RTC988; 80RTC83).



(151) (152)

Hydrolysis of 8-nitro-5-(β,β,β-trifluoroethoxy)-1,6-naphthyridine (**141**) gave 8-nitro-1,6-naphthyridin-5(6H)-one, which was further methylated to 8-nitro-6-methyl-1,6-naphthyridin-5(6H)-one (**16**) (81JHC941).

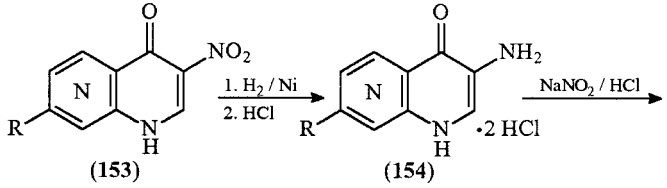


(141) (16)

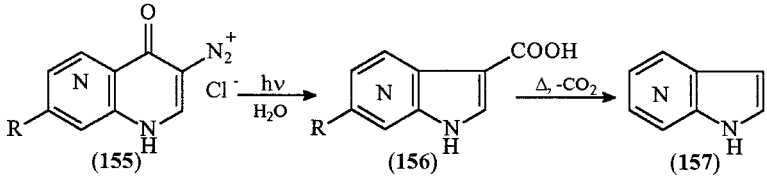
G. Ring Transformations and Annelations

1. *Ring Transformations*

Only a few examples are reported in the literature concerning ring transformations. The well-known photolytically induced ring contraction of 3-diaza-4-oxo-azines (53LA133, 53LA150; 55LA91) was successfully applied to the 3-diazo-4-oxo-1,X-naphthyridines (**155,** X = 5, 6, 7, 8). Photolysis of **155** [obtained from 3-nitro-1,X-naphthyridin-4(1H)-ones (**153**) by reduction of the 3-nitro group and subsequent diazotation of the compound (**154**)] gave, with nitrogen extrusion 4-,5-,6- and 8-azaindole 3-carboxylic acids (**156a**–**156d**) respectively. The latter were decarboxylated into the parent azaindoles(**157a**–**157d**) (55LA91; 58LA153; 56LA233; 60JCS1794).



(153) (154)

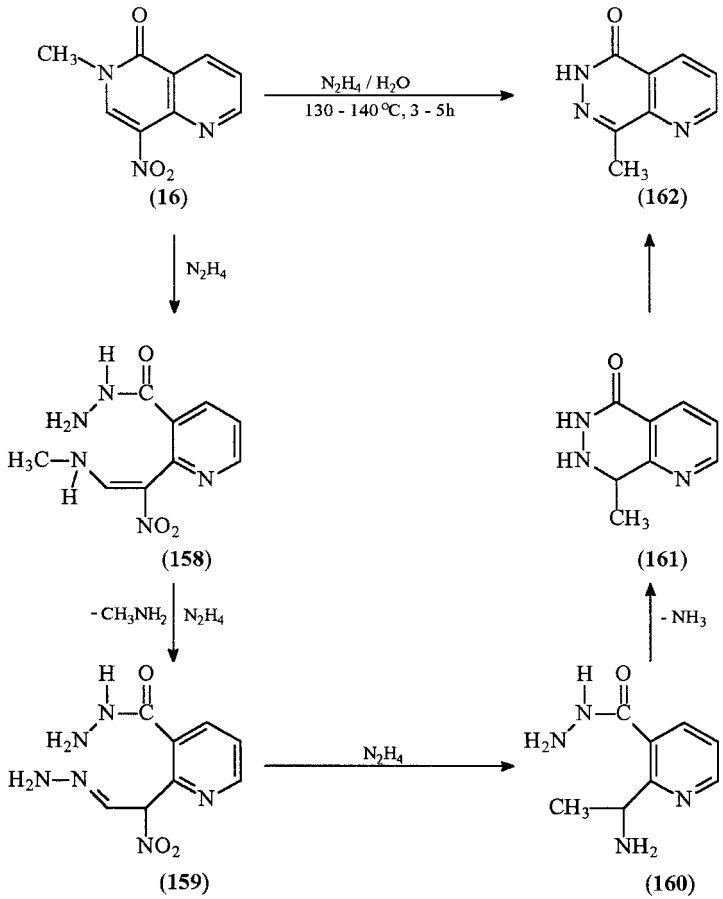


(155) (156) (157)

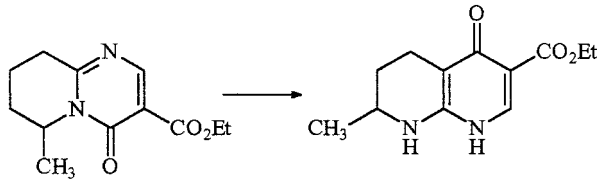
a. N = 5, R = H
b. N = 6, R = H
c. N = 7, R = H
d. N = 8, R = CO_2H

a. N = 4
b. N = 5
c. N = 6
d. N = 7

A hydrazine-induced ring transformation was observed with 8-nitro-6-methyl-1,6-naphthyridin-5(6H)-one (**16**). When **16** is heated with hydrazine hydrate 8-methylpyrido[2,3-*d*]pyridazin-5(6H)-one (**162,** 94%) is formed (86ZOR1793). The authors suggest that due to the influence of a strong electron-withdrawing C-8 nitro group on the carbonyl C-5 atom, the nucleophilic attack of hydrazine takes place at C-5, followed by opening the pyridine ring. A Wolff–Kishner-type reduction of **159** into **160** and a ring closure to the pyridazine ring gives **162: 16** → **158** → **159** → **160** → **161** → **162.** It has been argued (86ZOR1793) that for the occurrence of the ring contraction the presence of the nitro group is required, since in the hydrazinolysis of a somewhat similar compound, i.e., 4-aminoisoquinolin-1(2H)-one, no ring contraction was observed.



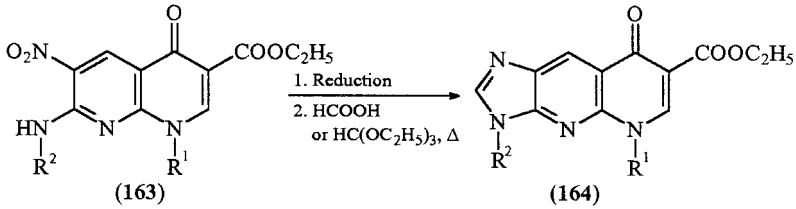
It is interesting that somewhat similarly 4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidine (**A**) was transformed into 5,6,7,8-tetrahydro-1,8-naphthyridin-4(1H)-one (**B**) by action of sec-amines (79H1407). Also in this transformation bond-breaking occurs between the ring nitrogen and the carbon of the carboxyl group.



(**A**) (**B**)

2. *Annelations*

Ortho diaminonaphthyridines, usually obtained by reduction of *ortho* nitro-aminonaphthyridines, are appropriate starting materials for constructing imidazonaphthyridines. Examples are the conversion of the 7-(substituted amino) 6-nitro-1,8-naphthyridin-4(1H)-one 3-carboxylates (**163a**/**163b**) in two consecutive steps, i.e., reduction of the amino group and a subsequent cyclization with formic acid or triethoxymethane, into the corresponding imidazo[4,5*b*][1,8]naphthyridine derivatives (**164a**/**164b**) (80CPB235).

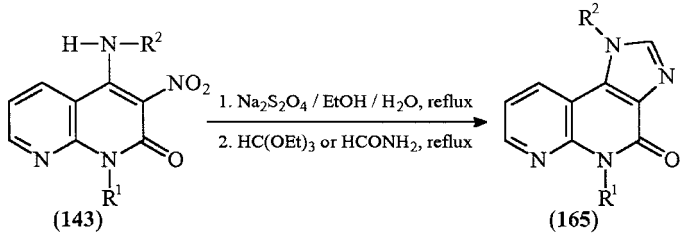


(**163**) (**164**)

a. $R^1 = C_2H_5$, $R^2 = C_6H_4$ -p-Cl

b. $R^1 = CH_2CH_2Cl$, $R^2 = CH_3$

In a very similar process (reduction and cyclization) a variety of 1-aryl (alkyl)-4-amino-3-nitro-1,8-naphthyridin-2(1H)-ones (**143a**–**143n**) were converted into the corresponding 1,5-disubstituted 1H-imidazo[4,5-*c*]naphthyridin-4(5H)-ones (**165a**–**165n**) (91JHC2029, 91MI2; 92JMC4866).



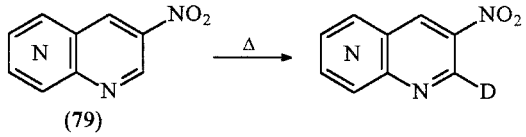
(143) (165)

	R^1	R^2	Yield (%)
a.	C_6H_5	H	58
b.	C_6H_5	CH_3	97
c.	C_6H_5	C_2H_5	88
d.	C_6H_5	$CH(CH_3)_2$	91
e.	C_6H_5	$CH_2C_6H_5$	87
f.	4-$MeOC_6H_4$	H	54
g.	3-$MeOC_6H_4$	H	50
h.	4-MeC_6H_4	H	52
i.	3-MeC_6H_4	H	37
j.	3-ClC_6H_4	H	47
k.	4-$EtOOCC_6H_4$	H	60
l.	3-$EtOOCC_6H_4$	H	48
m.	n-C_4H_9	CH_3	85
n.	n-C_4H_9	H	45

H. Deuterium Labeling

Hydrogen–deuterium exchange studies were performed for 3-nitro-1,5-naphthyridine (**79a**) and for 3-nitro-1,8-naphthyridine (**79b**) (83JHC9; 88MI1). Heating 3-nitro-1,5-naphthyridine (**79a**) (180°C, 5 h) in D_2O (83RTC511) gave 2-deuterio-3-nitro-1,5-naphthyridine. Similarly, H/D exchange in **79b** also occurred mainly in the C-2 position, both in neutral and in acid conditions. When **79b** was heated in D_2O or in 1.5% solution of DCl in D_2O at 200°C for 10 h, the reactivity order of the positions for H/D exchange was in D_2O: C-2 (100%) > C-4 (40%) > C-7 (35%) > C-5 ~ C-6 (0%); in DCl/D_2O: C-2 (60%) > C-4 ~ C-5 ~ C-6 ~ C-7 (0%). For the parent 1,8-naphthyridine this order was in D_2O : C-2,7 (95%) > C-3 ~ C-4 ~ C-5 ~ C-6 ~ C-7 (0%); in DCl/D_2O: C-2,7 (20%) > C-4,5 (10%) > C-3,6 (0%).

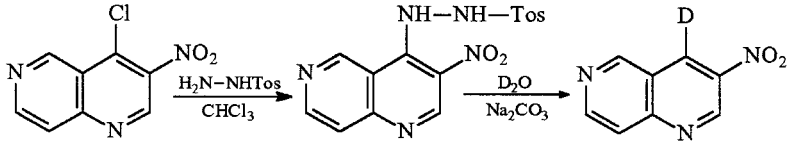
4-Deuterio-3-nitro-1,6-naphthyridine (**168**) was prepared from 4-chloro-3-nitro-1,6-naphthyridine (**166**) by a reaction with tosyl hydrazide and subsequent hydrolysis of the 4-tosylhydrazino derivative (**167**) with Na_2CO_3/D_2O solution (83RTC359). 7-Deuterio-1,8-naphthyridin-2(1H)-one was prepared by heating 1,8-naphthyridin-2(1H)-one with deuterium oxide at 230°C for 35 h (85JHC761). This deuterio compound could be converted into 2-chloro-(or 2-ethoxy-) 7-deuterio-3,6-dinitro-1,8-naphthyridine.



(79)

a. N = 5

b. N = 8



(166) (167) (168)

IV. Quantum-Chemical Calculations

FMO calculations using the MNDO method and electron-density calculations were performed to establish which calculations are in agreement with the experimentally observed regioselectivity of the S_NH amination of some nitronaphthyridines (see Section III,B).

The calculations of the π-electron energy for all positions in the studied nitronaphthyridines were carried out according to a simplified second-order perturbation Eq. (A) (94MI2).

$$\Delta E \approx 2\left[\frac{C_S^2\,(\mathrm{LUMO})}{|E^N_{\mathrm{HOMO}} - E^A_{\mathrm{LUMO}}|} + \frac{C_S^2\,(\mathrm{LUMO}+1)}{|E^N_{\mathrm{HOMO}} + E^A_{\mathrm{LUMO+1}}|}\right] \qquad \text{(A)}$$

Both the LUMO and LUMO + 1 energy levels of the nitronaphthyridines and the values of the coefficients at the carbon and ring nitrogen in the LUMO and LUMO + 1 orbitals were determined. Using $E_{\mathrm{HOMO}} = -11.9$ eV for ammonia, the values of the stabilization energy (ΔE) for each position of the nitronaphthyridines were calculated. The results of the cal-

culations are compiled in Table I. The results of calculations of the formal charges (electron densities) on all annular carbon and nitrogen atoms are shown in Table II. The FMO calculations nicely confirm the experimental results. With few exceptions, the amination occurs in those positions with the highest contribution of the π-electron stabilization energy (ΔE), in almost all cases the C-4 position. Since the electron-density calculations do not confirm the experimental results (see Table II) the conclusion seems justified that the regioselectivity of the S_NH amination is better predicted by the FMO calculations than by the electron densities on the different ring-carbon atoms in the nitronaphthyridines.

Similar calculations were also carried out for the S_NH methylamination reactions of 2-R-3-nitro- and 2-R-3,6-dinitro-1,8-naphthyridines (R = H, Cl, OCH_3, OH, NH_2, $NHCH_3$, NHPh). The calculations show that in these reactions the regioselectivity is also controlled by the interaction of the HOMO of methylamine and LUMO of the nitro-1,8-naphthyridines and not by the formal charges (97LAR2601, 97MI3).

The heats of formation of the intermediate methylamino-σ-adducts of 2-R-3-nitro- and 2-R-3,6-dinitro-1,8-naphthyridines (R = H, OCH_3, OH, NH_2, $NHCH_3$, NHC_6H_5, Cl) and transition states of the S_NH methylamination reaction of these nitro-1,8-naphthyridines were calculated by the PM3 method. The agreement between the calculated and observed results was found to be satisfactory (97LAR2601, 97MI4).

Also, the observed highly regioselective course in the S_NH substitutions in 2-R-3-nitro-1,8-naphthyridines (R = H, OH, Cl, NH_2, OEt) with the anion of chloromethyl phenyl sulfone was explained by MNDO quantum-chemical calculations showing that, like in the aminations, the interaction of HOMO of the nucleophile with LUMO of the nitronaphthyridines controls the regioselectivity (91JHC1075).

V. Physical and Spectroscopic Data

All nitronaphthyridines are solids with relatively high melting points (see Table III). Mononitronaphthyridines without other substituents are moderately soluble in hot water from which they can be recrystallized.

The pK_a value of 3-nitro-1,5-naphthyridine is 0.63. The ionization constants for protonation at N-1 (pK_1) and N-5 (pK_5) of 3-nitro-1,5-naphthyridine are pK_1 = 0.98 and pK_5 = 0.48 and for 3-nitro-1,5-naphthyridin-2(1H)-one (pK_a = 0.26) pK_1 = 6.35 and pK_5 = 0.67 were calculated using the modified Hammet equation. It was concluded by comparison of these results that protonation takes place at the ring-nitrogen in position 5 yielding **166a** and **166b** respectively (77KGS965).

TABLE I

π-Electron Stabilization Energy (ΔE) Calculated According to Eq. (A) for 3-Nitronaphthyridines

Compound	Values of ΔE when a molecule of NH_3 attacks position								Preferable positions for NH_3 attack under orbital control	Experimental data
	N-1	C-2	C-3	C-4	N-5 (C-5)	N-6 (C-6)	N-7 (C-7)	N-8 (C-8)		
3-nitro-1,5-naphthyridine	0.033	0.058	0.060	0.067	0.027	0.049	0.043	0.039	C-4 > C-2 > C-6 > C-7 > C-8	C-4
2-chloro-3-nitro-1,5-naphthyridine	0.036	0.065	0.062	0.069	0.026	0.046	0.042	0.038	C-4 > C-6 > C-7 > C-8	C-4
2-amino-3-nitro-1,5-naphthyridine	0.022	0.065	0.038	0.078	0.026	0.041	0.032	0.031	C-4 > C-6 > C-7 > C-8	C-4
3-nitro-1,5-naphthyridin-2(1H)-one	0.025	0.064	0.046	0.079	0.027	0.045	0.036	0.033	C-4 > C-6 > C-7 > C-8	C-4
2-ethoxy-3-nitro-1,5-naphthyridine	0.023	0.061	0.044	0.077	0.027	0.045	0.035	0.034	C-4 > C-6 > C-7 > C-8	C-4
4-amino-3-nitro-1,5-naphthyridine	0.015	0.054	0.024	0.063	0.034	0.049	0.038	0.043	C-2 > C-6 > C-8 > C-7	—
3-nitro-1,6-naphthyridine	0.034	0.066	0.060	0.070	0.040	0.032	0.043	0.033	C-4 > C-2 > C-7 > C-5 > C-8	C-4
2-chloro-3-nitro-1,6-naphthyridine	0.026	0.063	0.066	0.070	0.068	0.032	0.037	0.043	C-4 > C-5 > C-8 > C-7	C-4
2-amino-3-nitro-1,6-naphthyridine	0.021	0.071	0.035	0.081	0.039	0.027	0.030	0.027	C-4 > C-5 > C-7 > C-8	C-4
3-nitro-1,6-naphthyridin-2(1H)-one	0.026	0.072	0.045	0.082	0.039	0.029	0.035	0.029	C-4 > C-5 > C-7 > C-8	—
2-ethoxy-3-nitro-1,6-naphthyridine	0.024	0.069	0.044	0.079	0.040	0.029	0.035	0.029	C-4 > C-5 > C-7 > C-8	C-4
4-amino-3-nitro-1,6-naphthyridine	0.017	0.061	0.025	0.065	0.049	0.033	0.037	0.039	C-2 > C-5 > C-8 > C-7	—

8-amino-5-nitro-1,7-naphthyridine	0.018	0.040	0.051	0.021	0.028	0.069	0.020	0.062	C-6 > C-3 > C-2 > C-4	—
3-nitro-1,8-naphthyridine	0.032	0.058	0.060	0.068	0.043	0.049	0.045	0.024	C-4 > C-2 > C-6 > C-7 > C-5	C-4
2-chloro-3-nitro-1,8-naphthyridine	0.035	0.065	0.062	0.070	0.041	0.046	0.044	0.024	C-4 > C-6 > C-7 > C-5	C-4
2-amino-3-nitro-1,8-naphthyridine	0.020	0.063	0.035	0.079	0.043	0.041	0.033	0.019	C-4 > C-5 > C-6 > C-7	C-4
3-nitro-1,8-naphthyridin-2(1H)-one	0.024	0.063	0.045	0.079	0.043	0.045	0.038	0.021	C-4 > C-6 > C-5 > C-7	—
2-ethoxy-3-nitro-1,8-naphthyridine	0.022	0.061	0.044	0.078	0.044	0.046	0.038	0.021	C-4 > C-6 > C-5 > C-7	C-4
4-amino-3-nitro-1,8-naphthyridine	0.015	0.053	0.025	0.065	0.054	0.039	0.039	0.027	C-5 > C-2 > C-6 ~ C-7	—
1-*N*-ethyl-3-nitro-1,8-naphthyridin-2(1H)-one	0.014	0.019	0.042	0.072	0.062	0.058	0.044	0.023	C-4 > C-5 > C-6 > C-7	C-4
1-*N*-ethyl-3-nitro-1,8-naphthyridin-4(1H)-one	0.014	0.089	0.031	0.022	0.040	0.030	0.065	0.023	C-2 > C-7 > C-5 > C-6	—
3,6-dinitro-1,8-naphthyridine	0.028	0.054	0.061	0.065	0.065	0.061	0.054	0.028	C-4 ~ C-5 > C-2 ~ C-7	C-4
2-chloro-3,6-dinitro-1,8-naphthyridine	0.030	0.062	0.063	0.068	0.062	0.057	0.053	0.027	C-4 > C-5 > C-7	C-4 ~ C-5
2-amino-3,6-dinitro-1,8-naphthyridine	0.016	0.048	0.039	0.080	0.073	0.042	0.030	0.026	C-4 > C-5 > C-7	C-4
3,6-dinitro-1,8-naphthyridin-2(1H)-one	0.024	0.056	0.058	0.069	0.064	0.057	0.054	0.025	C-4 > C-5 > C-7	—
2-ethoxy-3,6-dinitro-1,8-naphthyridine	0.017	0.045	0.047	0.076	0.075	0.046	0.047	0.018	C-4 > C-5 > C-7	C-4 ~ C-5
1-*N*-ethyl-3,6-dinitro-1,8-naphthyridin-2(1H)-one	0.019	0.011	0.045	0.071	0.087	0.046	0.058	0.016	C-5 > C-4 > C-7	C-4

TABLE II

FORMAL ELECTRON CHARGES q ON THE ANNULAR ATOMS OF THE 3-NITRONAPHTHYRIDINES

Compound	Formal charge q of atoms								Preferable positions for NH_3 attack under charge control	Experimental data
	N-1	C-2	C-3	C-4	N-5 (C-5)	N-6 (C-6)	N-7 (C-7)	N-8 (C-8)		
3-nitro-1,5-naphthyridine	−0.1067	−0.0153	−0.1610	−0.0070	−0.1145	−0.0465	−0.1638	−0.0640	—	C-4
2-chloro-3-nitro-1,5-naphthyridine	−0.1055	0.0419	−0.1562	−0.0005	−0.1117	−0.0454	−0.1605	−0.0640	C-2	C-4
2-amino-3-nitro-1,5-naphthyridine	−0.2262	0.2161	−0.2387	0.0479	−0.0947	−0.0755	−0.1429	−0.0960	C-2 > C-4	C-4
3-nitro-1,5-naphthyridin-2(1H)-one	−0.2176	0.1960	−0.1961	0.0386	−0.0989	−0.0645	−0.1461	−0.0860	C-2 > C-4	C-4
2-ethoxy-3-nitro-1,5-naphthyridine	−0.2123	0.2001	−0.1978	0.0359	−0.0985	−0.0674	−0.1473	−0.0874	C-2 > C-4	C-4
4-amino-3-nitro-1,5-naphthyridine	−0.1683	0.0473	−0.3372	0.2601	−0.1326	−0.0655	−0.1515	−0.0782	C-4 > C-2	—
3-nitro-1,6-naphthyridine	−0.1164	0.0027	−0.1751	−0.0028	−0.0232	−0.1280	−0.0590	−0.1486	C-2	C-4
2-chloro-3-nitro-1,6-naphthyridine	−0.1150	0.0660	−0.1752	0.0090	−0.0322	−0.0872	−0.1293	−0.1751	C-2 > C-4	C-4
2-amino-3-nitro-1,6-naphthyridine	−0.2416	0.2404	−0.2609	0.0561	0.0021	−0.1528	−0.0433	−0.1814	C-2 > C-4	C-4
3-nitro-1,6-naphthyridin-2(1H)-one	−0.2282	0.2121	−0.2103	0.0424	−0.0054	−0.1415	−0.0436	−0.1710	C-2 > C-4	—
2-ethoxy-3-nitro-1,6-naphthyridine	−0.2228	0.2157	−0.2113	0.0392	−0.0056	−0.1438	−0.0455	−0.1722	C-2 > C-4	C-4
4-amino-3-nitro-1,6-naphthyridine	0.1734	0.0569	−0.3360	0.2622	−0.0234	−0.1428	−0.0502	−0.1605	C-4 > C-2	—
8-amino-5-nitro-1,7-naphthyridine	−0.1316	–0.0695	−0.1454	−0.1011	−0.2674	0.0754	−0.2487	0.2372	C-6 > C-8	—

3-nitro-1,8-naphthyridine	−0.0855	–0.0042	−0.1714	−0.0129	−0.0630	−0.1794	−0.0291	−0.0989	—	C-4
2-chloro-3-nitro-1,8-naphthyridine	−0.0859	0.0547	−0.1675	−0.0061	−0.0609	−0.1785	−0.0257	−0.0968	C-2	C-4
2-amino-3-nitro-1,8-naphthyridine	−0.2120	0.2354	−0.2580	0.0450	−0.0366	−0.2144	−0.0070	−0.1259	C-2 > C-4	C-4
3-nitro-1,8-naphthyridin-2(1H)-one	−0.1997	0.2078	−0.2070	0.0319	−0.0444	−0.1994	−0.0125	−0.1161	C-2 > C-4	—
2-ethoxy-3-nitro-1,8-naphthyridine	−0.1949	0.2116	−0.2081	0.0290	−0.0436	−0.2022	−0.0141	−0.1184	C-2 > C-4	C-4
4-amino-3-nitro-1,8-naphthyridine	−0.1404	0.0493	−0.3332	0.2556	−0.0573	−0.1997	−0.0206	−0.1078	C-4 > C-2	—
1-*N*-ethyl-3-nitro-1,8-naphthyridin-2(1H)-one	−0.2325	0.3523	−0.2367	0.0561	−0.0170	−0.2279	0.0101	−0.1835	C-4 > C-7	C-4
1-*N*-ethyl-3-nitro-1,8-naphthyridin-4(1H)-one	−0.1670	0.1159	−0.3292	0.3274	−0.0153	−0.2096	−0.0134	−0.1789	C-2	—
3,6-dinitro-1,8-naphthyridine	−0.0830	0.0106	−0.1673	−0.0064	−0.0064	−0.1672	0.0104	−0.0828	C-2 > C-7	C-4
2-chloro-3,6-dinitro-1,8-naphthyridine	−0.0856	0.0664	−0.1650	0.0012	−0.0038	−0.1680	0.0136	−0.0814	C-7 > C-4	C-4 ~ C-5
2-amino-3,6-dinitro-1,8-naphthyridine	−0.2154	0.2537	−0.2620	0.0629	0.0496	−0.2352	0.0390	−0.1193	C-4 > C-5 > C-7	C-4
3,6-dinitro-1,8-naphthyridin-2(1H)-one	−0.1861	0.2158	−0.1741	0.0160	0.0074	−0.1833	0.0211	−0.0963	C-7 > C-4 > C-5	—
2-ethoxy-3,6-dinitro-1,8-naphthyridine	−0.1991	0.2320	−0.2097	0.0413	0.0378	−0.2211	0.0336	−0.1120	C-4 > C-5 > C-7	C-4 ~ C-5
1-*N*-ethyl-3,6-dinitro-1,8-naphthyridin-2(1H)-one	−0.2258	0.3518	−0.2308	0.0568	0.0538	−0.2503	0.0665	−0.1821	C-7 > C-4 > C-5	C-4

TABLE III

MELTING POINTS OF NITRONAPHTHYRIDINES AND SOME DERIVATIVES: REFERENCES OF THEIR PREPARATIONS

Compound	Melting point (°C)	References
A. Nitronaphthyridines		
2-Nitro-1,5-naphthyridine	189–190	93LA471
3-Nitro-1,5-naphthyridine	183–184	63JCS4237
2-Nitro-1,6-naphthyridine	121–123	93LA471
3-Nitro-1,6-naphthyridine	159–160	63JCS4237
	161–162	89T2693
	163–164	83RTC359
8-Nitro-1,6-naphthyridine	144–145	63JCS4237
2-Nitro-1,8-naphthyridine	250–251	93LA471
3-Nitro-1,8-naphthyridine	247–248	79PJC1665
		76S691
3,6-Dinitro-1,8-naphthyridine	309–310	93LA471
2-Deuterio-3-nitro-1,5-naphthyridine	183–184	83RTC511
4-Deuterio-3-nitro-1,6-naphthyridine	163–164	83RTC359
2-Deuterio-3-nitro-1,8-naphthyridine	247–248	83JHC9
3-Nitro-2-phenyl-1,7-naphthyridine	120–121	57JOC138
3-Nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine	215–216	91JHC1075
B. Aminonitronaphthyridines		
2-Amino-3-nitro-1,5-naphthyridine	254–255 dec.	83RTC511
4-Amino-3-nitro-1,5-naphthyridine	228–229	83RTC511
		82MI1
2-Amino-3-nitro-1,6-naphthyridine	262	83RTC359
4-Amino-3-nitro-1,6-naphthyridine	298–299	83RTC359
		82MI1
8-Amino-5-nitro-1,7-naphthyridine	247–248 subl.	82MI1
2-Amino-3-nitro-1,8-naphthyridine	276–277	83JHC9
		82MI1
2-Amino-6-nitro-1,8-naphthyridine	337–339	77TL2087
4-Amino-3-nitro-1,8-naphthyridine	>350	79PJC1665
		83JHC9
2-(Methylamino)-3-nitro-1,8-naphthyridine	199–200	97LAR2601
4-(Methylamino)-3-nitro-1,8-naphthyridine	223–225	97LAR2601
2-(Phenylamino)-3-nitro-1,8-naphthyridine	173–174	97LAR2601
2-Amino-4-(methylamino)-3-nitro-1,8-naphthyridine	266–268 dec.	97LAR2601
4-Amino-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one	>300	91JHC2029
2,4-Diamino-3-nitro-1,5-naphthyridine	267–269	83RTC511
2,4-Diamino-3-nitro-1,6-naphthyridine	330 dec.	83RTC359
2,4-Diamino-3-nitro-1,8-naphthyridine	>350	83JHC9
2,4-Bis(methylamino)-3-nitro-1,8-naphthyridine	191–192	97LAR2601
4-(Methylamino)-2-(phenylamino)-3-nitro-1,8-naphthyridine	225–227	97LAR2601

TABLE III (*Continued*)

Compound	Melting point (°C)	References
2-(Diethanoloamino)-7-piperidino-3-nitro-1,8-naphthyridine	104–108	94EMJC735
2-Piperidino-7-(diethanoloamino)-3-nitro-1,8-naphthyridine	80–82	94EMJC735
2,7-Bis(piperidino)-3-nitro-1,8-naphthyridine	131–133	94EMJC735
2-Amino-3,6-dinitro-1,8-naphthyridine	>350	85JHC761
4-Amino-3,6-dinitro-1,8-naphthyridine	315–317	93LA471
2-(Methylamino)-3,6-dinitro-1,8-naphthyridine	234–236	97MI3
2-(Phenylamino)-3,6-dinitro-1,8-naphthyridine	299–303	97MI3
2,4-Diamino-3,6-dinitro-1,8-naphthyridine	>350	86JHC473
2,4-Bis(methylamino)-3,6-dinitro-1,8-naphthyridine	268–270	97MI3
C. Halogenonitronaphthyridines		
2-Chloro-3-nitro-1,5-naphthyridine	205	40MI1
	208–210 subl.	83RTC511
4-Chloro-3-nitro-1,5-naphthyridine	162–165	63JCS4237
2-Chloro-3-nitro-1,6-naphthyridine	142–143	83RTC359
4-Chloro-3-nitro-1,6-naphthyridine	139–140	63JCS4237
	139–141	83RTC359
4-Chloro-8-nitro-1,6-naphthyridine	182–183	63JCS4237
8-Chloro-5-nitro-1,7-naphthyridine	139–140	78JHC731
2-Chloro-3-nitro-1,8-naphthyridine	267–268 dec.	76S691
4-Chloro-3-nitro-1,8-naphthyridine	169–170	79PJC1665
4-Chloro-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one	228–232	91JHC2029
2,4-Dichloro-3-nitro-1,8-naphthyridine	188–189 subl.	98MI3
2,7-Dichloro-3-nitro-1,8-naphthyridine	201–203	94EJMC735
2,4-Dibromo-3-nitro-1,8-naphthyridine	233.5–234.5	98MI3
2-Chloro-3,6-dinitro-1,8-naphthyridine	204–206	85JHC761
4-Amino-2-chloro-3-nitro-1,5-naphthyridine	252–254	83RTC511
4-Amino-2-chloro-3-nitro-1,6-naphthyridine	>330	83RTC359
4-Amino-2-chloro-3-nitro-1,8-naphthyridine	>350	83JHC9
5-Amino-2-chloro-3,6-dinitro-1,8-naphthyridine	>330	86JHC473
D. Nitronaphthyridones, nitrohydroxynaphthyridones, and nitronaphthyridinediones		
3-Nitro-1,5-naphthyridin-2(1H)-one	272–274	56JCS(I)212
3-Nitro-1,5-naphthyridin-4(1H)-one	328–330 dec.	56JCS(I)212
	325–330	63JCS4237
	>360	55LA(593)91
3-Nitro-1,6-naphthyridin-2(1H)-one	>330	83RTC359
3-Nitro-1,6-naphthyridin-4(1H)-one	286	58LA153
		63JCS4237
8-Nitro-1,6-naphthyridin-4(1H)-one	256–257	63JCS4237
3-Nitro-1,7-naphthyridin-4(1H)-one	311–312	56LA233
	309–310	60JCS1794

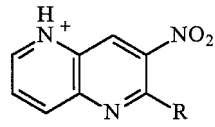
(*continues*)

TABLE III (*Continued*)

Compound	Melting point (°C)	References
5-Nitro-1,7-naphthyridin-8(7H)-one	>350 subl.	78JHC731
3-Nitro-1,8-naphthyridin-2(1H)-one	265–320 subl.	76S691
	324–328	66JCS(C)315
3-Nitro-1,8-naphthyrdin-4(1H)-one	>320 dec.	79PJC1665
		97LAR2601
3-Nitro-1,8-naphthyridin-4(1H)-one-7-carboxyl acid	314–319	58LA(612)153
4-Hydroxy-3-nitro-1,5-naphthyridin-2(1H)-one	>350 dec.	75JMC726
		77MI1
4-Hydroxy-3-nitro-1,6-naphthyridin-2(1H)-one	>370	75JMC726
		77MI1
4-Hydroxy-3-nitro-1,7-naphthyridin-2(1H)-one	344 dec.	75JMC726
		77MI1
4-Hydroxy-3-nitro-1,8-naphthyridin-2(1H)-one	288–289 dec.	75JMC726
		77MI1
3-Nitro-1,8-naphthyridin-2,7(1H,8H)-dione	>320	69GCI823
3-Nitro-1,8-naphthyridin-2,5(1H,8H)-dione	>320	72GCI253
3-Nitro-7-phenyl-1,8-naphthyridin-2(1H)-one	274–278	66JCS(C)315
2-Chloro-3-nitro-1,8-naphthyridin-7(8H)-one	240–242	94EJMC735
7-Chloro-3-nitro-1,8-naphthyridin-2(1H)-one	290 dec.	94EJMC735
7-Chloro-4-hydroxy-3-nitro-1,5-naphthyridin-2(1H)-one	252–254 dec.	96MI3
4-Hydroxy-3-nitro-7-phenyl-1,8-naphthyridin-2(1H)-one	245–246	66JCS(C)315
4-Hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1H)-one	296–298	94SC3289
3,6-Dinitro-1,8-naphthyridin-2(1H)-one	302–310 dec.	85JHC761
		87LAR2601
3,6-Dinitro-1,8-naphthyridin-2,7(1H,8H)-dione	>320	69GCI823
3,6-Dinitro-1,8-naphthyridin-2,5(1H,8H)-dione	>320	72GCI253
3,6-Dinitro-4-phenyl-1,8-naphthyridin-2,7(1H,8H)-dione	305–310 dec.	74GCI499
1-Ethyl-3-nitro-1,8-naphthyridin-2(1H)-one	166–168	93LA471
1-Ethyl-3-nitro-1,8-naphthyridin-4(1H)-one	213–215	93LA471
	207–209	79YZ155
6-Methyl-8-nitro-1,6-naphthyridin-5(6H)-one	191–192	81JHC941
	200–201	86ZOR1793
1-Ethyl-3,6-dinitro-1,8-naphthyridin-2(1H)-one	168–170	83LA471
E. Aminonitronaphthyridones		
4-Amino-3-nitro-1,5-naphthyridin-2(1H)-one	340–341	83RTC511
7-Amino-3-nitro-1,8-naphthyridin-2(1H)-one	>320	69GCI823
2-Amino-3-nitro-1,8-naphthyridin-5(8H)-one	>320	722GCI253
4-(methylamino)-3-nitro-1,8-naphthyridin-2(1H)-one	>290 dec.	97LAR2601
2-(methylamino)-3-nitro-1,8-naphthyridin-4(1H)-one	320–322 subl.	97LAR2601
2-Amino-3,6-dinitro-5-phenyl-1,8-naphthyridin-7(8H)-one	>320	74GCI499

TABLE III (*Continued*)

Compound	Melting point (°C)	References
4-Amino-1-ethyl-3-nitro-1,8-naphthyridin-2(1H)-one	285–286	93LA471
4-Amino-1-ethyl-3,6-dinitro-1,8-naphthyridin-2(1H)-one	260–262	93LA471
F. Alkoxynitronaphthyridines		
2-Ethoxy-3-nitro-1,5-naphthyridine	135.5–136	63RTC997
	134.5–136	80RTC83
2-Ethoxy-3-nitro-1,6-naphthyridine	157–159	83RTC359
2-Ethoxy-3-nitro-1,8-naphthyridine	130–131	83JHC9
2-Methoxy-3-nitro-1,8-naphthyridine	166–167	97LAR2601
2-Ethoxy-3,6-dinitro-1,8-naphthyridine	160–161	85JHC761
2-Methoxy-3,6-dinitro-1,8-naphthyridine	172–173	95MI1
4-Amino-2-ethoxy-3-nitro-1,5-naphthyridine	137–138	83RTC511
4-Amino-2-ethoxy-3-nitro-1,6-naphthyridine	202–203	83RTC359
4-Amino-2-ethoxy-3-nitro-1,8-naphthyridine	230–231	83JHC9
2-Methoxy-4-(methylamino)-3-nitro-1,8-naphthyridine	240–242	97LAR2601
4-Amino-2-ethoxy-3,6-dinitro-1,8-naphthyridine	239–240	86JHC473
5-Amino-2-ethoxy-3,6-dinitro-1,8-naphthyridine	243–244	86JHC473

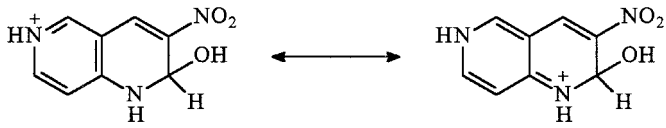


(166)

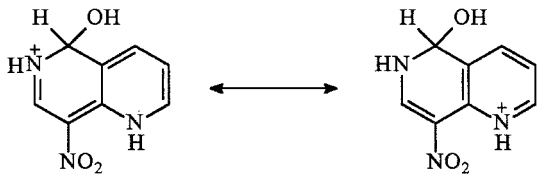
a. R = H ; **b.** R = OH

The pK_a values of 3-nitro-1,6-naphthyridine (pK_a = 2.32) and 8-nitro-1,6-naphthyridine (pK_a = 2.59) were reported (63JCS4237). In contrast to 3-nitro-1,5-naphthyridine cation (**166a**), the cations of 3-nitro-1,6-naphthyridine and 8-nitro-1,6-naphthyridine form in aqueous solution covalent hydrates. The most likely structures for the hydrated cations are presented as **167A**/**167B** and **168A**/**168B,** respectively (63JCS4237).

These results were strongly supported by the UV spectra of these compounds, showing a strong bathochromic shift of the long-wavelength bands of 64 and 36 mμ with respect to the neutral species (63JCS4237).



(167A) (167B)



(168A) (168B)

The ultraviolet spectrum of 3-nitro-1,8-naphthyridine in methanol: λ_{max} [mμ](log ε) = 206 (4.06), 238 (4.47), 311 (3.68), and 323 (3.65) showed bathochromic effect of the long-wavelength bands of 10 and 5 mμ with respect to the parent 1,8-naphthyridine (87MI2). The bathochromic effect of 3-nitro group in 1,8-naphthyridine was compared with the effects of some other substituents.

The mass spectra of the parent 3-nitro-1,X-naphthyridines (X = 5,6,7, and 8) and their amino and chloro derivatives feature as main fragmentation pathway the loss of a molecule of NO_2 from the molecular ions and further consecutive expulsion of two molecules of HCN. A second fragmentation pathway, although of much smaller intensity, is the loss of NO from the molecular ions, followed by consecutive expulsion of CO and HCN (82MI1; 89MI1).

$$\overset{-HCN}{\leftarrow}\ \overset{-CO}{\leftarrow}\ \overset{-NO}{\leftarrow}\ [M^+]\ \overset{-NO_2}{\rightarrow}\ \overset{-HCN}{\rightarrow}\ \overset{-HCN}{\rightarrow}$$

Ethoxy, aminochloro, aminoethoxy, and diamino derivatives of the 3-nitronaphthyridines show a more differentiated mass fragmentation. Besides the loss of NO_2, HCN, and NO, expulsion of OH, CO, C_2H_4, and O was observed as well.

Proton magnetic resonance spectra (in $CDCl_3$) of 3-nitro-1,5-naphthyridine (**84a**), 3-nitro-1,6-naphthyridine (**84f**), and 8-nitro-1,6-naphthyridine (**81**) have been measured and analyzed [66JCS(B)750].

84a: δ = 9.88(H-2), 9.35(H-4), 9.29(H-6), 7.82(H-7), 8.65(H-8), $J_{2,4}$ = 2.7Hz, $J_{4,8}$ = 0.9Hz, $J_{6,7}$ = 4.2Hz, $J_{6,8}$ = 1.8Hz, $J_{7,8}$ = 8.5Hz;
84f: δ = 9.81(H-2), 9.30(H-4), 9.63(H-5), 9.10(H-7), 8.19(H-8), $J_{2,4}$ = 2.6Hz, $J_{4,8}$ = 0,9Hz, $J_{5,8}$ = 0.8Hz, $J_{7,8}$ = 5.9Hz;
81: δ = 9.43 (H-2), 7.84(H-3), 8.56(H-4), 9.60(H-5), 9.30(H-7), $J_{2,3}$ = 4.2Hz, $J_{2,4}$ = 1.9Hz, $J_{3,4}$ = 8.5Hz.

The effect of substituents on chemical shifts in ^{1}H NMR spectrum of 4-chloro-3-nitro-1,6-naphthyridine (**78b**), when compared with those of the parent 1,6-naphthyridine, show that all corresponding proton signals in **78b** are shifted downfield in the range of 0.09 to 0.72 ppm. The downfield of H-2 is particularly large: 0.72 ppm (75MI1).

The ^{1}H NMR spectra of 2-nitro-, 3-nitro-, and 3,6-dinitro-1,8-naphthyridines and 37 of their substituted derivatives containing Cl, Br, OH, OCH_3, OC_2H_5, SH, SC_6H_5, NH_2, $NHCH_3$, NHC_6H_5, $N(CH_2)_4O$, and $CH_2CH{=}CH_2$, substituents have been measured in DMSO-d_6 solution (98MI1). In comparison with the parent 1,8-naphthyridine, the proton signals in these nitro-1,8-naphthyridines are shifted downfield from 0.19 to 1.20 ppm. For the di-, tri-, and tetra-substituted nitro derivatives, δ values were calculated on the basis of additivity values and compared with the experimentally established values. The differences between calculated and measured δ values are largely in the range of 0–3%.

^{1}H NMR spectra of amino-σ-adducts of 3-nitro-1,X-naphthyridines (X = 5, 6, and 8) and of 3,6-dinitro-1,8-naphthyridine and some of their 2-substituted derivatives in liquid ammonia are reported (83RTC359, 83RTC511, 83JHC9; 85JHC761; 87M1; 87MI3; 93LA471). The relevant data are presented in Table IV. Compared with the spectra in neutral solvents (DMSO or $CDCl_3$), nearly all the protons signals are shifted upfield. Especially the upfield shift of H-4 is considerable ($\Delta\delta$ = 2.55–4.61) due to the C-4 rehybridization from sp^2 in the nitronaphthyridines to sp^3 on adduct formation into their 4-amino-covalent σ-adducts. Some substituted 3,6-dinitro-1,8-naphthyridines (**87c**/**87d**) form in liquid ammonia a mixture of *mono*-σ-adducts, i.e., the 4-amino-σ-adducts and 5-amino-σ-adducts (see Table III).

Similarly, ^{1}H NMR spectra of some 3-nitro-1,8-naphthyridines in liquid methylamine were measured (97LAR2601) (see Table IV). They conclusively show that in this solution the covalent 4-methylamino-σ-adducts of those nitro compounds are present.

The infrared spectra of 3-nitro-1,7-naphthyridin-4(1H)-one; 5-nitro-1,7-naphthyridin-8(7H)-one; 8-chloro-5-nitro-1,7-naphthyridine; 3-nitro-1,8-naphthyridin-2(1H)-one; 3-nitro-1,8-naphthyridin-4(1H)-one; and 3-nitro-, 2-chloro-3-nitro-, 4-chloro-3-nitro-; and 4-amino-3-nitro-1,8-naphthyridines have been examined for the presence of structural characteristic vibrations in the C-H out-of-plane bending frequencies (78MI1; 79MI1). With few exemptions, these compounds showed ring bending (skeletal) vibrations at 680–740 cm^{-1}, three adjacent hydrogen absorptions at 750–795 and 805–885 cm^{-1}, two adjacent hydrogen absorptions at 780–855 cm^{-1}, and one hydrogen absorption at 795–810 and 885–920 cm^{-1}.

VI. Biological Activity and Uses

Platelets play an important role in hemostasis and are involved in the pathogenesis of many diseases, such as artherosclerosis and asthma. Moreover, an inadequately controlled aggregation may lead to vascular occlusion.

TABLE IV

^{1}H NMR DATA OF THE RING HYDROGENS OF SOME NITRONAPHTHYRIDINES AND THEIR 4- AND 5-AMINO-σ-ADDUCTS AND 4-METHYLAMINO-σ-ADDUCTS[a]

Compound	Solvent	Chemical shift δ (ppm)						
		H-2	H-3	H-4	H-5	H-6	H-7	H-8
3-Nitro-1,5-naphthyridine (**84a**)	DMSO	9.68	—	9.17	—	9.20	8.02	8.63
4-Amino-σ-adduct of (**84a**)	NH_3	8.41	—	5.36	—	8.25	7.27	7.56
	$\Delta\delta$	1.27	—	3.81	—	0.95	0.75	1.08
2-Amino-3-nitro-1,5-naphthyridine (**84b**)	DMSO	—	—	8.88	—	8.71	7.66	7.93
4-Amino-σ-adduct of (**84b**)	NH_3	—	—	5.31	—	7.98	7.15	7.15
	$\Delta\delta$	—	—	3.57	—	0.73	0.51	0.78
2-Chloro-3-nitro-1,5-naphthyridine (**84c**)	$CDCl_3$	—	—	8.83	—	9.09	7.78	8.39
4-Amino-σ-adduct of (**84c**)	NH_3	—	—	5.37	—	8.28	7.30	7.52
	$\Delta\delta$	—	—	3.46	—	0.81	0.48	0.87
3-Nitro-1,5-naphthyridin-2(1H)-one (**84d**)	DMSO	—	—	8.00	—	8.23	7.29	7.47
4-Amino-σ-adduct of (**84d**)	NH_3	—	—	5.45	—	8.15	7.31	7.31
	$\Delta\delta$	—	—	2.55	—	0.08	0.02	0.16
2-Ethoxy-3-nitro-1,5-naphthyridine (**84e**)	$CDCl_3$	—	—	8.65	—	8.82	7.58	8.10
4-Amino-σ-adduct of (**84e**)	NH_3	—	—	5.42	—	8.18	7.26	7.40
	$\Delta\delta$	—	—	3.23	—	0.64	0.32	0.60
3-Nitro-1,6-naphthyridine (**84f**)	$CDCl_3$	9.83	—	9.18	9.50	—	8.98	8.08
4-Amino-σ-adduct of (**84f**)	NH_3	8.45	—	5.12	8.45	—	8.23	7.02
	$\Delta\delta$	1.38	—	4.06	1.05	—	0.75	1.06
2-Amino-3-nitro-1,6-naphthyridine (**84g**)	DMSO	—	—	9.27	9.17	—	8.53	7.35
4-Amino-σ-adduct of (**84g**)	NH_3	—	—	5.07	9.17	—	8.53	7.35
	$\Delta\delta$	—	—	4.20	0.94	—	0.51	0.71
2-Chloro-3-nitro-1,6-naphthyridine (**84h**)	$CDCl_3$	—	—	8.85	9.45	—	8.98	7.95
4-Amino-σ-adduct of (**84h**)	NH_3	—	—	5.32	8.55	—	8.36	7.07
	$\Delta\delta$	—	—	3.53	0.90	—	0.62	0.88
2-Ethoxy-3-nitro-1,6-naphthyridine (**84i**)	$CDCl_3$	—	—	8.70	9.20	—	8.78	7.60
4-Amino-σ-adduct of (**84i**)	NH_3	—	—	5.32	8.42	—	8.22	6.95
	$\Delta\delta$	—	—	3.47	0.78	—	0.56	0.73
3-Nitro-1,6-naphthyridin-2(1H)-one (**47b**)	DMSO	—	—	9.11	9.38	—	8.77	7.61
4-Amino-σ-adduct of (**47b**)	NH_3	—	—	5.18	8.31	—	8.09	6.77
	$\Delta\delta$	—	—	3.93	1.07	—	0.68	0.84
3-Nitro-1,8-naphthyridine (**84j**)	DMSO	9.74	—	9.52	8.83	7.88	9.30	—
4-Amino-σ-adduct of (**84j**)	NH_3	8.57	—	5.14	7.82	7.07	8.30	—
	$\Delta\delta$	1.17	—	4.38	1.01	0.81	1.00	—

TABLE IV (*Continued*)

Compound	Solvent	Chemical shift δ (ppm) H-2	H-3	H-4	H-5	H-6	H-7	H-8
4-Methylamino-σ-adduct of (**84j**)	CH_3NH_2	8.81	—	5.42	7.81	6.95	8.25	—
	Δδ	0.93	—	4.10	1.02	0.93	1.05	—
2-Amino-3-nitro-1,8-naphthyridine (**84k**)	DMSO	—	—	9.20	8.38	7.32	8.92	—
4-Amino-σ-adduct of (**84k**)	NH_3	—	—	5.06	7.59	6.75	8.07	—
	Δδ	—	—	4.14	0.79	0.57	0.85	—
2-Chloro-3-nitro-1,8-naphthyridine (**84l**)	DMSO	—	—	9.43	8.72	7.85	9.27	—
4-Amino-σ-adduct of (**84l**)	NH_3	—	—	5.18	7.78	7.10	8.28	—
	Δδ	—	—	4.25	0.94	0.75	0.99	—
2-Ethoxy-3-nitro-1,8-naphthyridine (**84m**)	$CDCl_3$	—	—	8.63	8.22	7.45	9.08	—
4-Amino-σ-adduct of (**84m**)	NH_3	—	—	5.16	7.71	6.97	8.20	—
	Δδ	—	—	3.47	0.51	0.48	0.88	—
3-Nitro-1,8-naphthyridin-2(1H)-one (**22a**)	DMSO	—	—	8.93	8.83	7.37	8.68	—
4-Amino-σ-adduct of (**22a**)	NH_3	—	—	5.16	7.75	6.92	8.06	—
	Δδ	—	—	3.77	0.58	0.45	0.62	—
2-Methoxy-3-nitro-1,8-naphthyridine (**92e**)	$CDCl_3$	—	—	8.75	8.28	7.53	9.17	—
4-Methylamino-σ-adduct of (**92e**)	CH_3NH_2	—	—	4.26	8.69	7.73	9.17	—
	Δδ	—	—	4.49	0.41	0.20	0.00	—
2-Methylamino-3-nitro-1,8-naphthyridine (**92n**)	DMSO	—	—	9.23	8.44	7.36	8.95	—
4-Methylamino-σ-adduct of (**92n**)	DMSO	—	—	5.30	8.09	6.95	8.62	—
	Δδ	—	—	3.93	0.35	0.41	0.33	—
2-Phenylamino-3-nitro-1,8-naphthyridine (**92f**)	$CDCl_3$	—	—	9.12	8.19	a	9.12	—
4-Methylamino-σ adduct of (**92f**)	CH_3NH_2	—	—	5.41	a	a	a	—
	Δδ	—	—	3.71	—	—	—	—
3,6-Dinitro-1,8-naphthyridine (**87a**)	DMSO	9.91	—	9.76	9.76	—	9.91	—
4-Amino-σ-adduct of (**87a**)	NH_3	8.45	—	5.15	8.42	—	8.99	—
	Δδ	1.45	—	4.61	1.34	—	0.92	—
2-Amino-3,6-dinitro-1,8-naphthyr.(**87b**)	DMSO	—	—	9.47	9.37	—	9.58	—
4-Amino-σ-adduct of (**87b**)	NH_3	—	—	5.15	8.29	—	8.99	—
	Δδ	—	—	4.32	1.08	—	0.59	—
2-Ethoxy-3,6-dinitro-1,8-naphthyr. (**87c**)	$CDCl_3$	—	—	8.80	9.10	—	9.85	—

(*continues*)

TABLE IV (*Continued*)

Compound	Solvent	Chemical shift δ (ppm) H-2	H-3	H-4	H-5	H-6	H-7	H-8
4-Amino-σ-adduct of (**87c**)	NH_3	—	—	5.29	8.53	—	9.10	—
	Δδ	—	—	3.51	0.57	—	0.75	—
5-Amino-σ-adduct of (**87c**)	NH_3	—	—	8.49	5.13	—	8.49	
	Δδ	—	—	0.31	3.97	—	1.36	—
2-Chloro-3,6-dinitro-1,8-naphthyridine (**87d**)	$CDCl_3$	—	—	8.92	9.22	—	10.0	—
4-Amino-σ-adduct of (**87d**)	NH_3	—	—	5.30	8.55	—	9.11	—
	Δδ	—	—	3.62	0.67	—	0.89	—
5-Amino-σ-adduct of (**87d**)	NH_3	—	—	8.48	5.19	—	8.53	—
	Δδ	—	—	0.44	4.03	—	1.47	—
3,6-Dinitro-1,8-naphthyridin-2(1H)-one (**38**)	DMSO	—	—	8.84	9.11	—	9.38	—
4-Amino-σ-adduct of (**38**)	NH_3	—	—	5.15	8.36	—	8.81	—
	Δδ	—	—	3.69	0.75	—	0.57	—
1-Ethyl-3-nitro-1,8-naphthyridin-2(1H)-one (**90a**)	$CDCl_3$	—	—	8.46	8.10	7.35	8.79	—
4-Amino-σ-adduct of (**90a**)	NH_3	—	—	5.26	7.95	7.06	8.24	—
	Δδ	—	—	3.20	0.25	0.29	0.55	—
1-Ethyl-3,6-dinitro-1,8-naphthyridin-2(1H)-one (**90b**)	DMSO	—	—	9.18	9.34	—	9.60	—
4-Amino-σ-adduct of (**90b**)	NH_3	—	—	5.40	8.65	—	9.17	—
	Δδ	—	—	3.78	0.69	—	0.43	—

[a] The signals of these protons are overlapped by the signals of phenyl ring protons and cannot be exactly assigned.

It was discovered that 3-nitro-2-piperidino-, 3-nitro-7-piperidino-, and 7-*N*-diethanolamino-3-nitro-1,8-naphthyridin-2(1H)-ones and 2-diethanolamino-7-piperidino-3-nitro-1,8-naphthyridine showed remarkable activity to inhibit human platelet aggregation *in vitro* induced by arachidonic acid, collagen, and ADP. This activity was comparable to papaverine, dipyridamole, and ibuprofen (94EJMC735).

4-Hydroxy-3-nitro-1,5-, -1,6-, -1,7-, and -1,8-naphthyridin-2(1H)-ones possess antiallergic activity inhibiting the homocytotropic antibody–antigen-induced passive cutaneous anaphylaxis reaction. The 1,7-isomer possesses the best activity (75JMC726; 77MI1). These compounds are useful in the inhibition of the effects of certain types of antigen–antibody reactions and are therefore of value in the prophylaxis and treatment of diseases associated with allergic or immunological reaction, e.g., certain types of asthma and hay fever, and also in treatment of rhinitis.

Some of the 7-alkylamino- and arylamino-substituted derivatives of 1-ethyl-1,4-dihydro-6-nitro-4-oxo-1,8-naphthyridine-3-ethylcarboxylate showed nearly the same antibacterial activity as metronidazole against *Trichomonas vaginalis* (77MI2; 79YZ155).

Many derivatives of 4-hydroxy-3-nitro-1,X-naphthyridin-2(1H)-ones (X = 5,6,7, and 8) were claimed to have been used for treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia, and surgery as well as for treating neurodegenerative diseases, chronic pain, convulsion, anxiety, and opiate tolerance (96MI2).

Anti-mycobacterium avium activity *in vitro* of 3-carboxy-7-methyl-6-nitro-1-ethyl-1,8-naphthyridin-4(1H)-one (6-nitro derivative of nalidixic acid) was demonstrated (93MI1).

A number of nitronaphthyridines proved to be valuable intermediates in the synthesis of some antibacterial compounds (80CPB235), new broncholitators, antiflammatory and antiallergic agents (91MI2; 92JMC4866), and harmyrine (56LA233; 60JCS1794).

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 77

Chemistry of 1,2,4-Triazolopyrimidines III: 1,2,4-Triazolo[1,5-*c*]Pyrimidines

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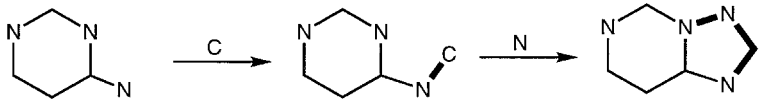
I. Introduction

The chemistry of one of the four possible classes of 1,2,4-triazolopyrimidines, namely 1,2,4-triazolo[1,5-*a*]pyrimidines, was reviewed in 1993 by G. Fischer [93AHC(57)81]. In two previous chapters published in this series we reviewed the chemistry of 1,2,4-triazolo[4,3-*a*]pyrimidines [99AHC(73)131] and their [4,3-*c*] congeners [99AHC(75)243]. In this chapter we survey the fourth and last class of 1,2,4-triazolopyrimidines. The literature has been inspected to issue number 26, Volume 129(1998) of *Chemical Abstracts*.

II. Synthesis

1,2,4-Triazolo[1,5-*c*]pyrimidines show many biological activities as well as medicinal and agrochemical applications (see Section VI). Such activities undoubtedly elicited efforts to diversify the methods of synthesizing additional members of these compounds possessing newer and more potent activities. The common approaches implemented so far to achieve this goal may collectively be categorized into (1) annulation of the 1,2,4-triazole ring onto a pyrimidine structure; (2) annulation of the pyrimidine ring onto a 1,2,4-triazole structure; (3) concurrent formation of both of the 1,2,4-triazole and pyrimidine rings; (4) intramolecular rearrangement of 1,2,4-



SCHEME 1

triazolo[4,3-*c*]pyrimidines; and (5) ring transformations of 1,3,4-thiadiazolo[3,2-*a*] and [3,2-*c*]pyrimidines.

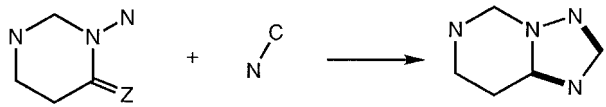
A. SYNTHESIS BY ANNULATION OF THE 1,2,4-TRIAZOLE RING ONTO A PYRIMIDINE STRUCTURE

Suitably functionalized pyrimidines were cyclized to 1,2,4-triazolo[1,5-*c*] pyrimidines according to the following schematically represented plans:

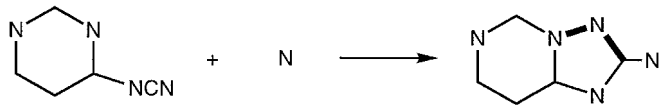
1. Three-bond formation through consecutive (3+1+1) atoms heterocyclization of 4(6)-aminopyrimidines with one carbon followed by one nitrogen (Scheme 1).
2. Two-bond formation through (3+2) atoms heterocyclization of 1(3)-aminopyrimidines having a leaving group at C6(4) with fragments containing one carbon and one nitrogen (Scheme 2).
3. Two-bond formation through (4+1) atoms heterocyclization of pyrimidines having an –N–C–N appendage at C4(6) with one nitrogen (Scheme 3).
4. Two-bond formation through (4+1) atoms heterocyclization of C2-blocked pyrimidines having an –N–C appendage at N1(3) with one nitrogen (Scheme 4).
5. Two-bond formation through (4+1) atoms heterocyclization of 1,6(3,4)-diaminopyrimidines with one carbon (Scheme 5).
6. One-bond formation through (5+0) atoms intramolecular heterocyclization of pyrimidines having an –N–N–C appendage at N1(3) and a leaving group at C4(6) (Scheme 6).

1. *Sequential Cyclization of 4-Aminopyrimidines with One Carbon Followed by One-Nitrogen Fragments*

Tisler and his group published the first synthesis of the parent unsubstituted 1,2,4-triazolo[1,5-*c*]pyrimidine **4** by transforming 4-aminopyrimidine **1**



SCHEME 2



SCHEME 3

to the dimethylaminomethyleneamino derivative then to the corresponding formamidoxime **2** followed by cyclization of the *O*-acetyl derivative of the latter (**3**) (76S833; 80AJC1147) (Scheme 7). A similar reaction sequence was employed to obtain **8;** the isolable *N,N*-dimethylaminomethylene-amino derivative **6,** however, was hydroximated to the amidoxime **7,** which was cyclodehydrated with polyphosphoric to give **8** (90JMC1230) (Scheme 8).

2. *Cyclization of 3-Amino-2-oxo- or 2-Thioxopyrimidines with Fragments Containing One Carbon and One Nitrogen*

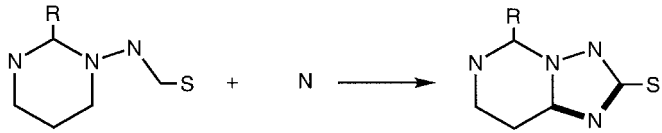
Treatment of 3-amino-4-oxoquinazolines (**9**) with cyanamide gave the 2-amino-1,2,4-triazolo [1,5-*c*]quinazolines **11** as a result of cyclodehydration of the intermediate 3-guanidino-4-oxoquinazolines **10** (68CB2106) (Scheme 9). Similarly, reaction of the 3-amino-4-thioxoquinazoline **12** with alkyl or aryl isothiocyanates yielded the mesoionic 1,2,4-triazolo[1,5-*c*]quinazolines **14** (84S881) (Scheme 10).

3. *Cyclization of 4-Cyanamidopyrimidines with One-Nitrogen Fragments*

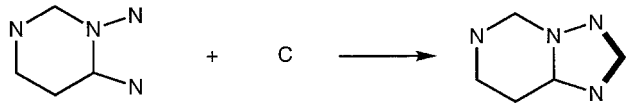
4-Cyanamidopyrimidine (**15**) was converted to the thioureido derivative **16** by reaction with hydrogen sulfide and ammonium hydroxide and then cyclized to **18** with hydrazine hydrate. Cyclization to **18** presumably took place by elimination of a molecule of ammonia from the aminoguanidine intermediate **17** (65JCS3357) (Scheme 11).

4. *Cyclization of C2-Blocked N-(Pyrimidin-3-yl)thioimidates with One-Nitrogen Fragments*

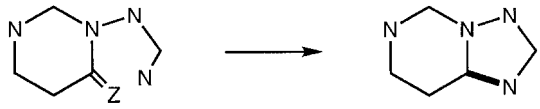
Photolysis of the 2-methyl-quinazolin-3-yl thioimidate **19** in the presence of butylamine produced an intricate mixture of products from which the



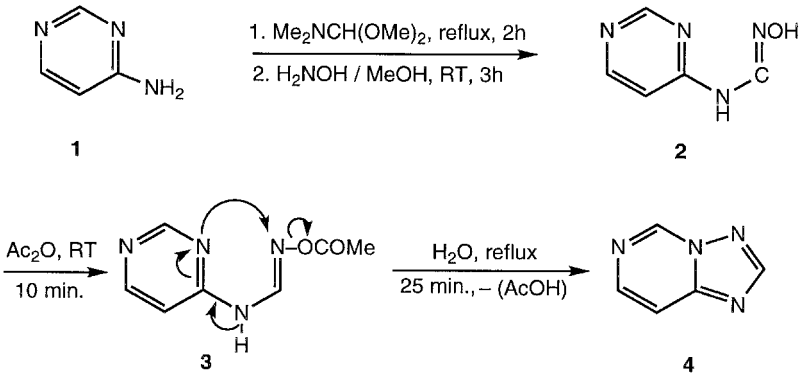
SCHEME 4



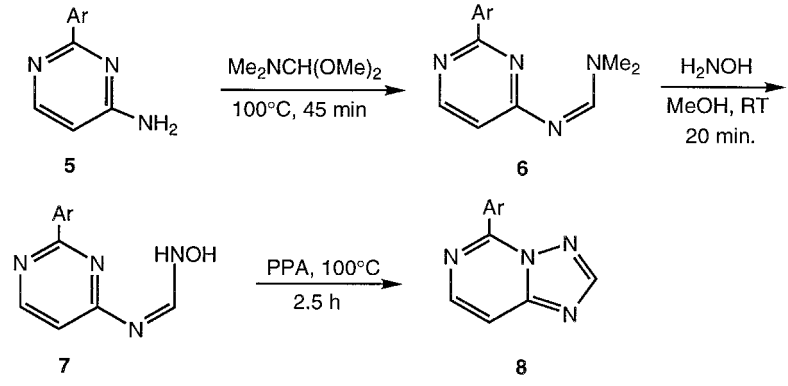
SCHEME 5



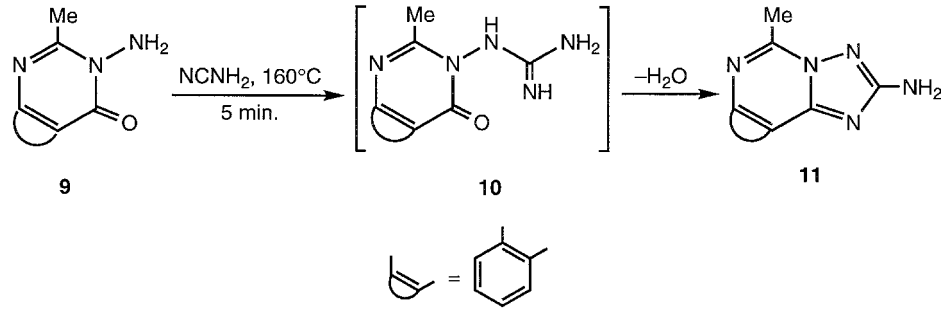
SCHEME 6



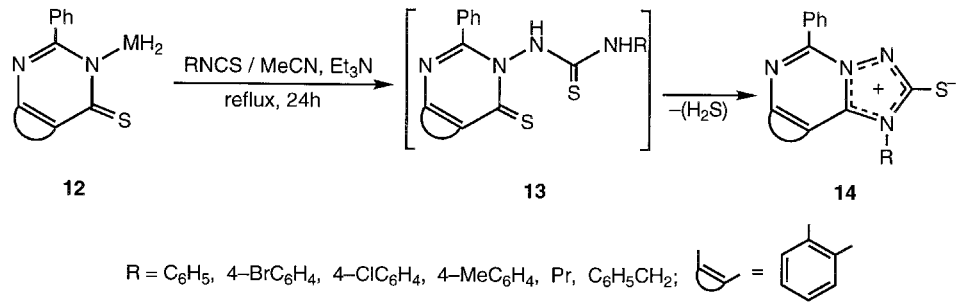
SCHEME 7



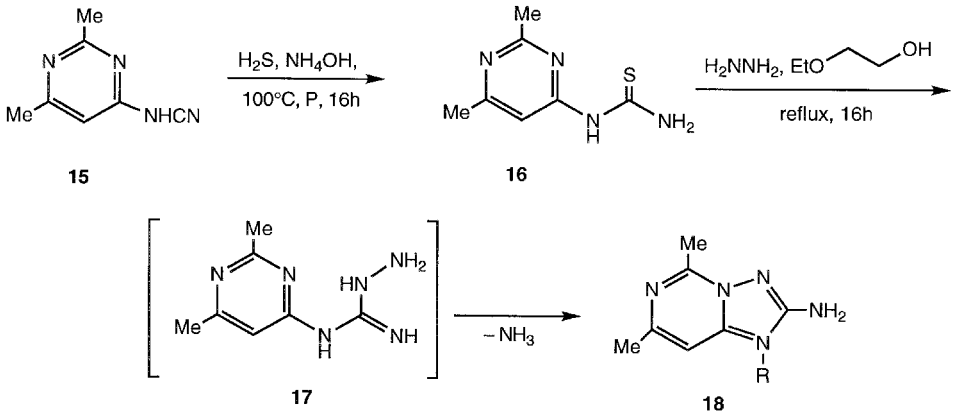
SCHEME 8



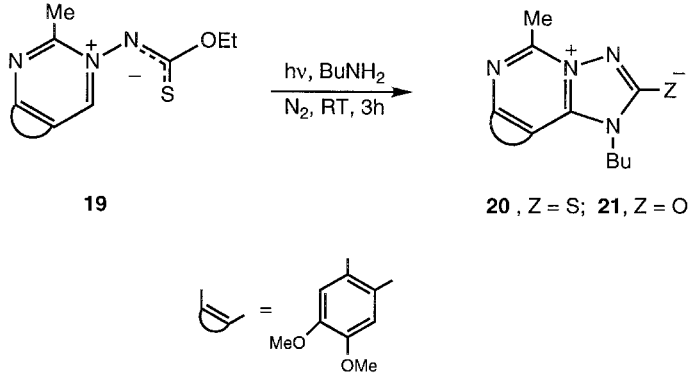
SCHEME 9



SCHEME 10



SCHEME 11



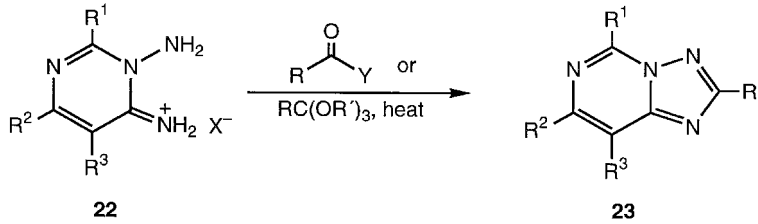
19 **20** , Z = S; **21**, Z = O

SCHEME 12

mesoionic 1-butyl-1,2,4-triazolo[1,5-*c*]quinazolinylium thiolate **20** (12%) and olate **21** (3.5%) were isolated [84JCS(P1)1143] (Scheme 12). Structures assigned to compounds **20** and **21** were corroborated by comparison with authentics prepared according to an unequivocal reaction pathway involving concurrent formation of the triazole and pyrimidine rings [84JCS(P1)1143] (see Scheme 39; Section II,C,5).

5. *Cyclization of 1,6(3,4)-Diaminopyrimidines with One-Carbon Fragments*

The two amino groups in 3,4-diaminopyrimidines **22** are properly disposed to cyclize with one-carbon cyclizing agents to readily afford 1,2,4-triazolo[1,5-*c*]pyrimidines **23.** Carboxylic acids (75JHC107; 79KGS262; 81JHC43; 93JSC405; 94JMC3828; 97JIC27, 97PHA753), acid anhydrides (75CPB844; 75JHC107; 97PHA753), acid chlorides (75JHC107; 92MI1; 97JIC27), esters (97PHA753), and orthoesters (75CPB844, 75M1111; 81JHC43; 92MI2; 98TL3865) were utilized to put this cyclization into effect (Scheme 13).



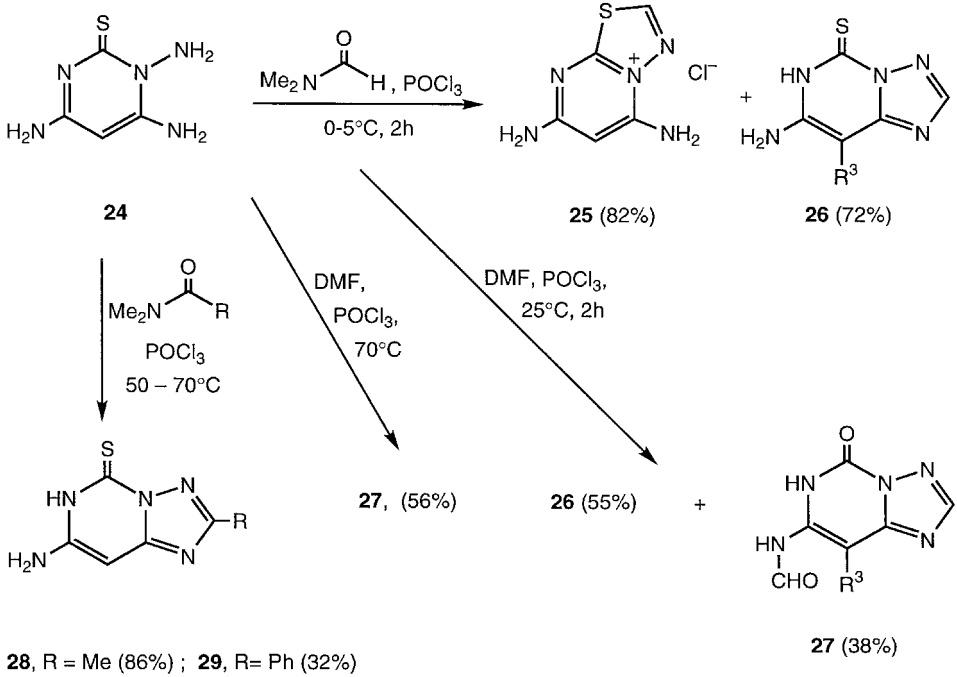
22 **23**

SCHEME 13

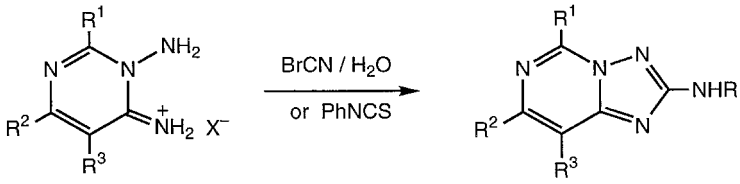
Heterocyclization of 1,4,6-triaminopyrimidine (**24**) with *N,N*-dimethylformamide and phosphoryl chloride (Vilsmeier reagent) was found to be temperature dependent (90JHC851). Carrying out the reaction at 0°–5°C gave a mixture of the 1,3,4-thiadiazolo[3,2-*a*]pyrimidinium chloride **25** (82%) and the 1,2,4-triazolo[1,5-*c*]pyrimidine **26** (7.2%) (Scheme 14). Elevation of the reaction temperature to 25°C caused **25** to undergo 1,3,4-thiadiazole ring transformation to afford **26** (55%) in addition to **27** (38%). Further elevation of the reaction temperature to 70°C exclusively produced **27** (56%). With *N*,*N*-dimethylacetamide or *N*,*N*-dimethylbenzamide and phosphoryl chloride, compound **28** or **29** was obtained as a single product in each case (90JHC851) (Scheme 14).

1,6-Diaminopyrimidines (**22**) were also cyclized with cyanogen bromide (90JHC851) or phenyl isothiocyanate (97PHA753) to give the corresponding 2-amino- or 2-anilino-1,2,4-triazolo[1,5-*c*]pyrimidines **30** and **31** respectively (Scheme 15).

1,6,-Diaminopyrimidines fused to a number of heterocycles (**35**) were also cyclized with one-carbon inserting agents to the corresponding heterocyclo-1,2,4-triazolo[1,5-*c*]pyrimidines **36** (75M1111; 81JHC43; 97JIC27).



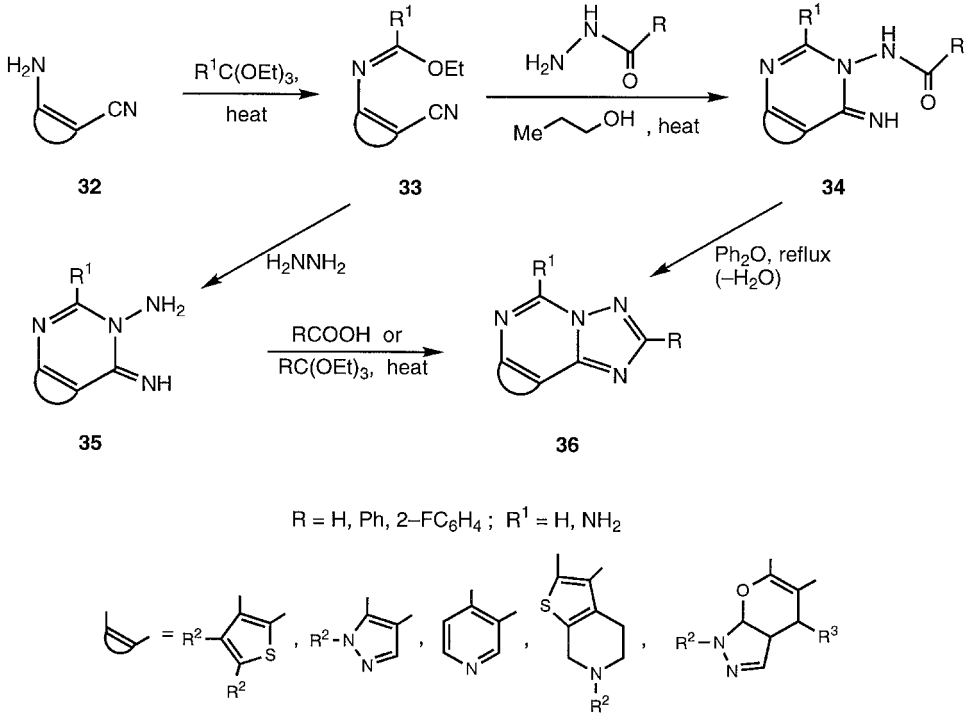
SCHEME 14



SCHEME 15

1-Acylamino-6-iminopyrimidines **34,** prepared from the appropriate β-cyanoimidate esters **33** and acylhydrazines, constitutionally contain the total carbon and nitrogen skeleton to effect their intramolecular cyclodehydration to **36** (93MI1, 93S1129; 94JHC1503) (Scheme 16).

Diethyl oxalate functioned as one-carbon rather than two-carbon cyclizing agent with the diamino-heterocyclopyrimidines **37** to give the triazo-lopyrimidines **38.** Diethyl malonate, ethyl acetoacetate, or ethyl



SCHEME 16

cyanoacetate also behaved as one-carbon cyclizing agents upon reaction with **37** to produce **39, 40,** and **41** respectively. Cyclization of **37** with 1,3-diketones gave **42** with elimination of a ketone molecule (97PHA753) (Scheme 17).

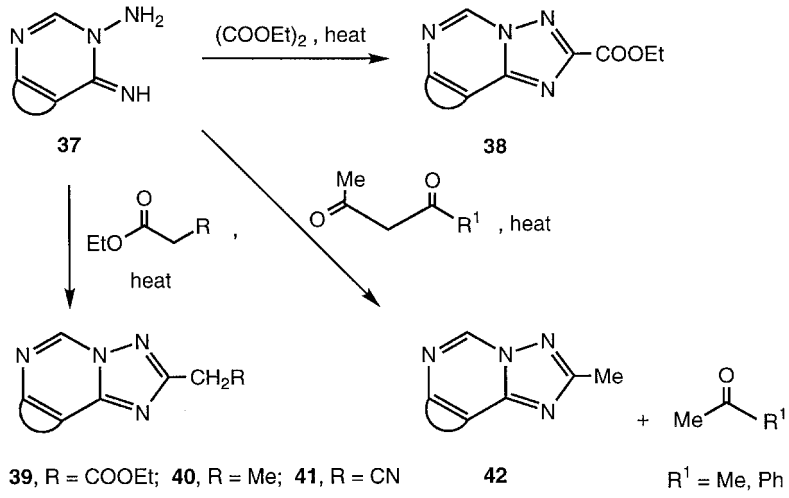
6. *Intramolecular Cyclization of 3-(1-amidino-, 1-thioureido-, or 4-thiosemicarbazido)-4-oxo- or 4-thioxopyrimidines*

Reaction of 1,3-benzoxazin-4-ones (**43, 44**) or trithioisatoic anhydride (**45**) with amidrazones (**46, 47**) or thiosemicarbazide (**48**) resulted in the formation of 3-(1-amidino)- (**49–51**) and 3-(1-thioureido)pyrimidines (**52**) respectively. Compounds **49–52** underwent thermal intramolecular cyclization to the corresponding 1,2,4-triazolo[1,5-*c*]quinazolines (**53–56**) [68CB2106; 76MI1; 80PHA582; 83MI1; 85H(23)2357] (Scheme 18).

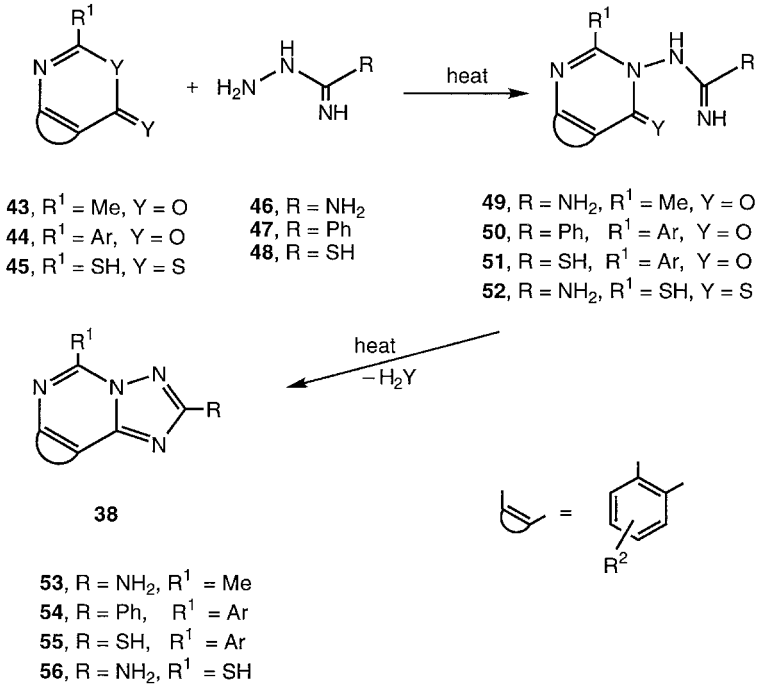
The mesoionic 1,2,4-triazolo[1,5-*c*]quinazolines **59** were obtained upon cyclization of the 4-thioxo-1,3-benzothiazines **57** with thiocarbohydrazine through the intermediate 3-(4-thiosemicarbazido)pyrimidines **58** (86-JHC43) (Scheme 19).

B. Synthesis by Annulation of the Pyrimidine Ring onto a 1,2,4-Triazole Structure

Two strategies have been used to construct the pyrimidine ring onto a triazole structure in order to produce 1,2,4-triazolo[1,5-*c*]pyrimidines:

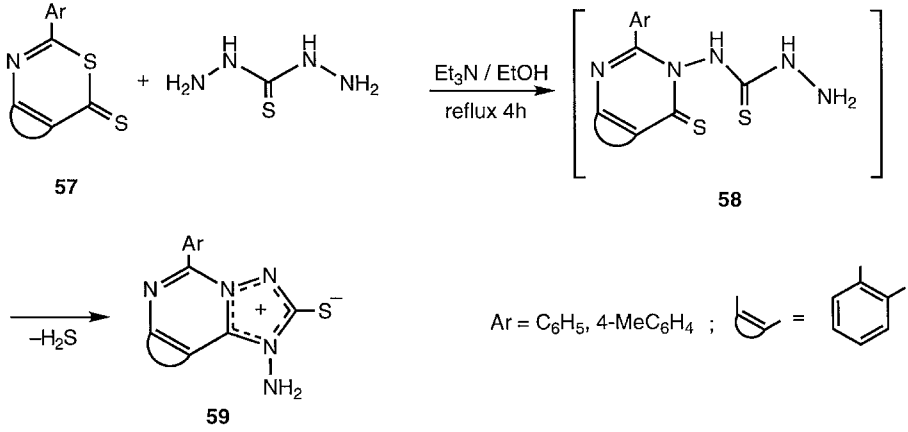


Scheme 17

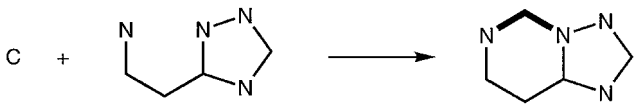


SCHEME 18

(1) two-bond formation through (5+1) atoms heterocyclization of 1,2,4-triazoles having a –C–C–N appendage at C3 by reaction with one-carbon cyclizing agents (Scheme 20); and (2) one-bond formation through



SCHEME 19



SCHEME 20

(6+0) atoms intramolecular heterocyclization of 1,2,4-triazoles having a –C–C–N–C appendage at C3 (Scheme 21).

1. *Cyclization of 1,2,4-Triazoles Having a –C–C–N Appendage at C3 with One-Carbon Cyclizing Agents*

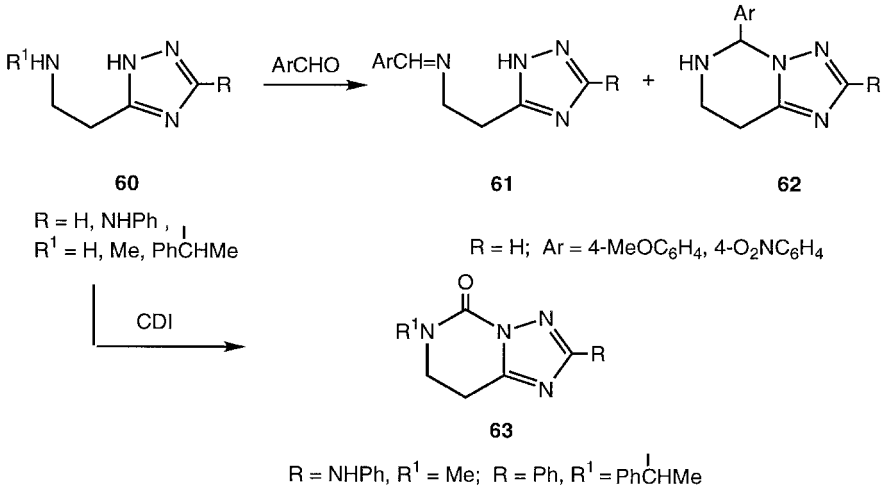
Cyclization of the 3-(2-aminoethyl)-1,2,4-triazoles **60** with aromatic aldehydes gave a mixture of the corresponding Schiff bases **61** and the 5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-*c*]pyrimidines **62.** Cyclization of **60** with carbonyl-1,1′-diimidazole (CDI) afforded the 5-oxo analogs **63** (92JPR630) (Scheme 22).

Attempted dehydrocyclization of the 6-acylhydrazinopyrimidine **65** by heating with polyphosphoric acid led, instead, to pyrimidine ring rupture, yielding the 1,1-diamino-2-nitro-2-(3-phenyl-1,2,4-triazol-5-yl)ethene **66.** Cyclocondensation of the latter with triethyl orthoformate gave the fully aromatic triazolopyrimidine **67** (94JHC1171) (Scheme 23).

1-Amino-2-(1,2,4-triazol-3-yl)benzene as well as its heterocyclic analogs (**70**), prepared from the corresponding 1-amino-2-cyano compounds (**68**) and acylhydrazine or from the 1-amino-2-carboxyhydrazides (**69**) and amidines, reacted with various one-carbon cyclizing reagents to give the tricyclic 1,2,4-triazolo[1,5-*c*]pyrimidines **71** (65JOC3601; 88JMC1014; 91JMC281; 93MI1; 94JHC1503) (Scheme 24).

Assignment of the 1,2,4-triazolo[1,5-*c*]pyrimidine structures to the products obtained from the previously described cyclizations and not the alternative [4,3-*c*] structures has been rationalized and corroborated on the basis of (a) preference of cyclization at the more nucleophilic triazole ring N2 rather than at its less nucleophilic N4 (65JOC3601; 88JMC1014), (b) inability of the obtained products to undergo acid- or base-catalyzed Dimroth rearrangement, a property characteristic of the thermodynamically less stable [4,3-*c*] isomers (91JMC281), (c) comparison with unequivocally prepared

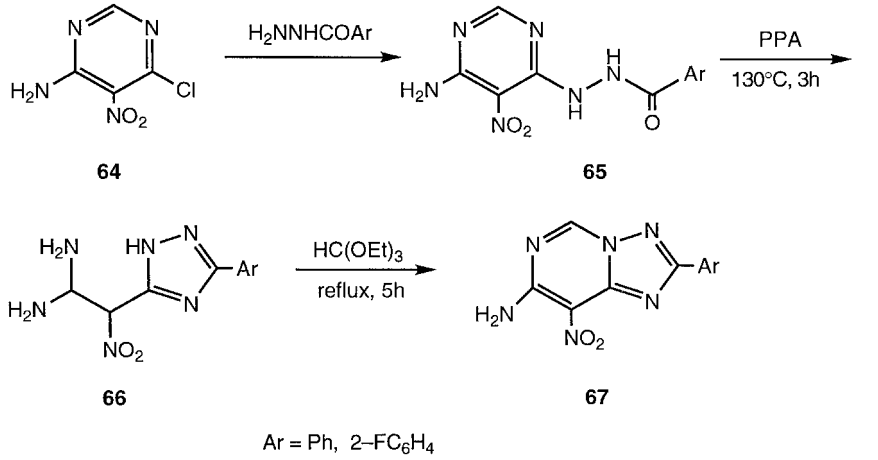
SCHEME 21



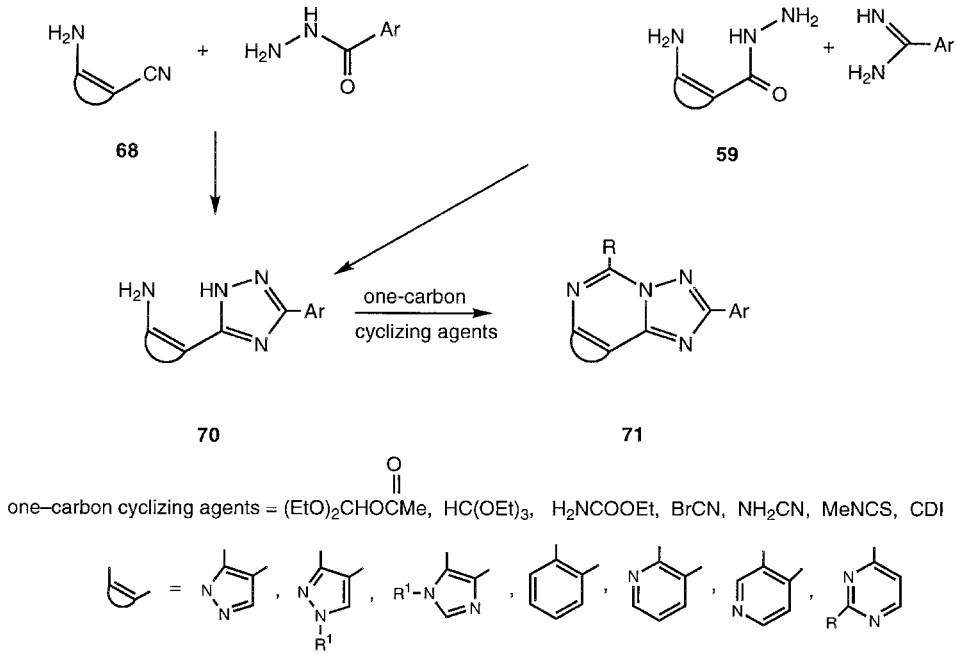
SCHEME 22

authentics (65JOC3601; 73TL1643; 94JHC1503), and (d) X-ray crystallographic analysis of the products (73TL1643).

A particularly interesting example of this method of synthesis is the cyclization of the 4-amino-3-(2-aminophyenyl)-1,2,4-triazoloes **73** with cyanogen bromide. Primarily, this reaction was applied to synthesize the 6-amino-1,2,4-triazolo[4,3-*d*]benzodiazepine hydrobromides **74;** the obtained products, however, were found to be the 1,5-diamino-1,2,4-triazolo-[1,5-*c*]quinazolinium bromides **77.** Structure elucidation of **77** was accomplished by direct



SCHEME 23



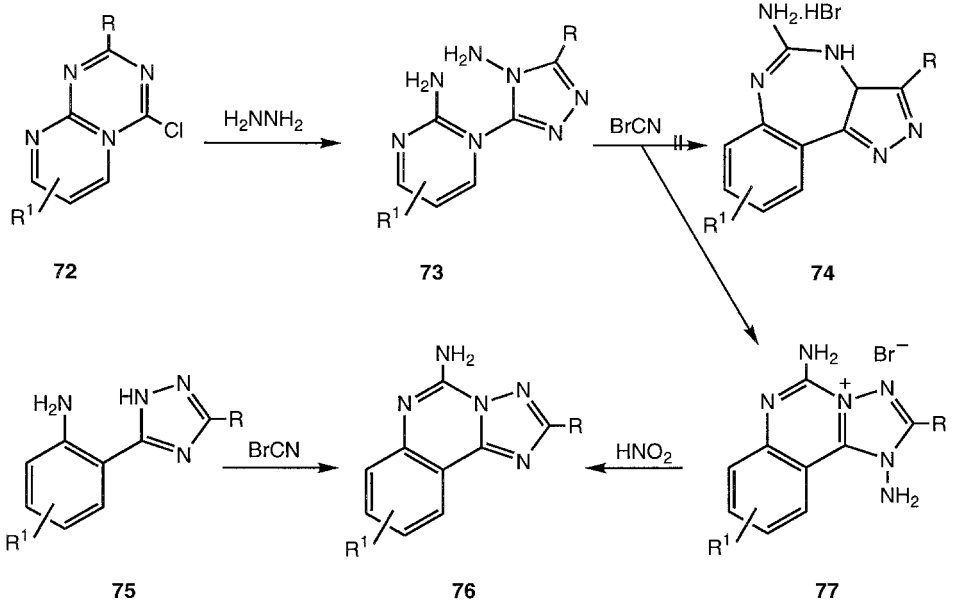
SCHEME 24

comparison of the deamination product **76** with the authentic prepared by cyclization of 3-(2-aminophenyl)-1,2,4-triazole **75** with cyanogen bromide [73TL1643; 79JCS(P2)1708] (Scheme 25). X-ray crystallographic analysis of the nitrate of **77** corroborated its structure [79JCS(P2)1708].

2. *Intramolecular Cyclization of 1,2,4-Triazoles Having a –C–C–N–C Appendage at C3*

Heating solutions of the 3-(5-formamidoimidazol-4-yl)-1,2,4-triazoles **79** caused their intramolecular cyclodehydration to the 1,2,4-triazolo[1,5-*c*]pyrimidines **80.** The starting compounds **79** were obtained by acid- or base-catalyzed pyrimidine ring hydrolysis of the 1,2,4-triazolo[4,3-*c*]pyrimidines **78** (65JOC3601) (Scheme 26).

2-(1,2,4-Triazol-3-yl)benzonitriles **81** provided starting materials for the synthesis of a number of 1,2,4-triazolo[1,5-*c*]pyrimidines according to this approach. The cyano group of **81** was converted, by two different reaction pathways, to the isocyanate function of **85** which then cyclized to the triazolopyrimidine **86** (75CB3799; 86EUP181282; 91JMC281). Thus, acid hydrolysis of the nitriles **81** to the carboxylic acids **82** and conversion of the latter to the acid azides **83** followed by a modified Curtius rearrangement gave the isocyanates **85** (75CB3799). The isocyanates **85** were also prepared

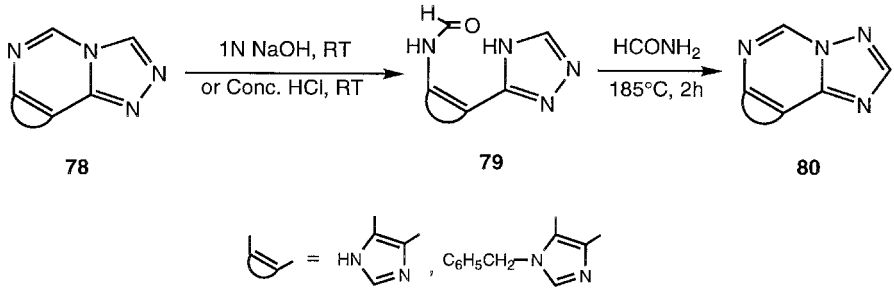


SCHEME 25

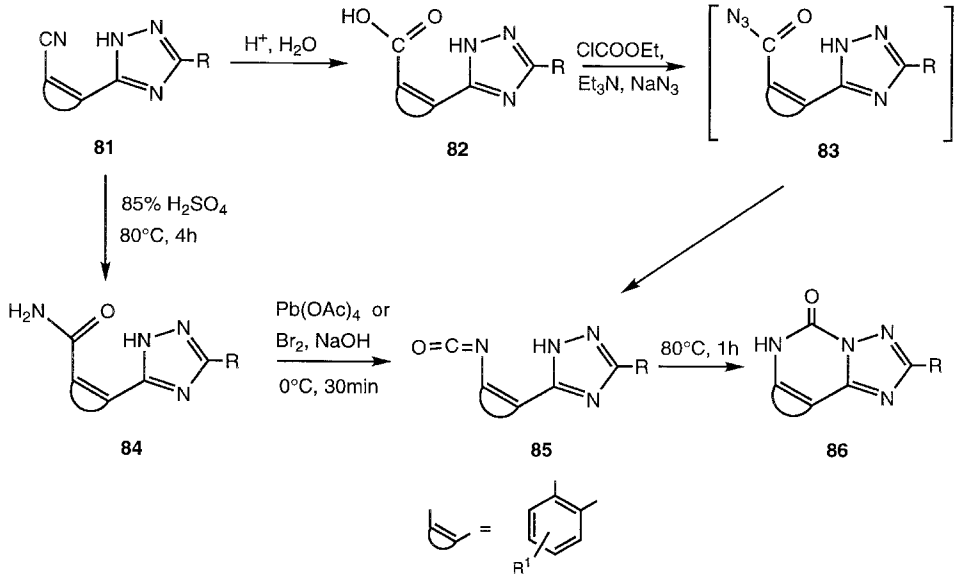
by partial acid hydrolysis of the nitriles **81** to the acid amides **84** followed by oxidation with lead tetraacetate (86EUP181282; 91JMC281) or by Hofmann rearrangement (91JMC281) (Scheme 27).

C. SYNTHESIS BY CONCURRENT FORMATION OF BOTH OF THE 1,2,4-TRIAZOLE AND PYRIMIDINE RINGS

Four general methods were used to achieve simultaneous formation of both of the triazole and pyrimidie rings of 1,2,4-triazolo[1,5-*c*]pyrimidines:

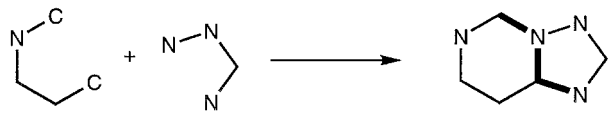


SCHEME 26

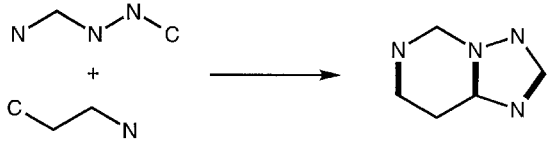


SCHEME 27

1. Double ring-closure comprising three-bond formation by (5+4) atoms heterocyclization. Two combinations of the reacting fragments are possible: (a) reaction of five-atom fragments consisting of four carbons and one nitrogen (C_4N) with four-atom fragments consisting of one carbon and three nitrogens (CN_3) (Scheme 28) and (b) reaction of five-atom fragments consisting of two carbons and three nitrogens (C_2N_3) with four-atom fragments consisting of three carbons and one nitrogen (C_3N) (Scheme 29).
2. Double ring-closure comprising three-bond formation by (6+3) atoms heterocyclization. This approach has always been carried out by reaction of six-atom fragments consisting of four carbons and two nitrogens (C_4N_2) with three-atom fragments consisting of one carbon and two nitrogens (CN_2) (Scheme 30).
3. Double ring-closure comprising four-bond formation by (7+1+1) atoms heterocyclization by reaction of fragments consisting of three carbons and four nitrogens (C_3N_4) with two one-carbon fragments (Scheme 31).



SCHEME 28



SCHEME 29

4. Double ring-closure comprising two-bond formation by intramolecular heterocyclization of (9+0) atoms open structures consisting of five carbons and four nitrogens (C_5N_4) (Scheme 32).

1. *Cyclization of C_4N_3 with CN_3 Fragments*

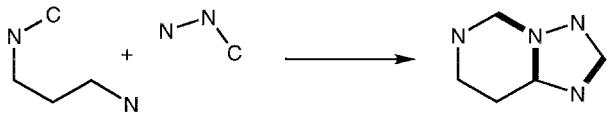
4-Isothiocyanato-3,3-dimethylbutan-2-one (**87**) provided the C_4N_3 fragment that gave, upon reaction with 2-ethylthiosemicarbazide (CN_3 fragment) (**88**), the 3-ethyl-1,6,7,8a-tetrahydro-2,5-dithioxo-8,8,8a-trimethyl-1,2,4-triazolo[1,5-*c*]pyrimidine **89** (76M1241) (Scheme 33).

2. *Cyclization of C_2N_3 with C_3N Fragments*

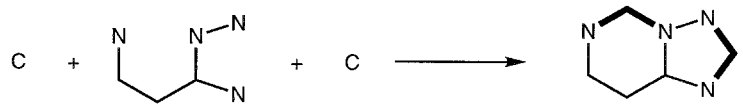
Reaction of ethoxymethylenemalononitriles (**90**) or ethyl ethoxymethylenecyanoacetates (**91**) (C_3N fragments) with hydrazones (**92**), derived from aldehydes or ketones and isothiosemicarbazides or aminoguanidines (C_2N_3 fragment), gave the 2,3-dihydro-1,2,4-triazolo[1,5-*c*]pyrimidines **94** through the occasionally isolable intermediates **93**. Elimination of a hydrogen or the lower alkane molecule from **94** gave the final products **95** [81BCJ1767, 81JOC3956; 85CPB2678; 86MI1; 87JCS(P1)1567; 88CPB1963, 88EUP275014, 88GEP(O)3702392; 89JHC763; 96JHC1285; 97JHC871] (Scheme 34). Achieving aromaticity and/or alleviating steric crowding at C2 is the mobilizing force for the latter elimination (81JOC3965).

3. *Cyclization of C_4N_2 with CN_2 Fragments*

2-Isocyanatobenzonitriles (as C_4N_2 fragments) (**96**) readily cyclized with acylhydrazines (CN_2 fragments) to the corresponding 1,2,4-triazolo[1,5-*c*]quinazolines **86** (87ZC373; 88JMC1014; 91JMC281) (Scheme 35). Similarly, imidates (**99**) derived from β-enaminonitriles (**98**) were cyclized with acylhydrazines to **101** (89MI1) (Scheme 36). 2-Ethoxycarbonylamino- and 2-ureidobenzonitriles as well as their heterocyclic congeners (**102**,

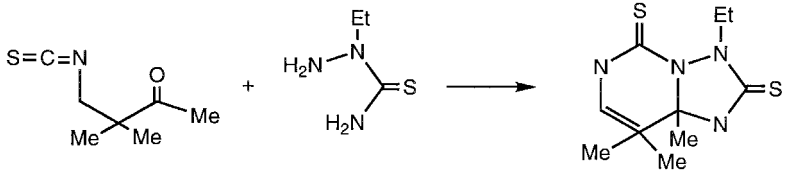


SCHEME 30



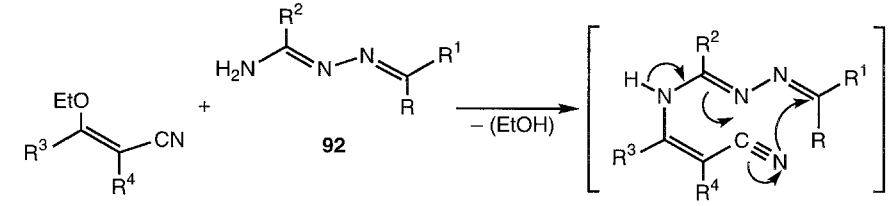
SCHEME 31

SCHEME 32

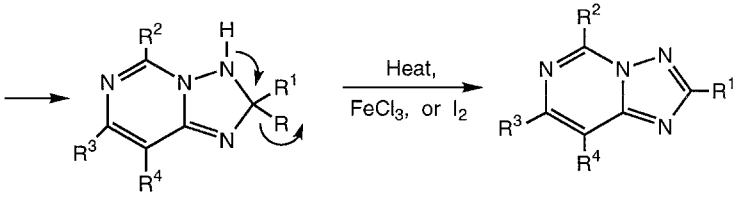


87 88 **89**

SCHEME 33



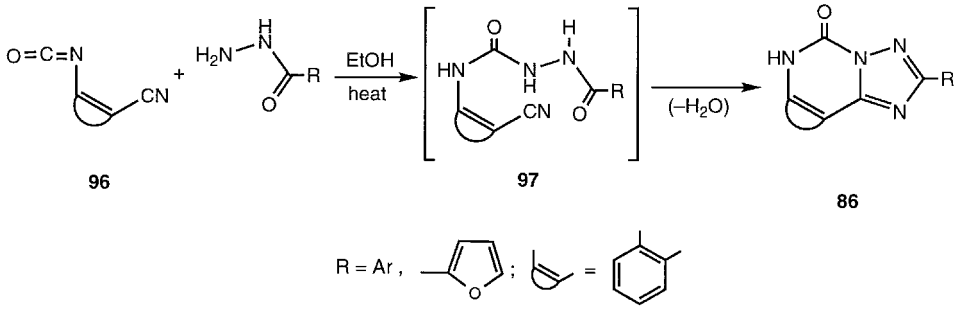
90, R = CN; **91**, R = COOEt **92** **93**



94 **95**

R = H, alkyl, aryl; R^1 = alkyl, aryl; R^2 = SMe, SCH_2Ph, NHR^5, NR^5_2; R^3 = H, Et; R^4 = CN, COOEt

SCHEME 34

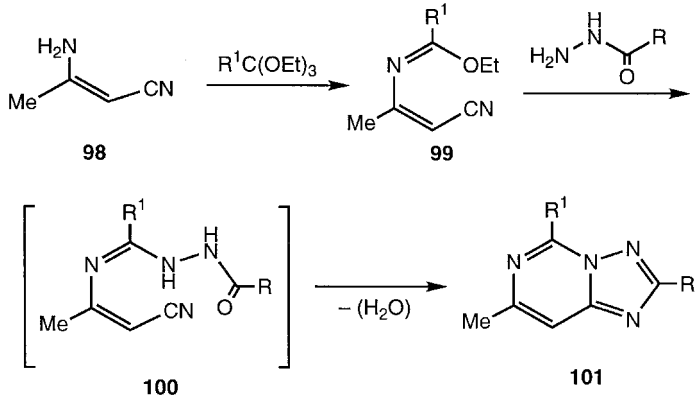


SCHEME 35

103) have also been cyclized with acylhydrazines to **86** (87USP4713383; 88EUP263071; 89JPR537, 89MI1; 91JMC281, 91JMC2899) (Scheme 37).

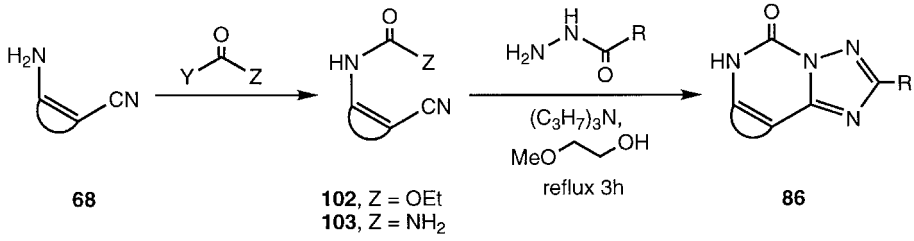
4. *Cyclization of C_3N_4 Fragments with Two One-Carbon Fragments*

Cyclization of the 5-(*N*-arylcarboxamido)-4-hydrazino-6methylpyrimidin-2-ones **104** with two molar equivalents of formaldehyde in the presence of pyridine caused the concomittant triazole and pyrimidine ring formation to yield the 4-aryl-1,3,4,10-tetrahydro-6-methyl-1,2,4-triazolo-[2,3,4-*c,d*]pyrimido[4,5-*d*]pyrimidine-5,8-diones **105** (89AP599) (Scheme 38).

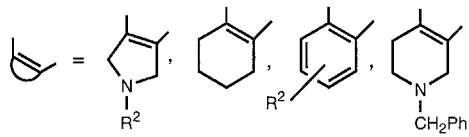


R = Me, Ph, 4–pyridyl; R^1 = Me, Et

SCHEME 36



Y = Cl, OEt; Z = OEt, NH_2; R = Ph, furyl, thienyl, pyridyl, pyrrolyl;

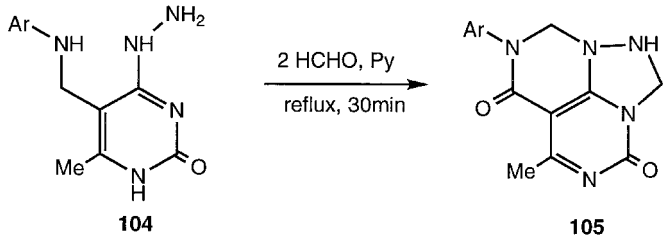


SCHEME 37

5. *Intramolecular Cyclization of C_5N_4 Fragments*

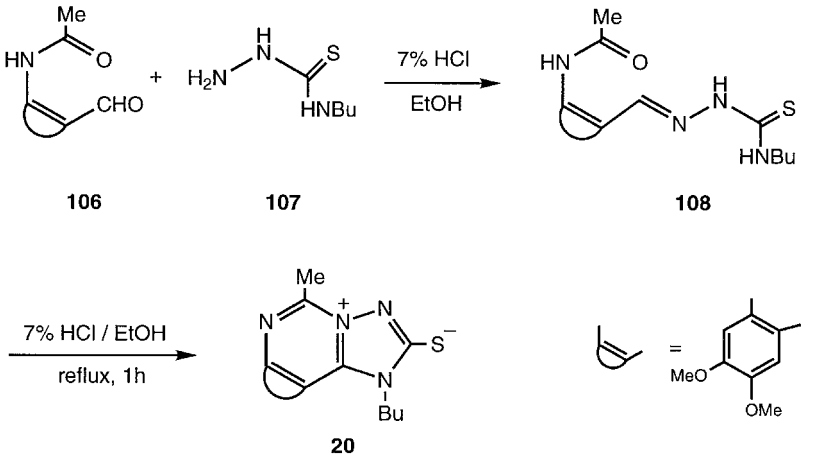
Cyclization of the thiosemicarbazone **108,** obtained from 2-acetamido-4,5-dimethoxybenzaldehyde **106** and 4-butylthiosemicarbazide (**107**), with ethanolic hydrochloric acid gave the mesoionic 1-butyl-1,2,4-triazolo[1,5-*c*]quinazolinylium thiolate **20** [84JCS(P1)1143] (Scheme 39), which was also obtained by photolysis of compound **19** [84JCS(P1)1143] (Scheme 12; Section II,A,4). Identity of both compounds corroborated the structure of **20** obtained by irradiation of **19.**

Reaction of 2-amino-2-(2-aminophenyl)acetaldehyde aroylhydrazones (**109**) with ethyl chloroformate gave the urethane derivatives **110.** The latter underwent condensative double ring-closure to the 1,2,4-triazolo[1,5-*c*]quinazolin-5-ones **86.** Carrying out a similar reaction between **109** and guanidine furnished the 5-amino congener **111** (93JHC11) (Scheme 40).



Ar = 4–ClC_6H_4, 4–EtC_6H_4

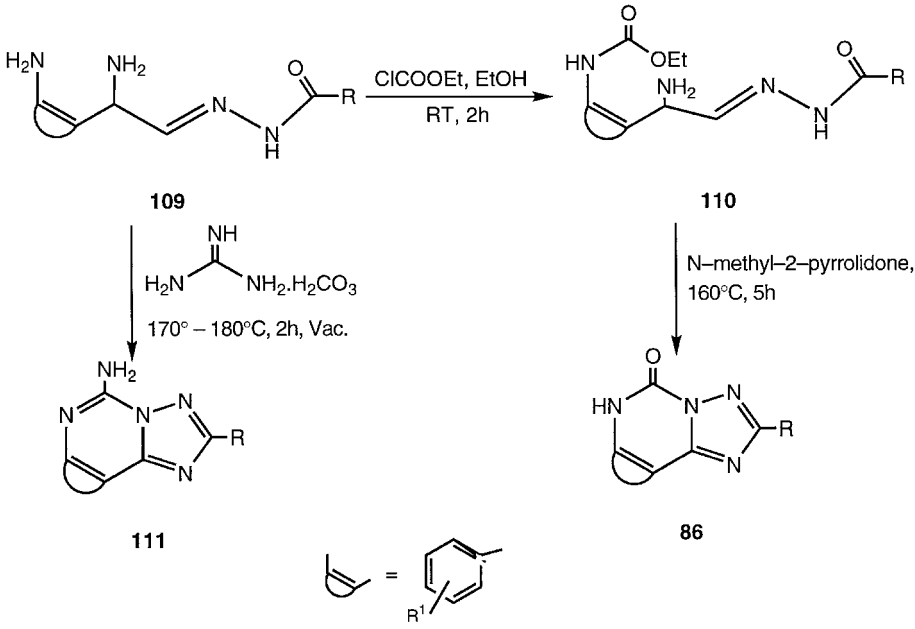
SCHEME 38



SCHEME 39

D. SYNTHESIS BY REARRANGEMENT OF 1,2,4-TRIAZOLO[4,3-*c*]PYRIMIDINES

The thermodynamically more stable 1,2,4-triazolo[1,5-*c*]pyrimidines **23** were frequently prepared by Dimroth rearrangement of their thermody-

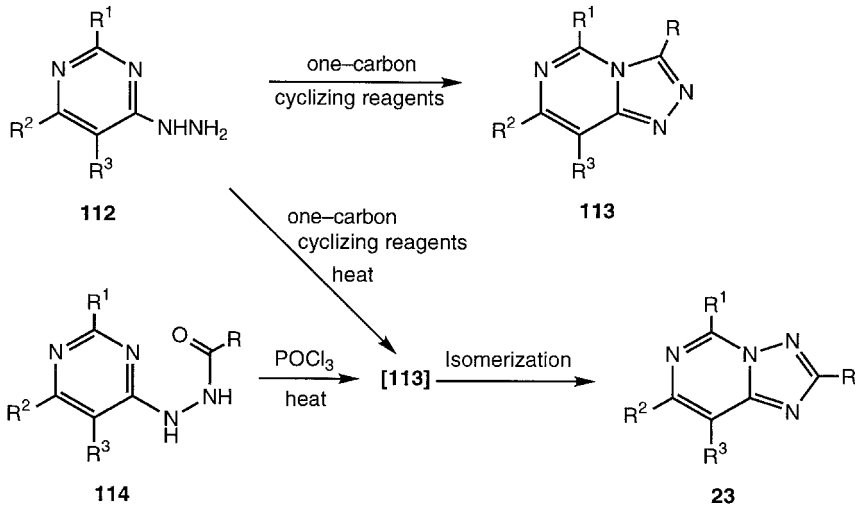


SCHEME 40

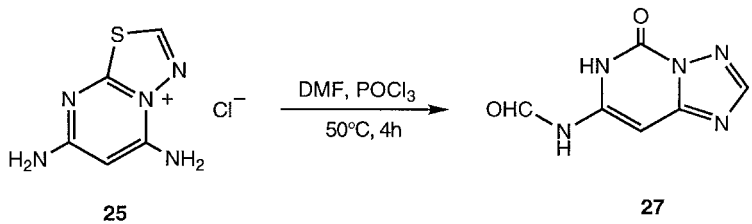
namically less stable [4,3-*c*] regioisomers **113.** Reaction conditions inducing these isomerization, electronic, and steric factors influencing their rates; the resulting ^{1}H NMR and UV changes; and operating mechanisms were discussed in the previous chapter of this review (Part II, Section III,A) [99AHC(75)243]. In many cases, however, preparation of 1,2,4-triazolo[1,5-*c*]pyrimidines (**23**) was attained in one-step by intramolecular cyclization of 4-acylhydrazinopyrimidines (**114**) (62BRP897870, 65JCS3357; 83EUP80176; 90T3897) or by cyclization of 4-hydrazinopyrimidines (**112**) with one-carbon cyclizing reagents at elevated temperatures [61BRP859287; 63JCS5642; 64BRP951652; 65JCS3369; 72GEP(O)2146076; 73CR(C)93; 74JHC975; 76S833; 77USP4053600; 79AJC2713; 80AJC1147; 81JHC43; 83USP4405780; 85GEP(O)3427823, 85USP4528288; 86TL3127; 89EUP343752, 89JHC687, 89JHC991; 90H(31)277, 90JMC1230; 94JMC2371). In these one-step syntheses, the 1,2,4-triazolo[1,5-*c*]pyrimidines **23** were obtained through the unisolable transiently formed [4,3-*c*] isomers **113** (Scheme 41).

E. Synthesis by Ring Transformation of 1,3,4-Thiadiazolo[3,2-*a*]- and -[3,2-*c*]Pyrimidines

Treatment of 5,7-diamino-1,3,4-thiadiazolo[3,2-*a*]pyrimidinium chloride (**25**) with Vilsmeier reagent gave the 7-formamido-1,2,4-triazolo[1,5-*c*]pyrimidin-5-one (**27**) (90JHC851) (Scheme 42). Compound **27** has presumably been formed via rupture of the 1,3,4-thiadiazole ring of **25** and



Scheme 41



25 **27**

SCHEME 42

subsequent recyclization with the C5–NH_2 group together with desulfurization and formylation of the C7–NH_2 function.

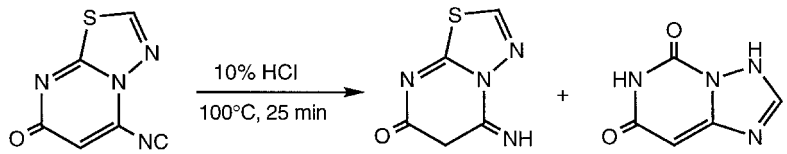
Heating the 5-isocyano-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one **115** with 10% hydrochloric acid gave a mixture of the 5-imino-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one **116** (10%) and the 1,2,4-triazolo[1,5-*c*]pyrimidine-5,7-dione **117** (35%) (91JHC489). Formation of **117** probably occurred through thiadiazole ring rupture of **116** and recyclization with its imino function together with desulfurization (Scheme 43).

Aminolysis of the 5-substituted-2-mercapto-1,3,4-thiadiazolo[3,2-*c*]-quinazolinium iodides **119** with butylamine afforded the mesoionic 1,3,4-triazolo[1,5-*c*]quinazolines **120** [77IJC(B)1110] (Scheme 44).

III. Reactions

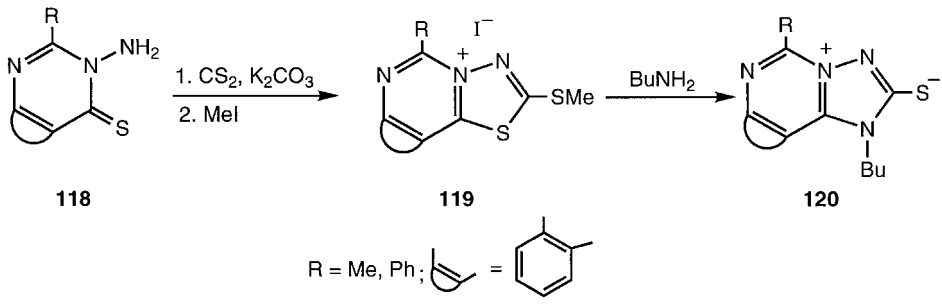
A. Isomerization (Dimroth Rearrangement)

Usually 1,2,4-triazolo[4,3-*c*]pyrimidines (**113**) undergo Dimroth rearrangement with acids, bases, or heat to the [1,5-*c*] regioisomers (**23**) according to the steps shown in Scheme 45 (see Part II, Section III,A) [99AHC(75)243]. The steps of this rearrangement may be reversible but the difference in thermodynamic stability usually mobilizes the reaction direction toward the formation of the thermodynamically more stable [1,5-*c*] regioisomers. Nevertheless, a case in which a retro-Dimroth rearrangement of the thermodynamically more stable 1,2,4-triazolo[1,5-*c*]pyrimidine **123** to its less stable [4,3-*c*] isomer **124** was reported (79KGS262) (Scheme 46).



115 **116** (10%) **117** (35%)

SCHEME 43



118 119 120

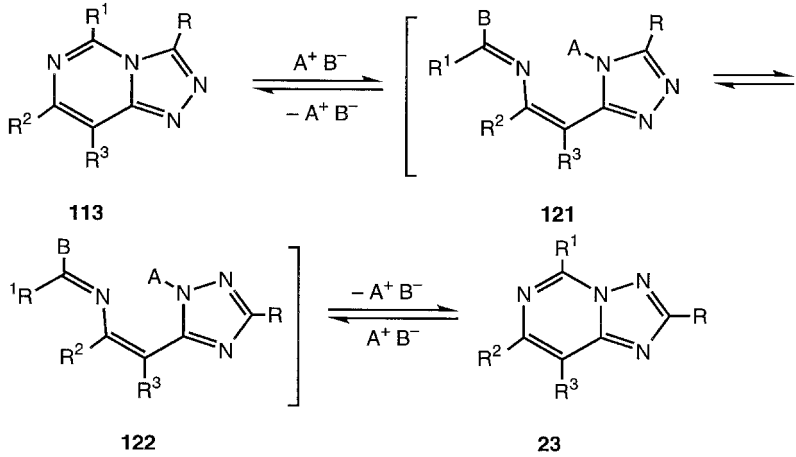
SCHEME 44

B. CLEAVAGE REACTIONS

1. *Pyrimidine Ring Cleavage*

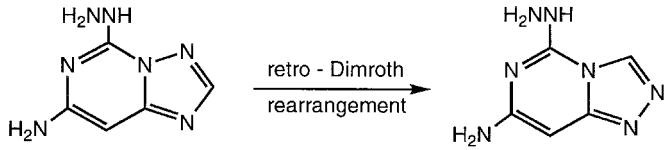
Cleavage of the pyrimidine ring of 1,2,4-triazolo[1,5-*c*]pyrimidines may take place with or without fragmentation. Thus, prolonged heating of compounds **23** with water effected cleavage of the N4-C5 bond without fragmentation to give the 1-acylamino-2-(1,2,4-triazol-3-yl)ethenes **125.** Fusion of compounds **125** caused reversal of this cleavage (78AJC 2505) (Scheme 47).

Heating the mesoionic 1-amino-2-thioxo-1,2,4-triazolo[1,5-*c*]quinazolines **59** with aromatic aldehydes and ethanolic hydrochloric acid resulted in the formation of Schiff bases and simultaneous pyrimidine ring cleavage



113 121 122 23

SCHEME 45



123 **124**

SCHEME 46

to afford the 4-arylideneamino-3-(2-aroylamino)phenyl-1H-1,2,4-triazolin-5-thiones **126.** Treatment of compounds **59** with phenacyl bromides under the same conditions produced the 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazine derivatives **127** (86JHC43) (Scheme 48).

Fragmentational cleavage of C5 of **128** was reported to take place through rupture of the N4-C5 and C5-N6 bonds upon acid-catalyzed hydrolysis to give **70** (65JOC3601; 93MI1; 94JHC1503) (Scheme 49).

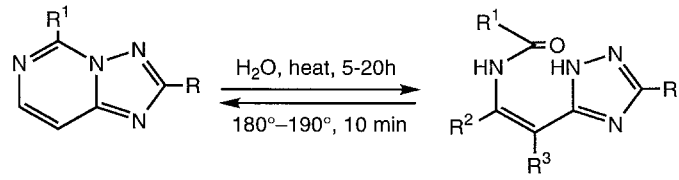
Hydrolytic fragmentation of the C5-N6 part took place upon heating 7-methyl-5-propyl-2-thioxo-1,2,4-triazolo[1,5-*c*]pyrimidine (**129**) with hydrochloric acid. 3-Acetonyl-5-mercapto-1,2,4-triazole (**130**) and butanoic acid were obtained as a result of N4-C5, C5-N6, and N6-C7 bond cleavages (65JCS3369) (Scheme 50).

2. *Triazole Ring Cleavage*

Treatment of the 1,5-diamino-1,2,4-triazolo[1,5-*c*]quinazolinium bromide **131** with sodium hydroxide gave the amidine **134** as a result of N1-C8a bond cleavage without fragmentation [79JCS(P2)1708] (Scheme 51).

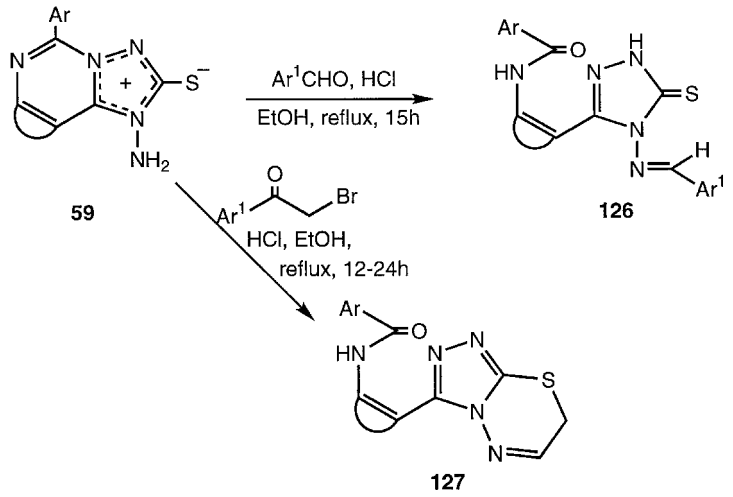
Triazole ring cleavage of the 7-amino-5-benzyl-5-mercapto-1,2,4-triazolo-[1,5-*c*]pyrimidinium iodide **135** at the N3-N4 bond occurred upon treatment with potassium carbonate to give the 4-amino-2-benzylmercapto-1-methyl-6-(*N*-methylcyanamido)pyrimidine **136** (85KGS421) (Scheme 52).

Attempted desulfurization of 7-methyl-3-propyl-2-thioxo-1,2,4-tri-



23 **125**

SCHEME 47



SCHEME 48

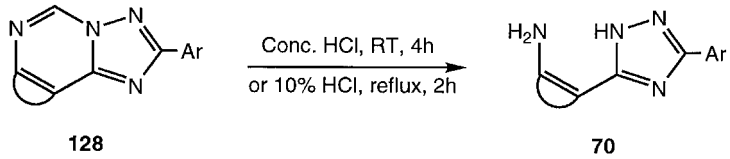
azolo[1,5-*c*]pyrimidine (**129**) with Raney nickel to **137** caused, instead, removal of the C2–N3 fragment of the system to give the 4-amino-6-methyl-2-propylpyrimidine **138** (65JCS3369) (Scheme 53).

C. ACYLATION AND ALKYLATION

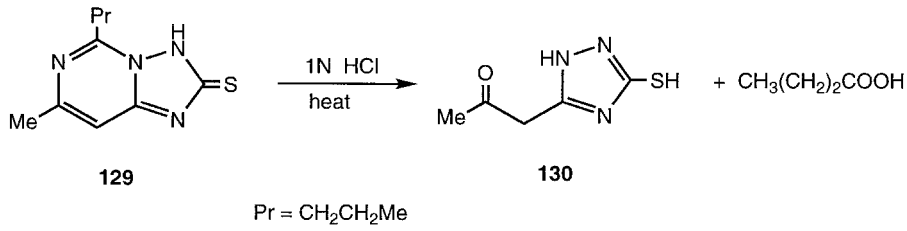
1. *N-Acylation*

Formylation, acetylation, and benzoylation of 1,2,4-triazolo[1,5-*c*]pyrimidines having an amino group at C2 (61BRP873223; 62BRP897870; 63JCS5642; 90JMC1230), C5 (84USP4483987), or C8 (68JOC530) with formic acid, acetic anhydride, or benzoyl chloride in the presence of pyridine afforded the corresponding acylamino derivatives.

2-Fluorophenylacetyl and 4-fluorophenylacetyl chlorides selectively acylated the C8-NH_2 group of 7,8-diamino-1,2,4-triazolo[1,5-*c*]pyrimidine **139** (94JHC1171) to give **140** (Scheme 54); N6 of the ring system probably renders the closer C7-NH_2 group less nucleophilic than the remoter C8-NH_2 function.



SCHEME 49



129 **130**

Pr = CH_2CH_2Me

SCHEME 50

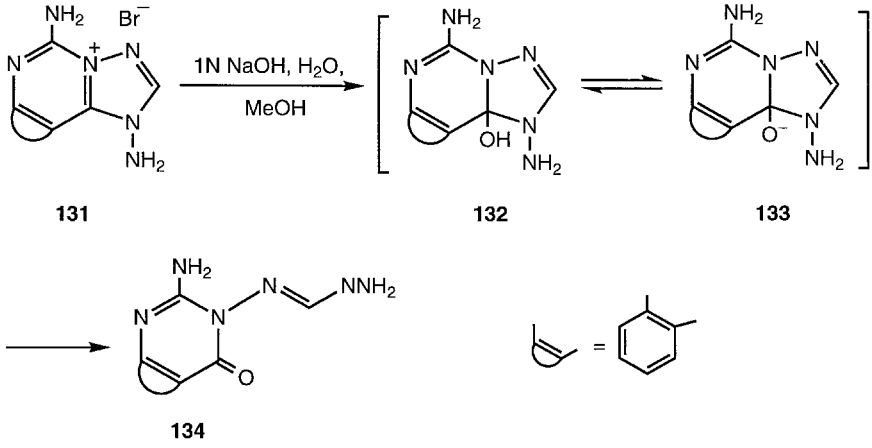
Acylation of 1,2,4-triazolo[1,5-*c*]quinazolin-5-one (**141**) with ethyl chloroformate occurred at N6 to afford the 6-ethoxycarbonyl derivative **142** (75CB3799) (Scheme 55). This result indicates that the amide tautomer (lactam tautomer) **141** prevailed over the corresponding imidic acid tautomer (lactim tautomer).

2. *N-Alkylation*

Methylation of the C2-NH_2 function of compounds **30** with dimethyl sulfate in the presence of sodium hydroxide gave the 2-methylamino derivatives **143** (63JCS5642) (Scheme 56).

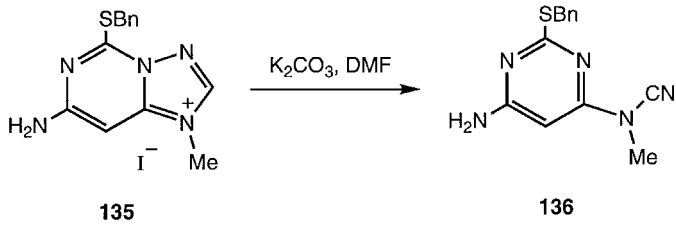
The 2-dimethylamino derivatives **147** were prepared by a three-step reaction pathway that comprised (a) methylation of the 2-acetamido derivative **144** with methyl iodide and sodium hydride to **145,** (b) mild acid-catalyzed N-deacetylation of **145** to **146,** and (c) further methylation of **146** to the 2-dimethylamino compound **147** (90JMC1230) (Scheme 57).

Skeletal methylation with methyl iodide in dimethlformamide methylated N1 of compound **148** to produce the methiodide **135** (85KGS421) (Scheme 58).



131 **132** **133** **134**

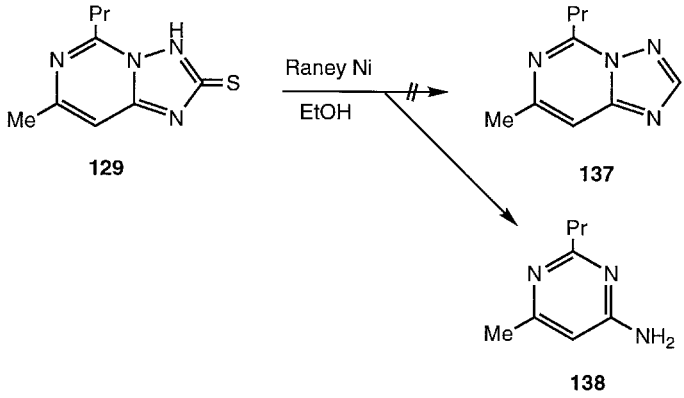
SCHEME 51



135 **136**

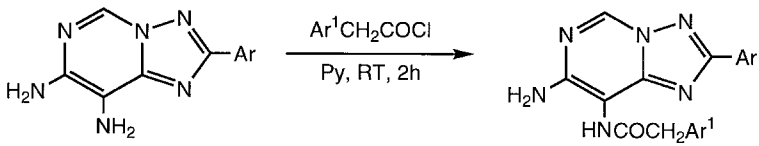
Bn = CH_2Ph

SCHEME 52



129 **137** **138**

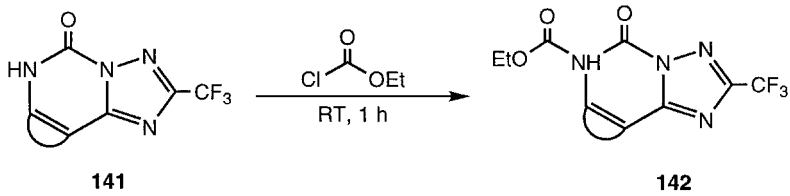
SCHEME 53



139 **140**

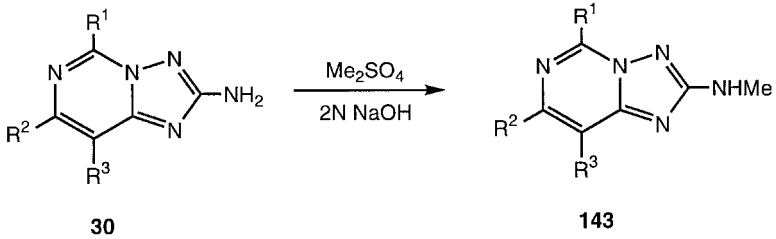
Ar = C_6H_5, 2–FC_6H_4; Ar^1 = 2–FC_6H_4; 4–FC_6H_4

SCHEME 54



141 **142**

SCHEME 55



30 **143**

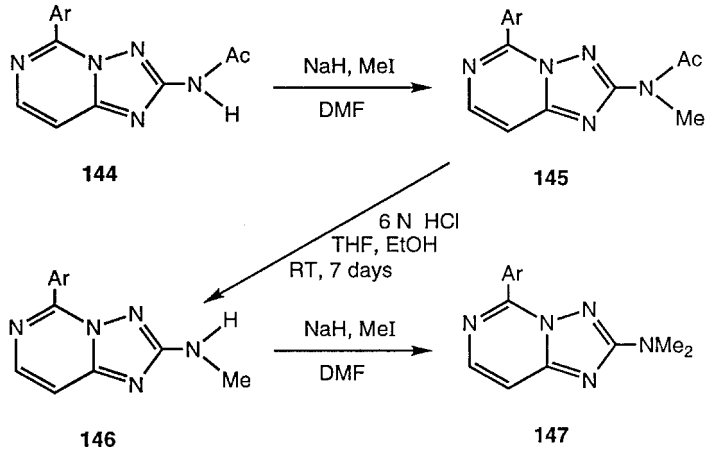
SCHEME 56

Finally, N6 alkylation as well as glycosylation of the 1,2,4-triazolo[1,5-*c*]pyrimidin-5-one **149** was performed with methyl iodide (83EUP80176), C1 activated glycofuranoses (89JIC686; 91T8949) and 3-deoxy-β-D-glycofuranoses (89JIC686) to give **150, 151,** and **152** respectively (Scheme 59).

3. *O-Alkylation*

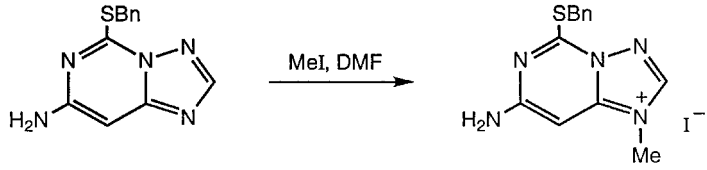
In the presence of potassium carbonate, alkyl halides reacted with the imidic acid tautomers **154** of 1,2,4-triazolo[1,5-*c*]pyrimidin-2-ones (**153**) to afford the 2-alkoxy derivatives **155** (85USP4528288; 94JMC2371) (Scheme 60).

Debenzylation of the benzyloxy groups in **156** and **158** to **157** and **159** respectively was achieved, without affecting the aromaticity of the system, by catalytic hydrogenolysis in the presence of palladium-on-charcoal (86TL3127; 89JHC991) (Scheme 61).



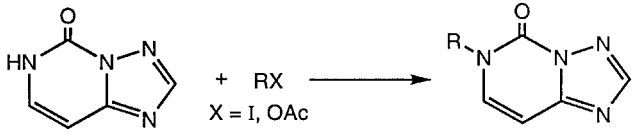
144 **145** **146** **147**

SCHEME 57



148 **135**

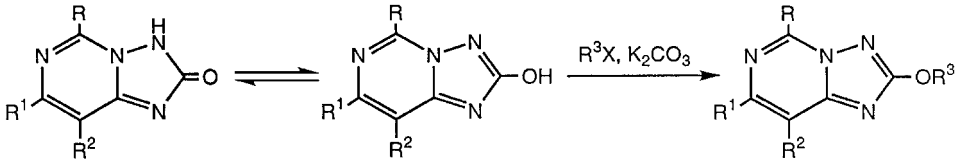
SCHEME 58



149

150, R = Me
151, R = β–D–glycofuranosyl
152, R = 3–deoxy– β–D–glycofuranosyl

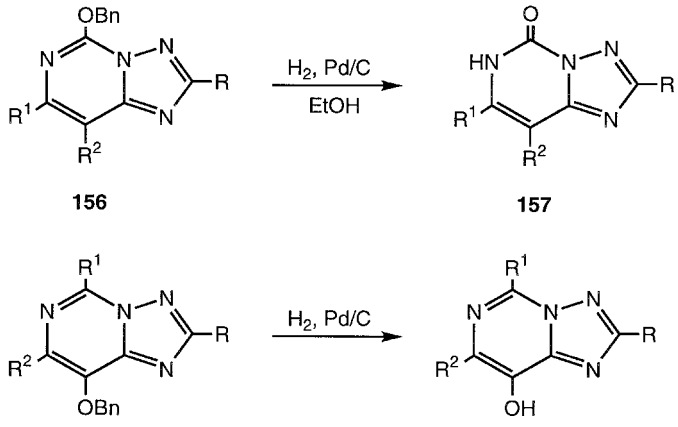
SCHEME 59



153 **154** **155**

R^3 = Me, CH_2COOEt, $(CH_2)_2COOEt$

SCHEME 60



156 **157**

158 **159**

SCHEME 61

4. *S-Alkylation*

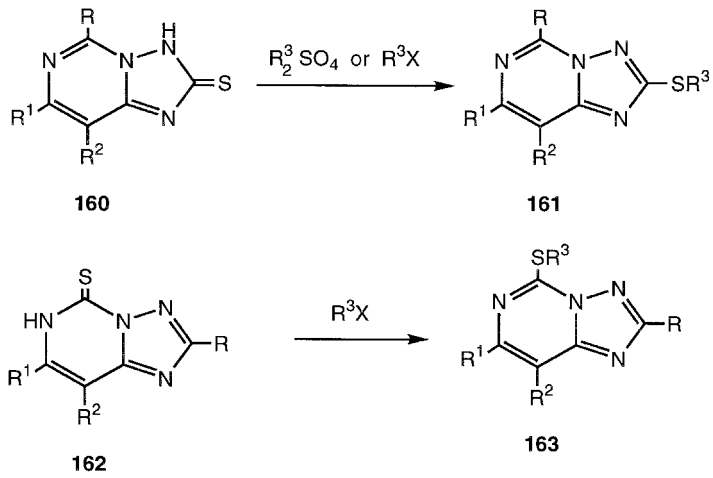
2-Alkylmercapto-1,2,4-triazolo[1,5-*c*]pyrimidines (**161**) were easily prepared by alkylation of the corresponding 2-thioxo compounds **160** with dialkyl sulfates in the presence of an alkali (62BRP897870; 65JCS3369) or with alkyl halides (79AJC2713; 84S881; 89EUP343752; 94JMC2371) (Scheme 62). The 5-alkylmercapto derivatives **163** were similarly prepared from the 5-thioxo compounds **162;** alkyl halides only were employed to accomplish this alkylation (79AJC1585; 85KGS421; 92KFZ30, 92KGS382; 94EUP582261) (Scheme 62).

D. Substituent Transformations

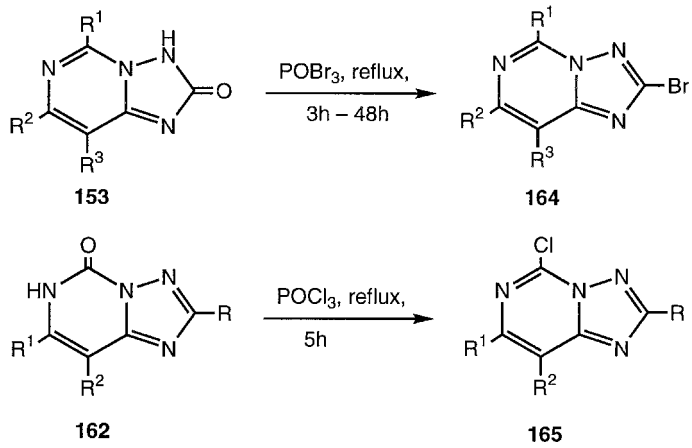
A fairly large number of 1,2,4-triazolo[1,5-*c*]pyrimidine derivatives were prepared via transformation of substituents attached to the skeleton of the parent system. The reported examples of such substituent transformation may collectively be categorized into the following types.

1. *Hydroxyl Group Transformations*

Imidic acid hydroxyl groups at C2 of 1,2,4-triazolo[1,5-*c*]pyrimidin-2-ones (**153**) were displaced with bromine upon treatment with phosphoryl bromide to give the 2-bromo derivatives **164** (62BRP897870; 65JCS3357). Treatment of the 5-oxo-1,2,4-triazolo[1,5-*c*]pyrimidines **156** with phosphoryl chloride afforded the corresponding 5-chloro derivatives **165** (79AJC1585; 80AJC1147; 88JMC1014) (Scheme 63).



Scheme 62



153 164

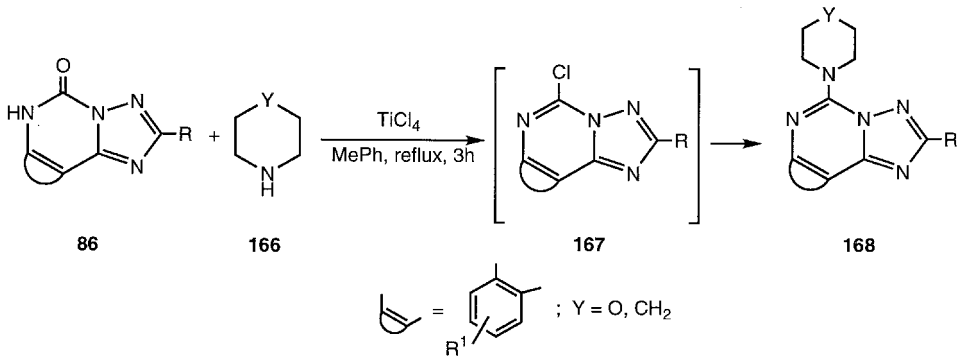
162 165

SCHEME 63

A one-step transformation of the C5-OH in **86** to the 5-(piperid-1-y)- or 5-(morpholin-4-yl) derivatives **168** was carried out by heating with the respective amines **166** in the presence of titanium tetrachloride. The reaction probably involved formation of the unisolable 5-chloro compounds **167** (93JHC11) (Scheme 64).

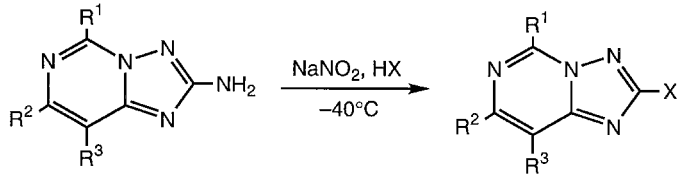
2. *Amino Group Transformations*

2-Amino-1,2,4-triazolo[1,5-*c*]pyrimidines (**30**) readily underwent Sandmeyer reaction to give the 2-bromo (**164**) (62BRP897870) and 2-chloro derivatives (**169**) (90JMC1230) (Scheme 65). The 5-amino congeners of **30** behaved analogously to give the 5-halo compounds (85EUP152841).



86 166 167 168

SCHEME 64



30 **164**, X = Br; **169**, X = Cl

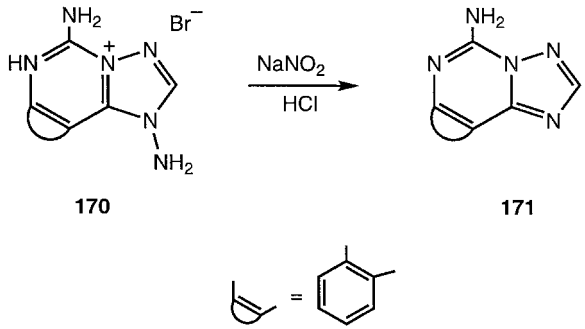
SCHEME 65

Treatment with nitrous acid caused deamination of the N1-NH_2 group of the 1,5-diamino-1,2,4-triazolo[1,5-*c*]quinazolinium bromide **170,** leaving the C5–NH_2 group intact to furnish **171** (73TL1643) (Scheme 66).

Aliphatic and aromatic aldehydes condensed with 2-amino- (62BRP898414), 5-amino- (80AJC1147), or 8-amino-1,2,4-triazolo[1,5-*c*]pyrimidines (68JOC530) to give the related Schiff bases. Treatment of the 2-amino-5-methyl-1,2,4-triazolo[1,5-*c*]quinazoline **11** with formaldehyde and piperidine in the presence of acetic acid gave the 2-hydroxymethyl-amino-5-(2-piperidinoethyl) derivative **172.** Utilization of aromatic aldehydes and piperidine in this reaction gave the 2-arylideneamino-5-styryl derivatives **173** (68CB2106) (Scheme 67).

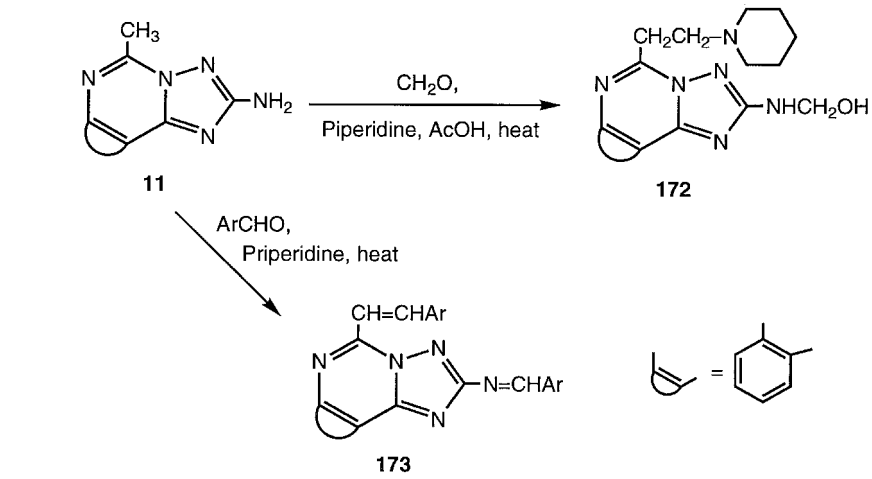
3. *Mercapto and Alkylmercapto Groups Transformations*

Oxidation of 2-mercapto-1,2,4-triazolo[1,5-*c*]pyrimidines (**174**) with chlorine or bromine in water (64BRP951652; 65JCS3369), with hydrogen peroxide and chlorine (95MIP1), as well as with sodium chlorate in hydrochloric acid (94JMC2371) gave the corresponding 2-sulfonyl halide derivatives **175**. Oxidation of the 2-alkylmercapto compounds **176** to the 2-alkylsufonyl derivatives **177** was made with ammonium peroxodisulfate and sulfuric acid



170 **171**

SCHEME 66



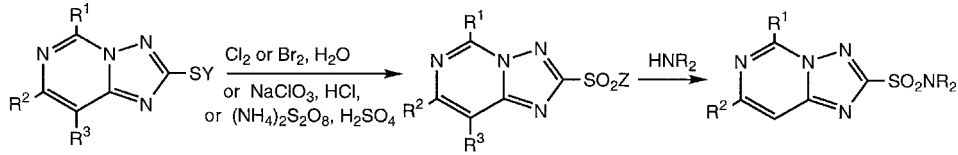
SCHEME 67

(62BRP897870; 65JCS3369). Reaction of the sulfonyl halides **175** or the alkylsulfonyl derivatives **177** with amines gave the respective 2-sulfonamido compounds **178,** many of which are agrochemically useful as herbicides (64BRP951652; 65JCS3369; 87EUP244948; 89EUP343752; 92USP5163995; 93USP5177206, 93USP5201938; 94JMC2371; 95USP5447905, 95USP5461161; 96MI1, 96MIP1; 97MIP1, 97USP5614469) (Scheme 68).

5-Mercapto and 5-alkylmercapto groups attached to 1,2,4-triazolo[1,5-*c*]pyrimidines (**179**) were easily displaced by amino (88JMC1014; 92KGS382), hydrazino (79KGS262; 92KGS382), hydroxy, and ethoxy functions (92KGS382) to give **180**–**183** respectively (Scheme 69).

4. *Halo Groups Transformations*

The halogen atom of 2-chloro- and 2-bromo-1,2,4-triazolo[1,5-*c*]pyrimidines (**164**, **169**) was displaced by alkoxy (65JCS3357), amino (65JCS3357;

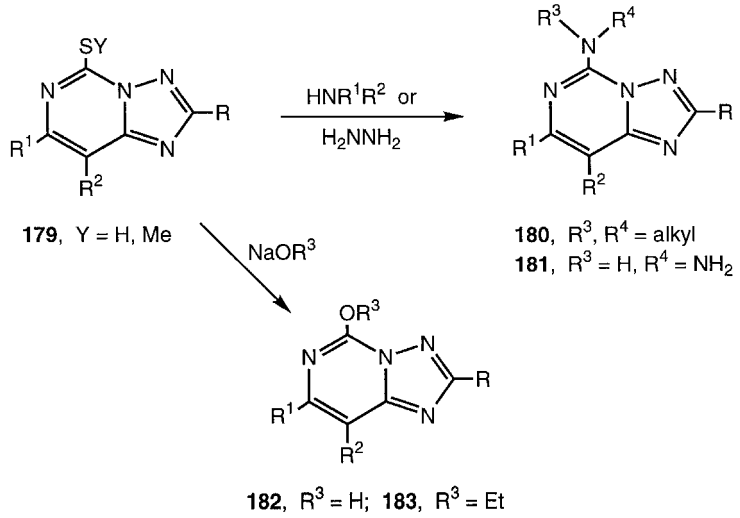


174, Y = H
176, Y = Me, Et

175, Z = Cl, Br
177, Z = Me, Et

178

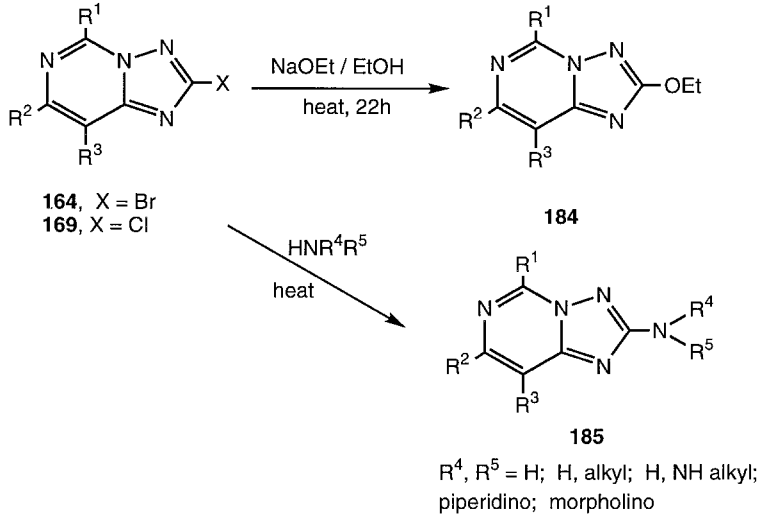
SCHEME 68



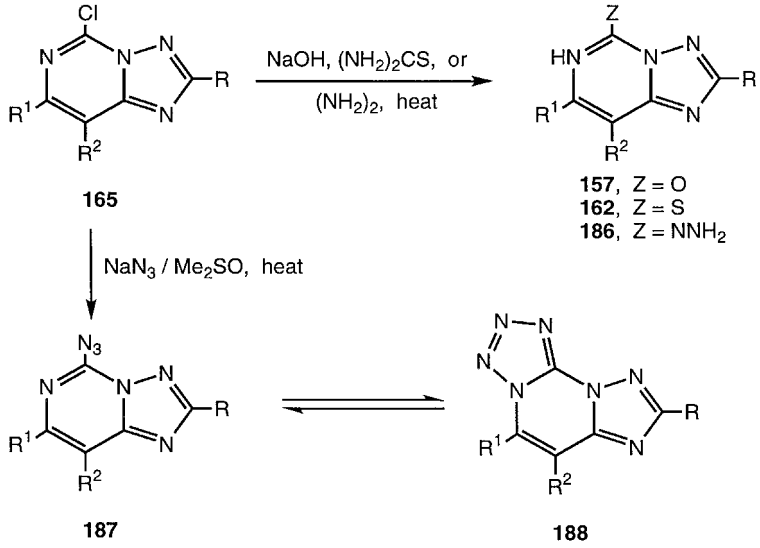
SCHEME 69

90JMC1230), and hydrazino groups (65JCS3357) to give **184** and **185** respectively (Scheme 70).

Reaction of 5-chloro-1,2,4-triazolo[1,5-*c*]pyrimidines (**165**) with sodium hydroxide, thiourea, or hydrazine hydrate (79AJC1585) or with sodium azide (85EUP152841) also caused the displacement of the chlorine atom to



SCHEME 70



SCHEME 71

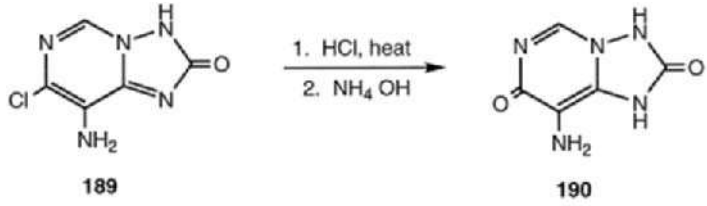
give the 5-oxo (**157**), 5-thioxo (**162**), 5-hydrazino (**186**), and 5-azido derivatives (**187**). The latter exists in equilibrium with the tautomeric tetrazolo[1,5-*a*]-1,2,4-triazolo[1,5-*c*]pyrimidine structure (**188**) (85EUP152841) (Scheme 71).

Heating the 8-amino-7-chloro-2-oxo-1,2,4-triazolo[1,5-*c*]pyrimidine **189** with hydrochloric acid caused hydrolysis of the chloro group yielding the 2,7-dioxo derivative **190** (68JOC530) (Scheme 72).

IV. Spectral and Electronic Properties

A. Infrared Spectra

The infrared spectra revealed the dominance of the 2-oxo (**153**) and 5-oxo (**157**) structures (amide or lactam tautomers) over the 2-hydroxy (**154**) and the 5-hydroxy (**192**) structures (imidic acid or lactim tautomers)



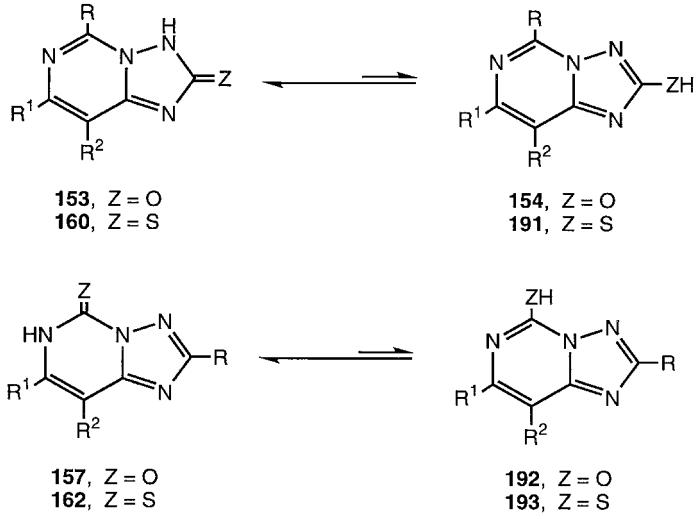
SCHEME 72

(65JCS3357; 68JOC530; 70CB3278; 75CB3799) (Scheme 72). The 2-thioxo (**160**) and 5-thioxo (**162**) tautomers also preponderated over the 2-mercapto (**191**) and 5-mercapto (**193**) tautomers (65JCS3369; 84S881; 86JHC43) (Scheme 73).

The infrared spectrum of 1,5-diamino-1,2,4-triazolo[1,5-*c*]quinazolinium bromide (**75**) showed two intense absorptions near 1700 cm^{-1}. These absorptions were interpreted, on the basis of deuteration experiments, to be due to ν $C{=}N^+$ coupled with δ NH_2 and other ring modes [79JCS(P2)1708].

B. Ultraviolet Spectra

Ultraviolet absorption spectra of 1,2,4-triazolo[1,5-*c*]pyrimidines differ markedly from those of the corresponding [4,3-*c*] regioisomers. Compounds of the latter system readily undergo Dimroth rearrangement during their preparation to isomers of the former system [99AHC(75)243]. UV spectral measurements have frequently been used to discriminate between structures belonging to both systems (63JCS5642; 65JCS3357, 65JCS3369; 68JOC530; 75JHC107; 78AJC2505; 81JHC43; 86TL3127; 89JHC687, 89JHC991; 91T8949; 98T3865). UV absorptions of compounds belonging to the [1,5-*c*] system occur at shorter wavelengths than those of the corresponding [4,3-*c*] compounds (63JCS5642; 65JCS3357, 65JCS3369; 89JHC687). At pH7, alkyl substituted 1,2,4-triazolo[1,5-*c*]pyrimidines showed a single absorption peak at 250–280 nm, which was, occasionally, accompanied by a minor inflexion (78AJC2505; 89JHC687; 98T3865). Bis{1,2,4-triazolo[1,5-*a*:1′,5′-*c*]}pyrimidines (**194**) showed five characteris-



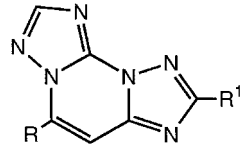
153, Z = O
160, Z = S

154, Z = O
191, Z = S

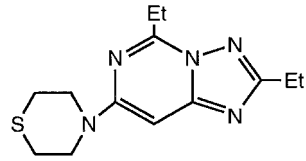
157, Z = O
162, Z = S

192, Z = O
193, Z = S

Scheme 73



194, R = H, Me; R^1 = H, Me, Ph



195

SCHEME 74

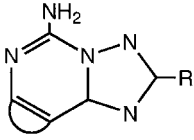
tic absorption bands at 214–219, 228–230, 256–258, 262–266, and 275–277 nm (80AJC1147) (Scheme 74).

Quantitation of the oral bronchodilator 2,5-diethyl-7-(tetrahydro-1,4-thiazin-4-yl)-1,2,4-triazolo[1,5-*c*]pyrimidine (R-836) (**195**) in plasma and urine of humans and experimental animals utilized reversed-phase HPLC and UV detection (88MI1).

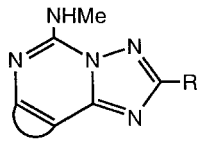
Comparison of the UV spectra of 5-amino-2-(2-furyl)-1,2,4-triazolo[1,5-*c*]quinazolines (**196**) and its 5-methylamino derivative (**197**) in neutral, acidic, and basic media with the spectra of the two tautomerically locked derivatives—2-(2-furyl)-5-dimethylamino-1,2,4-triazolo[1,5-*c*]quinazolines (**198**) (amino-locked tautomers) and the imino-locked tautomers 2-(2-furyl)-5-imino-6-methyl-1,2,4-triazolo[1,5-*c*]quinazolines (**199**)—indicated that compounds **196** and **197** are best represented as a mixture of their amino and imino tautomers (88JMC1014) (Scheme 75).

C. ^{1}H NMR SPECTRA

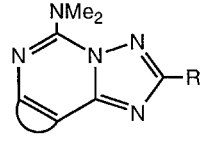
^{1}H NMR spectral measurements were utilized to a reasonable extent to distinguish between regioisomeric 1,2,4-triazolo[4,3-*c*] and [1,5-*c*]pyrimidines as well as to corroborate assigned structures (68JOC530; 70JOC3448; 75CB3799, 75JHC107; 76S833, 76TL1953; 78AJC2505; 79AJC1585,



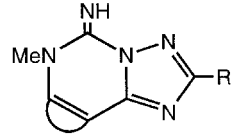
196



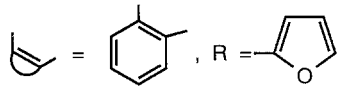
197



198



199



SCHEME 75

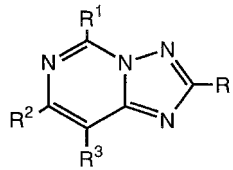
79AJC2713; 80AJC1147; 81AJC189, 81JHC43; 85CPB2678; 86TL3127; 89JHC687, 89JHC763, 89JHC991; 91JHC489; 94JMC2371; 98T3865). Adequate ^{1}H NMR data were reported to justify drafting the following guidelines that correlate the structural–chemical shifts relationship: (a) the decreasing order of magnitude of the chemical shifts (direction to higher fields) of the CH protons of the 1,2,4-triazolo [1,5-*c*]pyrimidines **23** is almost always C5-H > C2-H > C7-H > C8-H and (b) the same order is also valid for the chemical shifts of methyl groups of the various methyl derivatives of **23**, i.e., C5-Me > C2-Me > C7-Me > C8-Me (Scheme 76). The methylation product of the 1,2,4-triazolo[1,5-*c*]quinazoline **200** showed a nuclear Overhauser effect that indicated close spacial proximity between the methyl group protons and C7-H. Accordingly, methylation was decided to has taken place at N6 (**201**) and not at O5 (91JMC281) (Scheme 77).

D. ^{13}C NMR Spectra

The ^{13}C NMR spectral measurements of 1,2,4-triazolo[1,5-*c*]pyrimidines pinpointed that the order of chemical shifts of their carbons varies with the type and location of substituents they carry (87JHC805; 89JHC687, 89MRC1001; 90T3897; 91JMC281, 91T8949; 93JHC11; 96JHC1285).

E. Mass Spectra

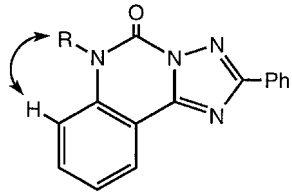
The mode of mass spectral fragmentation of 1,2,4-triazolo[1,5-*c*]pyrimidines has not been thoroughly studied. Most of the recorded measurements reported the molecular ion peaks and/or closely related fragments (e.g., M^++1, M^+−1… etc.) or documented the obtained mass/charge values without providing the probable structures [70JOC3348; 81JHC43, 81JOC3956; 84JCS(P1)1143, 84S881; 85CPB2678; 86JHC43, 86TL3127; 88CPB1963; 89JHC991; 90JMC1230; 91JMC2899; 93KGS1545; 97JHC871]. Fragmentation of the 5,7-dioxo-1,2,4-triazolo[1,5-*c*]pyrimidine **202** gave



23

R, R^1, R^2, or R^3 = H or Me

Scheme 76



200, R = H
201, R = CH_3

SCHEME 77

peaks corresponding to M^+, (M^+−HNCO), and HNCO (91JHC489) (Scheme 78).

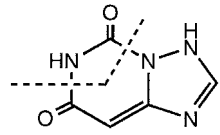
In the case of 2-substituted 7-amino-5-oxo- and 7-amino-5-thioxo-1,2,4-triazolo[1,5-*c*]pyrimidines **203,** however, the pattern of fragmentation was studied using high resolution electron impact mass spectrometery (90JHC851). Fragmentation of the molecular ions to the 1,2,4-triazole fragments **204**–**206** took place according to the two routes explained in Scheme 79. Fragments **204**–**206** underwent further fragmentation characteristic of 1,2,4-triazole species (Scheme 79).

F. X-RAY

X-ray crystallographic analysis has occasionally been used to confirm structures of 1,2,4-triazolo[1,5-*c*]pyrimidines [62AX231; 63JCS5642; 73TL1643; 79JCS(P2)1708; 90JMC1230, 90T3897]. X-ray analysis has also elucidated the regiochemistry of ribosylation of 5-oxo-1,2,4-triazolo [1,5-*c*]pyrimidine at the N6 position (91T8949).

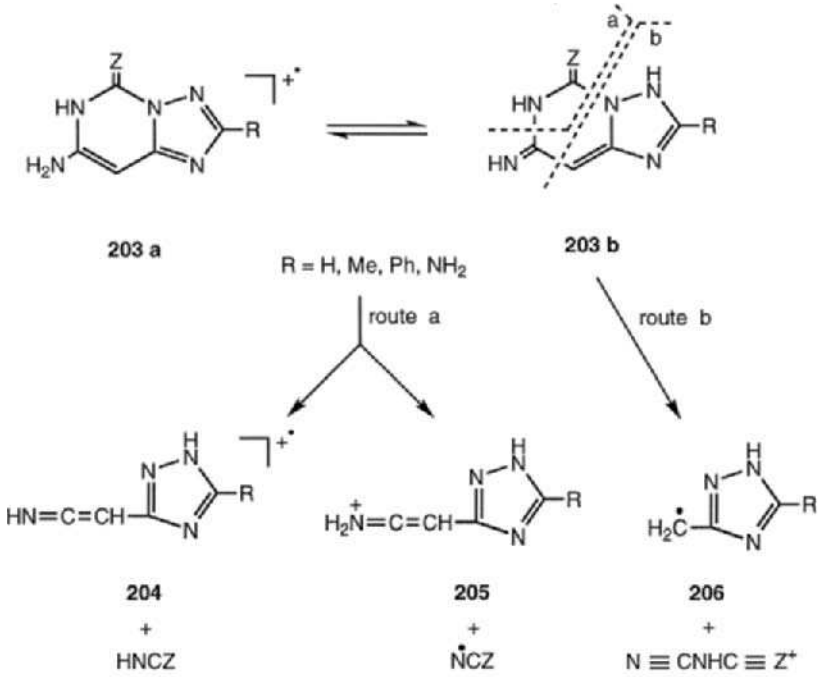
G. ELECTRONIC PROPERTIES

Electron density calculations of the parent unsubstituted 1,2,4-triazolo[1,5-*c*]pyrimidine suggested that N4 and N6 caused a decrease of the



202

SCHEME 78



SCHEME 79

electron density at C5 and increased, therefore, its electrophilicity. The calculations also explained the facile rearrangement of 1,2,4-triazolo[4,3-*c*]- to -[1,5-*c*]pyrimidines to be due to the larger interaction between the higher electron densities at N1 and N2 in the [4,3-*c*] isomers compared to the lesser interaction between the lower electron densities at N3 and N4 in the [1,5-*c*] isomers (71JHC643). Bond order, charge density distribution, energy terms, and charge separation indices were calculated for some mesoionic 7-oxo-1,2,4-triazolo[1,5-*c*]pyrimidines and compared with those of mesoionic purinones (73JHC479).

V. Molecular Modeling

Computer-generated energy-minimized molecular modeling was performed for some 1,2,4-triazolo[1,5-*c*]pyrimidines and quinazolines possessing adenosine antagonist activity. Superimposability of the obtained models with those of 8-arylxanthines suggested that both types of molecules bind to the same receptor site (88JMC1014; 94JMC2371).

VI. Applications

Similar to their [4,3-*c*] isomers [99AHC(75)243], 1,2,4-triazolo [1,5-*c*]pyrimidines displayed numerous biological and medicinal activities. In addition, the [1,5-*c*] isomers found useful agrochemical applications as herbicides.

A. Biological and Medicinal

1,2,4-Triazolo[1,5-*c*]pyrimidines exhibited antimicrobial activities ranging from antiviral (92KFZ30) and antibacterial (83MI1; 87EUP244948; 94EUP582261; 97PHA753), to antifungal (83MI1; 86MI1). Some compounds of this system were found to amplify the action of the antibiotic phleomycin (79AJC2713). Nucleosides carrying a 1,2,4-triazolo[1,5-*c*]pyrimidine base showed antiprotozoal activity against amastigotes of *Leishmania donovani* (89JIC686).

In connection with their medicinal applications and activities to the respiratory system they showed antiallergic (83EUP80176; 85USP4528288), antihistaminic [73BBA(304)693; 85GEP(O)3427823; 86EUP181282; 87USP4713383; 88EUP263071; 90JMC1230], bronchodilatory (62BRP897870, 62BRP898414; 84EUP121341; 86USP4591588; 87MI1, 87USP4639445; 89MI2), and respiratory-stimulant activities (62BRP898414).

Toward the cardiovascular and urinary tract, these compounds offer applications as hypotensives [72GEP(O)2146076; 73GEP(O)2261095; 87MI3; 91MI2; 93MI2; 94JMC2371, 94USP5358950; 98AF138], angiotensin II receptor antagonists (93EUP521768; 94JMC2371, 94USP5358950; 95MI1, 95MI2, 95MI3, 95MI4; 96JHC1307; 97BJP488, 97MI1), diuretics (64BRP951652; 83USP4405780; 84MI1, 84USP4483987; 85EUP152841; 87MI3; 88MI2; 89USP4866063; 91MI1, 91MI3; 92MI3), and renal vasodilators (84MI1; 88MI2; 91MI2).

The activities related to the central nervous system (CNS) include analgesic and sedative (62BRP897870, 62BRP898414), anticonvulsant (64BRP951652), tranquilizing (77USP4053600; 81USP4269980), anxiety modulating (86EUP181282; 87USP4713383; 88EUP263071; 91JMC2899), CNS stimulating (86EUP181282; 87USP473383), memory improving (86EUP181282), adenosine antagonist (80BJP359; 86EUP181282; 87MI2, 87USP4713383; 88JMC1014; 94MI1), and benzodiazepine antagonist activities (86EUP181282; 87USP4713383; 91JMC281).

Anti-inflammatory [62BRP897870, 62BRP898414; 73GEP(O)2261095; 74USP3850932; 77USP4053600), antitumor (92KFZ30), and radiation-protective (92KFZ30) properties were documented for some compounds of this system.

B. Agrochemical

1,2,4-Triazolo[1,5-*c*]pyrimidine-2-sulfonamides showed general or selective preemergence and postemergence herbicides (89EUP343752; 92USP163995; 93USP5201938; 95USP5447905, 95USP5461161; 96MIP1; 97MIP1, 97USP56114469).

VII. Conclusion

In two previous chapters published in this series we reviewed the chemistry of 1,2,4-triazolo[4,3-*a*]- and -[4,3-*c*]pyrimidines [99AHC(73)131; 99AHC(75)243]. The chemistry of the [1,5-*a*] system has been survyed in 1993 by G. Fischer [93AHC(58)81] and in this chapter we scrutinized the chemistry of the fourth and final system. The aforementioned chapters reviewed the methods of synthesis, reactions, spectral and electronic properties, and applications of 1,2,4-triazolopyrimidines. A very noticeable feature of these compounds is the ease of isomerization of the two kinetically favorable [4,3-*a*] and [4,3-*c*] systems to the thermodynamically more stable [1,5-*a*] and [1,5-*c*] systems respectively. Syntheses of the two former systems occasionally led to the latter regioisomeric systems. It is not uncommon, therefore, to encounter some erroneous structural assignments reported in ealier articles. Carefulness should, accordingly, be exercised regarding structure assignment to products of reactions designed to produce either of the two thermodynamically less stable [4,3-*a*] and [4,3-*c*] systems. Marked differences in UV, ^{13}C NMR, and ^{1}H NMR spectral properties provided tools of choice to distinguish between alternative structures and reassign incorrect ones. X-ray crystal analysis, whenever feasible, offered the conclusive evidence. Compounds of the four systems possessed valuable medicinal, agrochemical, and photographic applications.

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