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Organometallic Compounds of Furan, Thiophene, and Their Benzannulated Derivatives

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I. Introduction

Organometallic chemistry of heteroaromatic ligands is a relatively new and rapidly progressing subject of both pure and applied nature (93CCR237, 96CCR247, 97RCR389, 98CCR31, 99AHC, 99AHC1). Progress achieved in this field has been so great, especially in the 1990s, that it is difficult to reflect all the trends of development even in a monograph of moderate size. The aspects of synthesis, coordination modes of the heteroaromatic ligands and their modified reactivity in the complexed state, spectral and structural studies, theoretical computations, and use in various fields of fuel, materials, medicinal, and other branches of applied chemistry deserve special consideration. Here, we report on the trends in coordination modes and reactivity of the complexed furan, thiophene, selenophene, tellurophene, and their benzannulated derivatives. The material is grouped in such a way that nontransition organometallic derivatives are briefly considered first, but

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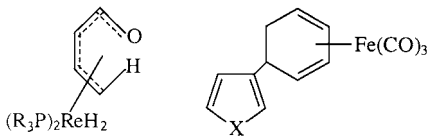
we then move across the transition metal series and whenever relevant cover the organolanthanide compounds. Synthesis details are not given as a rule, but most attention is paid to versatility of the coordination modes and trends in reactivity.

II. Organometallic Compounds of Furan

Furan is a heterocycle of low aromaticity (70T4505, 74AHC255). Chemically it resembles 1,3-dienes: It undergoes electrophilic substitution predominantly at the α-position, polymerizes in the presence of electrophiles, and undergoes Diels–Alder reactions (82MI1, 84MI5, 95MI1, 96KG867). Only seldom is 2,5-functionalization possible (94JA11153). The scope of chemical transformations is apparently narrow despite the high demand for variously derivatized furans in synthetic organic chemistry (natural products, pharmaceuticals, flavor or fragrance compounds).

Although according to *ab initio* data (79JMS87), furan is formally classified as a π-excessive ligand; it is not prone to π-complex formation. The only mention of η^5-furan complexes refers to the existence of $[Cp^*Ru(\eta^5\text{-}C_4H_4O)]Cl$ in solution [88JCS(CC)711], and sometimes such species are postulated as intermediates. In many cases coordination may lead to ring opening (93OM517), as in the reaction with $ReH_7(PPh_3)_2$, which causes cleavage of the C—O bond and formation of 1-oxapentadienyl species **1** [83JCS(CC)813]. Furan interacts with the tricarbonyl (cyclohexadienyl)iron cationic complex to yield the product of electrophilic substitution **2** (X = O) [74JOM(71)C11]. Additionally, there are the bridging η^1(C), η^2(C—C) $Fe_2(CO)_6$ complexes (91OM3363, 92OM3262).

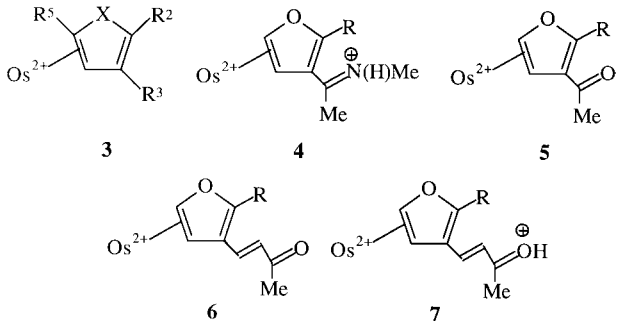


1 **2**

The overall impression of the poor donor ability of furan was changed somewhat when its organoosmium compounds were studied. The reactivity of the η^2-coordinated species appeared to be so various that many synthetic problems of derivatization were successfully solved. We give a detailed account of the transformations of organometallic species without paying attention to the decomplexation reactions and preparation of the corresponding substituted furan. This information can be easily found elsewhere (97CRV1953). The following chemistry enhances the range of derivatized furans. For furans, electrophilic attack is directed

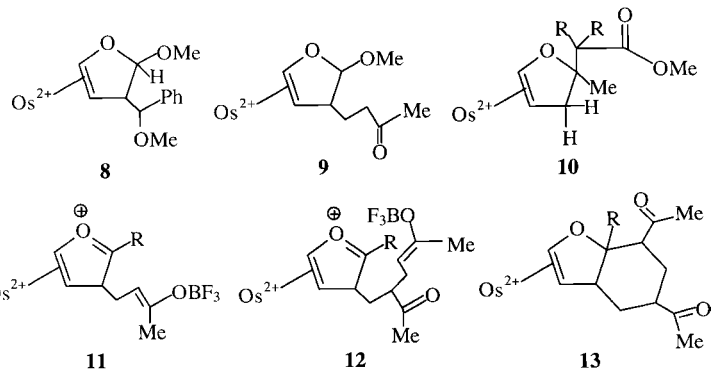
predominantly to position 2 (84MI3). Only under special conditions does the β orientation become possible (85SCI857). The η^2-complexation enhances the nucleophilic character of C3 atom, suddenly enabling facile β-electrophilic attacks. In addition, derivatization of furan is possible with some carbene complexes (99JA3065).

Reduction of $[Os(NH_3)_5(OTf)](OTf)_2$ with zinc amalgam or metallic magnesium in excess of a furan leads to complexes **3** (X = O, $R^2 = R^3 = R^5 = H$; R^2 = Me, $R^3 = R^5 = H$; $R^2 = R^5$ = Me, $R^3 = H$; $R^2 = R^5 = H$, $R^3 = CH_2OH$) (94JA5499, 97CRV1953, 98JA509). The η^2-coordination mode via C4 and C5 atoms of furans makes them susceptible to electrophilic attack at the β-carbons, hardly possible for uncoordinated furan. The properties of the heterocycle in **3** are similar to those of vinyl ether. The common α-electrophilic addition is blocked. Os^{2+} cation donates its π-electron density to furan and activates the β-carbon of the uncoordinated portion of the ring. Complexes **3** enter three major types of chemical reactions. First is C3-electrophilic substitution. Thus, species **3** (X = O, $R^2 = R^3 = R^5 = H$; R^2 = Me, $R^3 = R^5 = H$) interact with *N*-methylacetonitrilium triflate to yield the iminium substituted derivatives **4** (R = H, Me). On hydrolysis with water, **4** give the β-acetylfuran complexes **5** (R = H, Me). Vinylation is achieved in the reaction of **3** (X = O, R^2 = Me, $R^3 = R^5 = H$) with *trans*-4-methoxy-3-butene-2-one and a Lewis acid, the product being **6.** The latter is protonated by triflic acid at the ketone oxygen to give **7.**



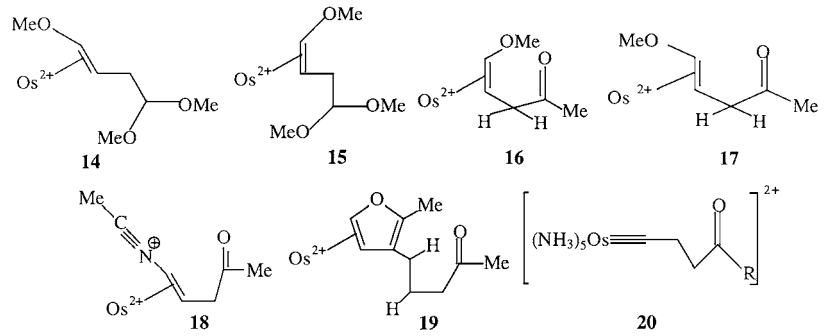
The second group of reactions is called vicinal difunctionalization. They embrace the C2 and C3 positions of the furan ring simultaneously. Thus, complex **3** (X = O, $R^2 = R^3 = R^5 = H$) reacts with benzaldehyde dimethyl acetal to give 4*H*-furanium cation (the product of electrophile addition at C4), which experiences further attack by the methoxide group with formation of the acetal **8** (95OM2861). This reaction is possible in the presence of the Lewis acid (BF_3–OEt_2). Reaction with methyl vinyl ketone in methanol, when run in identical conditions,

produces **9** (94JA5499). Attack to the α-position is observed even when the C2 atom is occupied with a methyl group as in **3** (X = O, R^2 = Me, $R^3 = R^5$ = H), provided that proton is used as the electrophile. At the first stage an excess of triflic acid and then methyl trimethylsilyl dimethyl ketene acetal are added. This sequence gives rise to **10** (R = Me) (98JA509). If in an identical sequence ((trimethylsilyl)oxy)propene is the nucleophile, then complex **10** (R = H) is obtained (98JA509). Difunctionalization can be brought about in a different manner. This so-called [2 + 2 + 2] Michael–Michael ring closure sequence was studied with complexes **3** (X = O, $R^2 = R^3 = R^5$ = H; R^2 = Me, $R^3 = R^5$ = H). The initial Michael addition with methyl vinyl ketone is followed by a Lewis acid to give **11** (R = H, Me). The second Michael addition followed to yield **12** (R = H, Me). The latter contains a potential benzofuran skeleton, and the ring closure to generate **13** (R = H, Me) is a consequence of an intramolecular nucleophilic attack.

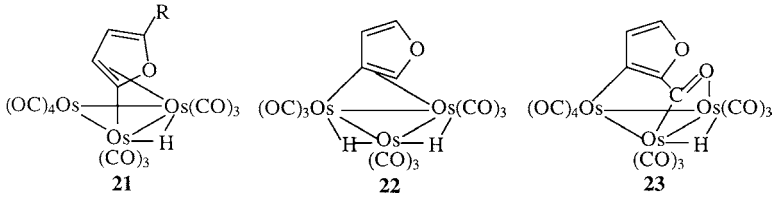


The third group of reactions is termed C3–C5 tandem difunctionalization (96JA5672, 98JA509). Protonation of **3** (X = O, $R^2 = R^3 = R^5$ = H) with triflic acid in methanol causes ring opening and formation of the *trans*- **14** and *cis*-4-methoxy-3-butenal dimethyl acetal complexes **15.** Under the same conditions, protonation of **3** (X = O, R^2 = Me, $R^3 = R^5$ = H) gives a mixture of *cis*- **16** and *trans*-5-methoxy-4-pentene-2-one complex **17.** Protonation probably occurs at C3 with subsequent ring opening. In acetonitrile, complex **3** (R^2 = Me, $R^3 = R^5$ = H) reacts with triflic acid to give **18,** where the nucleophilic ability of acetonitrile is evident. If the same reaction is conducted together with $BF_3 \cdot OEt_2$, species **19** regarded as a dimer of **3** (X = O, R^2 = Me, $R^3 = R^5$ = H) results. Protonation occurs along a pathway leading to the carbynes **20** (R = H, Me) when **3** (X = O, $R^2 = R^3 = R^5$ = H; R^2 = Me, $R^3 = R^5$ = H) react with triflic acid in methanol, dimethylformamide, acetonitrile, and acetone.

Thus, dearomatization of the furan heterocycle in the 4,5-η^2 complexes causes electrophilic addition mainly at the uncoordinated carbon C3. The other possibility

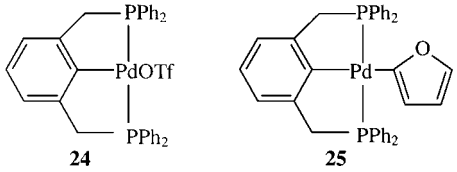


of functionalizing the vinyl ether moiety could be at oxygen. Preliminary experiments (98JA509) indicate the possibility of the attack of trimethylsilyl triflate at this center.

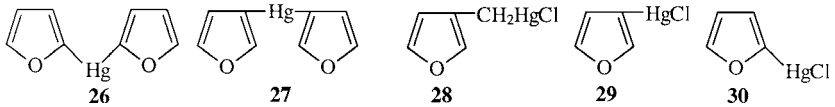


Furan [85JOM(297)341] and 2-methylfuran [91JOM(412)177] add oxidatively to $[Os_3(CO)_{10}(AN)_2]$ to yield **21** (R = H, Me). Complex **21** (R = H) on decarbonylation gives **22** [85JOM(297)341]. Another approach to **22** is the reaction of 2-formylfuran with $[Os_3(CO)_{10}(AN)_2]$ to produce first **23** [86JOM(311)371] and then **22** on thermal decarbonylation.

The reversible reaction of tri-*n*-butylstannylfuran with the cyclometallated palladium complex **24** yields the η^1(C) coordinated 2-furyl complex **25** (98JA11016).



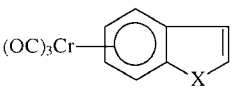
Photoelectron spectra of furyl mercury complexes **26–30** were studied [79JCS(D)2037].



III. Organometallic Compounds of Benzofurans

Although benzofuran is considered to be aromatic (70T4505), its electronic distribution [74JCS(P2)1893] is such that the π-donor ability is lower than in furan, i.e., it is less aromatic than furan. The influence of the heteroatom is limited by the five-membered cycle. The oxygen atom is a stronger σ-acceptor and a weaker π-donor than in furan. The furan ring of benzofuran is less π-excessive than the parent heterocycle, and the benzene and furan rings are fairly independent [72T3465, 83JMS(94)115]. Dibenzofuran is very stable (70T4505); its first ionization potential is π in nature [78ZN(A)1006]. The HOMO–LUMO transition reflects the dienic character of the five-membered ring [83JMS(94)115]. This leads to a general view of the electronic distribution in benzannulated five-membered heterocycles (84KGS1497, 85UKZ293). The π-electron delocalization is complete only for the carbocyclic constituent of the molecule. Thus, one may expect that coordination of metal carbonyls should occur via the π-conjugated carbocyclic system and the heteronucleus should take part in π-complex formation only with difficulty.

Chromium tricarbonyl complexes with benzofuran **31** (X = O), dibenzofuran **32** (X = O), and benzo[*b*]naphtho[2,3-*d*]furan **33** contain the η^6-coordinated $Cr(CO)_3$ fragment via the benzene ring [68JOM(14)359, 69JCS(B)1204, 75ADOC47, 82JCS(CC)467, 83JOM(255)317]. Species **31** and **32** are prepared from chromium hexacarbonyl, whereas **33** is made from $Cr(CO)_3(AN)_3$ [68JOM(14)359].



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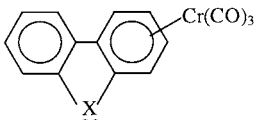

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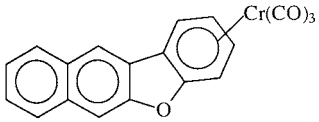

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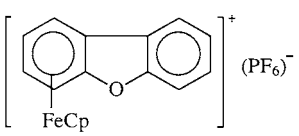
Reaction of dibenzofuran, ferrocene, and aluminum powder in the presence of aluminum chloride with subsequent hydrolysis and precipitation of the hexafluorophosphate salt gives **34** [80JOM(186)265]. When ferrocene and aluminum chloride are in excess, dicationic complexes **35** result. The reaction leading to **36** was also reported [84JOM(260)105].



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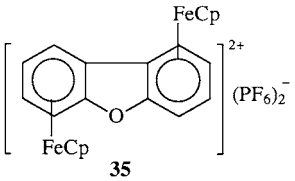

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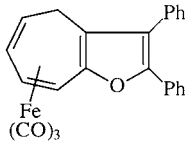

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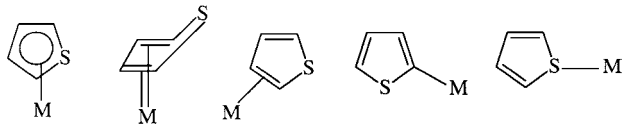
IV. Organometallic Compounds of Thiophene

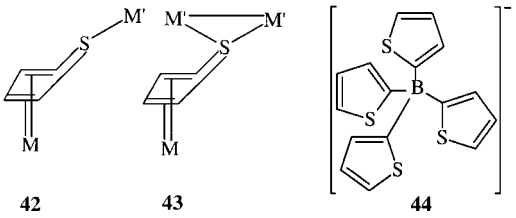
A. Introductory Remarks

The organometallic chemistry of thiophene has been studied the most comprehensively and systematically compared to the other five-membered monoheterocycles (72MI1, 88ACR387, 90CCR61, 91CI570, 91IECR2021, 91PIC259, 92CRV491, 92MI1, 94MI1, 95BSCB265, 96MI1, 98ACR109). It is aromatic (86MI1, 91T3949), although the extent of π-delocalization is substantially less than that of benzene. It is a classical example of the π-excessive heterocycle [68TCA247, 70MI1, 72TCA171, 73T3085, 75JCS(P2)974, 75JCS(P2)1223, 78JCP 5077, 78T3545, 82T3629, 83ACASH97, 83JCS(P2)135, 86MI1]. Selenophene (70AHC1, 73MI1, 82AHC127, 84MI4) and tellurophene [83JMS(105)233] generally have the same trends in electronic characteristics, although the organometallic species of these heterocycles are much less studied. Thus, there should be a reasonable balance between different π-coordination modes, namely η^5 (**37**), η^4 (**38**), and η^2 (**39**), (89JA5969), the latter two being possible and rather widespread because of the lower π-donor ability of thiophene compared to that of cyclopentadienyl. This leads to a high likelihood of the more localized π-coordination modes. σ-Coordination includes the η^1- (C-) 2-thienyl, **40,** and η^1- (S-) mode, **41.** The sulfur atom is a weak nucleophile, so that S-coordination, **41,** is not as probable, and metal–sulfur bonds are expected to be weak (86JA2294). The S-atom of the heteroring nearly acquires sp^3-hybridization in **41.** In fact there are few S-bonded complexes (89IC1183) where the thiophene is easily displaced by other weak ligands [85OM1909, 89JCS(CC)913, 90IC4380], but in a majority of cases they were postulated as intermediates, basically in reactions with subsequent cleavage of the C–S bonds. Such reactions as π-complexations followed by the nucleophilic attack lead to the ring-opened and sometimes completely desulfurized products.



37 **38** **39** **40** **41**

The most favorable coordination sites in thiophenes are the C2C3 and C4C5 double bonds (η^4-coordination, **38**). This type of coordination greatly enhances the nucleophilic power of the sulfur atom, which then gives rise to two new modes of binding the metal atoms, as in the η^4, S-μ_2-, **42,** and η^4, S-μ_3-species, **43.**



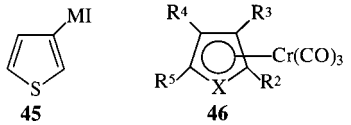
42 **43** **44**

Protonations of the uncomplexed thiophene at C2 is strongly preferred to S-protonation (81NJC505, 91JA4448). 2,5-Difunctionalizations are well known (86MI1), although deuterium exchange, for example, occurs only under highly basic conditions (84MI1) and is much slower for thiophene (60AK275) than for the coordinated heterocycle. The 3,4-substitutions are still unique for the uncomplexed thiophenes and when possible, they require special and stringent conditions [79MI1, 85JCS(P1)173, 85TL1149, 88MI1]. Sometimes attempts to obtain the 3-substituted species lead to opening of the thiophene ring (87AHC41). The coordinated thiophenes offer unique opportunities for further derivatizations.

A limited number of non-transition-metal derivatives of thiophene will be considered in this subsection. There are no short-range contacts between the lithium atoms originating from the $(LiO)_6$ cores and the sulfur atoms in $[Li{-}O{-}EMe_2(2\text{-}C_4H_3S)]_6$ (E = C, Si) (97OM5032), and evidence for π-interactions can be found in the X-ray crystal structures of these compounds. Theoretical computations show that σ-$(S^-)\,Li^+$ interactions are weak, whereas π-Li^+ contributions are considerable, in accord with the general reasoning on the electronic characteristics of uncomplexed thiophene.

The weakness of the η^1-coordination follows from the general structure determination of tetrakis(2-thienyl)borate, **44** (96IC7095). Counterions of potassium are η^5-coordinated, one cation per two thienyl substituents belonging to the neighboring anions.

3-Iodothiophene oxidatively inserts activated magnesium or zinc (obtained from their salts by lithium reduction) to yield **45** (M = Zn, Mg) (95JOC6658, 97JOC6921), which then reacts with electrophiles (e.g., aryl iodide) to generate the 3-substituted derivatives (3-arylthiophene). A similar process for 2-bromothiophene is known (92JA10087, 92TL5373, 93TL5955). 3-Bromothiophene also interacts with activated manganese (97TL993).



45 **46**

Thermolysis of the η^1-coordinated zirconium complex of thiophene $Cp_2Zr(SiMe_3)(C_4H_3S)$ is a thienyl ring cleavage reaction (92OM1646).

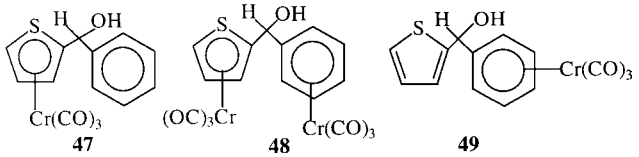
B. Group VI Metal Complexes

Chromium tricarbonyl complexes of thiophene, **46** ($X = S$, $R^2 = R^3 = R^4 = R^5 = H$), and its substituted derivatives may be obtained through either (i) the direct interaction of thiophenes with chromium hexacarbonyl [58CB2395, 58ZN(B)458, 60CB165, 66AICR1, 66CB1732, 68ICA12, 88JOM(338)211]; or (ii) the substitution reaction of thiophenes with complexes such as $(AN)_3Cr(CO)_3$ [71CR(C)2179, 71JOM(33)195, 74JOM(77)49, 74JOM(77)59] to give **46** ($X = S$; $R^2 = CH(OH)R$; $R^3 = SiMe_3$, Me; $R^4 = R^5 = H$) (97CB659) or with $(py)_3Cr(CO)_3$ in the presence of boron trifluoride etherate (66CB1732, 75JHC1055), or the reaction of thiophenes with tricarbonylchromiumnaphthalene to yield **46** ($X = S$, $R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^4 = R^5 = H$, $R^3 = Me$; $R^2 = Me_3Si$, Pr^i_3Si, Bu^tMe_2Si, $MeOCH_2$, $Me_3SiCH_2CH_2OCH_2$, $R^3 = R^4 = R^5 = H$) [94JOM(454)59, 95JCS(P1)97, 95JCS(P1)105]. The substitution reaction (ii) leads to higher yields of the η^5-complex than the direct interaction (i).

The α-carbon atom in **46** ($X = S$, $R^2 = R^3 = R^4 = R^5 = H$) has an enhanced electron density [74JOM(77)59, 75IZV84]. The π- and σ-systems of thiophene are modified in the complex. Complete delocalization among the four carbon atoms causes a greater polarization of the β-carbon atoms. Chromium is formally attached at the sulfur atom and the two double bonds [65IC1306, 76JOM(122)227]. This corresponds to an octahedral configuration of the complex. In the complexes, the electronic effects of a substituent may be transmitted toward the terminal carbonyls through the metal atom (75JHC1055). The stability of the η^5-coordinated $Mo(CO)_3$ thiophene complex with respect to that of the η^1(S) $Mo(CO)_5$ species follows from the results of theoretical computations (84JC400, 88SS320, 89JA40). The η^5-coordination of thiophene and 2,5-dimethylthiophene is not strong, and these heterocycles may be substituted by $P(OMe)_3$ in ligand exchange reactions of **46** ($X = S$, $R^2 = R^3 = R^4 = R^5 = H$) [96JCS(D)3959].

The range of the known reactions of tricarbonylchromium thiophene is perhaps broader than that of the uncomplexed thiophene (94MI2). They include electrophilic H─D exchange (76DAN1365) and metalation with *n*-butyllithium [83JOM(244)C21], often in combination with an electrophilic quench. Thus, with excess *n*-butyllithium followed by D_2O, 2,5-dideuterium tricarbonylchromium derivative is formed via the lithiated intermediates. Reaction of the dilithium compound with trimethylchlorosilane gives 2,5-bis(trimethylsilyl)thiophene tricarbonylchromium (76DAN1365). If an equimolar mixture of **46** ($X = S$, $R^2 = R^3 = R^4 = R^5 = H$) and *n*-butyllithium is used, only one hydrogen is replaced. For **46** ($X = S$, $R^2 = Me$, $R^3 = R^4 = R^5 = H$), the sluggish reaction requires refluxing with excess reactant (59ZOB2034) or the presence of tetramethylethylenediamine [74JOM(69)327]. The lithio derivatives of thiophenes may be quenched with other electrophiles. Thus, the reaction of tricarbonyl(η^5-2-lithiothiophene)chromium(0) with excess benzaldehyde yields **47** [94JOM(454)59]. The same transformation

is observed for 2-thiophenecarboxaldehyde and 2-selenophenecarboxaldehyde. The reaction of tricarbonyl(η^5-2-lithiothiophene)chromium(0) with tricarbonyl (η^6-benzaldehyde)chromium(0) yields **48.** The first tricarbonyl group in **48** to be decomplexed is the one belonging to the thiophene moiety to give **49,** whereas the complete decomplexation can be achieved only photochemically.

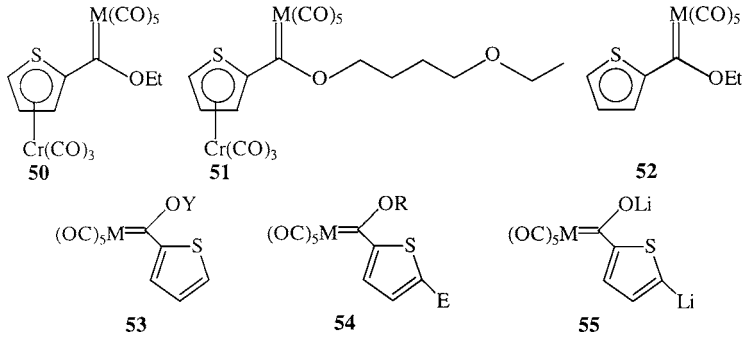


47 **48** **49**

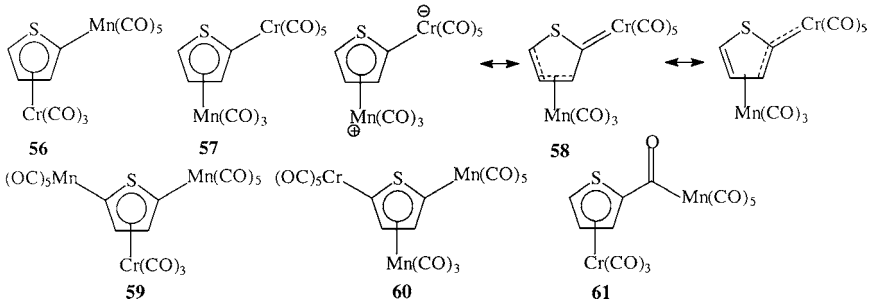
Complex **46** (X = S, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) when deprotonated with *n*-butyllithium gives **46** (X = S, $R^2 = R^5 = Me$, $R^3 = Li$, $R^4 = H$), an example of lithiation that takes place at the β-position [95JCS(P1)97]. The product was quenched by a variety of electrophiles (MeI, MeOTf, Me_3SiCl, Me_3SnCl) to give **46** (X = S, $R^2 = R^5 = Me$, $R^3 = Me$, Me_3Si, Me_3Sn). Another combination of the lithiation and electrophilic quench for **46** (X = S, $R^2 = R^3 = R^5 = Me$, $R^4 = H$) gives **46** (X = S, $R^2 = R^3 = R^5 = Me$; $R^4 = COOMe$, $SiMe_3$). The 2-(dimethyl-*t*-butylsilyl)thiophene complex **46** (X = S, $R^2 = Bu^tMe_2Si$, $R^3 = R^4 = R^5 = H$) is lithiated at C5, and then it can be quenched by electrophiles [D_2O, MeI, $(MeS)_2$, PhNCO, I_2, $CH_2{=}CHCH_2Br$, ClCOMe] to yield **46** (X = S, $R^2 = Bu^tMe_2Si$, R^5 = D, Me, SMe, CONHPh, $CH_2CH{=}CH_2$, COMe). Species **46** (X = S, $R^2 = Bu^tMe_2Si$, $R^5 = Me$, $R^3 = R^4 = H$) is lithiated/quenched (methyl iodide) to give **46** (X = S, $R^4 = R^5 = Me$, $R^2 = Bu^tMe_2Si$, $R^3 = H$). Protodesilylation of the latter leads to **46** (X = S, $R^2 = R^3 = Me$, $R^4 = R^5 = H$). Further combination of the same two reactions using chloroformate affords **46** (X = S, $R^2 = R^3 = Me$, $R^5 = MeOOC$, $R^4 = H$). This reaction shows that α-silyl groups attached to the thiophene ring are very labile (92SL135). In this sense, complexes **46** (X = S, $R^2 = Me$, $R^3 = R^4 = H$, $R^5 = R_3Si$, $R_3 = Me_3$, Et_3, Pr^iMe_2, Bu^tMe_2, Pr^i_3) are of interest, because in the subsequent combinations of lithiation and electrophilic quench, there is a competition between the desilylation and β-electrophilic substitution [95JCS(P1)105]. If R = Me, desilylation predominates. Yet, for R = Et and a more bulky trialkylsilyl group, the two reactions are simultaneous, and if Et_3SiCl is used as an electrophilic quench, the 2,3-disubstituted product **46** (X = S, $R^2 = Me$, $R^3 = Et_3Si$, $R^4 = R^5 = H$) occurs together with **46** (X = S, $R^2 = Me$, $R^3 = R^5 = Et_3Si$, $R^4 = H$). As the bulk of the substituent increases, the fraction of the trisubstituted η^5-coordinated thiophene grows.

The lithiated $Cr(CO)_3$ derivatives of thiophene may react with organometallic species. Their interaction with hexacarbonyls of chromium and tungsten

and further alkylation with Et_3OBF_4 in THF gives metallic monocarbenes **50** (M = Cr, W) and **51** (M = Cr, W) [97JCS(D)2177]. It is remarkable that the origin of **51** (M = Cr, W) is due to the cleavage and insertion of the resultant tetrahydrofuran molecule into the ethoxy substituent of **50** (M = Cr, W). Complexes **50** (M = Cr, W) may lose the tricarbonylchromium group to yield **52** (M = Cr, W). Reaction of 2-lithiothiophene with $M(CO)_6$ (M = Cr, W) yields species **53** (Y = Li, H) (92JA2985). Further reaction of **53** (M = W, Y = Li) with lithium (di-*iso*-propyl)amide, and then D_2O and aqueous hydrochloric acid gives **54** (E = D, R = H) with deuteration exclusively at position 5. Dilithio **55** was also trapped in the reaction with benzaldehyde followed by quenching with water and subsequent ethylation with Meerwein salt to give **54** [R = Et, E = CH(OH)Ph]. A range of species starting from simple thiophene aminocarbenes [71JCS(A)1974] to the oligomers containing a thiophene ring [99JOM(583)111] is known.

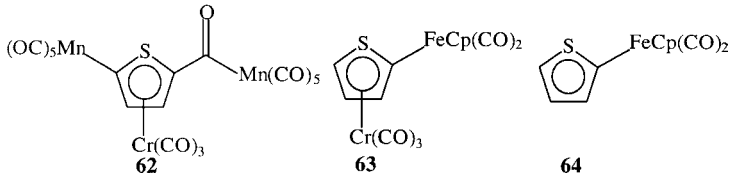


The reaction of **46** (X = S, Se, R^2 = Li, $R^3 = R^4 = R^5$ = H; X = S, R^2 = Me, $R^3 = R^4$ = H, R^5 = Li) with $Mn(CO)_5X$ (X = Cl, Br) yields complexes such as **56** and **57,** the latter being the main product (93AGE710, 93OM4250, 95ADOC219). The metal exchange of **56** to **57** is spontaneous. Species **56** is characterized by a classically η^5-coordinated heteroring, whereas the thiophene ring in **57** is allylic in character, and there is some contribution of the carbene counterpart for the η^1 (C) (σ) coordinated $Cr(CO)_5$ grouping, as illustrated by resonance forms **58.** The reaction of **46** (X = S, $R^2 = R^5$ = Li, $R^3 = R^4$ = H) with $Mn(CO)_5Br$ yields the trimetallic complex **59** with the η^5:η^1:η^1 coordination mode. Now the transformation of **59** to **60** is possible but reversible. The σ-bonded chromium-carbon in **60** again has some carbene character. Complexes **56** and **59** insert carbon monoxide to yield **61** and **62,** respectively, whereas **57** and **60** are inert toward CO.



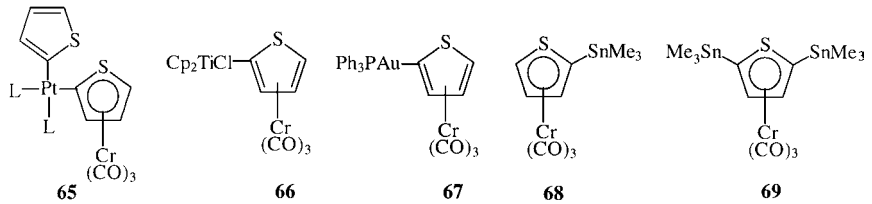
56 **57** **58** **59** **60** **61**

The π-complex **63** was obtained by the condensation of chromium hexacarbonyl with the thiophene σ-derivative of dicarbonylironcyclopentadienyl **64** (76IZV153, 79IZV900). The presence of the electron-donor iron-containing substituent facilitates π-coordination.



62 **63** **64**

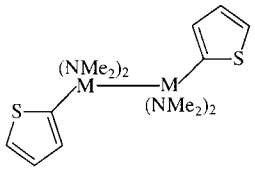
Reaction of the tricarbonylchromium complex of 2-lithiothiophene with *cis*-$[PtL_2Cl_2]$ ($L = PMe_3$, CO; L_2 = dppe) gives complexes **65** ($L = PMe_3$, CO; L_2 = dppe) [97JCS(D)2955]. A similar reaction with $TiCp_2Cl_2$ proceeds differently and gives **66;** with chloro(triphenylphosphine)gold(I), species **67** is obtained. When the starting complex reacts with trimethylstannylchloride, complexes of 2- and 2,5-di-Me_3Sn thiophene derivatives, **68** and **69,** result.



65 **66** **67** **68** **69**

2-Lithiothiophene and $M_2Cl_2(NMe_2)_4$ (M = Mo, W) give species **70** (M = Mo, W) with the η^1(C) coordination mode [94JCS(CC)1634, 97JA1634]. Tungsten derivatives of 3-methyl- and 2,5-dimethylthiophene are also η^1(C) coordinated in a related manner. A similar reaction course was observed for $W_2I(NMe_2)_5$. Species **70** based on tungsten, thiophene, and 2,5-dimethylthiophene react with *tert*-butanol or $Me_2(CF_3)COH$ to give the ring-opened structures, such as **71.**

With CO_2, compounds **70** based on tungsten and thiophene give **72.** With carbon monoxide, $W_2(\mu\text{-CCHCHCHS})(\sigma\text{-2-thiophene})(NMe_2)_4(CO)_3$ results, while the 2,5-dimethylthiophene derivative gives $W_2(\mu\text{-CCHCHCMeS})(\sigma\text{-2,5-}Me_2C_4H_2S)(NMe_2)_4(CO)_3$.



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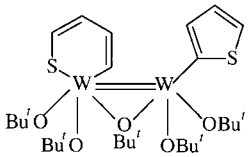

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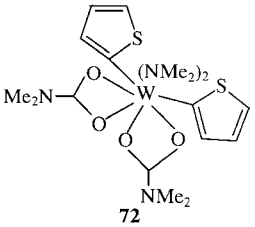
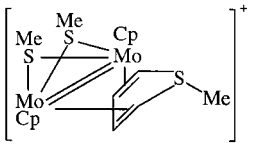


72

The trend of thiophene to form thiophenium cations on interaction with transition metal derivatives, in particular transition metal thiolates, is well-documented [73JCS(CC)583, 75JCS(D)197, 75JCS(D)2283, 85MI2, 96OM325]. One such reaction of acetylenic compound, $CF_3C{\equiv}CH$, with the binuclear species $[Cp_2Mo_2(\mu\text{-SMe})_3(AN)_2]BF_4$ gave rise to a unique coordination mode of thiophenium, designated as $\mu\text{-}\eta^2{:}\eta^2$, **73** (99OM2055). Reactions of a sulfur-bridged $Mo_2(CO)_2(\mu\text{-S})_3$ cluster with thiophene causes extraction of the sulfur heteroatom from the heterocycle to produce a $Mo_2(CO)_2(\mu_3\text{-S})_4$ cluster (91JA1416). Complex $Cp_2Mo_2Co_2S_3\,Co(CO)_4$ causes desulfurization of thiophene by an unknown route (94JA4357).

Molybdenum complexes of the derivatives of thiophene are known. Thus, the 3-CH_2Cl-thiophene reacts with $CpMo(CO)_3^-$ to yield **74,** which on photolysis or thermolysis undergoes decarbonylation and rearrangement of the coordinating moiety to yield **75** [69IC2535, 72JOM(44)1]. 2,5-Bis[2-(diphenylphosphino)ethyl] thiophene reacts with $Mo(CO)_3$(cycloheptatriene) to give **76** (93IC5652). The oligomeric derivatives of thiophene **77** (R = H, Ph) react with $[Mo_2Cp_2(CO)_4]$ to yield **78** (R = H, Ph) [98JCS(D)1893].



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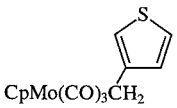

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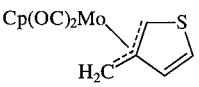

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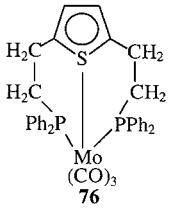

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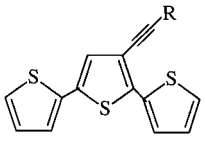

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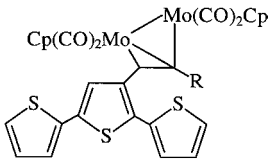
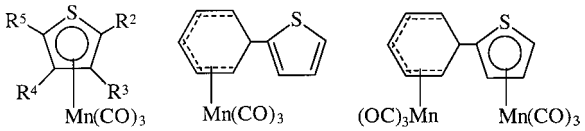


78

C. Group VII Metal Complexes

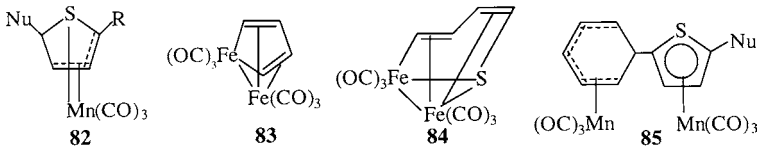
The η^5-coordinated $Mn(CO)_3$ cationic complexes of thiophenes follow mainly from the direct interaction of a heterocyclic ligand with $Mn(CO)_5X$ (81HCA1288). The first successful synthesis of **79** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^5 = Me$, $R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Me$) occurred with $Mn(CO)_5Cl$ in the presence of $AlCl_3$ or $AlBr_3$ [67JOM(9)135]. Application of $Mn(CO)_5OSO_2CF_3$ allowed an increase in the yield of **79** ($R^2 = R^3 = R^4 = R^5 = H$) (84JA2901). Further improvement employed the reaction of thiophene, 2- and 3-methyl-, and 2,5-dimethylthiophene with $Mn(CO)_5BF_4$ to yield **79** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$) (96OM325, 97OM5688). 2-Silatranylthiophene reacts in the same fashion to yield **79** [$R^2 = Si(OCH_2CH_2)_3N$, $R^3 = R^4 = R^5 = H$] (97OM1749). A sequence of transformations leading to the dinuclear complex incorporating η^5-coordination via the thiophene ring includes (i) the reaction of 2-thienylmagnesium bromide with (benzene)$Mn(CO)_3^+$ to yield **80,** and (ii) the reaction of **80** with $Mn(CO)_5BF_4$ to yield **81.**



79 **80** **81**

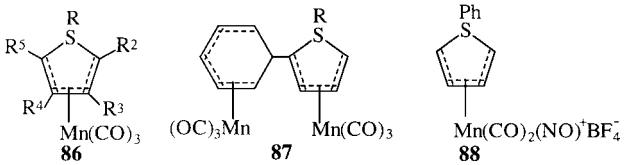
Complexes **79** show several types of chemical reactions (87CCR229). Nucleophilic addition may proceed at the C2 and S atoms. In excess potassium cyanide, **79** ($R^2 = R^3 = R^4 = R^5 = H$) forms mainly the allyl sulfide complex **82** (R = H, Nu = CN) (84JA2901). The reaction of sodium methylate, phenyl-, and 2-thienyllithium with **79** ($R^2 = R^3 = R^4 = R^5 = H$) follows the same route. The fragment consisting of three coplanar carbon atoms is described as the allyl system over which the π-electron density is delocalized. The sulfur atom may participate in delocalization to some extent. Complex **82** (R = H, Nu = CN) may be protonated by hydrochloric acid to yield the product where the 2-cyanothiophene has been converted into 2,3-dihydro-2-cyanothiophene. The initial thiophene complex **79** ($R^2 = R^3 = R^4 = R^5 = H$) reacts reversibly with tri-*n*-butylphosphine followed by the formation of **82** [R = H, Nu = P(*n*-Bu)$_3$]. Less basic phosphines, such as methyldiphenylphosphine, add with much greater difficulty. The reaction of **79** ($R^2 = R^3 = R^4 = R^5 = H$) with the hydride anion [BH_4^-, $HFe(CO)_4^-$, $HW(CO)_5^-$] followed by the formation of **82** (R = Nu, H) has also been studied in detail. When the hydride anion originates from $HFe(CO)_4$, the process is complicated by the formation of side products **83** and **84.** The 2-methylthiophene complex **79**

($R^2 = Me$, $R^3 = R^4 = R^5 = H$) adds the hydride anion in a similar fashion, whereas **79** ($R^2 = R^5 = Me$, $R^3 = R^4 = H$) does not enter this kind of reaction (87OM591). Nucleophilic addition to the cationic complexes **79** [$R^2 = Si(OCH_2CH_2)_3N$, $R^3 = R^4 = R^5 = H$] occurs preferentially at the C5 position of the thiophene ring to yield **82** [$R^2 = Si(OCH_2CH_2)_3N$, Nu = H, CN, $P(O)(OR)_2$]. The reaction of **81** with sodium borohydride or sodium cyanide gives **85** (Nu = H or CN, respectively) (97OM1749). All the transformations observed are indicative of an enhanced reaction ability of the thiophene ring in **79** with nucleophiles under quite mild conditions. Nucleophilic addition distorts the aromatic stability of the heterocyclic ring.



82 **83** **84** **85**

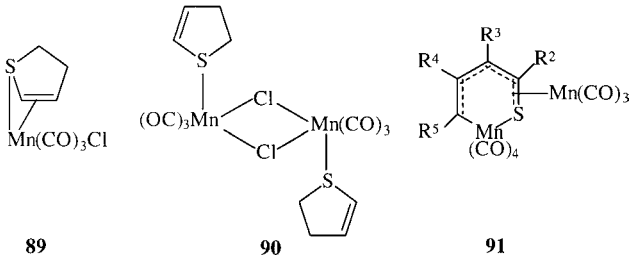
Organometallic nucleophilic reagents change the reaction pattern drastically. Thus, the reaction of **79** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$) with organocuprates $LiCuR_2$ (R = Me, Ph) gives **86** ($R^2 = R^3 = R^4 = R^5 = H$, R = Me, Ph; $R^2 = R^5 = Me$, $R^3 = R^4 = H$, R = Me, Ph) (96OM325). The sulfur atom therein is charged positively, and the ligand is η^4-coordinated to the $Mn(CO)_3$ moiety. Grignard reagents, RMgBr (R = Me, Et, Ph), also attack the sulfur atom (97OM1749). Thus, **79** [$R^2 = Si(OCH_2CH_2)_3N$, $R^3 = R^4 = R^5 = H$] yields **86** [$R^2 = Si(OCH_2CH_2)_3N$, $R^3 = R^4 = R^5 = H$, R = Me, Et, Ph]. The same reaction is valid for **81** to give the S-substituted products **87** (R = Et, Ph). Such a situation appears general and is observed for species **79** ($R^2 = R^3 = R^4 = R^5 = H$, $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$) in their reactions with RMgBr (R = Ph, Et) affording **86** ($R^2 = R^3 = R^4 = R^5 = H$; R = Ph; $R^2 = Me$, $R^3 = R^4 = R^5 = H$, R = Ph; $R^2 = R^5 = Me$, $R^3 = R^4 = H$, R = Me, Ph). The same type product as **87** ($R^2 = R^3 = R^4 = R^5 = CF_3$, $R = C_6F_5$) follows from the other type of reaction of $[Mn(CO)_4(\mu\text{-}SC_6F_5)]_2$ with $CF_3C{\equiv}CCF_3$ [73JCS(CC)583, 75JCS(D)197]. Reaction of **86** ($R^2 = R^3 = R^4 = R^5 = H$, R = Ph) with nitrosyl tetrafluoroborate gives the product of ligand exchange, **88** (97OM1749).



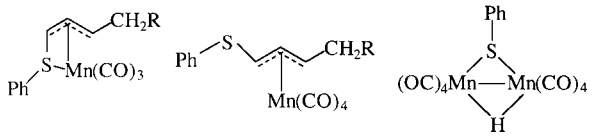
86 **87** **88**

Passage of gaseous hydrogen chloride through a solution of **79** ($R^2 = R^3 = R^4 = R^5 = H$) causes formation of the reduced forms for which structures **89** and **90**

have been postulated (84JA2901). Reduction of the cations **79** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$) with cobaltocene results in the insertion of manganese into the C–S bond (96AGE212, 97OM5688) to yield **91** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$), where the $Mn(CO)_3$ framework is coordinated to a metallocyclic ring. Species of type **79** do not react with molecular hydrogen, whereas the *S*-phenyl neutral complexes **86** (R = Ph, $R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$) enter this reaction to afford the ring-opened products **92** (R = H, Me), **93** (R = H, Me), **94** [99JOM(579)385]. A similar reaction course is taken by the 1-phenyl-3-methylthiophene and 1-phenyl-3,4-dimethylthiophene complexes.

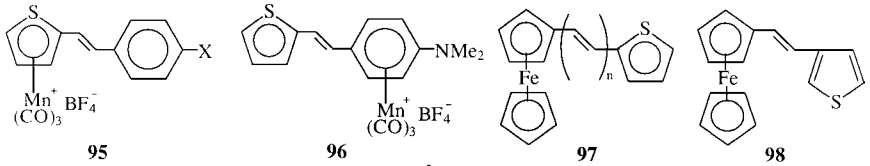


89 **90** **91**

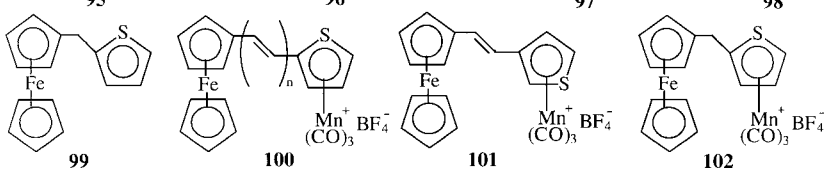


92 **93** **94**

(*E*)-2-[2-(Phenyl)ethenyl]thiophene and its 4-substituted derivatives react with $[(\eta^6\text{-}C_{10}H_8)Mn(CO)_3]BF_4$ to give **95** (X = H, Me, Br, MeO, NO_2) (99OM1091). Coordination is of the η^5-type via the thiophene ring. However, when $X = NMe_2$, then η^6-coordinated product **96** results. Ferrocenes **97–99** on reaction with $[(\eta^6\text{-}C_{10}H_8)Mn(CO)_3]BF_4$ give **100** (n = 0, 1, and 2), **101,** and **102,** respectively.

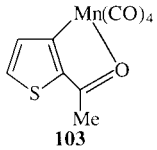


95 **96** **97** **98**



99 **100** **101** **102**

When acetylthiophenes are subjected to orthomanganation, formation of the 2,3-, **103,** and 3,4-, **104,** metallocycles is observed [88JOM(349)197]. Complex **103** contains two coplanar five-membered heterocycles with octahedral manganese. Complex **104** is also planar. In both cases, substantial delocalization of the π-electron density follows from the structural parameters.



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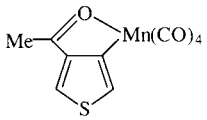
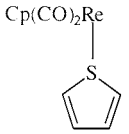


104

$Cp(CO)_2Re(THF)$ forms the complex **105** upon reaction with thiophene (89JA8753, 91OM2436). Similar species are known for 2- and 3-methyl-, 2,5-dimethyl, and tetramethylthiophene (91IC1417). Thiophene in **105** is S-coordinated, and the sulfur atom is pyramidal. Treatment of **105** with $Fe_2(CO)_9$ produces **106,** where the thiophene ligand is bridge-coordinated via the sulfur atom to rhenium and four carbon atoms of the dienic system with iron (the η^4:η^1 coordination mode). The pyramidal nature of the sulfur atom is preserved. The η^4-coordination of thiophene separates the dienic and sulfur counterparts of the ligand and decreases the π-electron delocalization, which leads to the enhanced basicity of the sulfur atom.



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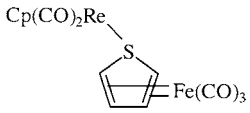
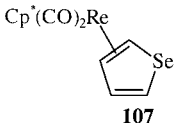


106

In contrast to the situation with thiophene, reaction of selenophene with $Cp^*(CO)_2Re(THF)$ yields complex **107** containing the η^2-coordinated ligand. The noncoordinated selenium atom appears to be able to form a bond with the $W(CO)_5$ framework in the product **108** (L = CO) (90JA7811). The triphenylphosphine derivative **108** ($L = Ph_3P$) is obtained from **107** and $W(CO)_4(PPh_3)(THF)$. Methylation of the selenophene ring in $[Cp^*Re(CO)_2(\eta^2\text{-}C_4H_4Se)]$ is achieved with Me_3OBF_4, the η^2-coordination being retained. 2,5-Dimethylselenophene under similar conditions gives the η^1(Se) coordinated product. 2-Methylselenophene gives a mixture of the η^1(Se) and η^2(C4═C5) coordinated isomers (91JA5651).



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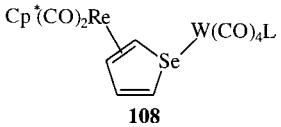
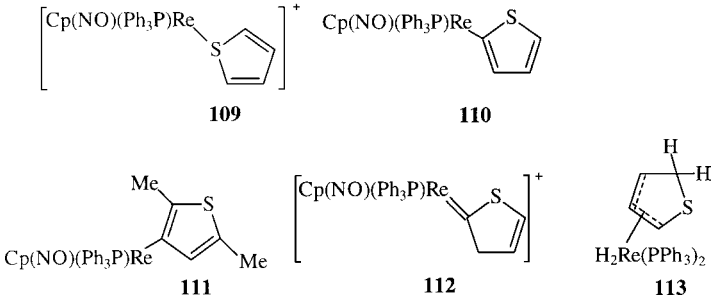


108

The ligand substitution reaction of CH_2Cl_2 in $Cp(NO)(Ph_3P)Re(ClCH_2Cl)^+$ by thiophene and 2,5-dimethylthiophene yields the η^1 (S) coordinated complex of type **109** (94JA5190, 94OM5132). Proton abstraction from **109** gives a neutral η^1(C) 2-thienyl complex, **110.** Such a reaction becomes impossible in case of the 2,5-dimethylthiophene analog of **109.** However, use of a strong base such as potassium hydroxide in methanol gives **111.** An attempted transformation of **109** to **110** by protonation with triflic acid leads, however, to the thienylcarbene complex cation **112** where the aromaticity is disrupted.



Thiophene reacts with $ReH_7(PPh_3)_2$ aided by the H-acceptor (3,3-dimethyl-1-butene) to give the thioallyl species **113** (92JA10767). Further reaction of **113** with trimethylphosphine yields organometallic products with a cleaved C─S bond.

Diphenyl-2-thienylphosphine is expected to serve as a bidentate ligand by coordination of either the phosphorus and sulfur atoms or the phosphorus atom and π-electrons of the heteroring. Reaction of this phosphine with $[Re_2(CO)_{10}]$ yields the species where both the sulfur and phosphorus atoms serve as the donor sites (96OM786).

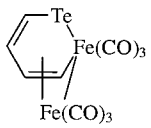
D. Group VIII Metal Complexes

1. *Iron*

The reaction of thiophene with iron carbonyls is quite peculiar. Thus, with $Fe_3(CO)_{12}$ at elevated temperatures, elimination of the sulfur atom from the heterocycle and substitution by the iron atom takes place. The final product of the reaction is ferrole, **83** [60JA4557, 60JA4749, 61JA3600, 65MI1, 68JA1995, 76JOM(108)213, 77AX(B)344, 77JOM(129)105]. The first step is the insertion of the iron atom into the thiophene ring to yield thiaferrole, **84** (88OM1171). Analogous complexes of 2-methyl- and 2,5-dimethylthiophene were obtained. Thiaferrole species may be obtained from **64** containing a 2-thienyl-ligand σ-bonded to the

iron atom (76IZV153, 79IZV900, 82ZOB1571). The latter reacts with $Fe_3(CO)_{12}$, and complex **84** is formed.

The similarity of the electronic structures of thiophene and tellurophene [72JCS (P1)199] implies that their chemistry toward $Fe_3(CO)_{12}$ should be the same. Thus, tellurophene produces [$Fe_3Fe_2(CO)_9$], ferrole **83,** and **114** [72JOM(42)C87, 96JCS (D)1545]. The same trend is observed in the reactions of the derivatives of tellurium and selenium heterocycles [97JCS(D)1579, 98JCS(D)3947].



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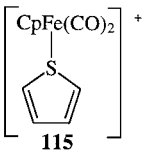


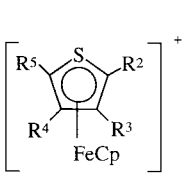
115

Interaction of the iron metal atoms with thiophenes (thiophene, 2-methyl-, and 2,5-dimethylthiophene) in the vapor phase at 77 K with subsequent heating in a carbon monoxide atmosphere also leads to the formation of ferrole **83** [76JOM(118)37, 77CJC3509]. The iron cyclopentadienyl ring is planar and all the bonds have multiple character.

As mentioned, thiophenes are weak σ-donors. Only a few S-bonded complexes of thiophene and 2,5-dimethylthiophene are known. As a rule, they are poorly described because of their extreme lability. Examples include [Fe(η^1-C_4H_4S)$(CO)_2$(Cp)](BF_4) [84JOM(276)55] or [CpFe$(AN)_2$(2,5-$Me_2C_4H_2S$)] [84JOM(272)417, 86JOM(316)335]. With compound [Fe(η^2-$H_2C{=}C(Me_2)$)$(CO)_2$(Cp)](BF_4) the isobutene is displaced by thiophene to yield the η^1 (S) coordinated species, **115,** where the heterocyclic ligand is labile (87IC3424). Thiophene in this complex can be quantitatively substituted by CD_3NO_2. Thiophene, 2-methyl-, 3-methyl-, and 2,5-dimethylthiophene react with CpFe(dppe)I in the presence of thallium hexafluorophosphate to yield the S-coordinated species of type [CpFe(dppe)(C_4H_4S)]PF_6 (96P2825).

The ligand exchange between the cation of η^6-chlorobenzene-η^5-cyclopentadienyliron and thiophene, 2-methyl-, 3-methyl-, or 2,5-dimethylthiophene gives the η^5-coordinated **116** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$) [85JOM(288)89]. Reactions of a similar nature are known [76ZN(B)25, 77JOM(141)99, 80JOM(186)265]. Complexes containing the cyclopentadienyl framework such as CpFe$(AN)_2$(η^5-C_4H_4S) [83JOM(248)C9, 86JOM(316)335] have also been reported. The thiophene π-complex **117** with a rare $+2$ charge containing two heterocyclic molecules coordinated to a transition metal atom has been prepared [75JOM(84)37]. According to cyclic voltammetry, the complex is reduced reversibly in two one-electron steps. Such electrochemical behavior reveals the possibility of isolation of

bis(tetramethylthiophene) iron(0). Tetramethylthiophene reacts with the carborane complex $(C_8H_{10})Fe(Et_2C_2B_4H_4)$ to yield the sandwich $(\eta^5\text{-}C_4Me_4S)Fe(Et_2C_2B_4H_4)$ (91IC3957).



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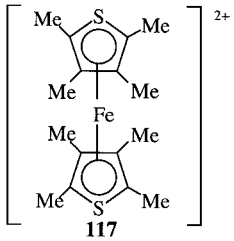
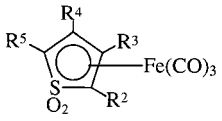


117

In contrast to thiophene, its derivatives and analogues, thiophene 1,1-dioxide is not subject to desulfurization in its reactions with iron carbonyls. Thus, the structure of tricarbonyliron(η^4-3,4-dimethylthiophene 1,1-dioxide) **118** ($R^2 = R^5 = H$, $R^3 = R^4 = Me$) has been determined [77JOM(128)389]. Not only the η^4- but η^5-tricarbonyliron species of thiophene 1,1-dioxide are possible. Indeed, photochemical synthesis of $LFe(CO)_3$ (L = thiophene 1,1-dioxide and its 2,5-dimethyl and tetraphenyl derivatives) has proven successful, **118** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Ph$) [72JCS(CC)501]. Decomposition of complex **118** ($R^2 = R^5 = Me$, $R^3 = R^4 = H$) by triethylamine oxide in an aprotic medium proceeds via the intermediate **119** [76JCS(CC)657]. Irradiation of 3,4-dibromo-2,5-dimethylthiophene 1,1-dioxide in the presence of iron pentacarbonyl yields iron tricarbonyl complexes containing one or two bromine atoms [79JOM(165)357, 81JOM(207)343]. Reaction of thiophene with tricarbonyl (cyclohexadienyl)iron cationic species gives **2** (X = S) [74JOM(71)C11].



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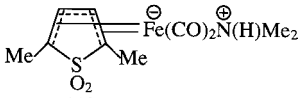
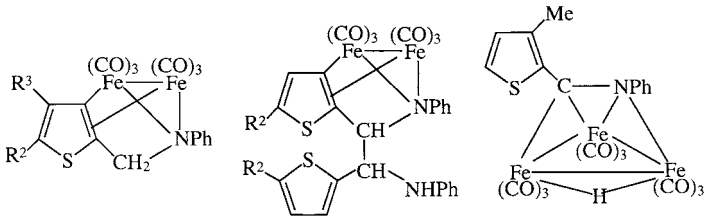


119

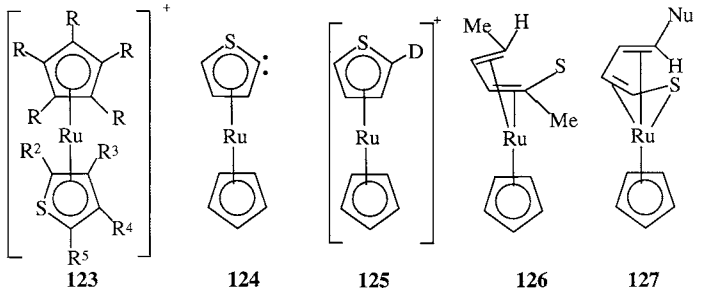
Other derivatives of thiophene, for which iron carbonyls do not cause ring opening but on the contrary reveal the unique donor properties of the heteroring, are the azomethine derivatives [97OM3109, 99JOM(579)211]. Thus, $Fe_2(CO)_9$ causes cyclometalation of *N*-(2-thienylmethylidene)aniline and its 5-methyl analogue to yield species **120** ($R^2 = H$, Me; $R^3 = H$) and **121** ($R^2 = H$, Me). The thiophene ring participates in a $\eta^1 : \eta^2$ bridging function. The 3-methyl-2-thienyl analogue reacts differently, giving a mixture of isomers **120** ($R^2 = Me$, $R^3 = H$) and **120** ($R^2 = H$, $R^3 = Me$), and species **122.**



120 **121** **122**

2. *Ruthenium and Osmium*

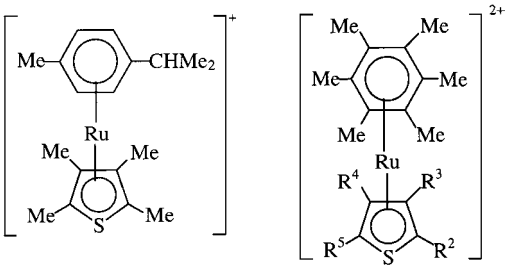
The reaction of thiophene with $[(\eta^5\text{-Cp})Ru(PPh_3)_2Cl]$ and $AgBF_4$ gives **123** ($R^2 = R^3 = R^4 = R^5 = H$, $R = H$) [85JA5569, 87OM1897, 88JOM(355)359]. 3-Methylthiophene with $[Cp^*RuCl]_n$ yields **123** ($R^2 = R^4 = R^5 = H$, $R^3 = Me$, $R = Me$) [88JCS(CC)711]. Cation **123** is stable but undergoes very slow substitution of thiophene by benzene, tri(*n*-butyl)phosphine, acetonitrile, and *tert*-butylisocyanide, an indicator of a rather strong thiophene metal bond. Kinetic studies of base-promoted H–D exchange with a series of **123** ($R^2 = R^3 = R^4 = R^5 = H$, $R = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$, $R = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$, $R = H$) showed that the hydroxide ion induces deprotonation of the thiophene in the rate-determining step (85JA5569, 87OM1146). Then rapid D^+ transfer from the solvent (CD_3OD) to the intermediate, **124,** takes place leading to the deuterated product, **125.** H–D exchange occurs most rapidly at the 2 and 5 positions, then at the 3 and 4 positions, and finally at the methyl groups. Reaction of cationic complex **123** ($R^2 = R^5 = Me$, $R^3 = R^4 = H$, $R = H$) with metal hydrides such as $LiAlH_4$, $Na[(MeOCH_2CH_2O)_2AlH_2]$, and $NaBHEt_3$ leads to the formation of the hydride adduct (87AGE909, 89OM14, 92OM922) followed by cleavage of the C–S bond and formation of the butadienethiolate ligand, **126.** The ruthenium atom is coordinated to all four carbon atoms and the sulfur atom. Hydride addition to the related complexes **123** ($R^2 = R^3 = R^4 = R^5 = H$, $R = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$, $R = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$, $R = H$; $R^2 = R^3 = Me$, $R^3 = R^4 = H$, $R = H$; $R^2 = R^3 = R^5 = Me$,



123 **124** **125** **126** **127**

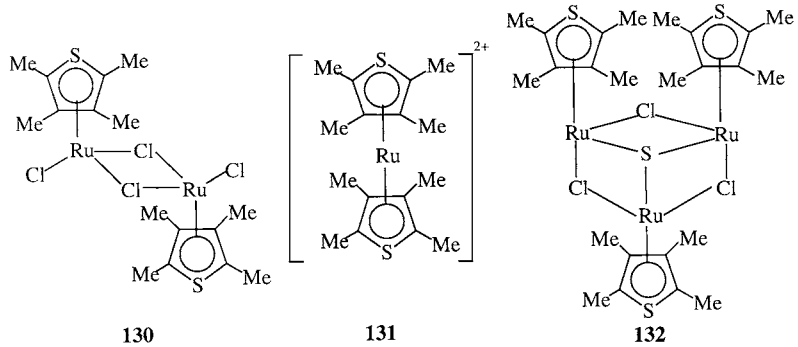
$R^4 = H$, $R = H$) gives similar butadienethiolate complexes. π-Complexation of thiophene in compounds of the type **123** activates the heterocycle relative toward other nucleophiles, such as OMe^-, SMe^-, SEt^-, $S(i\text{-}Pr)^-$, and $CH(COOMe)_2^-$. The products **127** include the ring-opened butadiene–thiolate framework.

Treatment of di-μ-chlorobis[chloro(*p*-cymene)ruthenium(II)] with tetramethylthiophene in the presence of $AgPF_6$ leads to the formation of **128.** Reaction of a suitable thiophene with $[(C_6Me_6)RuCl_2]_2$ yields the dicationic complexes, **129** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Me$) (92JA8515). Electrochemical or chemical reduction of **129** ($R^2 = R^5 = Me$, $R^3 = R^4 = H$) generates Ru(0) compounds [Ru(η^4-2,5-$Me_2C_4H_2S$)(η^6-C_6Me_6)]. On protonation the latter gives [Ru(η^4-2,5-$Me_2C_4H_2S$-2H)(η^6-C_6Me_6)]$^+$. If the sandwich η^5-coordinated complexes undergo base hydrolysis or aminolysis, the C–S bond is cleaved (93OM3273, 95OM2923).



128 **129**

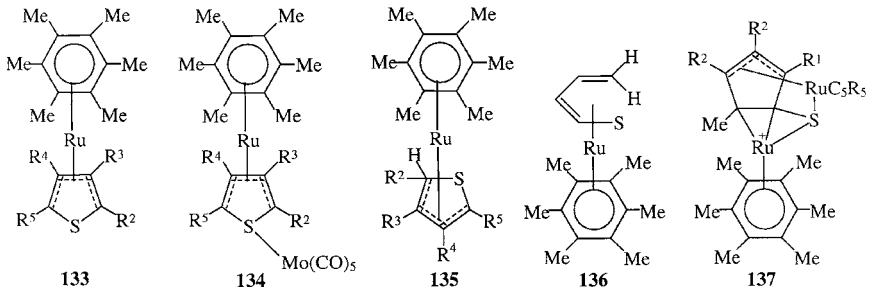
Thermal arene exchange of tetramethylthiophene with $[(p\text{-cymene})RuCl_2]_2$ affords **130** (89JA8828), which on reaction with $AgBF_4$ and excess tetramethylthiophene yields **131.** The Ru–S thiophenic cluster, **132,** was synthesized by reaction of **130** with $(Me_3Si)_2S$ followed by anionic metathesis and formation of the PF_6^- salt. The coordination geometry around each ruthenium atom is pseudooctahedral.



130 **131** **132**

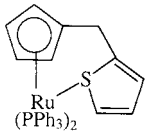
Reaction of $[Ru(\eta^5\text{-}C_4Me_4S)(\mu\text{-}Cl)Cl]_2$ (89JA8828, 91OM270) with [9]aneS_3 and NH_4PF_6 gives $[Ru(\eta^5\text{-}C_4Me_4S)(\kappa^3\text{-}[9]aneS_3)](PF_6)_2$ [99JOM(575)242]. The latter with nucleophiles ($Y = H^-$, $AlkO^-$, CN^-) experiences a change in the coordination mode of thiophene as a result of the formation of $[Ru(\eta^4\text{-}C_4Me_4S\text{-}Y)(\kappa^3\text{-}[9]ane\text{-}S_3)](PF_6)$, where the *exo*-nucleophilic attack is directed to the C2 atom of the heteroring. Moreover, the η^5-coordinated thiophene was observed in $[(\eta^5\text{-}Me_4C_4S)Ru(H_2O)_3]^{2+}$ (91OM270) and $[(\eta^5\text{-}C_4H_4S)Ru(PPh_3)_2]^{2+}$ [86JOM(316)C35].

Thus, the majority of the η^5-coordinated ruthenium complexes appear to be cationic and electrophilic. The reactivity of the η^5-coordinated ruthenium complexes is restricted, in particular, with respect to protonation. However, it appeared possible to convert the η^5- into the η^4-thiophene by means of chemical reduction where the nucleophilic function of the heterocycle is increased considerably (89JA8828). Thus, complexes **129** undergo chemical two-electron reduction with cobaltocene to give the neutral derivatives **133** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Me$). The sulfur atom then is a relatively strong nucleophile, and reaction of **133** ($R^2 = R^3 = R^4 = R^5 =$ Me) with $[Mo(CO)_5(THF)]$ gives **134,** consistent with the basicity of **133.** Reactions of the same η^4-coordinated species with protic agents (such as NH_4PF_6) go in two directions: a redox process to yield **129** and molecular hydrogen, and protonation at the α-position of the heteroring to yield **135** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Me$). The product **135** ($R^2 = R^3 = R^4 = R^5 = H$) then undergoes C–S scission to yield the thiapentadienyl species **136** (93JA4943). Tetramethylthiophene in this set of transformations behaves differently (95JA6396). Thus, **133** ($R^2 = R^3 = R^4 = R^5 = Me$) reacts with $[CpRu(AN)_3]PF_6$ to yield **137** ($R^1 = R^2 = Me$, $R = H$). In the same manner, complexes **137** ($R^1 = Me$, $R^2 = H$, $R = H$; $R^1 = H$, $R^2 = Me$, $R = H$; $R^1 = R^2 = Me$, $R = Me$) were obtained.



The η^1(S) coordination of thiophene was proposed for $[(\eta^5\text{-}Cp)Ru(PPh_3)_2(\eta^1\text{-}C_4H_4S)]^+$ prepared from $[CpRu(PPh_3)_2Cl]$, thiophene, and $AgBF_4$ (76JA689,

84JA5379, 85OM1909). However, this complex undergoes the η^1–η^5 transformation to yield **123** ($R = R^2 = R^3 = R^4 = R^5 = H$) simply on standing in solution (85OM1909). Thiophene is S-coordinated in $[Ru(NH_3)_5(C_4H_4S))]^{2+}$ (76JA689), as well as in **138** (85OM1909), where thiophene is a part of the chelating ligand. Reaction of thiophene, 2- and 3-methylthiophene, 2,5-dimethylthiophene, and tetramethylthiophene with $Cp(CO)_2RuCl$ in the presence of silver tetrafluoroborate gives a series of the S-coordinated cationic complexes **139** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^5 = Me$, $R^3 = R^4 = H$; $R^2 = R^3 = R^4 = R^5 = Me$) (93OM680) that are not stable and are air sensitive. The electron-releasing methyl groups tend to strengthen the η^1-S coordination.



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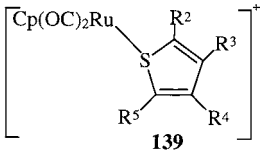
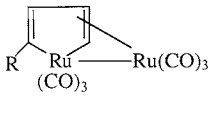


139

The reaction of thiophene with $Ru_3(CO)_{12}$ leads to the disintegration of the heteroring and formation of **140** ($R = H$) and **141** ($R = H$) [92JCS(D)2423, 94AGE1381]. 2-Methylthiophene reacts differently and yields both the product of the C–H bond cleavage as a mixture of exo-, **142,** and endo-, **143,** isomers, cluster **140** ($R = Me$), and the product of the C–S bond cleavage, **141** ($R = Me$).



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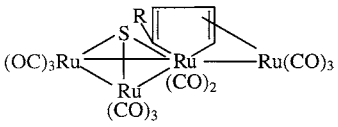

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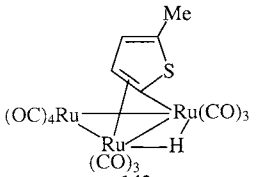

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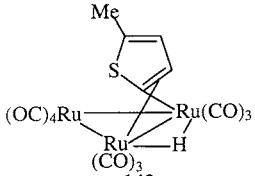
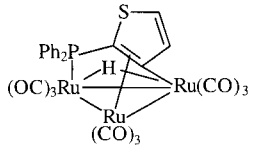


143

Reaction of diphenyl-2-thienylphosphine with $Ru_3(CO)_{12}$ gives the η^1(P):η^2:η^1(C) coordinated species, **144,** along with cluster **145** where two ligand molecules participate in coordination, one via the phosphorus atom and the C=C bond of the heteroring, and the other via the phosphorus atom only. P-Coordination in the products of such an interaction is known [95JOM(488)85]. Complex **144,** the main product, interacts with carbon monoxide to yield the P-coordinated cluster, **146,**

which in turn decarbonylates to regenerate **144.** The stability of **144** is somehow related to the enhanced reactivity of thiophene with respect to electrophiles compared to that of benzene (79MI2). Additional evidence in favor of this statement is the formation of the tetranuclear cluster **147** upon thermolysis of **144** where the cleavage of the P—C bond occurred. A μ_4-bridged thiophyne coordination is unique in this sense compared to the μ_3-thiophyne and μ_2-thienyl coordination modes in the Group VIII cluster chemistry [89OM1408, 90JCS(CC)1568, 91JOM(412)177, 92JCS(D)2423].



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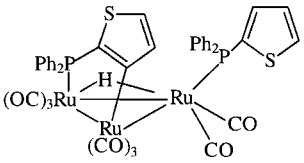

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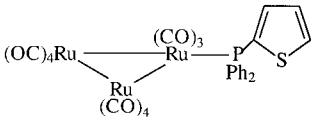

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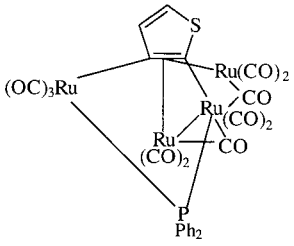
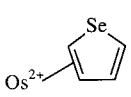


147

Of special interest for material chemistry are oligothienylacetylide complexes of ruthenium(II) (99OM1930).

Selenophene reacts with $[Os(NH_3)_5(OTf)](OTf)_2$ and zinc amalgam to give the η^2-coordinated species **148** (99OM1559), analogously to the thiophene derivative (89JA5969). The η^2-osmium thiophene complexes experience electrophilic addition basically at the vacant α-carbon site (97JA8843). With triflic acid, **148** gives the product of protonation, a selenophenium complex **149,** where a shift of the η^2-coordinated metal occurs. With acetaldehyde, diethyl acetal, and *tert*-butyldimethylsilyltriflate, the direction of the electrophilic attack is the same, and another selenophenium species, **150,** is formed. Methylation with methyltriflate occurs, however, at the sulfur atom to give **151,** which then undergoes ring cleavage on reaction with *n*-Bu_4NBH_4 to yield **152.**



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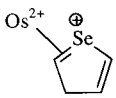

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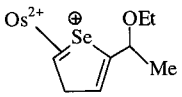

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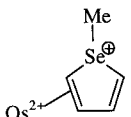

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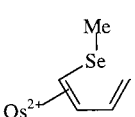
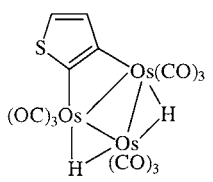


152

Interaction of thiophene with $[Os_3(CO)_{12}]$ gives cluster **153** with its doubly bridged ligand in which carbon (both C2 and C3)–osmium σ-type bonds are formed (89OM1408). Thiophene may be incorporated in its dehydrogenated form in the cluster $[Os_3(\mu\text{-}H)_2(\mu\text{-}C_4H_2S)(CO)_9]$ (90OM6). A broad variety of such products based on the oligomers of thiophene is known [94JOM(479)159]. The reaction of thiophene and 2-methylthiophene with $[Os_3(CO)_{10}(AN)_2]$ leads to the splitting of the C─H bonds in position 2 and formation of hydrido products by oxidative addition, **154** (R = H, Me) [90JCS(CC)1568, 91JOM(412)177]. The sulfur atom occupies the *exo* position relative to the $Os(CO)_4$ group. Despite the predominance of the *exo* species, there occurs a rapid equilibrium between the *exo* and *endo* isomers. This suggests an intermediate S-bonded thienyl complex. Meanwhile, selenophene and tellurophene yield **155** (E = Se, Te) under similar circumstances with cleavage of the selenium (tellurium)–carbon bond and donation of six electrons by the selenophene or tellurophene ring. Cases of C─S, C─Se, and C─Te bond cleavage in similar products are described [91JOM(419)63].



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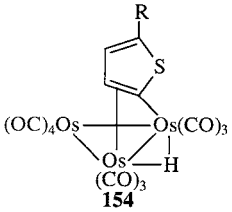

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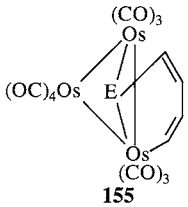
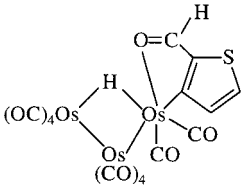


155

2-Formylthiophene reacts with $[Os_3(CO)_{10}(AN)_2]$ to yield cluster **156** where the C2 atom takes part in the carbon–osmium σ-bond (89OM1408). It was shown [86JOM(311)371, 92JOM(436)351], however, that 2-formylthiophene reveals a twofold manner of reacting, giving both the product of the cleavage of the C─H bond of the formyl group, **157,** and that of the heterocyclic framework, **156.** Thermolysis of **157** leads to the decarbonylation and formation of the thiophene-2,3-diyl compound, **158.**



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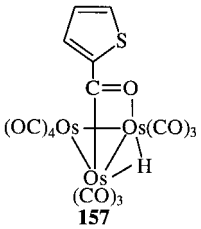

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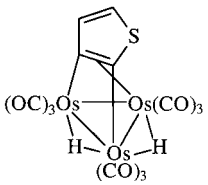
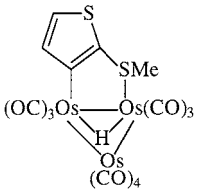


158

Activation of a C─H bond in 2-methylthiothiophene results in species **159** [99JOM(580)370]. Decarbonylation gives a mixture of isomers **160** and **161.**

Photolysis of **159** leads to a migration of the SMe group to the bridging position and formation of **162.** This product can be further decarbonylated to **163,** which is also the product of photolysis of **159** and **161.**



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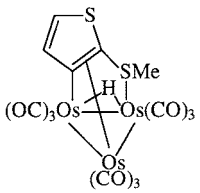

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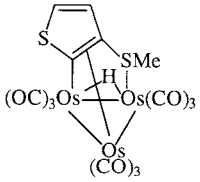

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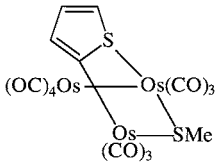

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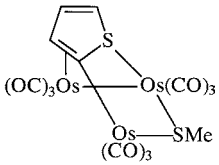
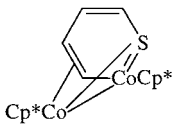


163

3. *Cobalt*

Thiophene reacts with [$Cp^*Co(C_2H_4)$] to cleave the C─S bond and yield **164** (92OM2698, 97P3115).

Photolysis of 2,5-dimethylthiophene 1,1′-dioxide with $CpCo(CO)_2$ gives **165,** whereas flash-vacuum pyrolysis gives **166** and **167** among the other products [87JOM(324)57]. Further flash-vacuum pyrolysis of **166** finally yields the species with coordinated dimethylcyclobutadiene (85OM389, 93AHC123). Phenyl-2-thienylacetylene in a reaction with Cp_2Co yields a mixture of two isomers, **168** and **169** [77JOM(135)229].



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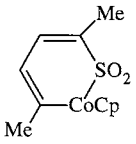

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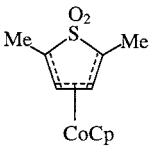

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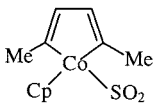

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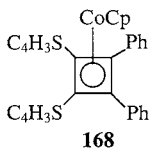

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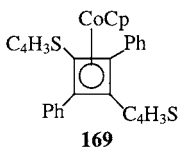
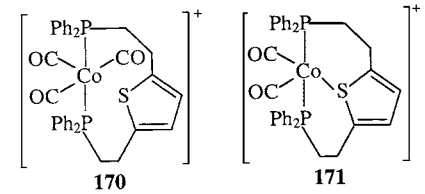


169

2,5-Bis[2-(diphenylphosphino)ethyl]thiophene (L) on reaction with $Co_2(CO)_8$ yields $[Co(CO)_3L][Co(CO)_4]$, which exchanges anions with $NaBPh_4$ to give **170** (93IC5652). When product **170** is heated at reflux, complex **171** results with coordination to both phosphorus sites and the sulfur atom of the thiophene ring. The latter bond is so tight that the reaction could not be reversed by excess carbon monoxide. Diphenyl-2-thienylphosphine reacts with $[Co_2\{\mu\text{-}C_2(COOMe)_2\}(CO)_6]$ to yield **172** and **173** [99JOM(573)272]. The same ligand with $[Co_3(\mu_3\text{-}CMe)(CO)_9]$ gives **174** and **175.**



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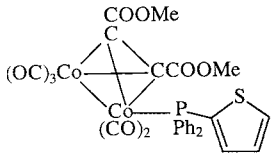

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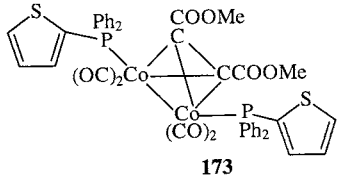

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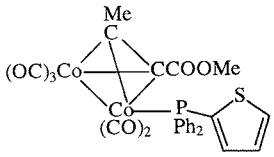

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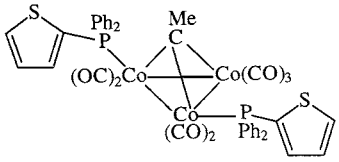
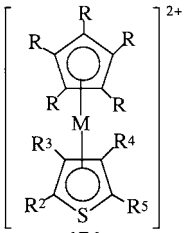


175

4. *Rhodium and Iridium*

Complex **176** (R = Me, M = Ir, $R^2 = R^3 = R^4 = R^5 = H$) was obtained from $[Cp^*Ir(acetone)_3](BF_4)_2$ (88OM686) and is stable with respect to the ligand substitution reactions. 2,5-Dimethylthiophene and especially tetramethylthiophene react with $[MCp(solv)_3]^{2+}$ (M = Rh, Ir) to give **176** (R = H, M = Rh, Ir, $R^2 = R^3 = R^4 = R^5 = Me$; M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) [78JCS(D)849, 78JCS(D)857]. Complexes **176** (particularly those with M = Ir, R = H, $R^2 = R^3 = R^4 = R^5 = Me$) are active hydrogenation catalysts. The η^5-complex $[(Ph_3P)_2Rh(\eta^5\text{-}C_4H_4S)]$ is known as well, where the heterocycle is not strictly planar [86JOM(316)C35]. Thiophene is a weaker donor than the cyclopentadienyl anion. As a consequence, its η^5-complexes contain a weaker metal–heterocycle bond. If, however, the center is a 4d or 5d metal (typically, iridium or rhodium), the interaction of d-orbitals with

extended orbitals of the sulfur atom becomes stronger (94OM2628, 97P3219). This interaction is strengthened by the donor ligands present in the coordination sphere. In such circumstances, the π-back donation from the vacant π^*-orbitals of the heteroring to the 4d or 5d metal orbitals becomes appreciable. Tellurophene reacts with $[RhCp^*Cl_2]_2$ and silver triflate to yield the η^5-complex **177** [97JCS(D)1579]. The η^5-selenophene complex is also known (94OM4474).



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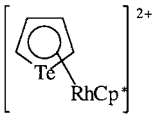
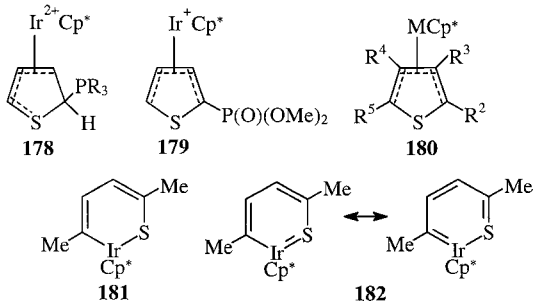


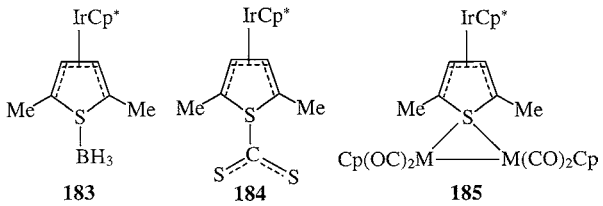
177

Activation of the thiophene ring was studied in the iridium complex **176** (R = Me, M = Ir, $R^2 = R^3 = R^4 = R^5 = H$) (88OM1491). This compound undergoes reaction with trimethyl-, methyldiphenyl-, and triphenylphosphine followed by formation of the η^4-complexes **178** ($R_3 = Me_3$, Ph_2Me, Ph_3). Reaction with trimethoxyphosphine leads to **179,** but with $NaBEt_3H$ hydride addition to the thiophene ligand does not occur; instead there is a two-electron reduction of the iridium complex to the neutral complex **180** (M = Ir, $R^2 = R^3 = R^4 = R^5 = H$). Two-electron reduction of **176** (R = Me, M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) also produces **180** (M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) where the heterocycle is coordinated only via four carbon atoms (90JA199, 90P1883). Chemical reduction is accomplished by Cp_2Co or $Na[H_2Al(OCH_2OCH_2OMe)_2]$. The process was also conducted electrochemically. The elongated carbon—sulfur bonds and expressed donor character of the sulfur heteroatom characterize complexes **180.** Nucleophilic properties of the sulfur atom in the η^4-species stem from the substantial metal-sulfur antibonding interaction (94OM2628). This change of the coordination mode thus implies activation of the heteroring. Similar synthetic approach gave **180** (M = Ir, $R^2 = Me$, $R^3 = R^4 = R^5 = H$; $R^3 = Me$, $R^2 = R^4 = R^5 = H$; $R^2 = R^3 = R^4 = R^5 = Me$). Isomer **180** is thermodynamically unstable with respect to the open-chain isomer **181** (89OM2277) and is converted to it in the presence of basic alumina gel or amines as catalysts, or under UV photolysis (92AOC479). Isomer **181** may be oxidized by Cp_2Fe^+ to restore **176.** Isomerization results in the insertion of the iridium atom into one of the C—S bonds of the η^4-coordinated thiophene. Delocalization of the π-electron density from the ring onto the iridium atom and planarity is illustrated by resonance structures **182** (97OM2448, 97OM3819). Iridathiabenzene is separately studied as a reductant and ligand (97OM606, 99JA595).



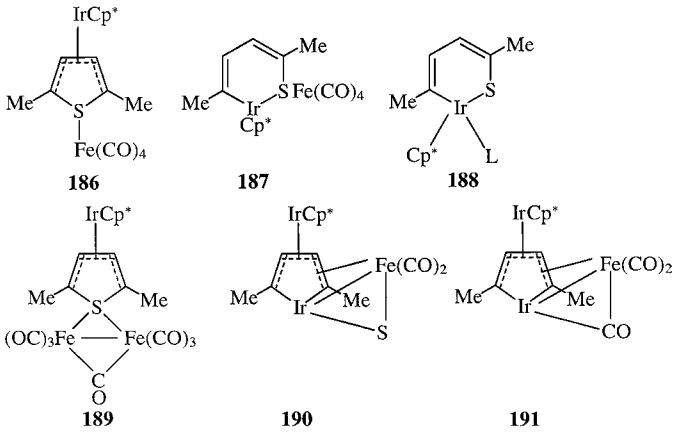
The rhodium analog **176** (R = Me, M = Rh, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) also can be reduced by dicyclopentadienyl cobalt or electrochemically to give the analogue of **180** (M = Rh, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) but not that of **181.** The tetramethylthiophene analogue of **180** (M = Rh, $R^2 = R^3 = R^4 = R^5 =$ Me) is also known (89OM2739, 91OM1002, 92JA1732, 92JA8515, 92OM3497, 93JA4943).

The sulfur atom in the η^4-complexes possesses unusual donor properties, and **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) forms the BH_3 adduct **183** extremely easily. The isomer **181** reacts with borane followed by ring closure to yield adduct **183.** It may be prepared directly from **176** (M = Ir, R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) when it contains two BF_4^- ions and is reduced by $Na[H_2Al(OCH_2CH_2OMe)_2]$. With carbon disulfide both isomers **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and **181** form the S-coordinated adduct **184** [95ICA(235)61]. This reaction highlights the enhanced basicity of the sulfur heteroatom in the η^4-coordinated thiophene. Other Lewis acids coordinated via the sulfur atom are Me_3O^+ and Et_3O^+ (90OM849). Complex **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) reacts with $Cp(OC)_2M{\equiv}M(CO)_2Cp$ (M = Mo, W) and forms **185** as the major product (90OM879, 92AOC479). The bridging thiophene ligand preserves its coordination relative to iridium while both molybdenum atoms are bonded via the sulfur atom of the heterocycle. This is the $\eta^4{:}\eta^1$(S)-μ_3-coordination mode.

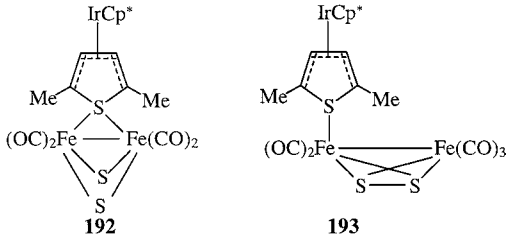


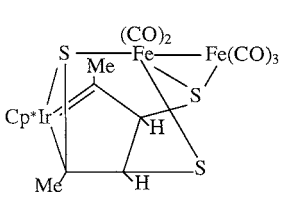
Both isomers, **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and **181,** react with $Fe(CO)_5$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$ to form a wide variety of products (91JA2544). In **186,** 2,5-dimethylthiophene fulfills a bridging function maintaining its η^4-coordination to the iridium site and coordinating in an η^1-(S) fashion to the $Fe(CO)_4$ group. This is an example of the $\eta^4{:}\eta^1$(S)-μ_2-coordination mode. In **187,** the

heterocycle is η^1-coordinated relative to the iridium atom and η^1-coordinated to the iron atom and thus serves as a bridge. Species **188** (L = CO) is described in detail later. In **189** the thiophene moiety is η^4-coordinated to iridium and S-coordinated to two iron atoms. The compounds **190** and **191** are ring-opened, which is typical for the reactions of thiophenes and their complexes with the iron-containing organometallics. Compound **190** retains the sulfur atom, but sulfur is completely eliminated in **191.**



The η^5-coordinated species **176** (R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and its η^4-descendant **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) give rise to a variety of products on interaction with $(\mu\text{-S})_2Fe_2(CO)_6^{2-}$ [96JOM(522)21]. Thus, **176** (R = Me, M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) gives the η^4:η^2, **192,** and η^4:η^1, **193,** derivatives, whereas **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) yields a ring-opened structure, **194.** The same reaction course is observed for the ring-opened isomer of **180,** species **181,** but in this case the other product $Cp^*Ir(2,5\text{-}Me_2C_4H_2S)S_2Fe(CO)_4$ is formed with an unidentified structure. Reaction of **176** (M = Ir, R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) with $(\mu\text{-CO})(\mu\text{-}n\text{-BuS})Fe_2(CO)_6^-$ gives **195** and **188** (L = CO) implying that initially **176** (M = Ir, R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) is reduced to **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and **181,** and then the η^4-species experiences nucleophilic attack.





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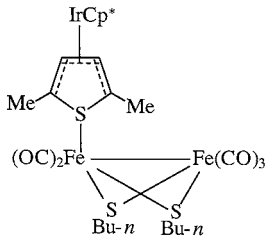
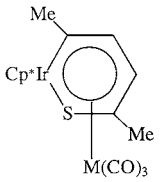


195

Isomers **180** (M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) and **181** react together (89OM2277, 90JA199, 92AOC479), but the products may be based on any of them in different reactions [90OM849, 90P1883, 92OM992, 95ICA(235)61]. Thus, reactions of **180** (M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) and **181** with $(AN)_3M(CO)_3$ (M = Cr, Mo, W), (η^6-toluene)$Mo(CO)_3$, or [(η^6-ClPh)FeCp]PF_6 give the η^6-coordinated iridathiabenzene complexes, **196** (M = Cr, Mo, W) and **197** (95JA6362). However, $Co_4(CO)_{12}$ gives clusters **198** and **199** (96OM1414); $Co_2(CO)_8$ gives **198, 199,** and **200** [92AX(C)2120], and (η^6-$C_6H_3Me_3$)$Co_4(CO)_9$ gives **201,** the η^6-iridathiabenzene product.



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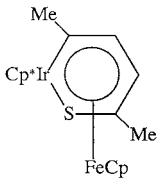

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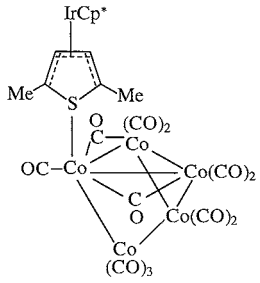

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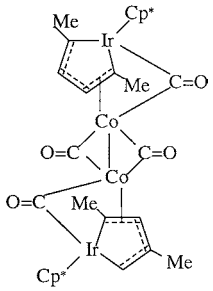

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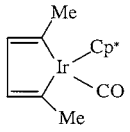

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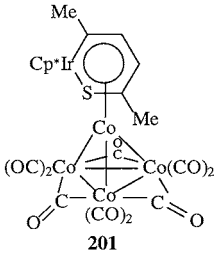

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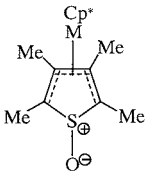
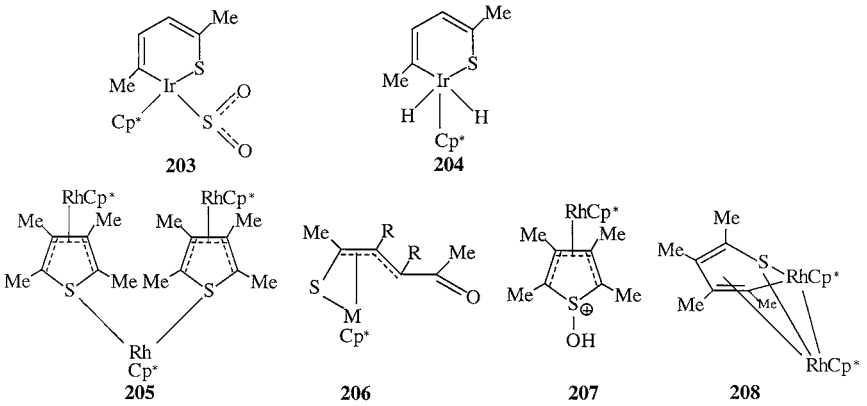


202

Reaction of **180** (M = Rh, $R^2 = R^3 = R^4 = R^5 = Me$) with dry oxygen occurs via the sulfur atom to yield the *S*-oxide complex **202** (M = Rh) (90JA2432, 92JA8521). A species similar to **202** (C_5Me_4H instead of Cp^*) is formed in the base hydrolysis

of $[(C_5Me_4H)Rh(\eta^5\text{-}C_4Me_4S)]$. A weak acid, NH_4PF_6, converts the corresponding Rh analogue of **206** into $[(C_5Me_4H)Rh(\eta^4\text{-}C_4Me_4S^+\text{-}OH)]PF_6$. These results show that although nucleophilic additions generally proceed at position 2 of the heteroring [84JA2901, 88JOM(355)359, 93IC3528], initially nucleophilic attack may well be directed at the sulfur atom, the most electropositive site (85MI1). When the thiophene is coordinated to the rhodium center, the electrophilic character of the sulfur atom (79PAC901) is enhanced, so that sulfur may become a supersulfonium ion.



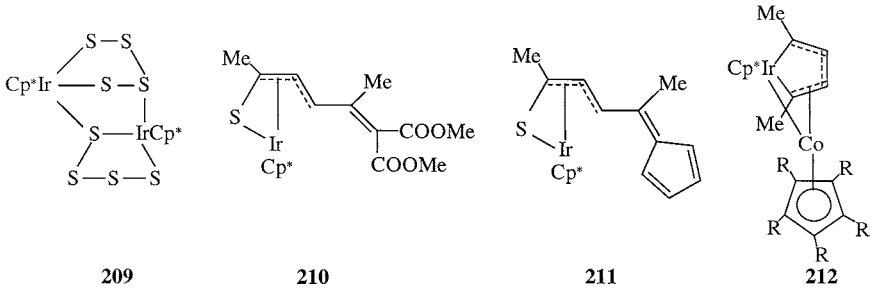
Both isomers **180** (M = Ir, $R^2 = R^5 = Me$, $R^3 = R^4 = H$) and **181** react with P-donor ligands and carbon monoxide yielding the 18-electron adducts **188** (L = PMe_3, PMe_2Ph, $PMePh_2$, PPh_3, $P(OPh)_3$, CO). The structure of **188** is such that the six-membered ring is no longer planar [92AX(C)2120] as in **181.** Deviation from planarity has been proven in the series of related occasions (92JA151, 92JA1732, 93OM1583, 93OM2740, 95JA6362, 96OM2727). Both isomers interact with sulfur dioxide to afford adduct **203.** Also, isomer **181** undergoes oxidative addition of hydrogen resulting in the dihydride, **204,** formation (90P1883).

The η^4-coordinated complex of tetramethylthiophene, **180** (M = Rh, $R^2 = R^3 = R^4 = R^5 = Me$) (89OM2739), in the solid state slowly rearranges into a species with a mixed η^4:η^1 coordination mode, **205** (92JA1732). Solutions of **205** on interacting with air give the *S*-oxide, $[Cp^*Rh(\eta^4\text{-}C_4Me_4SO)]$ (90JA2432).

As mentioned earlier, the possible products of the η^4-complexes include ring-opened structures. This includes isomer **181** and some of its derivatives, for example, **187, 188, 196, 197, 203,** and **204,** as well as the products of interaction with organoiron, **180, 191,** and **194,** and organocobalt, **199, 200,** and **201,** compounds. They have already been discussed together with the variously characterized η^4-complexes. Examples of the ring-opening reactions based on the η^4- and η^5-species are given next.

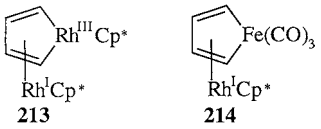
Ring-opened products sometimes include the η^5- and η^4-descendants simultaneously. Thus, the η^5-tetramethylthiophene rhodium complex **176** (M = Rh, R = Me, $R^2 = R^3 = R^4 = R^5 =$ Me) (91OM1002) is easily hydrolyzed by aqueous potassium hydroxide to yield **206** (M = Rh, R = Me), the thiolate complex with the thiophene ring opened (90JA2432, 90OM2875, 92JA8521). The reaction is reversible. When triflic acid is added as a protonating agent, first the ring is regenerated back to the η^4-coordinated entity with the S–OH bond, **207,** and then with excess triflic acid, **176** (M = Rh, R = Me, $R^2 = R^3 = R^4 = R^5 =$ Me) is regenerated. The $[(C_5Me_4Et)Rh(\eta^5\text{-}Me_4S)]^{2+}$ complex undergoes a similar hydrolysis $\rightleftharpoons$ protonation cycle. Reaction of **180** (M = Rh, $R^2 = R^3 = R^4 = R^5 =$ H) with $Fe_3(CO)_{12}$ gives the ferrole-related products (89OM2739). Thermolysis of **205** gives the ring-opened product **208** (90JA2432).

Both isomers **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and **181** interact with sulfur, S_8, to yield the dimer **209** [95ICA(235)61] and with oxygen to produce the acylthiolate species similar to **206** (M = Ir). Interrelationship of the η^5-, η^4-, and ring-opened structures can be traced from the set of transformations that follow [96JOM(512)149]. The reaction of the η^5-coordinated complex **176** (M = Ir, R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) with phenyllithium gives **206** (M = Ir) where the source of the oxygen atom could be the THF used as a solvent. The reaction with the malonate ion $^-CH(COOMe)_2$ proceeds similarly and gives **210,** whereas that with $(n\text{-}Bu)_4N^+OH^-$ leads to **204** and **206** (M = Ir, R = H). If the reducing agent in the transformation of **176** (M = Ir, R = Me, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) to **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) is dicyclopentadienyl cobalt, species **211** is formed in small amount. Both isomers, **180** (M = Ir, $R^2 = R^5 =$ Me, $R^3 = R^4 =$ H) and **181,** on further interaction with dicyclopentadienyl cobalt yield **212** (R = H). Similar reaction with $Cp^*Co(C_2H_4)$ gives **212** (R = Me) (96OM1223).



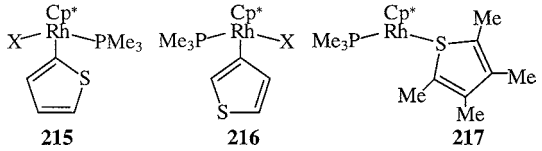
209 **210** **211** **212**

Chemical reduction of **177** by dicyclopentadienyl cobalt is different from that of a thiophene derivative and leads to the removal of a heteroatom to yield **213.** The latter reacts with tellurophene and $Fe_3(CO)_{12}$ to give **214** [97JCS(D)1579].



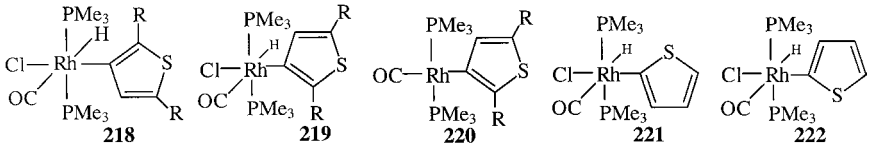
213 **214**

Photochemical reaction of thiophene with [$Cp^*Rh(PMe_3)(PhH)$] yields the product of C—H bond activation, **215** (X = H) (92JA151). Reaction of 2-thienyllithium with $Cp^*Rh(PMe_3)X_2$ (X = Cl, Br) yields **215** (X = Cl, Br). Reduction of **215** (X = Cl) by $LiHBEt_3$ gives **215** (X = H). The rhodium bromide precursor, $Cp^*Rh(PMe_3)Br_2$, on reaction with thienyllithium gives **216** (X = Br), which can be reduced to **216** (X = H) by $LiHBEt_3$. The latter rapidly rearranges to **215** (X = H). Tetramethylthiophene in the reaction with $Cp^*Rh(PMe_3)(PhH)$ behaves differently and gives the S-coordinated product **217.**



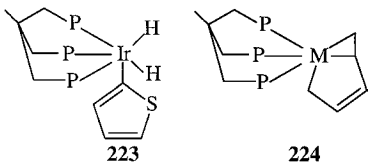
215 **216** **217**

2,5-Dimethylthiophene reacts photochemically with *trans*-$Rh(PMe_3)_2(CO)Cl$ to yield the isomeric products **218** (R = Me) and **219** because of C—H activation of thiophene (96OM872) as well as species **220** (R = Me). Unsubstituted thiophene in similar conditions gives five products, the 3-thienyl activated isomers **218** (R = H) and **219** (R = H), the 2-thienyl isomers, **221** and **222,** and 2-thienyl analogs of **220** (R = H).



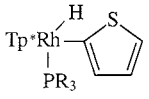
218 **219** **220** **221** **222**

Thiophene reacts with [(triphos)IrH] to yield the products of both C—H, **223,** and C—S, **224,** activation [95JOM(504)27]. Thermolysis of **223** gives **224** (M = Ir) via an intramolecular transformation.



223 **224**

The pentamethylcyclopentadienyl derivatives of rhodium Cp^*RhL ($L = PMe_3$, C_2H_4) oxidatively add thiophene preferentially via the C—S activation route compared to that based on the C—H activation [88OM1171, 94JOM(472)311]. The Tp^* derivatives by contrast yield mainly the latter. $Tp^*Rh(PEt_3)$ acts almost selectively and forms exclusively **225** (R = Et), whereas $Tp^*Rh(PMe_3)$ forms a major amount of **225** (R = Me) and minor amount of **226** (96OM2678).



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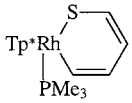

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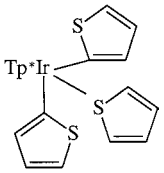
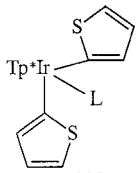


227

Thiophene enters a thermal reaction with $[Tp^*Ir(C_2H_4)_2]$ to yield complex **227** where one of the heterocyclic ligands is η^1-(S-) coordinated, while the other two are η^1-C coordinated [94JA4519, 95JOM(504)197, 99OM139]. 2- and 3-methylthiophenes react similarly. The S-coordinated thiophene is labile and can be easily replaced to yield species **228** (L = PMe_3, CO). Complex **227** on hydrogenation gives **229,** which on thermolysis forms complexes **230** and **231** with the bridging thiophene ligands. Thiophene interacts with $Tp^*IrH_2(C_2H_4)$ to yield **232.** As before, the ligand substitution of PMe_3 or AN leads to elimination of the S-bound heterocycle to yield **233.** Reaction of thiophene or 2- and 3-methylthiophene with $Tp^*Ir(\eta^4\text{-}CH_2C(Me)C(Me)CH_2)$ gives **232** and analogs, whereas 2,5-dimethylthiophene forms species **234.**



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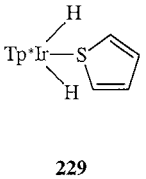

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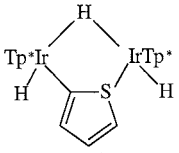

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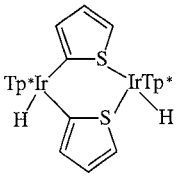

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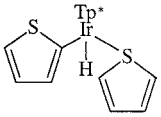

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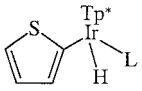

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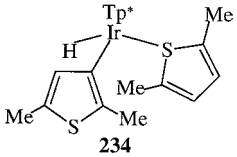
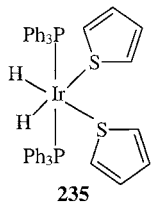


234

The switch in coordination mode was observed on thermolysis of the S-coordinated species **235** to give **236** (94OM721).



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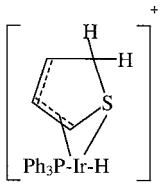
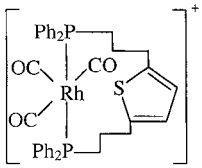


236

Cases of the S-coordinated rhodium and iridium are quite scarce. To complete the picture, we next consider the possibilities of S-coordination using complicated derivatives of thiophene. 2,5-[Bis(2-diphenylphosphino)ethyl]thiophene is known to contain three potential donor sites, two phosphorus atoms and the sulfur heteroatom, the latter being a rather nucleophilic center (93IC5652). A more typical situation is coordination via the phosphorus sites. It is also observed in the product of the reaction of 2,5-bis[3-(diphenylphosphino)propyl]thiophene (L) with the species obtained after treatment of [(cod)Rh(acac)] with perchloric acid (95IC365). Carbonylation of $\{[Rh(cod)L][ClO_4]\}_n$ thus prepared yields **237.** Decarbonylation of **237** gives a mixture of **238** and the S-coordinated species **239.** Complete decarbonylation gives **240,** where the heterocycle is η^4-coordinated. The cycle of carbonylation $\rightleftharpoons$ decarbonylation is reversible.



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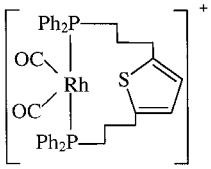

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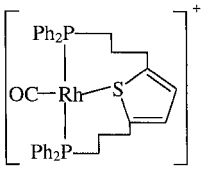

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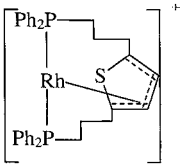
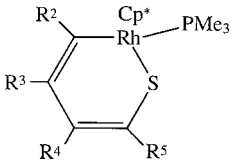


240

2,5-Dimethylthiophene reacts with $[Cp^*Rh(PMe_3)_3]$ to give **241** ($R^2 = R^5 =$ Me, $R^3 = R^4 = H$) (91JA559, 97P3115). Similar products result from 2- and 3-methylthiophenes. Reaction of thiophene with $[Cp^*Rh(PMe_3)H_2]$ under photochemical conditions gives (η^2-C,S-C_4H_4S) and $Cp^*Rh(PMe_3)$(2-thienyl)H (92JA151). The 2-thienyl product transforms to the butadienethiolate species on warming. In contrast to the photochemical reaction, thermal reaction of thiophene, 2- and 3-methylthiophene, and 2,5-dimethylthiophene with $Cp^*Rh(PMe_3)(Ph)H$ gives the ring-opened rhodium(III) complexes **241** ($R^2 = R^3 = R^4 = R^5 = H$; $R^2 =$ Me, $R^3 = R^4 = R^5 = H$; $R^2 = R^5 =$ Me, $R^3 = R^4 = H$) (90JA2432, 91JA559, 92JA151). The dienic group and the sulfur atom are planar but the rhodium atom is above the plane. A localized dienic structure is observed in the six-membered metallocycle. Complex **215** (X = H) formed in the corresponding photochemical reaction with thiophene appears unstable and gradually rearranges to **241** ($R^2 = R^3 = R^4 = R^5 = H$).



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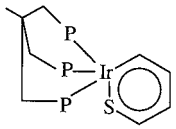
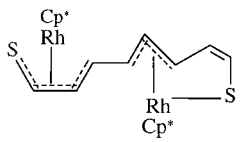


242

Reaction of thiophene with (triphos)RhH_3 gives **224** (M = Rh) (95JA4333). Thiophene reacts with the η^4-benzene species [(triphos)Ir(η^4-C_6H_6)]BF_4 to yield the ring-opened product **242** containing the planar, π-delocalized iridathiabenzene ring [93JA2731, 96JCS(D)801, 97P3003, 97SL643].

Chemically reactive 16-electron species, such as Cp^*RhPMe_3 (94OM4448) or (triphos)MH (M = Rh, Ir) (95JA4333) as a rule activate thiophene and its derivatives by way of C–S bond insertion. The C–S activation thus produces metallacycles, while C–H activation yields thienyl(hydride) organometallic species (98OM65). Both kinds of activation may proceed simultaneously; the first is thermodynamically more favorable, and the second is kinetically competitive (91JA559, 92JA151, 94JA4370, 95JA11704, 96OM2905, 97P3073).

Thermal reaction of thiophene with $Cp^*Rh(C_2H_4)_2$ yields product **243** not only with C–S cleavage but with C–C coupling (92AGE357, 92JA9851). The same reaction run photochemically gives not only **243** (still the main product) but also a small quantity of **244.** A similar thermal reaction of 2-methoxythiophene gives **245–247,** the monomer **245** being the main product. All these species result from insertion of the Cp^*Rh framework into the C–S bond of thiophene.



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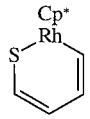

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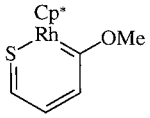

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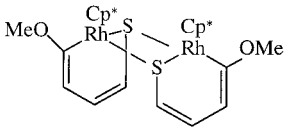

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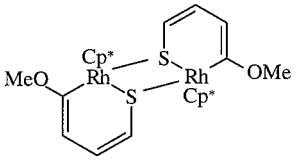
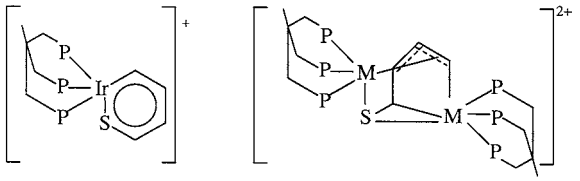


247

Thiophene reacts with [(triphos)Ir(η^4-C_6H_6)]BPh_4 differently depending on the nature of the reaction medium [93JA2731, 95JCS(CC)921]. Thus, in THF the

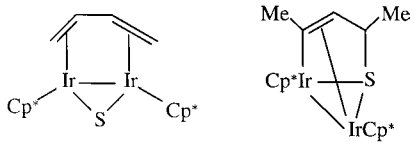
iridabenzene species **248** is formed. In dimethyl sulfoxide the reaction yields dimer **249** (M = Ir). Reaction of thiophene with [(triphos)Rh(Cl)(C_2H_4)] and $TlPF_6$ gives **249** (M = Rh).



248 **249**

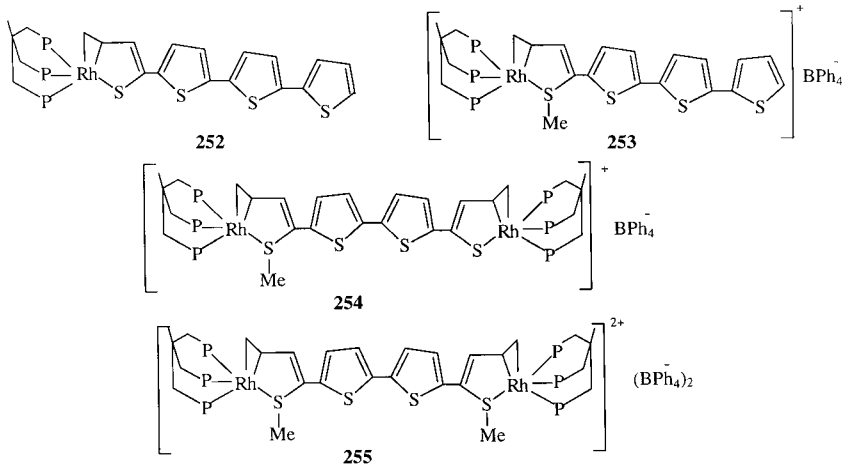
Thus, there are two major directions for thiophene ring-opening upon interaction with the mononuclear rhodium(I) and iridium(I) species: formation of the delocalized planar rhoda- or iridathiabenzene ring or the coordinated thiabenzene framework. Metallacycles of the types **241** and **244** deviate from planarity. Their formation is due to the insertion of the 16-electron framework [$Cp^*Rh(PMe_3)$] into derivatives of thiophene (91JA559, 92JA151, 95JA11704, 96OM2905). Some planar but localized structures are also known (94JCS(CC)557). Thus, thiophene oxidatively adds via the C, S-route to [Ir(cod)(PMe_3)$_3$]Cl to yield the ring-opened (Me_3P)$_3$ClIr(SCHCHCHCH)(93OM1583). Selenophene reacts with $Cp^*Rh(PMe_3)$ PhH at elevated temperature to yield a ring-opened product, where rhodium has inserted to the carbon–selenium bond (97OM2751).

A solution of the complex [Cp^*IrH_3]$_2$ in neat thiophene upon heating gives **250** where the heterocyclic molecule is cleaved and two iridium atoms are bridged separately by the butadiene and sulfide groups (94JA198). 2-Methylthiophene in a similar reaction yields **251** (*tert*-butylethylene was added to the reaction mixture as a hydrogen acceptor) (99OM134).



250 **251**

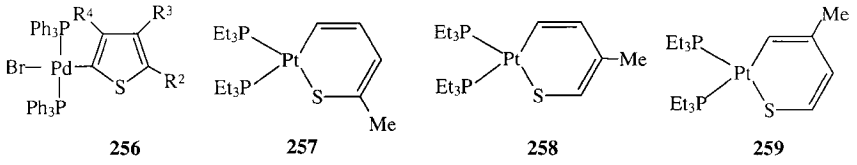
2,2′,5′,2″:5″,2″-Quaterthiophene, a representative of the oligomers of thiophene [97JPC(A)4437] reacts with the labile 16-electron species [(triphos)RhH] to yield **252** (97OM1517). The sulfur atom bonded to rhodium has expressed nucleophilic properties and attack by methyl iodide followed by $NaBPh_4$ gives the thioether **253.** The latter reacts with [(triphos)RhH] to give the binuclear complex **254** that can be further methylated to give **255.**



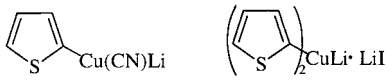
5. *Nickel Group Complexes*

The data on complex formation by metals of the nickel group (Ni, Pd, Pt) is scarce. 2-Bromo-, 2,4- and 2,5-dibromo-, 2,3,5-tribromo-, and tetrabromothiophene react with $Pd(PPh_3)_4$ to yield the η^1- (C-) coordinated species **256** [97JOM (531)175] ($R^2 = R^3 = R^4 = H$; $R^2 = R^3 = H$, $R^4 = Br$; $R^2 = R^4 = H$, $R^3 = Br$; $R^3 = R^4 = H$, $R^2 = Br$; $R^2 = R^3 = Br$, $R^4 = H$; $R^2 = R^3 = R^4 = Br$). This type of oxidative addition has also been studied for a series of thienyl ligands formed from 2-bromothiophene or 2-bromo-3-methylthiophene [80JOM(188)121].

Thiophene and its derivatives react with the platinum(0) complex $[Pt(PEt_3)_3]$, the latter experiencing the oxidative insertion into the carbon–sulfur bond of the heterocycle giving rise to the ring-opened products (93JA12200, 95JA2179). Thus, 2-methylthiophene yields **257** (97P3185) where insertion takes place to the H(C)─S bond, whereas 3-methylthiophene yields isomers **258** and **259.** Reactions of tris(2-thienyl)phosphine (L) with $(cod)Pt^{II}Me_2$ give the *cis*-L_2PtMe_2, platinum(II) complex, where the ligand is coordinated via the phosphorus site (82JOC1489). Dimeric complexes of platinum with acetylide oligothienyl bridges [97JCS(D)4283] are of applied interest as the conducting materials.

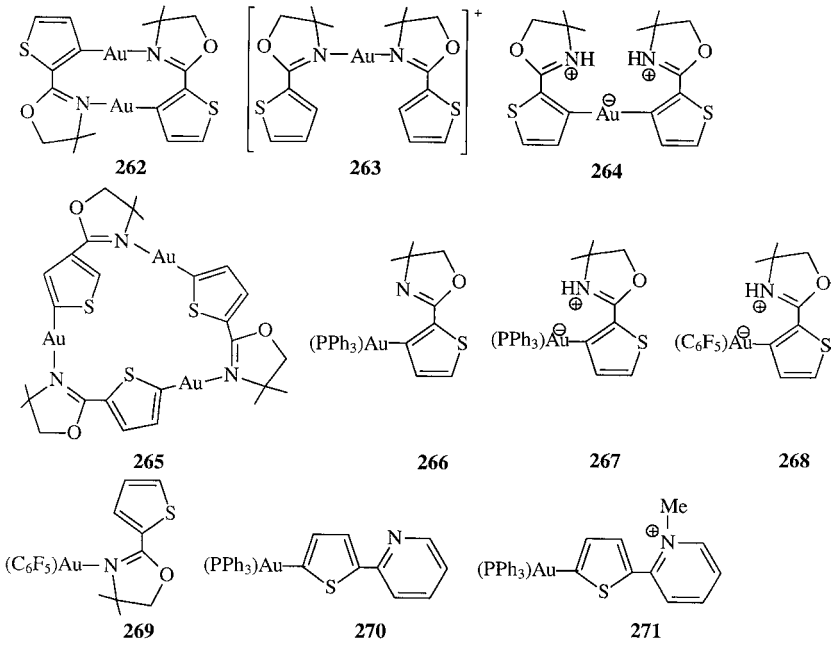


The η^1(C) coordinated organocopper compounds **260** and **261** were obtained from 2-lithiothiophene and copper cyanide and iodide, respectively (99OM1571).



260 **261**

The ligand 2-(4′,5′-dihydro-4′,4′-dimethyloxazolin-2′-yl)thien-3-yllithium is of interest from the viewpoint of the competition between the donor functions of oxazoline and thiophene rings. On reaction with [AuCl(tht)] it produces the neutral dimer **262** (97OM3324). Both the η^1(C) function of the thienyl and the traditional N-function of oxazoline are utilized in this species. Protonation of **262** by triflic acid leads to a mixture of products. In **263** the thienyl framework is not coordinated, whereas in **264** the oxazoline function is excluded because of protonation of the nitrogen atoms. Reaction of the lithiated starting ligand with [AuCl(tht)] may proceed further to yield **265,** a neutral trimer. With [AuCl(PPh_3)], the complex where only the thienyl grouping is utilized in coordination, **266,** results. Protonation of this complex unequivocally occurs at the ring nitrogen atom, **267,** and does not disrupt the thienyl donor function. This type of reaction occurs by the same route when [Au(C_6F_5)(tht)] and then triflic acid are used, the product being **268.** If, however, the ligand 2-(4′,5′-dihydro-4′,4′-dimethyloxazolin-2′-yl)thien-5-yllithium is employed, the neutral species with N-coordination, **269,** results. It is interesting in this respect that 2-(2′-pyridyl)thien-5-yllithium with [AuCl(PPh_3)] gives the thienyl 2-coordinated product, **270,** which on alkylation with CF_3SO_3Me reacts at the N-site and yields **271.**

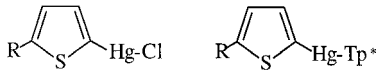


262 **263** **264**

265 **266** **267** **268**

269 **270** **271**

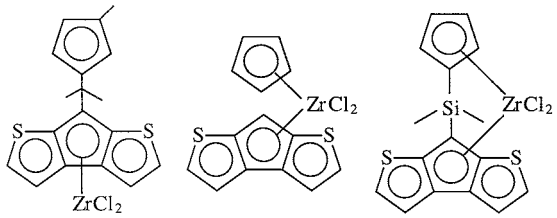
Interaction of the thiophene-containing organomercury compounds **272** (R = H, Me, Et) [74MI1, 79JCS(D)2037] with potassium tris(3-methylpyrazolyl) borate (KTp^*) yields **273** [96JOM(515)213].



272 **273**

V. Organometallic Compounds of Benzothiophenes

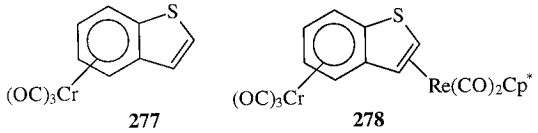
The electronic structure of annulated thiophenes is such that the π-electron density is delocalized mainly in the carbocyclic counterpart, while the heteroring is only slightly involved (84KGS1497, 85UKZ293). Therefore the η^6-coordination is expected to be the major mode [60JA4557, 68JOM(14)359, 73JOM(61)249, 80JOM(186)265]. In the cyclopentadienyl-annulated derivatives, **274–276,** coordination is inevitably via the carbocycle (84JC226, 98JA10786). The corresponding complexes are effective in terms of activity and stereospecificity in propene polymerization.

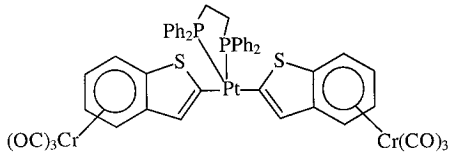


274 **275** **276**

The η^6-coordinated tricarbonylchromium series of benzo-, dibenzo-, and benzo[*b*]naphtho[2,1-*d*]thiophenes results when $Cr(CO)_3(AN)_3$ and a ligand interact [68JOM(14)359, 69JCS(B)1204, 75MI1, 82JCS(CC)467, 83JOM(255)317, 92AX(C)266]. Lithiation of the η^6-chromiumtricarbonyl–benzothiophene complex occurs at the C2 position [84MI1, 87JOM(336)C44, 89OM1688, 93AHC123]. Tricarbonylchromium(benzothiophene) **277** was treated with *n*-butyllithium, and the product was methylated by methyl iodide to give tricarbonylchromium(2-methylbenzothiophene) [87JOM(336)C44]. When *n*-butyllithium was used in excess, tricarbonylchromium(2,7-dimethylbenzo-thiophene) was isolated as the basic product. The thiophene moiety in η^6-coordinated benzothiophene species **277** retains its donor potential, so that further η^2-coordination with respect to $Re(CO)_2Cp^*$ appears possible when **277** interacts with $Cp^*(CO)_2Re(THF)$ and yields **278** [95ICA(240)393]. This coordination mode is the consequence of the electron-withdrawing properties of the tricarbonylchromium moiety increasing the

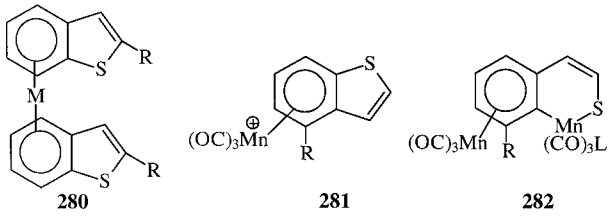
π-acceptor function of the C2C3 double bond. Lithiated benzothiophene can be quenched by [Pt(dppe)Cl_2] to give **279** [97JCS(D)2955].





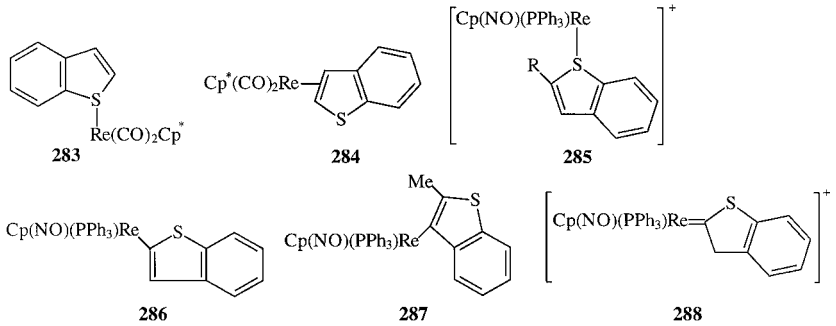
The vapor-phase reaction of benzothiophene, 2-methylbenzothiophene, or 2-trimethylsilylbenzothiophene with chromium atoms and also in the case of the latter ligand with molybdenum atoms gives the η^6-coordinated sandwich complexes **280** (M = Cr, R = H, Me, $SiMe_3$; M = Mo, R = Me) [95JOM(494)241].

Manganese and rhenium derivatives present a wider variety of coordination modes. The η^6-species of benzothiophene and its 7-methyl- and 7-ethyl-derivatives **281** (R = H, Me, Et) are the products of the reaction of the ligand with $Mn(CO)_5Br$ and $AgBF_4$ (94OM3972, 95OM2613, 97OM5604). The species **281** may be reduced by cobaltocene in the presence of carbon monoxide. The resultant homodinuclear complex **282** (L = CO) is formed as a result of ring opening at the S—C_{Ph} bond (96AGE212, 97OM5604, 98OM2067). The same reduction course is observed under a nitrogen atmosphere in the presence of trimethyl- or triethylphosphite, the products being **282** [L = $P(OMe)_3$, $P(OEt]_3$]. Perhaps this method of ring opening is more intrinsic for the η^6-precursors (88OM1491).



$Cp^*(CO)_2Re(THF)$ forms η^1(S) coordinated complexes such as **283** with dibenzo- and benzothiophene (88OM686, 91IC1417, 92OM3328). Compound **283** is formed in an equimolar mixture with 2,3-η^2-isomer **284** [91JA4005, 95ICA(240)393]. Mutual conversion of isomers **283** and **284** occurs instantaneously. Benzothiophene and 2-methylbenzothiophene react with $Cp(NO)(PPh_3)Re(ClCH_2Cl)^+$ and yield the η^1(S) coordinated species **285** (R = H, Me)

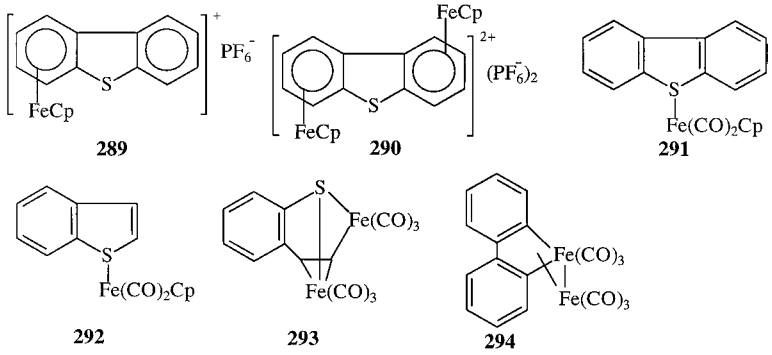
(94JA5190). Upon deprotonation by bases, **285** (R = H) transforms to **286,** and **285** (R = Me) goes to **287** because the C2 position is occupied. Protonation of **286** with triflic acid occurs at position 3 of the heteroring to form the benzothienyl carbene complex **288,** and deprotonation reverts it to **286.** This kind of process is a rarity for the uncomplexed benzothiophenes (81AHC171).



283 **284** **285**

286 **287** **288**

For the organoiron derivatives, the expected trend is ring opening, although the η^6- and η^1-coordination modes are also known. Thus, dibenzothiophene on interaction with ferrocene, Al, $AlCl_3$, and ammonium hexafluorophosphate gives the η^6-coordinated species **289** [80JOM(186)265]. In excess ferrocene, the homodinuclear species **290** results. The η^1(S) coordinated species **291** and **292** were described (87IC3424). Isobutene is readily displaced from $[Fe(\eta^2\text{-}H_2C{=}CMe_2)(CO)_2Cp]BF_4$ by the related benzannulated thiophenes. S-Coordinated benzo- and dibenzothiophene (L) occur also in the complexes $[CpFe(dppe)L]PF_6$ resulting from interaction of the relevant ligands with CpFe(dppe)I and $TlPF_6$ (96P2825). Reaction of benzothiophene with $Fe_3(CO)_{12}$ gives benzothiaferrole, **293** (88OM1171). X-ray structural analysis of the monophosphine derivative of this complex substantiates the $(CO)_6$ structure contrary to the $(CO)_5$ arrangement proposed earlier (61JA3600, 89JA8753). Dibenzotellurophene causes ring opening and removal of the tellurium heteroatom to give **294** [96JCS(D)1545].

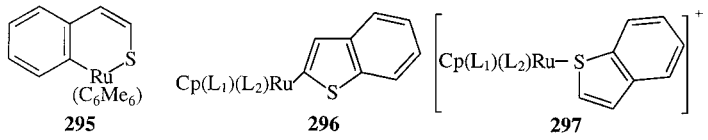


289 **290** **291**

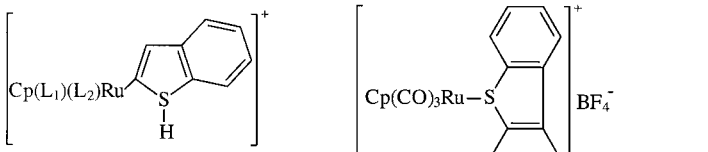
292 **293** **294**

The η^6-coordination mode remains quite typical for the organoruthenium chemistry of benzannulated thiophenes. Thus, the dicationic complexes $[Cp^*RuL](PF_6)_2$ were obtained as a result of the interaction of $[Cp^*RuCl_2]$, $AgPF_6$, and benzothiophene (L) (88OM686, 89JA8828). The monocationic complex $[Cp^*RuL]X$ (88OM686, 88OM1491) was also synthesized. In both species, the η^6-coordination via the benzene ring takes place (90NJC331, 93OM3504, 94JMC287). Benzothiophene forms the η^6-coordinated complex with $Ru(C_6Me_6)^{2+}$ that further undergoes ring opening to yield **295** [96JCS(D)4493].

Benzothiophene is lithiated with *n*-butyllithium at position 2 of the heteroring (79MI1, 84MI2). 2-Lithiobenzothiophene on reaction with $Cp(PMe_3)RuX$ ($X = Cl, O_3SCF_3$) or $Cp(CO)(PPh_3)RuCl$ produces the η^1(C) coordinated products **296** [$L_1L_2 = (PMe_3)_2, (CO)(PPh_3)$] (93IC1871). Protonation with triflic acid causes the change in the coordination mode to η^1(S) in the product **297** ($L_1L_2 = (PMe_3)_2$, $(CO)(PPh_3)$). For the combination $L_1L_2 = (CO)(PPh_3)$, the process was demonstrated to proceed via the η^1(C) species **298.** Thus, protonation is accompanied by the cleavage of the Ru—C bond and attachment of the proton to the C2 atom. The η^1(S) coordinated benzo- and dibenzothiophene, e.g., **299,** can be obtained from excess heterocycle, $Cp(CO)_2RuCl$ or $Cp(CO)(PPh_3)RuCl$, and $AgBF_4$. The η^1(S) coordination ability increases in the series dibenzothiophene > benzothiophene > thiophene (92OM922, 93OM680).

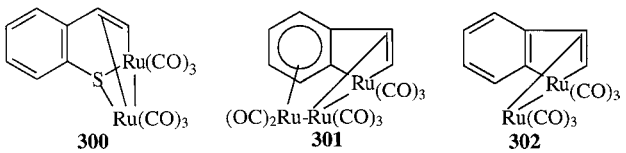


295 **296** **297**



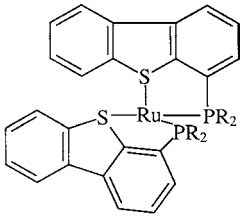
298 **299**

Ring opening of the heteroring (C—S bond cleavage), **300,** or even ring opening with elimination of the heteroatom, **301** and **302,** happens in the reaction of benzothiophene with $Ru_3(CO)_{12}$ (94AGE1381).



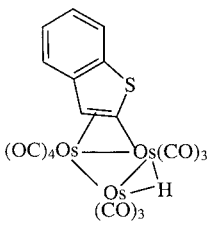
300 **301** **302**

$RuCl_2(PPh_3)_2$ reacts with 4-R_2P-dibenzothiophene (R = Ph, *p*-Tol) and forms **303,** in which the dibenzothiophene ligand is coordinated to ruthenium via the phosphorus and sulfur atoms [84JA5379, 87JOM(318)409]. The donor ability of the sulfur atom is relatively weak. Complex **303** (R = Ph) is able to add carbon monoxide and yield the monocarbonyl adduct.



303

Osmium derivatives usually give rise to the bridged and mixed coordinated species. Thus, benzothiophene reacting with $[Os_3(CO)_{10}(AN)_2]$ gives rise to a diversity of the products of oxidative addition [99ICA(285)277], including a μ,η^2-coordinated cluster where the ligand is a three-electron donor, **304** [95OM2238, 99ICA(285)277]. Another product of C–H activation, **305,** could be prepared from **304** on thermolysis. The ligand performs its triple bridging role in **305.** Ring-opened product **306** is also formed and furthermore produced on prolonged standing of **304** in chloroform. The ligand in **306** is a six-electron donor, three electrons from the bridging sulfur atom and three from the μ,η^2-vinyl framework. $[Os_3(CO)_{10}(\mu\text{-}C_8H_6Te)]$ has a similar structure [97ICA(254)119]. Dibenzothiophene in this reaction yields only species **307** where only one benzene group participates in coordination, as a μ_3,η^2-ligand similar to benzene.



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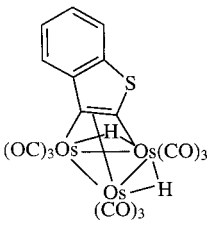

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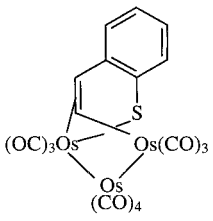

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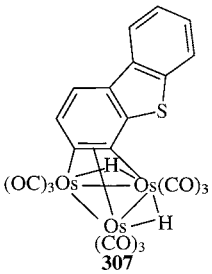
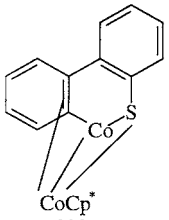


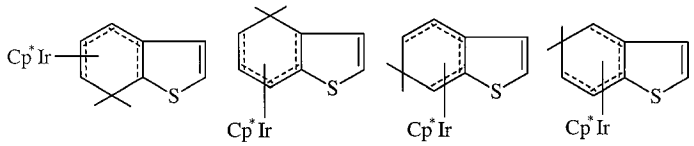
307

Benzothiophene and dibenzothiophene with $Cp^*Co(C_2H_4)_2$ give products where the carbon–sulfur bond has been cleaved, such as **308** [94JOM(472)311, 97P3115].



308

The η^6-coordinated iridium complexes, $[Cp^*IrL](BF_4)_2$ (L = benzothiophene, 2-methyl-, 3-methyl-, and 2,3-dimethylbenzothiophene) were obtained as a result of interaction of $[Cp^*Ir(acetone)_3](BF_4)_2$ with various benzothiophenes (88OM686, 89JA8828). Dicationic iridium complexes react with hydrides, such as $NaBH_4$, to form isomers **309–312.** Hydride attacks the benzothiophene ring predominantly at the 7 position, but noticeable amounts of isomers are formed because of the attack at the 5 and 6 sites. The iridium dications react with nucleophiles followed by formation of $[Cp^*Ir(L \cdot Nu)]^+$ (L = benzothiophene, 3-methylbenzothiophene; $Nu = OMe^-$, $CH(COOMe)_2^-$, SEt^-). Four isomers of the type **309–312** are again formed. Excess $Ph_3C^+BF_4^-$ leads to immediate regeneration of the initial dication. The same kind of reaction takes place between the dications and trimethylphosphine, which predominantly adds at the 7 position of the coordinated ring.

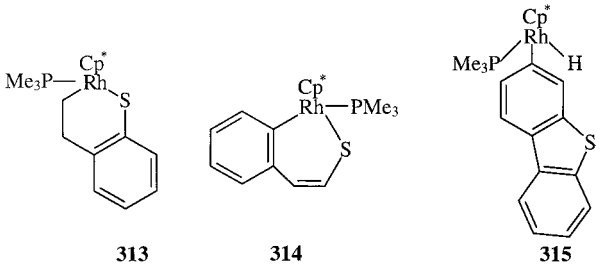


309 **310** **311** **312**

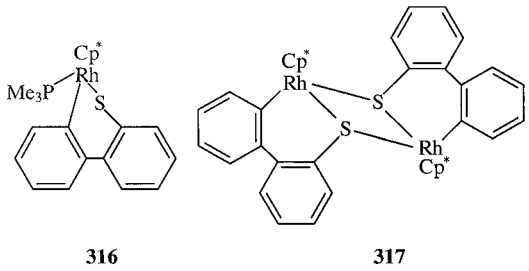
The rhodium and iridium complexes of dibenzothiophene (L) reveal an interesting case of linkage isomerism (91IC5046). Thus, the η^1(S) coordinated species $[MCp^*LCl_2]$ on thermolysis with silver tetrafluoroborate afford the η^6-coordinated dicationic species.

Three groups of researchers are studying the reactions of C,S-cleavage of benz-annulated thiophenes sometimes preceded by η^1(C), η^1(S) or other types of coordination (89P1431, 91MI1, 92JA5187, 92OM3328, 93CJC199, 93IC3766, 94OM553). Benzo- and dibenzothiophene on thermolysis with $Cp^*Rh(PMe_3)$ give the ring-opened product where the metal has inserted to the C—S bond (92JA151). Benzothiophene with $Cp^*Rh(PMe_3)(Ph)(H)$ follows the CS activation route to yield **313** (91JA559). 2-Methylbenzothiophene also gives a product similar to **313** due to sulfur vinyl bond insertion. Thermolysis of **313** gives the more thermodynamically stable Rh(III) product of the sulfur—aryl bond insertion **314** (95JA11704). Dibenzothiophene in contrast gives the products of C—H, **315,**

and C—S, **316,** activation, **315** gradually transforming to **316** upon standing (96OM2905, 97OM1912, 97P3115). 4,6-Dimethyl- and 4,6-diethylbenzothiophene give the η^1(S) coordinated species. The C—S cleavage reaction between dibenzothiophene and $Cp^*Rh(C_2H_4)$ gives dimer **317.**

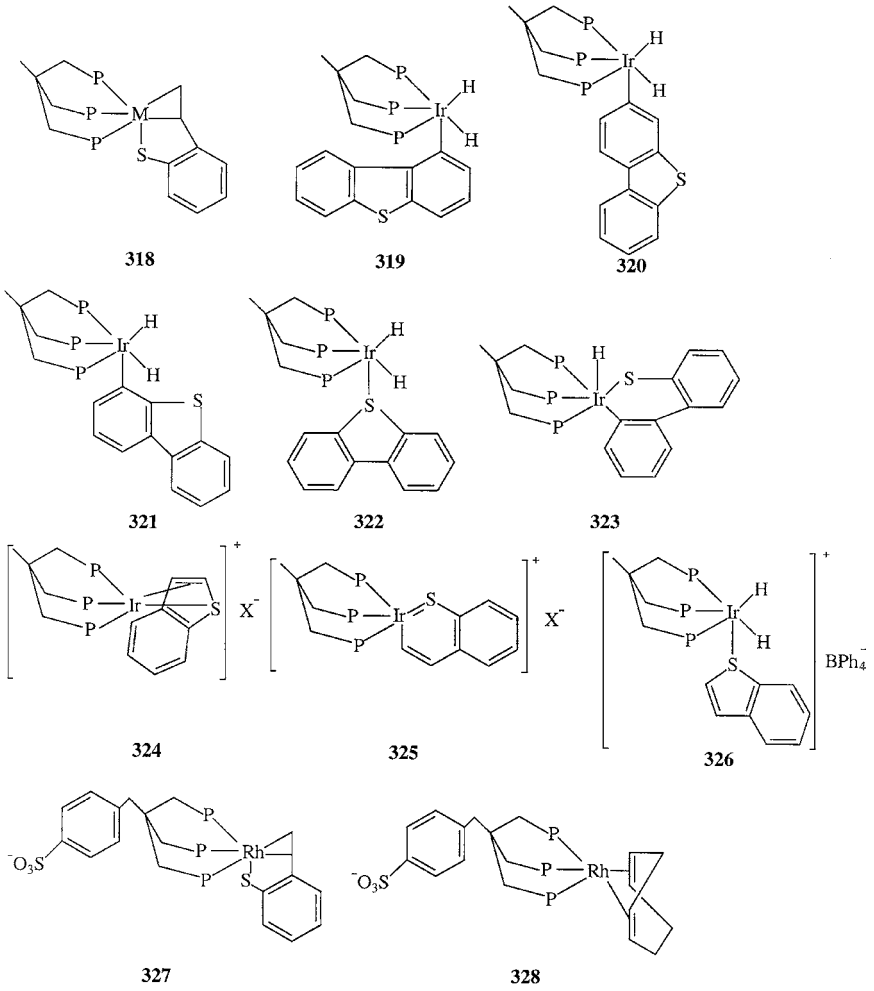


313 **314** **315**



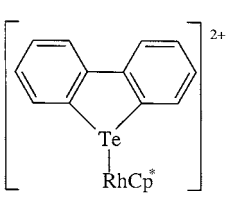
316 **317**

Benzothiophene with the unsaturated 16-electron species, [(triphos)RhH] and [(triphos)IrH], gives the ring-opened products **318** (M = Rh, Ir) where the metal has inserted to the C2—S bond (the 2-vinylthiophenolate) (95JA8567, 95OM4390, 97OM3109). The CS-cleavage by [Ir(triphos)H] is also known for 2-methylbenzothiophene [97JOM(541)143]. The same product follows from [(triphos)RhH_3] but with evolution of hydrogen gas (95JA4333, 97OM5696). An iridium analogue has also been described (93JA7505). Dibenzothiophene on thermolysis with (triphos)$Ir(H)_2Et$ yields isomeric η^1(C) coordinated species **319** and **320** (95OM2342). Protonation of **321** with triflic acid leads to a switch in the coordination mode to η^1(S) and formation of **322.** Elevated temperatures produce the CS insertion species **323** [95JOM(504)27]. Benzothiophene reacts with [(triphos)Ir(η^4-C_6H_6)]X (X = BF_4, PF_6) to give the η^3-coordinated species **324** (93JA7505, 94JA4370). Thermolysis of the product gives **325** (X = BPh_4, PF_6). Hydrogenation of **324** (X = BPh_4) leads to a change in the coordination mode to η^1(S), **326.** The product of the cleavage of the CS bond, **327,** is obtained from benzothiophene and **328** (97JA4945).



Dibenzotellurophene, $[RhCp^*Cl_2]_2$, and silver triflate yield the η^1(Te) coordinated product **329** [97JCS(D)1579]. In the absence of silver triflate, species **330** is formed. Reduction of **329** with dicyclopentadienyl cobalt results in **331.** If, however, this process is conducted in the presence of $Fe_3(CO)_{12}$, ring-opened products **332** and **333** are isolated.

A ring-opening process was also found for the product of interaction of dibenzothiophene with $[(dippe)NiH]_2$, **334,** in which molecular hydrogen was evolved (97JA10855). Other ring-opened products with nickel were also studied (83JOC2963, 86JA7763, 89JOC4848, 90S89, 93JOC2407). One was from dibenzothiophene and $Pt^o(PEt_3)_3$, **335** (93JA12200, 95JA2179, 97OM3216, 97P3185).



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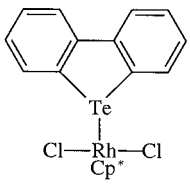
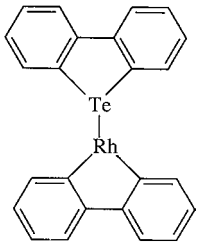


330



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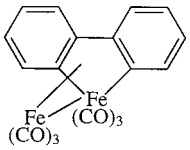

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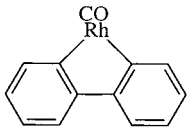
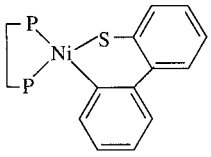


333

It is a six-membered thiaplatinacycle, the product of insertion into the C—S bond, **336,** based on benzothiophene. The corresponding thiaplatinacycles from 2-, 3-, and 4-methylbenzothiophene and 4,6-dimethyldibenzothiophene are similar (99OM1680). Meanwhile, 4,6-dimethylbenzothiophene also produces products of C—H oxidative addition, **337,** which is η^1(S) coordinated. Other phosphines, namely, PMe_3, $Ph_2P(CH_2)_2PPh_2$ [98JCS(CC)61], and PPh_3 (98OM3216), enter the same type of ring opening.



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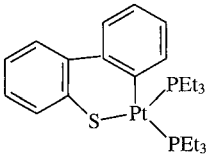

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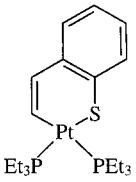

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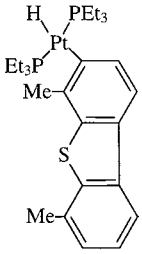

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VI. Conclusion

1. Furan is typically η^1(C) coordinated in a series of organometallic compounds. However, it is its η^2(C═C) coordination that opened a perspective toward a broad series of derivatized furans. It can be a bridging ligand forming η^1(C):η^2 (C═C) bridges. It enters into ring opening reactions. However, the intrinsic η^5-donor

function of π-excessive heterocycles is suppressed and the data on its existence are still controversial.

2. Benzannulated furans are coordinated preferentially at the aromatic ring (η^6-mode).

3. A wide range of coordination modes attests to the versatility of thiophene ligands. There are η^5-complexes, and some of them can be reduced to the η^4-species. In the latter, the nucleophilicity of the sulfur atom is greatly enhanced, thereby making this group of organometallic compounds a source of the various bridging coordination modes (e.g., η^4, S–μ_2 or η^4, S–μ_3) or remarkable ring opening reactions. The η^2-coordinated thiophenes also contain a highly activated heterocycle that can be derivatized or ring-opened. The η^1(C) pattern is widespread, but η^1(S) species are scarce if not included in the composition of a bridge. There are several pathways for direct ring opening. In addition, the μ-η^2:η^1 and μ-η^2:η^2 modes of binding organometallic frameworks were observed.

4. Benzothiophenes offer a much wider variety of organometallic representatives than benzofurans. Alongside the classical η^6 mode there occur η^1, η^2, bridging, and ring-opened patterns.

Abbreviations

[9]aneS_3	1,4,7-trithiacyclononane
AN	acetonitrile, CH_3CN
Bu^t	*tert*-butyl, CMe_3
cod	1,5-cycloctadiene
Cp	cyclopentadienyl, C_5H_5
Cp^*	pentamethylcyclopentadienyl, $C_5(CH_3)_5^-$
dippe	$(i\text{-}Pr_2PCH_2)_2$
dppe	diphenylphosphinoethane, $Ph_2P(CH_2)_2PPh_2$
Et	ethyl, C_2H_5
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
Me	methyl, CH_3
Nu	nucleophile
OTf	triflate, $CF_3SO_3^-$
Ph	phenyl, C_6H_5
Pr^i	*iso*-propyl, $CHMe_2$
THF	tetrahydrofuran, C_4H_8O
tht	tetrahydrothiophene
Tp^*	hydrotris(3,5-dimethyl-1-pyrazolyl)borate
triphos	$MeC(CH_2PPh_2)_3$

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 78

Monocyclic Furazans and Furoxans

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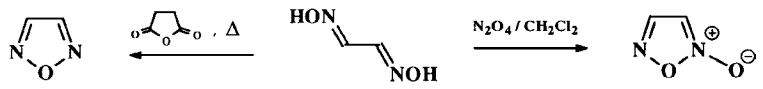
I. Introduction

Furazans (1,2,5-oxadiazoles) and furoxans (1,2,5-oxadiazole-2-oxides) have been known since the second half of the 19th century [96CHEC(II,4)229]. The synthesis of the parent compound **1** was achieved in 1964 (64JA1863, 65JOC1854), whereas the preparation of **2** was reported only recently (94MC7). In recent years, the emphasis of research has been directed more and more toward the utilization of these compounds as reactive intermediates in organic synthesis. Furazans and furoxans became of interest for preparing pharmacologically and agrochemically active agents. Additionally, a series of powerful explosives was synthesized on their basis. Various aspects of the chemistry of furazans and furoxans and of annulated derivatives (e.g., benzofurazans, benzofuroxans) have been reviewed repeatedly [81AHC251, 90CHE1199, 90KGS1443, 91MI1, 92CCC978, 92MI1, 92MI2, 94HOU648, 95H2095, 95JHC371, 96CHEC(II,4)229, 96MI1, 96MI2, 97MI1, 97MI2, 97MI3, 97MI4, 97MI13, 97MI14, 99RCR137, 99UK154]. This review covers the chemistry of *monocyclic* furazans and furoxans. The aim is to present a general picture of more than a century of development in this field. This review focuses more on the reactivity of side-chain functional groups than on the ring synthesis. A liberal selection of examples for preparations and reactions is offered. Because of the enormous amount of literature no exhaustive coverage of this field is intended. This freedom of choice is reasonable only because truly exhaustive reviews have been published in past (see the references just given).

II. Parent Compounds and Monosubstituted Furazans and Furoxans

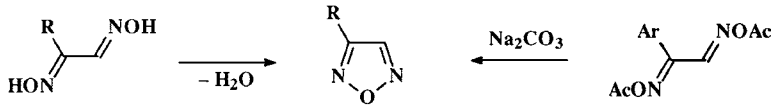
A. Synthesis

Furazan **1** was first prepared and characterized in 1964 by melting glyoxime **2** with succinic anhydride in 57% yield (64JA1863, 65JOC1854). Its *N*-oxide, furoxan **3,** has been in a focus of attention for chemists for more than a century, but was synthesized only in 1994 by oxidation of **2** with dinitrogen tetroxide in dichloromethane in 45% yield (94MC7) (Scheme 1). The *N*-oxide cannot be prepared by direct oxidation of furazan.



1 **2** **3**

Scheme 1



4 **5** **6**

R = CH_3 (45%) (88ZOR423, 92CHE927, 92KGS1101), adamant-1-yl (71%) (87ZOR2571), Ph (87%) (23G698, 65JOC1854), *p*-$CH_3C_6H_4$ (75%) (23G698), *p*-ClC_6H_4 (82%) (23G698), thien-2-yl (64%) (92CHE927, 92KGS1101, 97MI5), CH_2CO_2H (29%) (96ROC734, 96ZOR766), $CH_2CH_2CO_2H$ (65%) (1891CB1165), CH_2OAc (38%) (81ZOR1112)

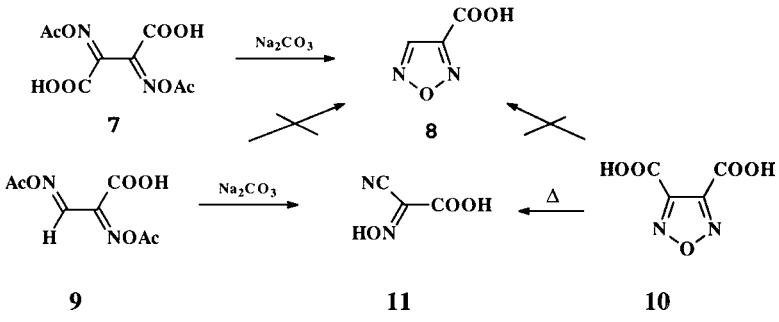
SCHEME 2

The cyclization of monosubstituted glyoximes **4** using a variety of dehydrating agents is a widely utilized method for the preparation of monosubstituted furazans **5** (Scheme 2). Acetic (23G698, 65JOC1854, 81AHC251, 87ZOR2571), succinic (65JOC1854, 92CHE927, 92KGS1101, 97MI5), and phthalic anhydride (65JOC1854, 88ZOR423), sulfuric acid (1891CB1165), and thionyl chloride (81ZOR1112, 96ROC734, 96ZOR766) may be used as dehydrating agents.

Base-promoted cyclization of *O*-acylated glyoximes **6** also affords furazans **5** (for example, Ar = Ph, 30%) (1891CB1215) (Scheme 2). The decarboxylation and ring closure of diacetyl glyoxime **7** with base to give the acid **8** was unexpected (1891CB1215). An attempt to cyclize diacetyl glyoxime **9** (1892CB904) as well as the decarboxylation of furazandicarboxylic acid **10** afforded only the ring-opened product **11** (1895CB69) (Scheme 3).

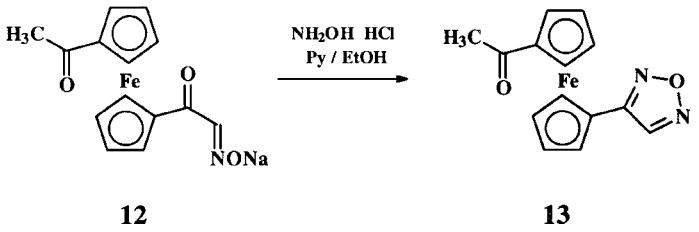
Interestingly, the ferrocene derivative **12** reacted with $NH_2OH \cdot HCl$ in pyridine to give furazan **13** in 46% yield (86ZOB1110) (Scheme 4).

Ring opening with subsequent recyclization to compound **15** occurred when 3,4-bis(hydroximinomethyl)furoxan **14** was heated in water; prolonged heating afforded the nitromethyl derivative **16** (Scheme 5). Ring opening on attack by ammonia on the furoxan **14** led to the intermediate **17,** which may be recyclized to hydroxamic acid **18** (75LA1029).



7 **8** **9** **11** **10**

SCHEME 3



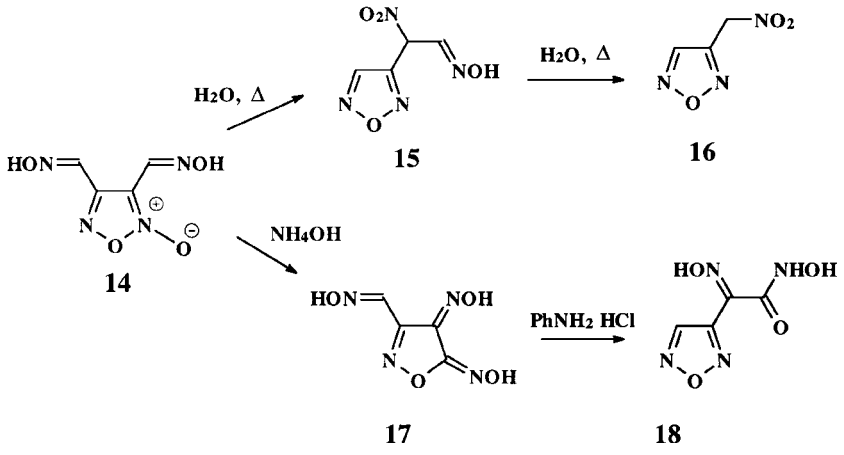
12 **13**

SCHEME 4

The furazan ring is stable under the conditions used to reduce the nitro group to the amine (Scheme 6). Thus, on treatment of compound **19** with $SnCl_2$ in HCl, the nitro group was reduced and the cyano group underwent hydrolysis and decarboxylation yielding salt **20** (30G721).

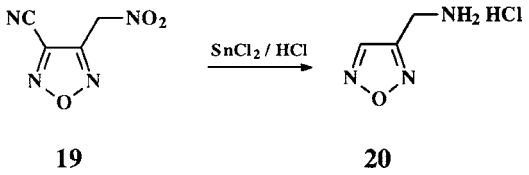
The most convenient method for preparing monosubstituted furoxans is oxidation of the corresponding glyoximes **4.** The glyoxime conformation is known to determine its reactivity. *E,Z*-Glyoximes—earlier referred to as *amphi*-glyoximes—usually gave 4-R-furoxans **21.** Thus, 4-arylfuroxans (**21,** R = Ar) were synthesized by the action of N_2O_4 on monoaryl *E,Z*-glyoximes (**4,** R = Ar) (23G25, 36G119) (Scheme 7). Since then both the mechanism and the selectivity of this reaction have been studied (79BAU2118, 79IZV2295). The oxidation may be carried out with a mixture of nitric and acetic acid (88CHE217, 88KGS258), cerium ammonium nitrate (70HCA1883), and lead tetraacetate (66MI1), as well as electrochemically (in this case, the 3-isomer was formed as a by-product) (83ZC29, 92MI1, 92MI2).

Dehydration of nitro oxime **22** bearing an electron-donating substituent with oleum gave the furoxan **21** (R = C_3H_7) in 20% yield (77BRP1474693).



14 **15** **16** **17** **18**

SCHEME 5



19 **20**

SCHEME 6

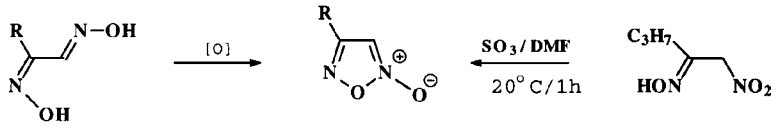
In contrast to 4-monosubstituted furoxans, only a small number of 3-monosubstituted derivatives has been reported until recently. 3-Arylfuroxans **23** were synthesized by oxidation of *Z,Z*-glyoximes **4** (earlier referred to as *anti*-glyoximes) on the action of nitric acid (27G124, 29G266) or a solution of $K_3Fe(CN)_6$ in aqueous NH_4OH (97HAC7) (Scheme 8). The reaction of nitro oxime **15** bearing an electron-withdrawing substituent with $SOCl_2$ gave the furoxan **24** in 41% yield (75LA1029). A 2:1 mixture of *E*- and *Z*-isomeric furoxan-3-aldoximes **26** was prepared from the salt **25** in 75% yield (73LA898) (Scheme 8).

A new general synthesis of 3-substituted derivatives has been reported (99MC13) (Scheme 9). Thus, the nitro group of furoxan **27** underwent a facile hydride replacement on treatment with $NaBH_4$ in EtOH to give 3-monosubstituted furoxans **23.** The result of this reaction is independent of the nature of R.

It should be noted that the oxidation of 3-amino-4-phenylfuroxan by CF_3CO_3H gives a mixture of the furoxan **23** (R = Ph) with 3-nitro-4-phenylfurazan and 3-nitro-4-phenylfuroxan (82BAU573, 82IZV646).

B. REACTIVITY

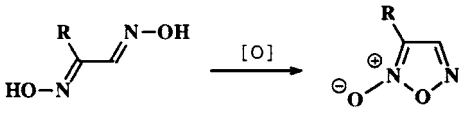
Neither furazan **1** nor the *N*-oxide **3** are suitable starting materials for the preparation of other derivatives of these ring systems because they undergo ring cleavage reactions quite easily. Alkylation of **1** with trimethyloxonium tetrafluoroborate (64JA1863, 65JOC1854) or dimethyl sulfate (74AJC1917) produced



E,Z-**4** **21** **22**

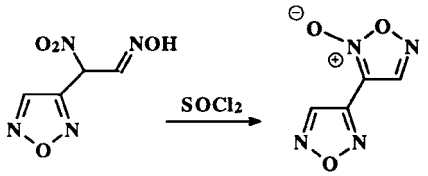
R = Ph (35–90%) (23G25, 36G119, 79BAU2118, 79IZV2295), *p*-$CH_3C_6H_4$ (50%), *p*-ClC_6H_4 (24%), *p*-BrC_6H_4 (50%), thien-2-yl (22%) (97HAC7), 3-R-adamant-1-yl (60–71%) (88CHE217, 88KGS258), CO_2H (100%) (26G247), Cl (49%) [63T(S)143, 92MI1, 92MI2], $C(NOH)NO_2$ (47%) (93CHE952, 93KGS1117)

SCHEME 7

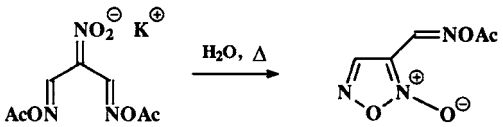


Z,Z-**4** **23**

R = Ph (50%), *p*-$CH_3C_6H_4$ (34%), *p*-BrC_6H_4 (24%), thien-2-yl (13%)



15 **24**

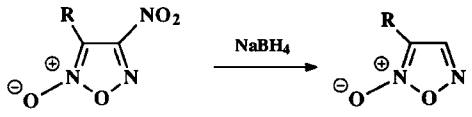


25 **26**

SCHEME 8

the *N*-2 quaternary salts. Furazan **1** forms coordination compounds of type [M (furazan)$_3$] ($SbCl_5$)$_2$, with M = Mg^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, and Ni^{2+} [78ZN(B)1120].

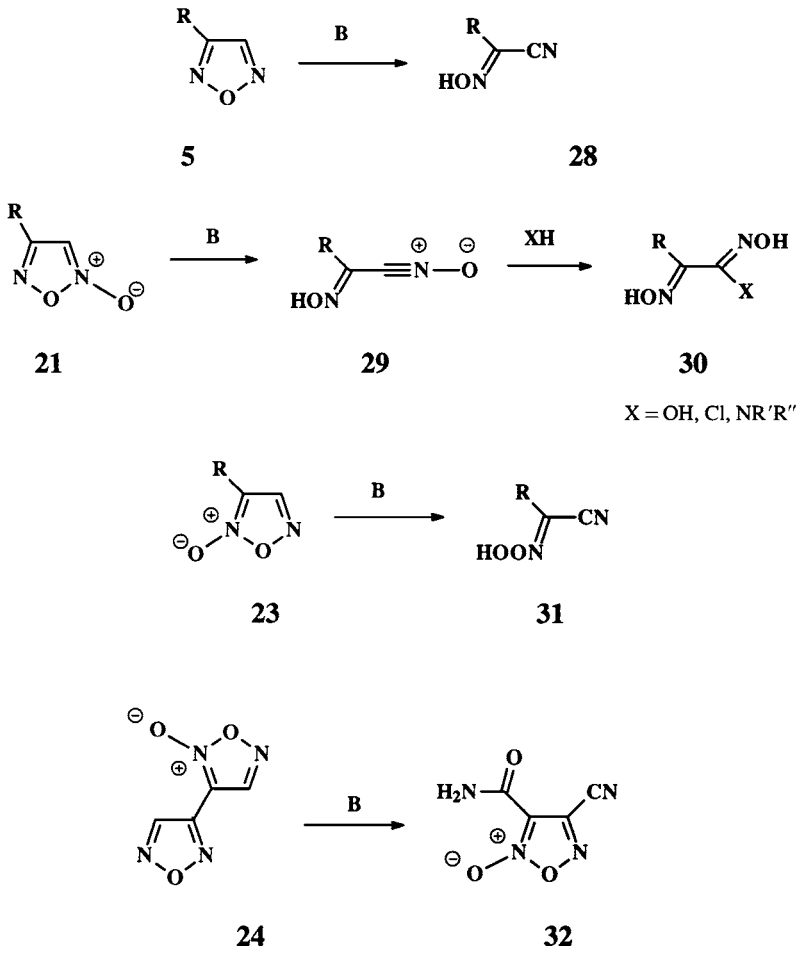
All monosubstituted furazans and furoxans are quite sensitive to bases, which cause ring-opening reactions with the formation of nitriles **28** (from **5**) (1891CB1165, 1891CB1215, 23G698, 65JOC1854, 74MI1, 78ANL385, 87ZOR2571, 96MC246, 97HAC7, 98MC135), nitrile oxides **29** (from 4-substituted furoxans **21**) (28G191, 36G114, 41G693, 66FCF62, 70HCA1883, 71MI1,



27 **23**

R = Me, Et, Ph, CO_2Et

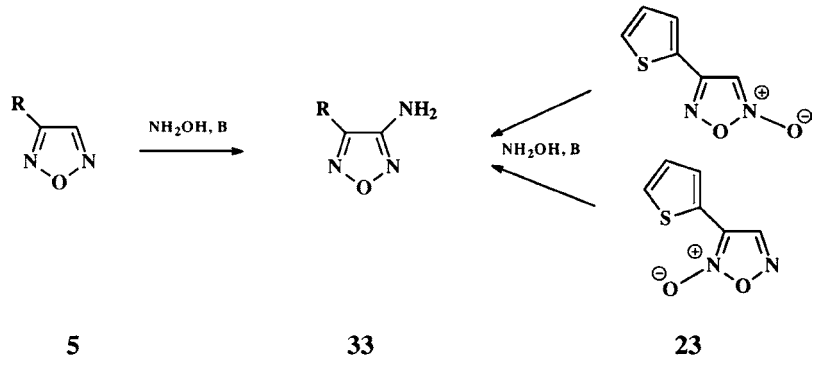
SCHEME 9



SCHEME 10

72JOC593), and *aci*-nitro compounds **31** (from 3-substituted furoxans **23**) (27G124) (Scheme 10). Base attack is favored at the position adjacent to the more highly electron-withdraw-ing substituent. Usually the nitrile oxide **29** reacts further with nucleophilic reagents present in the reaction mixture to give glyoximes **30.** Both rings in furazanylfuroxan **24** were opened on treatment with base and the intermediate formed then cyclized to give nitrile **32** (75LA1029).

The furazan ring-cleavage reaction occurred when **1** or **5** was treated with Ac_2O at elevated temperatures to produce acylated derivatives of **28** (65JOC1854). Ring opening with subsequent recyclization also occurred when furoxan **3** was reacted with H_2SO_4 to give 3,4-bis(hydroximinomethyl)furoxan **14** (94MC7). Further



5 **33** **23**

R = CH_3, thien-2-yl, 3-aminofurazan-4-yl

SCHEME 11

examples of nucleophilic attack on monosubstituted furazans leading to ring cleavage and subsequent transformation to aminofurazans **33** have been described (88ZOR423, 96MC246, 97MI5). An unusual formation of **33** was found to occur on treatment of 3-thien-2-yl- and 4-thien-2-ylfuroxan with NH_2OH in aqueous KOH (97HAC7) (Scheme 11).

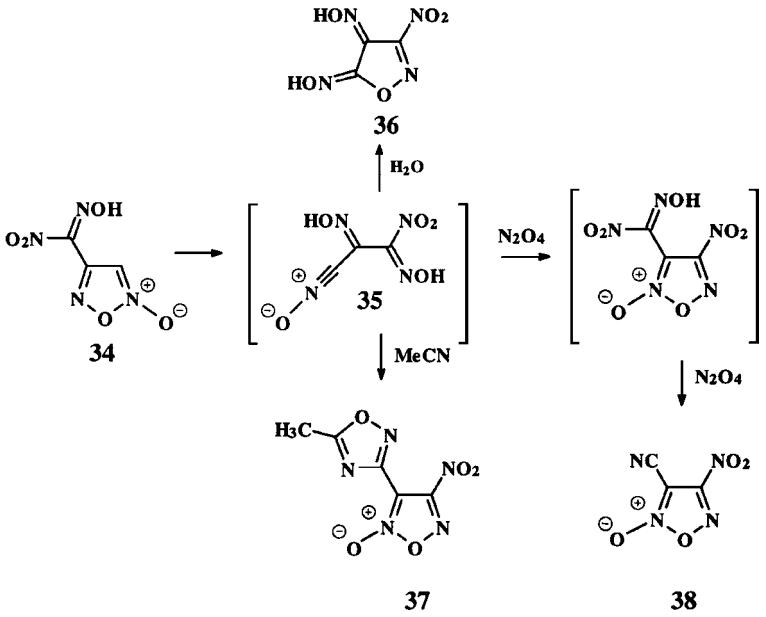
Furoxan nitrolic acid **34** was converted into isoxazoline **36** (96% yield) on storage in CH_2Cl_2 solution in the presence of water (93CHE1099, 93KGS1283) (Scheme 12). The intermediate **35** could be trapped as [3 + 2] cycloaddition product **37.** Reaction of nitrolic acid **34** with an excess of N_2O_4 also occurred via **35,** giving 3-cyano-4-nitrofuroxan **38.**

3-Arylfuroxans **23** (R = Ar) underwent isomerization to 4-arylfuroxans **21** during electrolysis via formation of a cation radical (86BAU1543, 86IZV1691). The thermal isomerization of 4-arylfuroxans **21** afforded 3-arylfuroxans **23** (79BAU2118, 79IZV2295, 83G811).

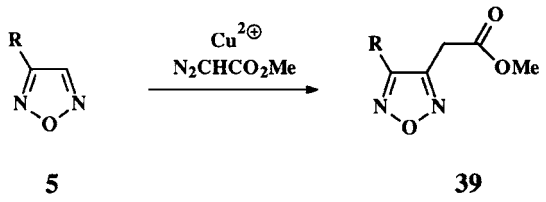
There is a single example of an electrophilic reaction at the ring carbon of a furazan.

Thus, insertion of methoxymethylcarbene in the C–H bond of a furazan occurred on thermolysis of **1** or **5** with methyl diazoacetate in the presence of copper stearate to give methoxycarbonylmethylfurazans **39** in 9–12% yields (89BAU2640, 89IZV2876) (Scheme 13).

Oxidation of methylfurazan **5** (R = Me) with potassium permanganate under acidic conditions gave the corresponding carboxylic acid **8** in 40% yield, which was converted into the methyl ester by the reaction with methanol and HCl in 65% yield (92CHE927, 92KGS1101). The vinyl ether **41** was synthesized by vinyl exchange reaction from hydroxymethylfurazan with vinyl acetate (85ZOR1357) (Scheme 14). The starting material can be obtained by several different routes (30G721, 85ZOR1357); however, the use of ester **40** is particularly suitable.

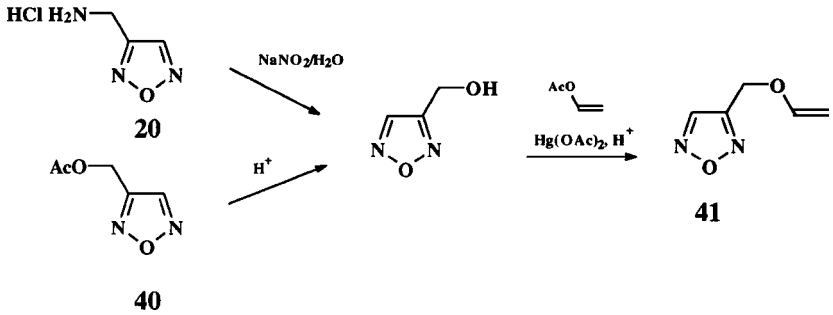


SCHEME 12

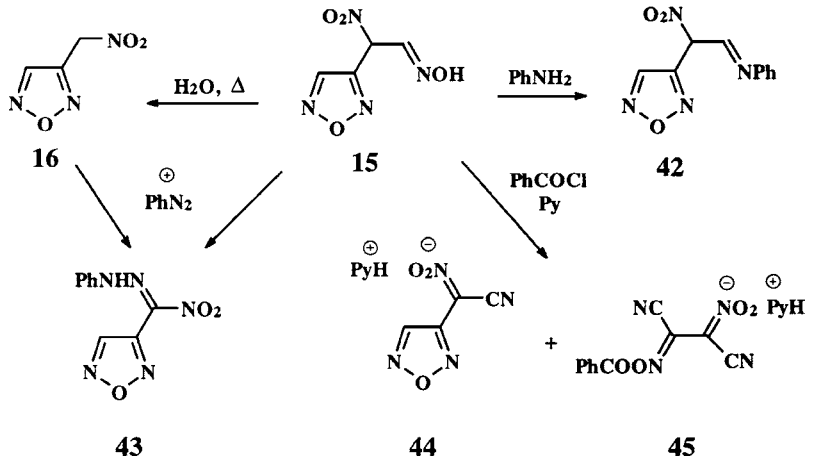


R = H, Ph, thien-2-yl

SCHEME 13



SCHEME 14

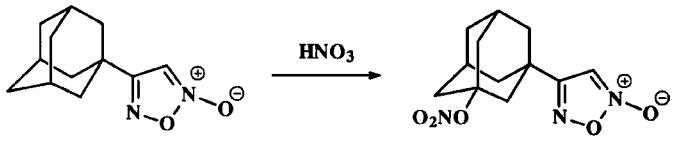


SCHEME 15

Elimination of the hydroxyaminomethyl moiety from nitro oxime **15** by treatment with a diazonium salt gave hydrazone **43** (75LA1029) (Scheme 15). The same product was obtained by coupling the diazonium salt with the compound **16.** On heating in aniline, oxime **15** was transformed into Schiff base **42.** Acylation of the oxime **15** with benzoyl chloride in pyridine led to a mixture of furazan **44** and dinitrile **45.**

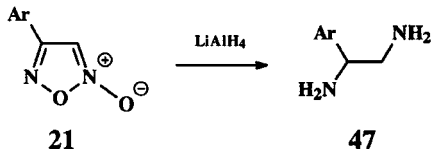
Electrophilic substitution in phenylfurazan and phenylfuroxan occurred in the benzo ring, predominantly at the 4-position. For example, bromination of phenylfurazan with bromine in the presence of Ag_2SO_4/H_2SO_4 yielded *p*-bromophenyl products in 82% yield (78ANL385). Similar results were obtained on nitration with fuming nitric acid, which gives nitro or dinitro products (74MI1, 83G811). Nitrating 4-adamantylfuroxan in nitric acid (d 1.5) at 26°C for 2 hours afforded the nitrate **46** in 78% yield (88CHE217, 88KGS258) (Scheme 16).

In the presence of an acid, 4-arylfuroxans **21** (R = Ar) are reduced with $SnCl_2$ to yield furazans **5** (36G119). With a stronger reducing agent, such as Zn/AcOH, the furoxan ring was cleaved to afford the corresponding glyoxime **4** (36G119). Diamines of type **47** were prepared from **21** using $LiAlH_4$ (57CB2124) (Scheme 17).



46

SCHEME 16



SCHEME 17

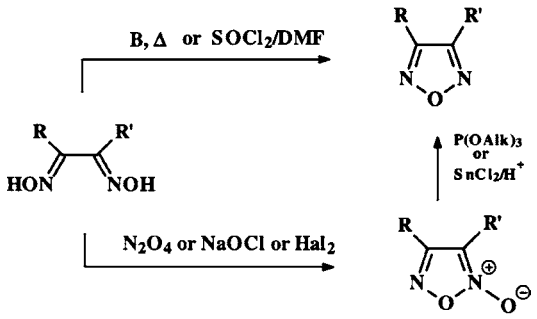
III. Alkylfurazans and -Furoxans

A. SYNTHESIS

Furazans and furoxans bearing aliphatic substituents have been prepared by standard procedures (Scheme 18). Thus, the dehydration of glyoximes to furazans is usually carried out by heating with aqueous base or with a mixture of $SOCl_2$/DMF (1895CB69, 33G334, 73IZV842, 74URP435240, 78URP591468). Treatment of alkylfuroxans with $P(OAlk)_3$ or $SnCl_2$ afforded the corresponding furazans [32G432, 64CB575, 69JCS(C)1901]. The syntheses of alkylfuroxans are usually carried out by oxidation of glyoximes with N_2O_4, NaOCl, or halogens (28G329, 59TAL235, 74URP422736, 75MI1, 76URP481617, 80URP721430, 80URP721431, 90BAU551, 90IZV630, 97T1751).

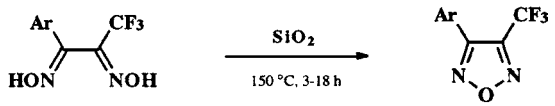
An unusual method for the preparation of 3-(trifluoromethyl)-4-aryl-furazans **49a,b** in 47–77% yield has been reported (99H627) (Scheme 19). Thus, dehydration of 1,1,1-trifluoroalkane-2,3-dione dioximes **48a,b** was accomplished on heating with silica gel. If, as in **48b,** Ar was an electron-withdrawing moiety, the conversion proceeded more smoothly. The dehydration of the same dioximes using traditional methods failed.

Vinyl azides **50** (73CJC2406) and vicinal vinyl nitro compounds of type **51** (57JOC456, 75MI1) can be precursors for furoxans and furazans (Scheme 20).



R, R′ = Me, Et, Pr, Bu, $ArCH_2$, Ar, CH_2Hal

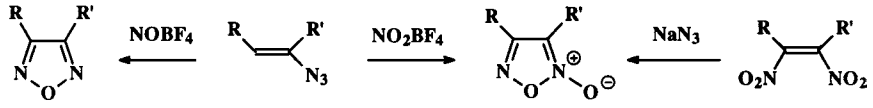
SCHEME 18



48a,b **49a,b**

a: Ar= *p*-Tol; **b**: Ar = *p*-$O_2NC_6H_4$

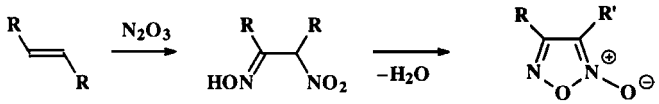
SCHEME 19



50 **51**

R, R′ = Me, Pr, Bu

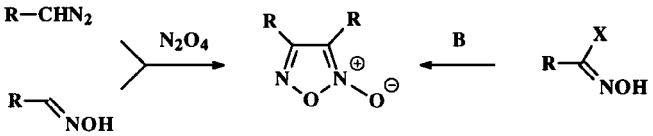
SCHEME 20



52

R, R′ = Me, Et, Pr, Ar, CH_2OH

SCHEME 21



R = CCl_3, CF_3, $C(NO_2)_2F$, C_2F_5, C_3F_7, Me, Et, Pr, $FcCH_2$ and others

X = Cl, Br, NO_2

SCHEME 22

Addition of N_2O_3 to alkenes and dehydration of the intermediate nitro oximes **52** is another efficient pathway to furoxans (35JPR277, 73CJC2406, 74GEP(O) 2336403, 77BRP1474693, 91LA1211) (Scheme 21).

The common methods for the preparation of furoxans are treatment of diazomethanes and aldoximes with N_2O_4, and base-promoted dimerization of nitrile oxides (73HCA457, 73MI1, 74IZV2513, 75JOC2626, 80DOK636, 80MI2, 84JOC919) (Scheme 22).

The choice of a pathway for the synthesis of certain compounds is determined by the presence of functional groups at the alkyl substituent.

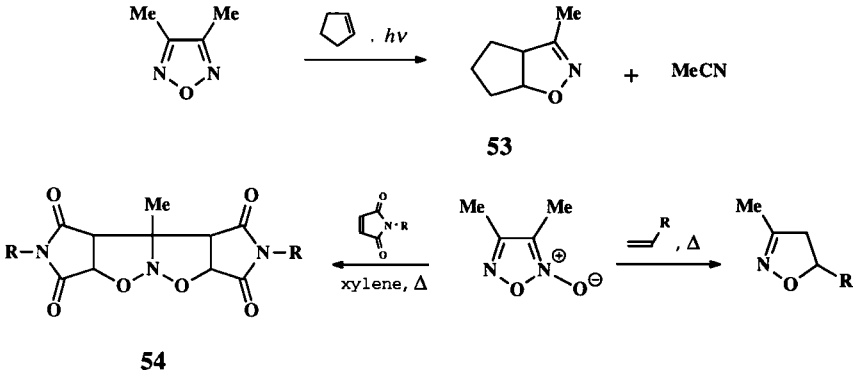
Because of the difficulties encountered in preparing starting materials, further data on the synthesis of these compounds are rare. Exceptionally, 3,4-dimethylfurazan [63OS(IV)342] and 3,4-dimethylfuroxan (1890CB3490, 80URP721430) were synthesized in a straightforward manner from commercially available dimethylglyoxime.

B. Reactivity

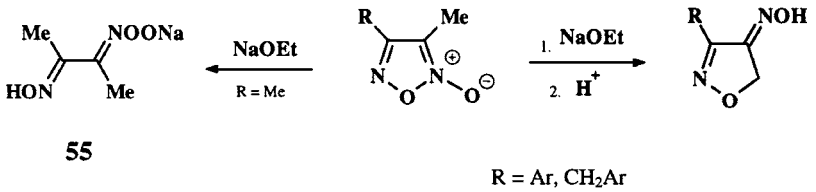
Few reports describe reactions of the ring of alkylfurazans and furoxans.

Cantrell and Haller have found that dimethylfurazan on irradiation in the presence of excess cyclopentene gives bicycle **53** [68JCS(CC)977]. Mitchell and Paton have observed retro cyclization of dimethylfuroxan at elevated temperatures. The generated nitrile oxide could be trapped by electron-rich alkenes to give isoxazolines (79TL2443). With male-imides in refluxing xylene dimethylfuroxan reacts as nitrone to give tetracycles **54** in yields up to 70% (85T727) (Scheme 23).

Furoxans bearing a methyl group at C-3 give hydroximino derivatives of isoxazolines on treatment with NaOEt (Angeli rearrangement) (81G167, 89AP513) (Scheme 24). In contrast, under similar conditions dimethylfuroxan affords salt **55** [63T(S)143]. On heating with aqueous alkali, alkylfuroxans are decomposed.

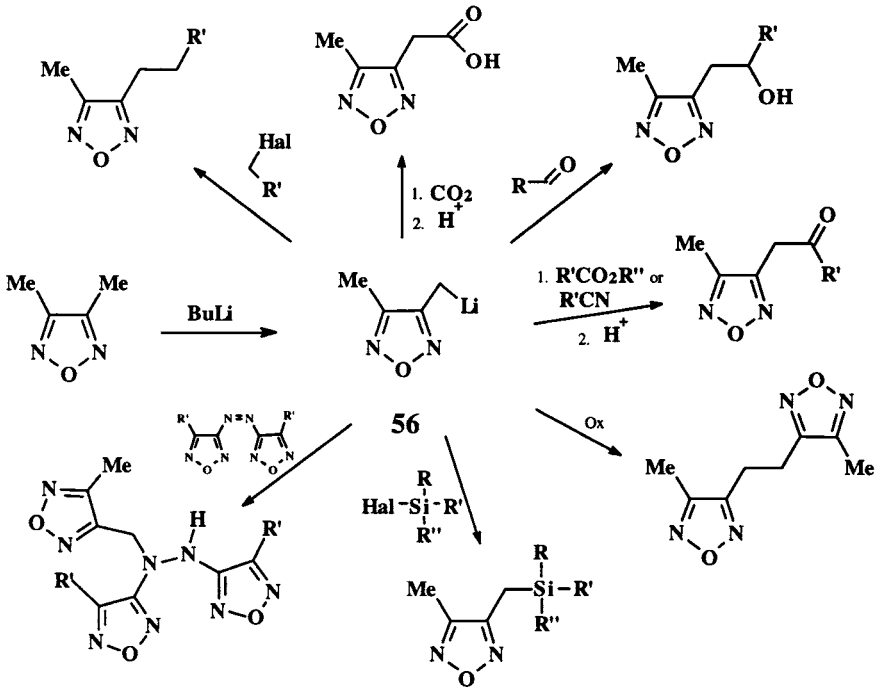


SCHEME 23

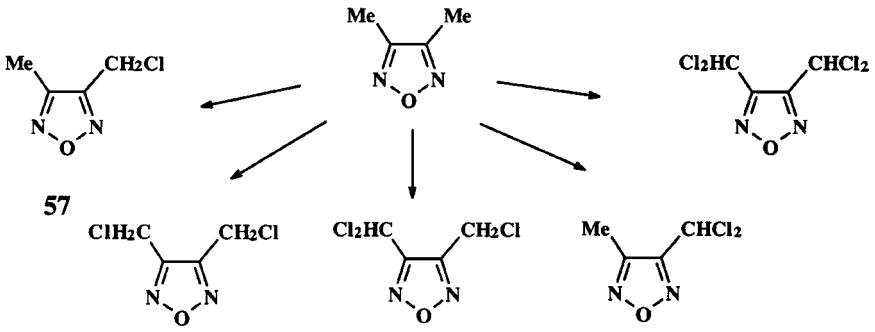


SCHEME 24

Under standard conditions, condensations of a methyl group on furazan and furoxan rings with aromatic aldehydes was not feasible. However, alkyl substituents on the furazan and the furoxan ring can undergo functional transformations that depend on the electron-withdrawing properties of the rings. Micetich provided the first method for lithiation of 3,4-dimethylfurazan (70CJC2006). This compound readily underwent lithiation with *n*-butyllithium at the methyl group. The lithiated intermediate **56** reacts with electrophiles at −55°C to give a variety of α-functionalized alkylfurazans (Scheme 25) (92BAU281, 92IZV365, 99MI5, 000UP6). The electrophile can be an alkyl halide, a chlorosilane, a carbonyl compound, a nitrile, or an ester, and an azo compound. Oxidative coupling of **56** with I_2, copper(II) chloride, or 1,2-dibromoethane afforded 1,2-difurazanylethane. A



SCHEME 25



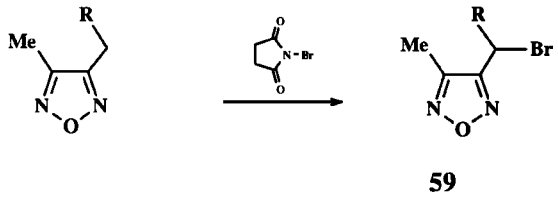
SCHEME 26

similar procedure using two equivalents of BuLi and two equivalents of an electrophile offers an access to α,α′-difunctionalized derivatives.

Under mild conditions the methyl group at the furazan ring is resistant to chlorination. Vigalok and co-workers reported, however, that at 150–155°C with a high excess of Cl_2 dimethylfurazan yielded a mixture of halo derivatives (77CHE25, 77KGS30, 78ZOR1255) (Scheme 26). When dimethylfurazan was treated with one equivalent of SO_2Cl_2 in the presence of benzoyl peroxide (BPO) or azobis(isobutyronitrile) (AIBN) only **57** was formed (77CHE25, 77KGS30, 96WO29328). A second equivalent of SO_2Cl_2 afforded α,α′-dichloro compound **58** (96WO29328).

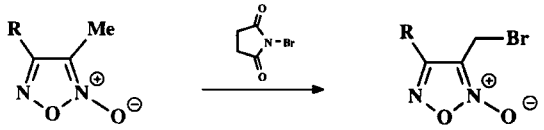
Treatment of alkylfurazans with NBS in the presence of BPO or AIBN gave α-bromoalkyl derivatives **59** (81GEP2919293, 84JMC1201) (Scheme 27). Similar results were obtained with 3-methylfuroxans (95JHC811, 96HCA1803, 98JMC5393).

An alternative synthesis of α-haloalkyl derivatives is based on the transformation of hydroxymethylfurazans and -furoxans. Thus, treatment of hydroxymethyl compounds with thionyl chloride gave α-chloro products [95GEP(O)4401150, 96IZV1782, 96RCB1692]. Hydroxymethylfuroxans reacted with phosphorus tribromide (77H1173), thionyl bromide, or a mixture of NBS and methyl sulfide to give bromo derivatives (98JMC5393). The chlorine atom in α-chloroalkyl groups underwent exchange with other halogen atoms (80MI3, 96IZV1782, 96RCB1692). These α-haloalkyl derivatives are excellent starting materials for side-chain-substituted furazans and furoxans through classical nucleophilic substitution reactions. The halogen atom is readily replaced by a wide range of oxygen, sulfur, nitrogen, phosphorus, and carbon nucleophiles to give the corresponding products in good yields [77CHE25, 77H1173, 77KGS30, 78ZOR1255, 80MI3, 81GEP2919293, 84JMC1201, 95GEP(O)4401150, 95JHC811, 96HCA1803, 96IZV1782, 96WO29328, 96RCB1692, 98JMC5393, 000UP3] (Scheme 28).



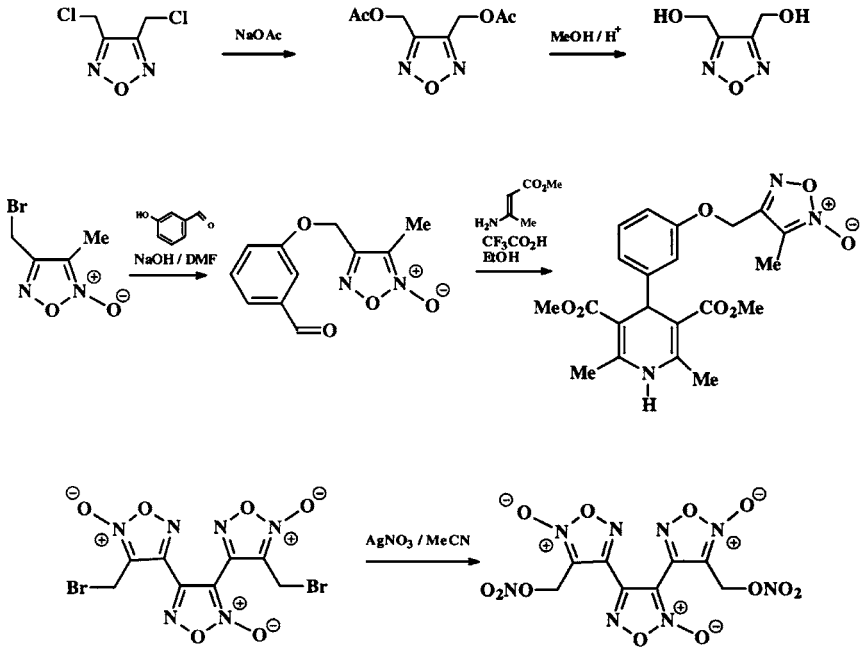
59

R = H, Me, Et

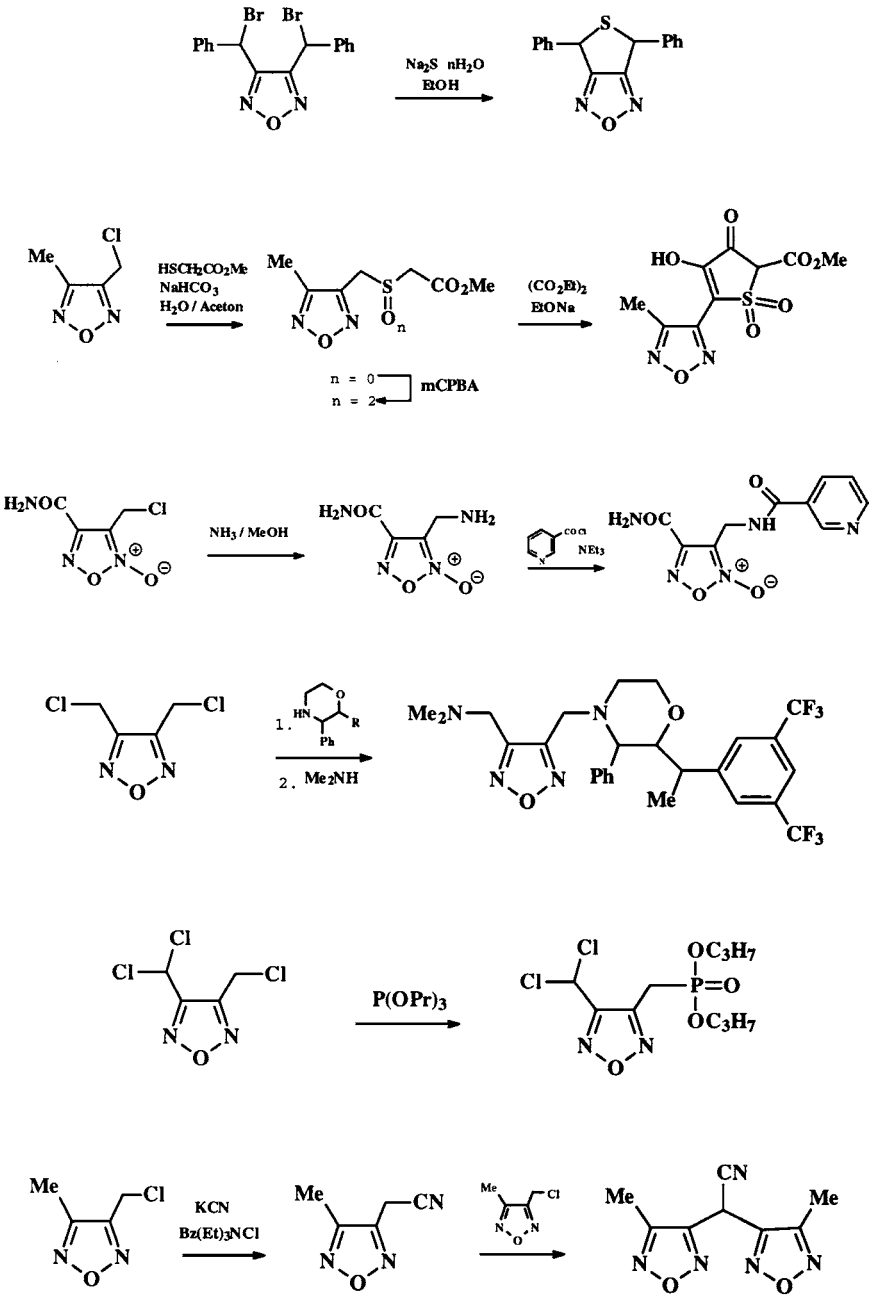


R = Me, Ph, CH=NOH, $CONH_2$, OEt, OPh

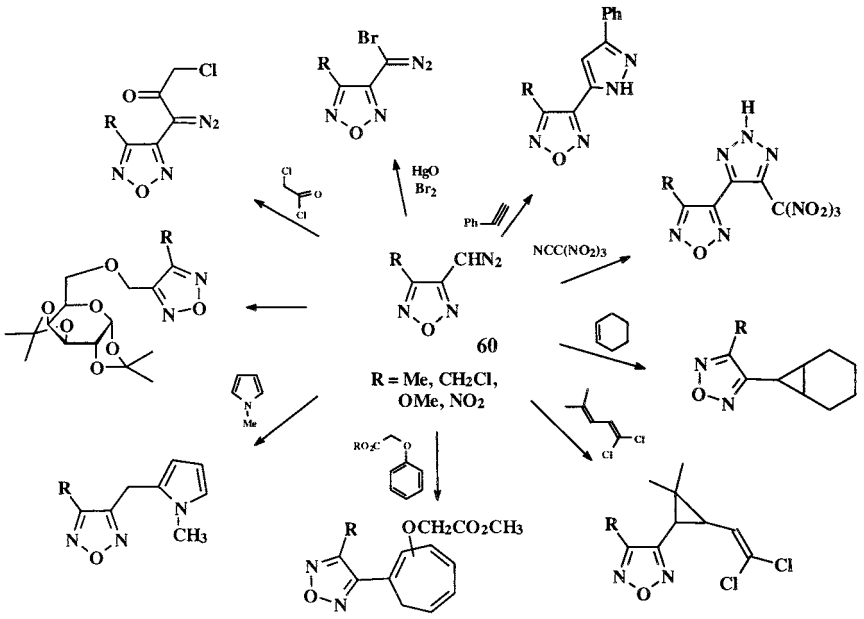
SCHEME 27



SCHEME 28



SCHEME 28 (*Continued*)



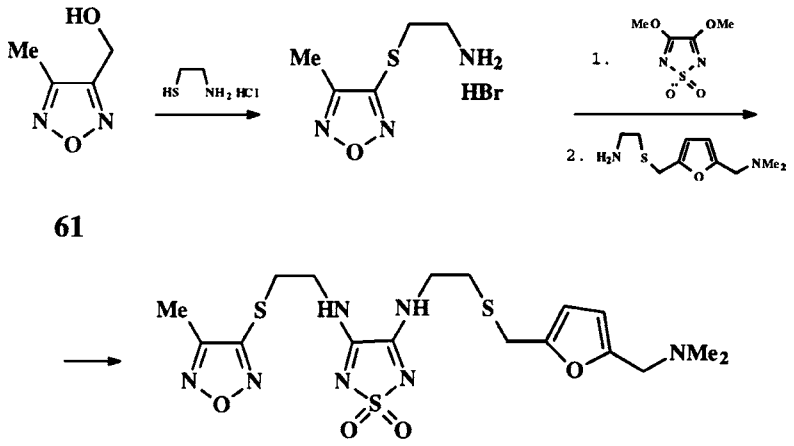
SCHEME 29

Sheremetev and co-workers employed diazo compounds of type **60,** prepared from the corresponding amines in moderate yields as alternative excellent precursors for the preparation of side-chain-functionalized derivatives (Scheme 29). Several furazans bearing reactive groups or cyclopropyl or five-membered heterocyclic substituents have been prepared by standard procedures (99MI6).

Side-chain functionalities react in an expected manner. For example, treatment of hydroxymethylfuroxan with HNO_3 and H_2SO_4 gives the corresponding nitro ester (96IZV1782, 96RCB1692).

Reaction of 2-aminoethanethiol hydrochloride with hydroxymethylfurazan **61** in 48% aqueous hydrobromic acid (reflux, 24 h) gave a salt that on treatment with an equimolar amount of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide and another amine gave compound **62** (84USP4471122) (Scheme 30).

When 3,4-dihydroxymethylfurazan was reacted with aldehydes, ketones, vinyl acetate, vinylic ethers, or ethynyl ketones in the presence of a catalyst, dioxepanes of type **63** were formed in 50–80% yields (81ZOR1047, 82ZOR1319, 84CHE846, 84KGS1044, 85ZOR1357, 90BAU920, 90IZV1031) (Scheme 31). Under similar conditions as well as on treatment with acrylonitrile, hydroxymethylfurazan afforded linear ethers (82ZOR1319, 85ZOR1357).

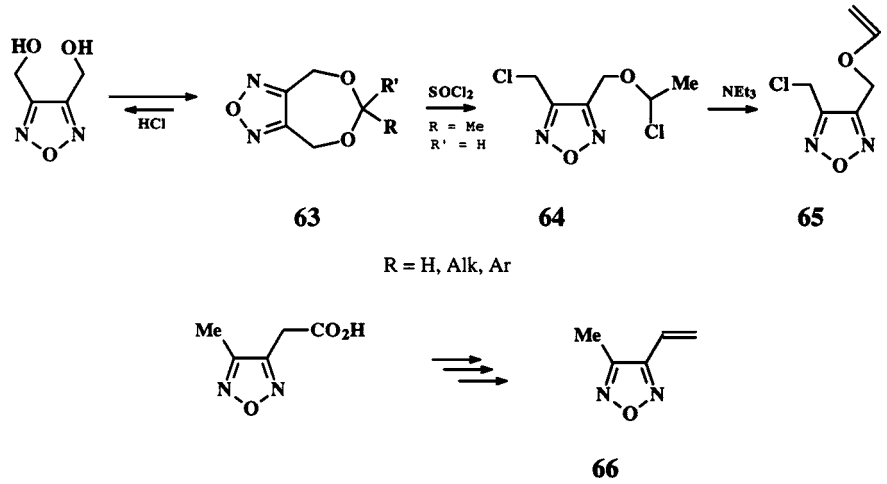


61

62

SCHEME 30

Dioxepanes **63** were hydrolyzed with aqueous hydrochloric acid to the starting diol. A thionyl chloride promoted ring-opening of dioxepane **63** to intermediate **64** has been reported. When treated with base, compound 64 can be transformed into vinylic ether **65** in 58% yield (81ZOR1047) (Scheme 31). 3-Methylfurazan-4-acetic acid was converted to the vinyl derivative **66** via an esterification, reduction, mesylation, and base elimination sequence (81JHC1247) (Scheme 31).

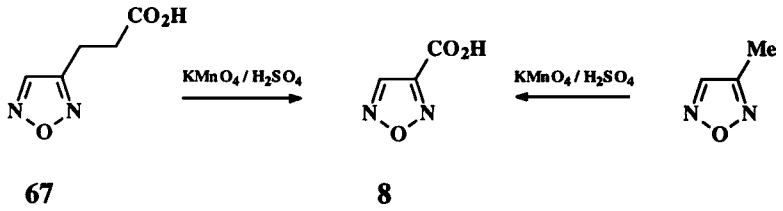


63 64 65

R = H, Alk, Ar

66

SCHEME 31



67 **8**

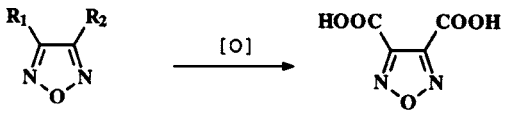
SCHEME 32

IV. Furazanic and Furoxanic Acids

A. SYNTHESIS

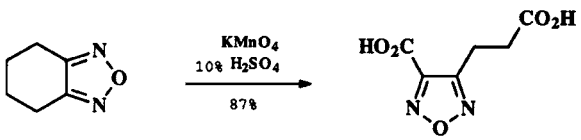
The preparation of furazancarboxylic acid **8** by treating furazan-β-propionic acid **67** with potassium permanganate in sulfuric acid was reported by Wolff and Gans in the 19th century (1891CB1165) (Scheme 32). Strelenko *et al.* reported the oxidation of methylfurazan, which with the same reagent gives furazancarboxylic acid in 40% yield (92CHE927, 92KGS1101) (Scheme 32). The acid **8** is also available from furazan-3-carbo-nitrile (e.g., with aqueous sodium hydroxide) (31G943).

Oxidation of 3,4-dimethylfurazan (1895CB69), 3-ethyl-4-methylfurazan (42G333), and 1-(4-methylfurazan-3-yl)-ethanone (22G289) with $KMnO_4$ under acidic conditions gives 4-methylfurazan-3-carboxylic acid. Dicarboxylic acid **10** has been prepared by oxidative side-chain degradation of different pre-cursors (1895CB69, 46G3, 61BCJ270, 79CHE261, 79KGS319) (Scheme 33). Under mild



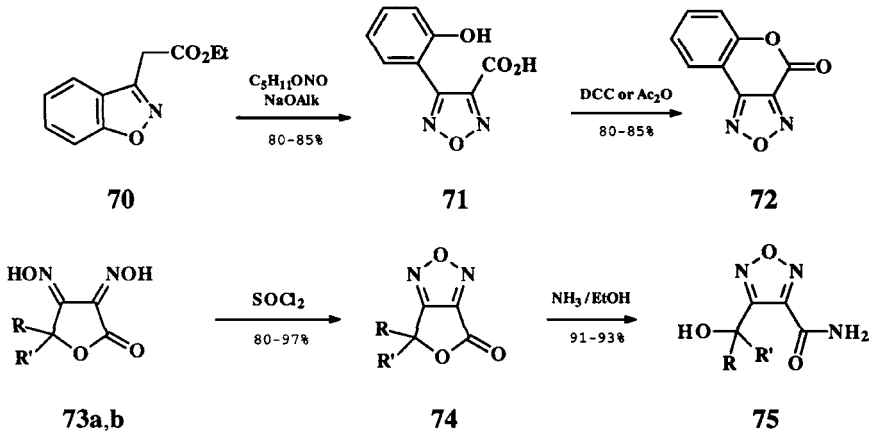
10

R^1, R^2 = Me, Et, Ac, CO_2H, $CH_2CH_2CO_2H$



68 **69**

SCHEME 33



R, R′ = H, Me

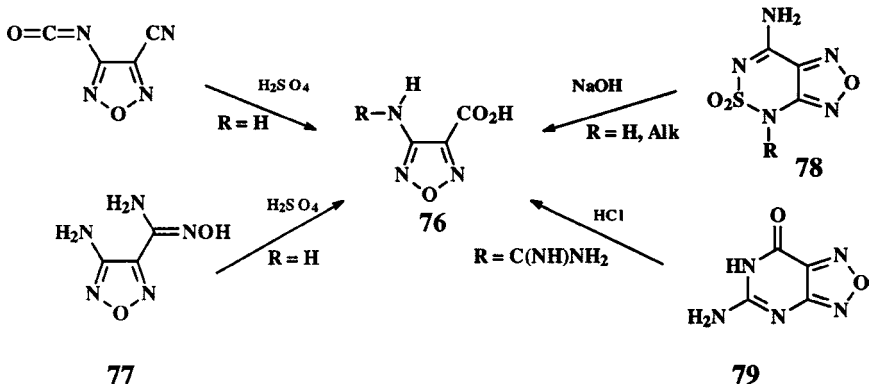
SCHEME 34

conditions, oxidation of fused furazan **68** afforded dicarboxylic acid **69** (61BCJ270).

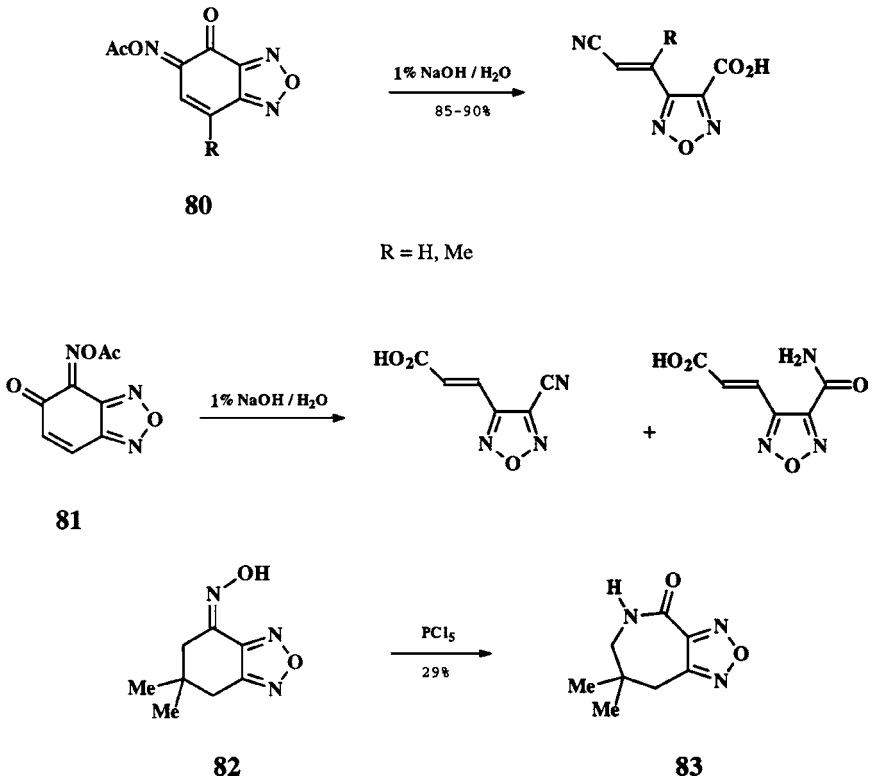
4-Phenylfurazan-3-carboxylic acid was synthesized by oxidation of 3-methyl-4-phenylfurazan (82CHE21, 82KGS27).

In the course of the nitrosation of benzisoxazole **70,** furazancarboxylic acid **71** was isolated as the main product (83JHC385) (Scheme 34). Lactonization to **72** could be effected with DCC or Ac_2O. Other lactones, such as **74,** have been prepared by dehydration of glyoximes **73** with $SOCl_2$ in dioxane. These compounds were used in the synthesis of amides **75** (79S977) (Scheme 34).

Several approaches to 4-amino-3-furazancarboxylic acid are known (Scheme 35). Thus, saponification of isocyanatofurazancarbonitrile with conc. sulfuric acid



SCHEME 35

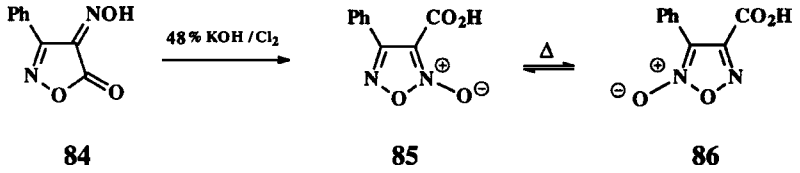


SCHEME 36

yields acid **76** (30LA43). The carboxamidoxime **77** reacts similarly (31G575, 94CHE608, 94CHE470, 94KGS534, 94KGS693). *N*-Alkylated derivatives of aminofurazancarboxylic acid were also obtained from 1,2,6-thiadiazine dioxide derivatives **78** with sodium hydroxide (81MI1, 83H2351). Ring-opening reactions of the pyrimidine ring in **79** yield guanidine derivative **76** [R=C(NH)NH_2] [84T879].

The Beckmann rearrangement in *O*-acetylated oximes **80** and **81** gave a series of unsaturated furazanic acids (75G723) (Scheme 36). A similar rearrangement of oxime **82** with PCl_5 afforded azepine **83** (90CCC245, 99RCR137, 99UK154).

There are two isomeric 3(4)-methyl and 3(4)-phenyl furoxancarboxylic acids. The straightforward approach to these compounds involved hydrolysis of the corresponding esters or amides (72JHC577). The phenyl derivatives (**85, 86**) have been prepared from isoxazol-4,5-dione-4-oxime **84** (90LA335) (Scheme 37). Both acids are also available from the corresponding carbinols and aldehydes by oxidation with Jones' reagent (91LA1211, 93FA48).



84 **85** **86**

SCHEME 37

Utilizing a common strategy for benzofuroxan synthesis, the related annulated furoxan **88** has been obtained from azidonitro compound **87** by heating in ethanol (83LA1901) (Scheme 38).

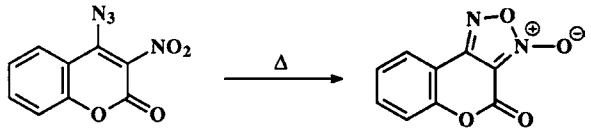
Treatment of nitrolic acid **34,** which is in turn available from hydroximino malonaldehyde dioxime (N_2O_4 in CH_2Cl_2, 20 min, 10–15°C), with TFA gives furoxan-4-carboxylic acid in 35% yield (93CHE952, 93KGS1117) (Scheme 39).

A set of methodologies has been extended to the preparation of furoxan-3,4-dicarboxylic acid diesters. Some of these routes are outlined in Scheme 40 (58JA4333, 67ZOR1201, 72CPB97, 76AP781, 83JOC5384, 83T2247, 86BCJ2827, 86T1407, 89JOC5277, 91JA1364, 91TL3075, 93IZV147, 93RCB131, 94IZV103, 94JA6513, 94MI4, 94RCB98). Similar approaches have been used for the preparation of furoxan-3,4-dicarboxamides (82EUP54873, 83JOC5384, 89TL3193). Hydrolysis of furoxan-3,4-dicarboxylic acid diesters under acidic conditions is a route to monoesters (09LA52). In contrast to *furazan*dicarboxylic acid, *furoxan*dicarboxylic acid is unstable.

Pyridylfuroxancarboxamides **90** were prepared from the corresponding glyoximes **89** on treatment with NaOCl (93EUP575754) (Scheme 41).

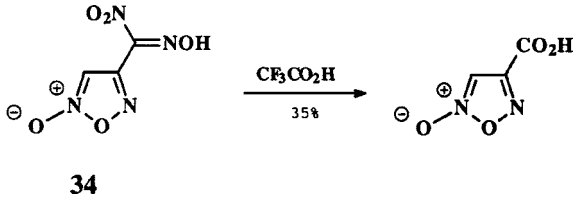
One-pot procedures were utilized for the preparation of hydroxymethylfuroxancarboxylic acid derivatives **91** and **92** starting from the cyclic glyoxime **73a** (Scheme 42) [94GEP(O)4307105, 94WO20478, 95WO19355].

Treatment of ethyl acrylate with sodium nitrite/sulfuric acid yields ethyl 4-nitrofuroxan-3-carboxylic acid, albeit in low yield (97ROC1140, 97ZOR1216). Furoxancarbonitriles were prepared by oxidation of cyano glyoximes (31G51, 31G943, 75LA1029, 93CHE1099, 93KGS1283, 95EUP683159, 97CHE927,



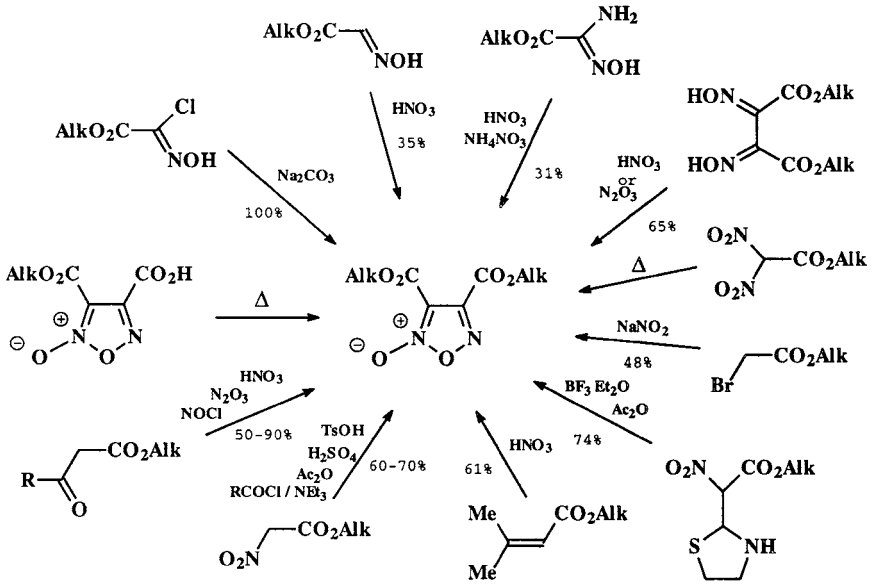
87 **88**

SCHEME 38

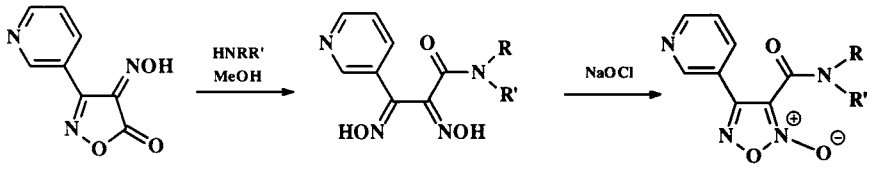


34

SCHEME 39

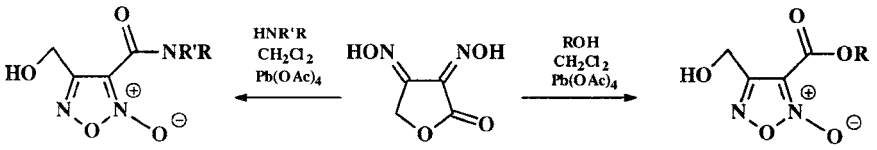


SCHEME 40



89 **90**

SCHEME 41



91 **73a** **92**

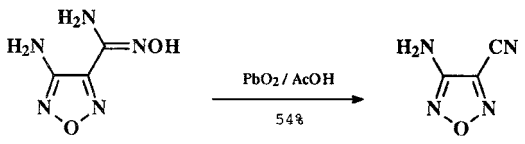
SCHEME 42

97KGS1115), by destructive nitration of cyano acetic acid derivatives (25LA7, 62T79, 73USP3832249, 75JCED135), and by dehydration of hydroxyaminomethyl and carboxamido derivatives (75LA1029, 90LA335, 98AF212).

3-Amino-4-cyanofurazan has been prepared by treatment of amidoxime **77** with PbO_2 in acetic acid (94CHE608, 94KGS693) (Scheme 43).

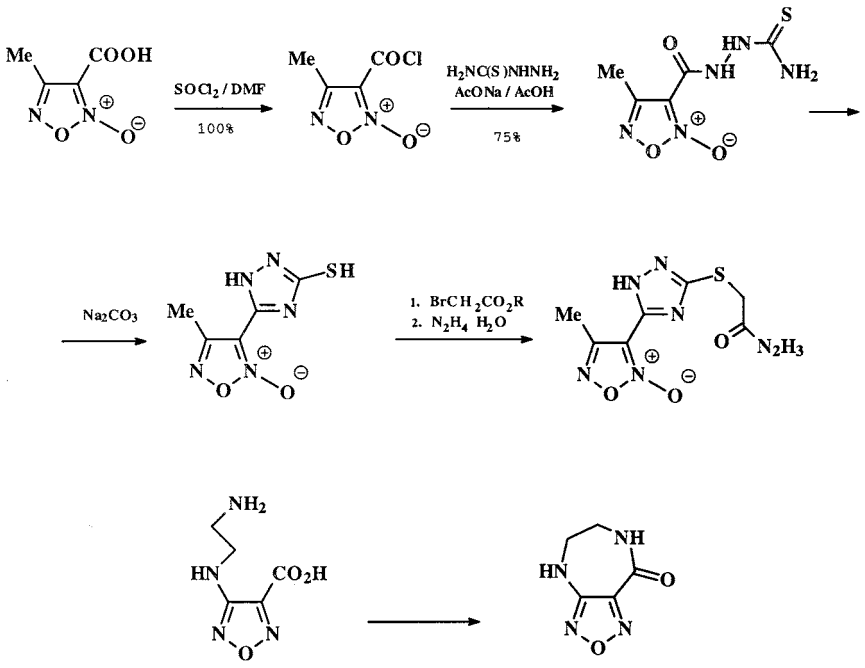
B. REACTIVITY

Both isomeric methylfuroxancarboxylic acids have pK_a values of 1.3 (72JHC577). Methylfurazancarboxylic acid has pK_a 1.6 (as an acid) (72JHC577) and pK_{aBH+} 5.2 (as a base) (81CHE27, 81KGS35). The proton of 2,4-dinitrobenzoic acid is of comparable acidity (p$K_a = 1.425$). Dissociation constants, absorption spectra, and the electrochemical behavior of 4-aminofurazan-3-carboxylic acid have been reported (83H2351). The distribution of furazanmonocarboxylic acid derivatives between different solvents [92JCS(P2)1643] and the electrochemical behavior have been investigated (83ZOB2511). The carboxylic group on the ring can be converted to the corresponding acid chloride (46G3, 67USP3322751, 68BRP1124920, 73FA624, 90LA335, 92AF921, 92ZOR422, 93ZOR400, 98JMC5393], ester [71FA241, 83JHC385, 90LA335, 92CHE927, 92KGS1101, 92ZOR422, 98MC238, 98JMC5393), amide (09LA80, 46G3, 64CB575, 67USP3322751, 68BRP1124920, 69TL3619, 71FA241, 72JHC577, 77FA789, 82EUP54873, 83JHC385, 90LA335, 92ZOR422, 93ZOR400, 95JMC4944, 98JMC5393), and hydrazide (71FA241, 72JHC577, 73FA624, 79CHE261,



77

SCHEME 43

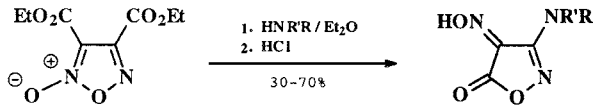


SCHEME 44

79KGS319, 97MI3, 97MI4, 97MI14) in good yields. These routes are illustrated in Scheme 44.

It should be noted that furoxan amides and hydrazides could only be prepared in aqueous solution. In ether solution, reaction of diethyl furoxandicarboxylate with amines and hydrazine derivatives have been shown to give isoxazolones **93** (Scheme 45) (08CB3512, 09LA52, 09LA80).

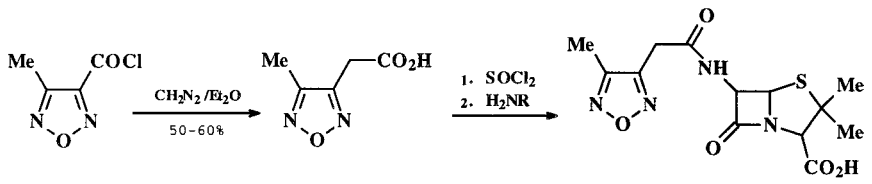
Methylfurazancarboxylic acid chloride was transformed into the corresponding acetic acid **66,** which was used for the preparation of penicillanic acid derivatives (Scheme 46) (67USP3322751).



93

R, R′ = H, Me, Et, $(CH_2)_5$, NHPh

SCHEME 45



66

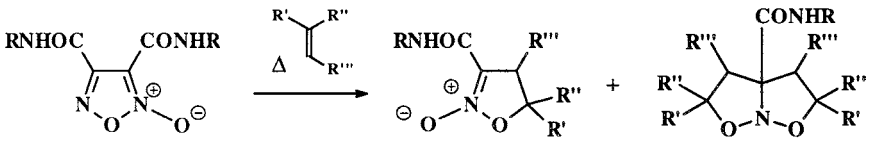
SCHEME 46

Amides and hydrazides behave normally in the Hofmann and Curtius rearrangements (see section on amines). The deoxygenation of derivatives of furoxancarboxylic acids to the corresponding furazans has been accomplished with triethyl phosphite (64CB575), a mixture of Zn/AcOH (68T395), $SnCl_2$/HCl/AcOH (31G943, 94IZV679, 94RCB630), and sodium borohydride/ethanol (96BAU1692, 96IZV1782, 96RCB1692). Treatment of phenylfurazancarboxylic acid with ethyl chloroformate and subsequent reduction with sodium borohydride yields the corresponding carbinol (91LA1211).

The acids lose carbon dioxide when heated above their melting points. Decarboxylation of furazancarboxylic acids was accompanied by ring opening to give the corresponding α-hydroximinoacetonitriles (1895CB69, 75G723, 83JHC385). Furoxancarboxylic acids on thermolysis generated the corresponding α-hydroximinoacetonitrile oxides (25G453, 74TL627, 85T727, 90LA335, 93FA48, 98PHA758), which could be trapped with dipolarophiles to give the corresponding cycloadducts. When amide **94** was refluxed in xylene with dipolarophiles, isoxazoline oxides **95** and bicycles **96** were obtained in low to moderate yields (Scheme 47) (85T727).

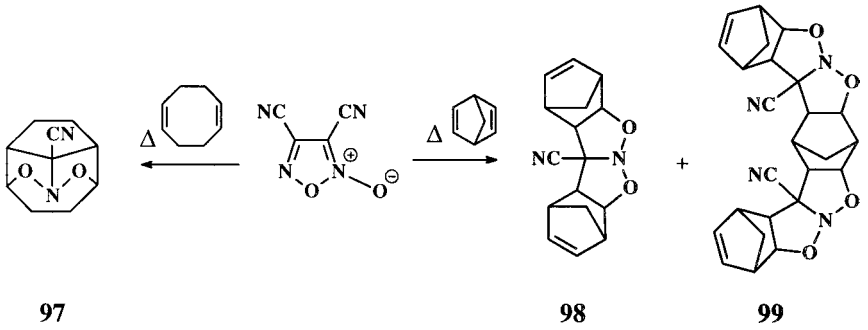
Interestingly, the intramolecular cycloadduct **97** (15%) was obtained from the reaction of 3,4-dicyanofuroxan with 1,5-cyclooctadiene. In contrast, with norbornadiene only intermolecular products **98** (30%) and **99** (14%) were obtained (85T727) (Scheme 48).

Nitrile groups attached to the furazan and furoxan rings are susceptible to nucleophilic reagents. The nitrile group was easily reacted with azides (68USP3386968,



94 **95** **96**

SCHEME 47



97 **98** **99**

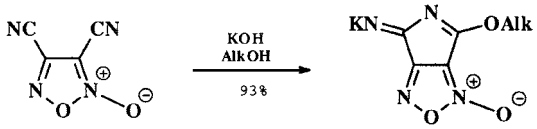
SCHEME 48

94CHE608, 94KGS693, 97CHE973, 97KGS1115), hydroxylamine (82H1063, 94BAU382, 94CHE608, 94IZV444, 94KGS693, 97CHE927, 97KGS1115), hydrazines (73USP3740947, 82H1063, 94CHE608, 94KGS693, 95IZV1559, 95RCB1499), and alcohols (75LA1029, 99ZOR315). Note that 3,4-dicyanofuroxan on treatment with an alcoholic solution of KOH afforded a bicyclic salt (Scheme 49) (75LA1029).

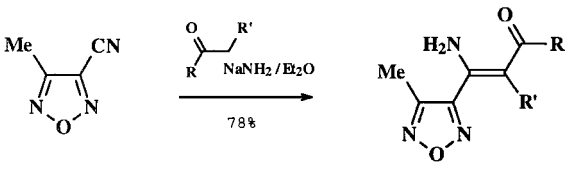
Enolate anions react with 3-cyano-4-methylfurazan giving enamines (Scheme 50) (75JAP(K)50049271, 77H1985, 78BCJ3059, 82H221).

The reaction of 3-amino-4-cyanofurazan with β-dicarbonyl compounds in the presence of catalytic amounts of nickel acetylacetonate ($Ni(acac)_2$) gave labile enamines that on treatment with acetic acid afforded fused pyridines of type **100** in 80–95% total yields (Scheme 51) (94MC57). Further syntheses of furazanopyridines can be found in the review by Sheremetev (99RCR137, 99UK154).

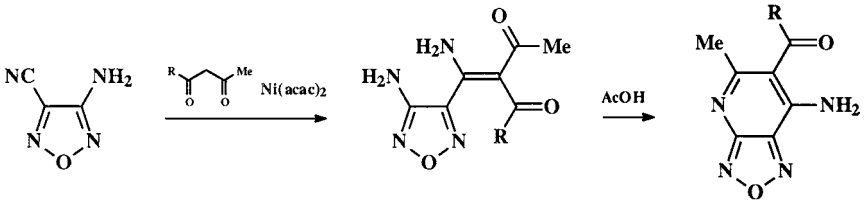
There have been several reports concerning the reactions of furazans and furoxans bearing cyano (94CHE608, 94KGS693, 97CHE973, 97KGS1115, 97MI10, 98CHE1220, 98KGS1430, 99ZOR315), imidic ester (93IZV1776, 93RCB1700, 99ZOR315), amidoxime (90T3941, 94BAU382, 94CHE470, 94IZV118, 94IZV444, 94KGS534, 94RCB114, 97CHE927, 97KGS1115), and chlorooxime (92CHE581, 92KGS687, 94CHE370, 94KGS420) groups, producing a variety of hetaryl derivatives, as illustrated in Scheme 52.



SCHEME 49

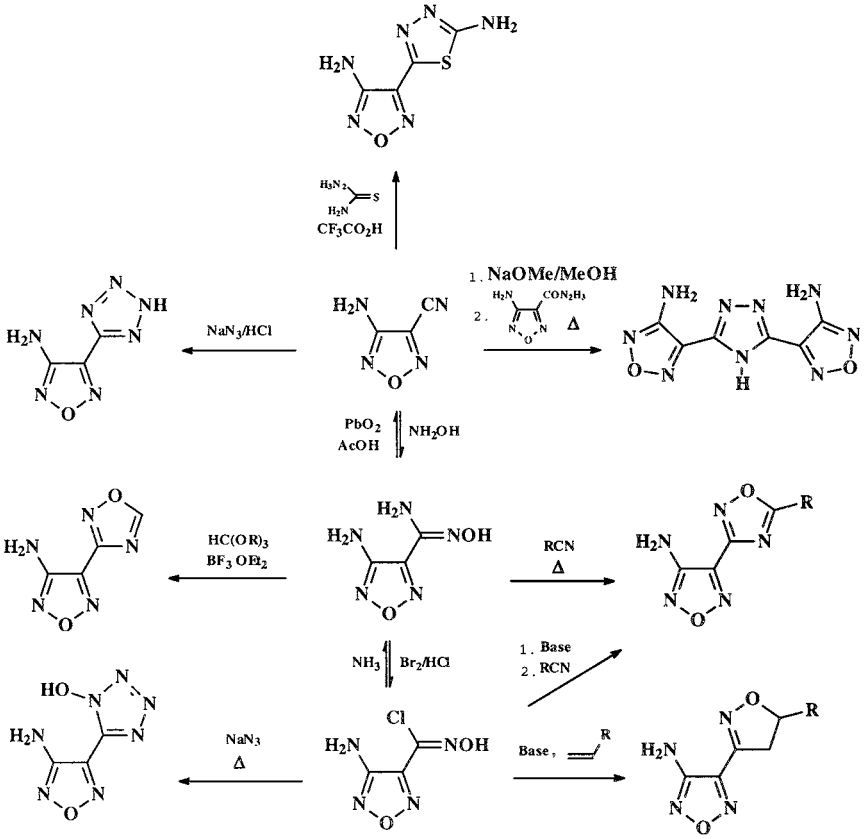


SCHEME 50

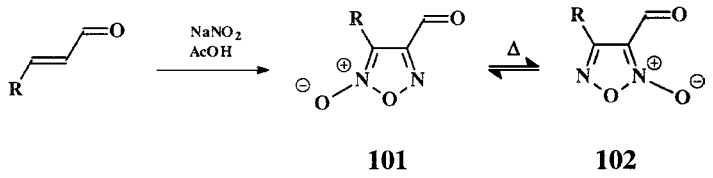


100

SCHEME 51



SCHEME 52



101 **102**

R = Me (40%), Pr (51%), Ph (%)

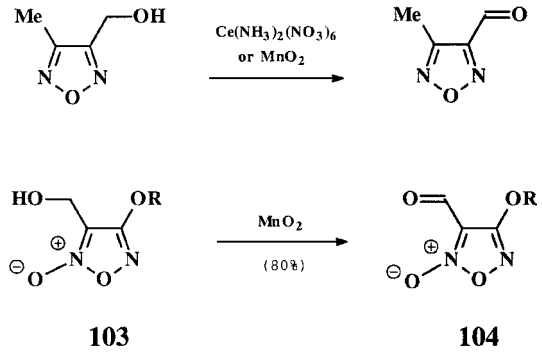
SCHEME 53

V. Furazan and Furoxan Aldehydes and Ketones

A. SYNTHESIS

Gasco and co-workers found that furoxan-4-aldehydes **101** can be synthesized, in moderate yield, by direct treatment of the corresponding acrolein derivatives with dinitrogen trioxide (Scheme 53) (89JHC1345, 92AF921). Thermally induced isomerisation gives the 3-isomers **102.** 3-Methylfurazan-4-aldehyde was also obtained by oxidation of the corresponding furazanmethanol with ceric ammonium nitrate in 3.5 N nitric acid at 50°C for 6 hours (Scheme 54) (84JMC1201). Manganese dioxide oxidation in $CHCl_3$ after 4 hours at room temperature gave the aldehyde in 55% yield (92AF921). Furoxan-3-methanols **103** have also been employed in the synthesis of furoxan aldehydes **104.** The manganese dioxide dehydrogenation gave furoxan-3-carbaldehydes **104** without significant isomerization (96HCA1803).

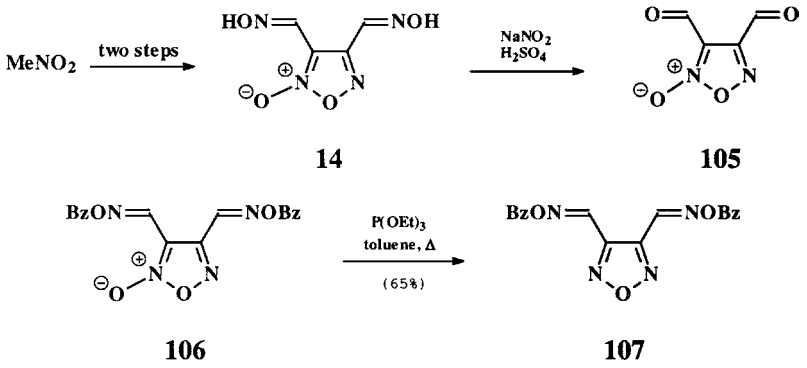
Furoxan dialdehyde **105** has been prepared from the bisaldoxime **14** by desoximation with nitrous acid. The bisaldoxime **14** was prepared by a two-step procedure from nitromethane [25LA7] (Scheme 55). The benzoylated oxime **106**



103 **104**

R = Et, Ph

SCHEME 54



SCHEME 55

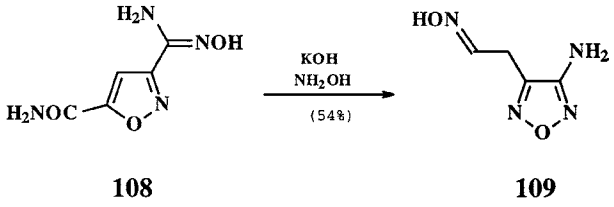
can be reduced to the corresponding furazan **107** by heating with triethyl phosphite (75LA1029).

The mononuclear heterocyclic rearrangement (MHR) of isoxazole-3-amidoxime **108** in the presence of a base and hydroxylamine with concomitant removal of the amide moiety affords furazan acetaldoxime **109** (Scheme 56) (91CHE651, 91KGS827).

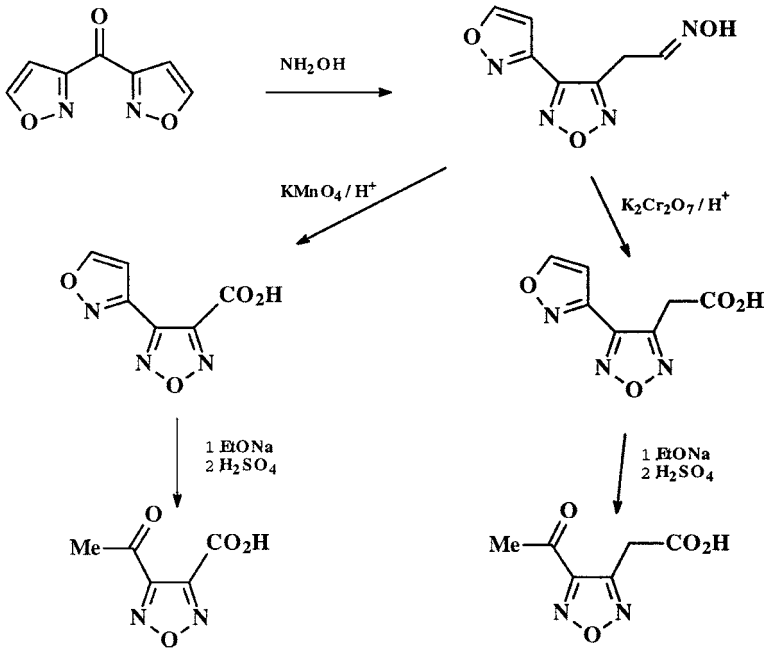
An elegant synthesis of a wide range of carbonyl derivatives of furazan from di-3,3′-isoxazolyl ketone with MHR as key step was developed in 1946 by Quilico and Freri (46G3). The intermediate acetaldoxime derivative was produced in 85% yield. It was converted regioselectively into the functionalized acetylfurazans (Scheme 57).

β-Keto derivatives and their oximes have also been prepared from various isoxazoles with an α-oxime group in the side chain at 3-position via MHR [33G159, 37G779, 38G792, 39G391, 83JCS(P1)483, 91CHE651, 91KGS827] (Scheme 58). Further information on these rearrangements can be found in the reviews of Ruccia *et al.* (81AHC141) and Andrianov *et al.* (90CHE1199, 90KGS1443).

In a synthetic approach to acetylfurazans and their *N*-oxides, an oximation and dehydration or oxidation of 3-hydroximinopentan-2,3-dione resulted in the formation of the furazan ring [22G289, 37G388, 87JCS(P2)523] (Scheme 59).

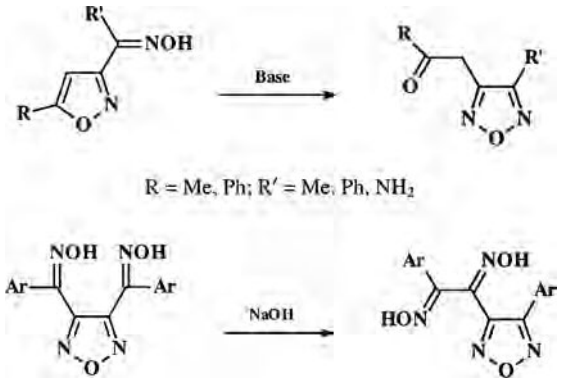


SCHEME 56

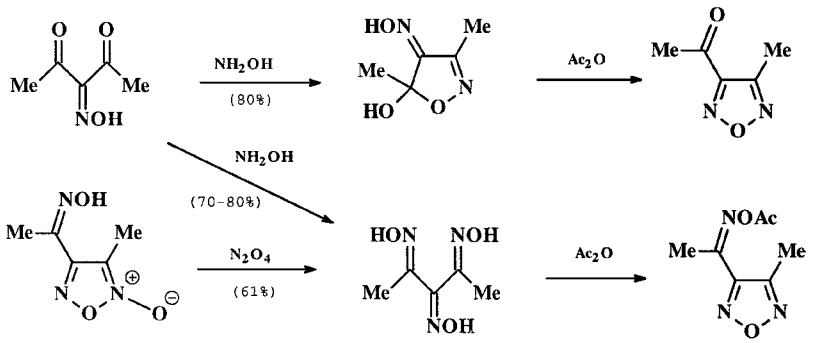


SCHEME 57

A traditional and widely used method for the synthesis of diacylfuroxans is the reaction of methyl ketones with a nitrosating/nitrating source (Scheme 60). Thus, a wide variety of aliphatic (66TL1727, 68JOC866, 74BSF1691, 87MI1, 99KGS1259), aromatic (55JA4233, 77MI2, 92JHC87, 94BCJ757, 95AJC1969, 95ZOB1378, 99H895), and heterocyclic (32G436, 54JOC1897, 58JOC1024, 61JOC5239, 63JOC3542, 68JHC379, 77CHE1356, 77KGS1692, 85ZOB1565,



SCHEME 58



SCHEME 59

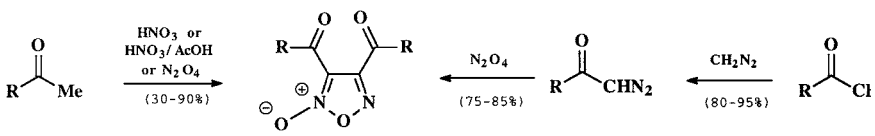
91CHE656, 91KGS833, 94IZV485, 94RCB445, 99KGS1619) methyl ketones are nitrosated and oxidized by the action of nitric acid, or diluted nitric acid in acetic acid solution, or dinitrogen tetroxide, to the corresponding symmetrical diacylfuroxans in good to excellent yields. The mild reaction conditions and commercial availability of the reagents make this an attractive method. A detailed study of the conversion of methyl ketones into furoxans has been carried out [85JCS(P2)1643]. A complementary synthesis is based on the nitrosation/nitration of diazoketones (Scheme 60) (68RZC289, 71CHE804, 71KGS859, 71SC121, 72URP350795, 77CHE1356, 77KGS1692, 77MI2).

Brittelli and Boswell described the synthesis of di(cycloalkanoyl)furoxans by treatment of ethynyl cycloalkanes with nitronium tetrafluoroborate (81JOC312, 81JOC316). Although the aliphatic precursors gave good yields of the corresponding furoxans, rections with ethynyl-substituted aromatic compounds failed. A furoxan bearing cage moieties **110** was prepared under similar conditions (Scheme 61) (98H271).

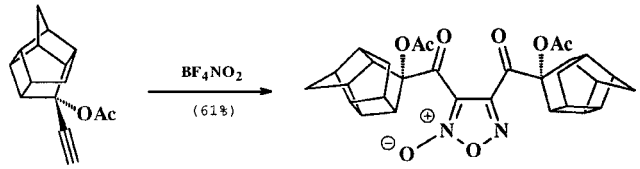
All these furoxan derivatives may be reduced to the corresponding furazans with $SnCl_2$/HCl/AcOH (64FRP1329349, 77RZC1531, 94IZV679, 94RCB630).

B. REACTIVITY

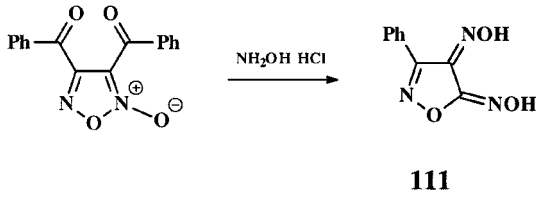
Aldehydes and ketones of furazans and furoxans have many properties resembling those of the aryl derivatives. Reduction of the carbonyl compounds with



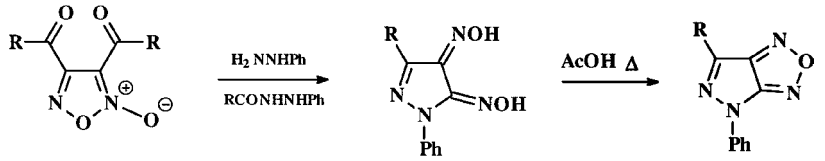
SCHEME 60



SCHEME 61

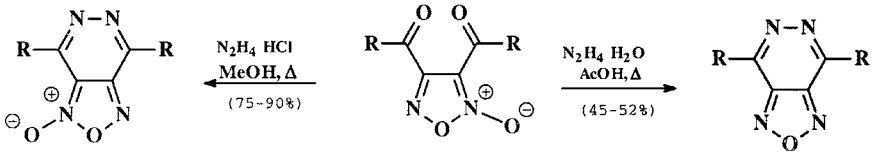


111

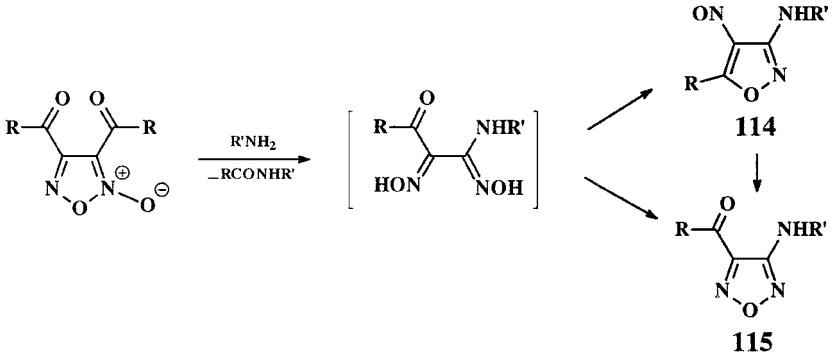


112 **113**

SCHEME 62



SCHEME 63



SCHEME 64

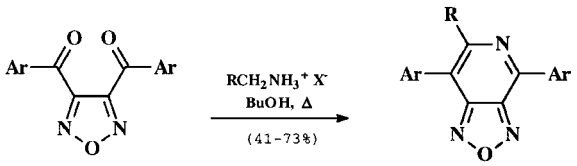
sodium borohydride gives the corresponding alcohols (77H1173, 96IZV1782, 96RCB1692). The aldehydes and ketones can be converted into their oximes in the normal way, and the oximes have been used to prepare several other functionalized derivatives [25LA7, 75LA1029, 83JCS(P1)483, 84JMC1201, 88BAU2571, 88IZV2848, 88LA1017, 96HCA1803, 97MI11, 97ROC1760]. 3,4-Dibenzoylfuroxane was found to react with hydroxylamine in organic solvents to form isoxazole **111** in 35–43% yield (Scheme 62) (000HEC35). Reaction of hydrazine and its derivatives with furazans and furoxans bearing a carbonyl function is more complex and different types of products are obtained. Thus, low-basicity hydrazines such as phenylsulfonyl (89JHC1345, 89MI2) and dinitrophenyl hydrazine (54JOC1897, 68JOC866) gave the usual hydrazones. Treatment of monoacylfuroxans with phenylhydrazine proceeded in a similar way, whereas reaction of diacylfuroxans yielded pyrazole derivatives **112** and **113** (Scheme 62) (69JHC317). Earlier papers considered the alternate isoxazole structure for the pyrazoles (58JOC1024, 61JOC5239, 68JOC866). Further details on furazans fused to five-membered rings can be found in the review of Sheremetev (95JHC371).

Reaction of diacylfuroxans with hydrazine dihydrochloride gave furoxanopyridazines (55JA4233, 77MI2, 99KGS1259), whereas treatment with hydrazine hydrate in acetic acid afforded furazanopyridazines (Scheme 63) (92JHC87).

Diacylfuroxans underwent degradative amination with aqueous ammonia, alkyl, and aryl amines to form either the corresponding nitrosoisoxazoles **114** or aminofurazans **115,** depending on the nature of the substituent R and reaction conditions (Scheme 64). At a high temperature, furazans **115** were formed exclusively (1892RTC258, 10LA297, 10RTC275, 25G72, 28G26, 69JHC317, 78CHE503, 78KGS616).

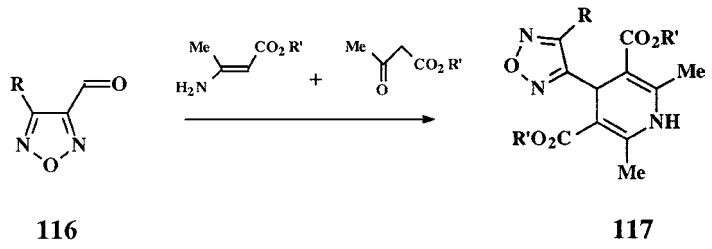
A variety of furazanopyridines have been obtained by the treatment of dibenzoylfurazan with methylamines bearing electron-withdrawing substituents (Scheme 65) (79S687, 80S842, 99H895).

A modified Hantzsch synthesis has been utilized for the preparation of 1,4-dihydropyridines (Scheme 66). Thus, condensation of formylfurazans **116** with an acetoacetic ester and aminocrotonic acid ester in isopropanol at reflux led to 1,4-dihydropyridine derivatives **117** in about 70% yield (92AF921). Both isomeric furoxan aldehydes reacted in a similar way.



R = CN, CO_2Alk, COPh

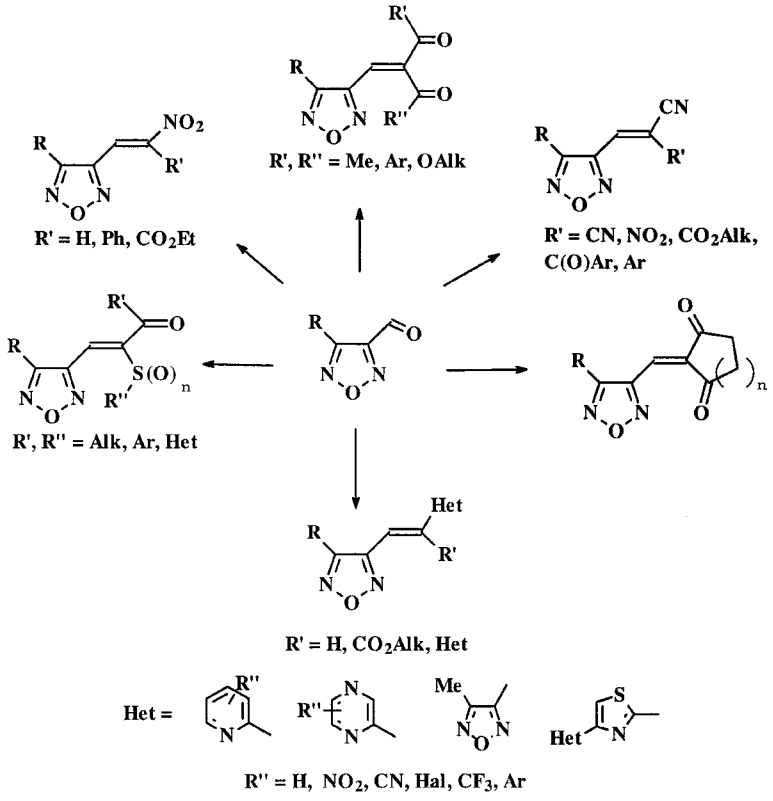
SCHEME 65



116 **117**

R = Me, Ph; R′ = Me, Et

SCHEME 66



R = Me, Ph, NHAc, NO_2

SCHEME 67

Standard condensation reactions of formylfurazans with a variety of active methylene compounds have been performed to give reactive ylidene derivatives (99MI7) (Scheme 67). Yields ranging from 8% to 95% have been obtained.

Ylidene-substituted furazans, which may be used in some cases without purification, are excellent building blocks for the construction of heteroaryl substituted derivatives. Simple variations in the substituents on the furazan ring, the active methylene compounds, and reagents can lead to a variety of products (99MI7) (Scheme 68).

Haloacetyl groups have also a synthetic potential. Thus, pesticidal (alkylthio)-vinyl esters of phosphorus acid derivatives have been prepared by the introduction and subsequent displacement of two chlorine atoms in the acetyl moiety attached to the furazan ring (Scheme 69) [73GEP(O)2144393].

Bromine atom in bromoacetylfurazans and furoxans (93IZV744, 93RCB708) is readily displaced by various sulfur nucleophiles (98IZV137, 98RCB139). A variety of thiazoles has been obtained by the treatment of bromoacetyl compounds with thiourea (Scheme 70) (96UP1, 98IZV137, 98RCB139).

Indoles **118** (99IZV400, 99RCB398) and indolizines **120** (99IZV2375, 99RCB2349) have been obtained by the condensation of suitably functionalized pyridinium salts **119** and aniline derivatives (Scheme 71).

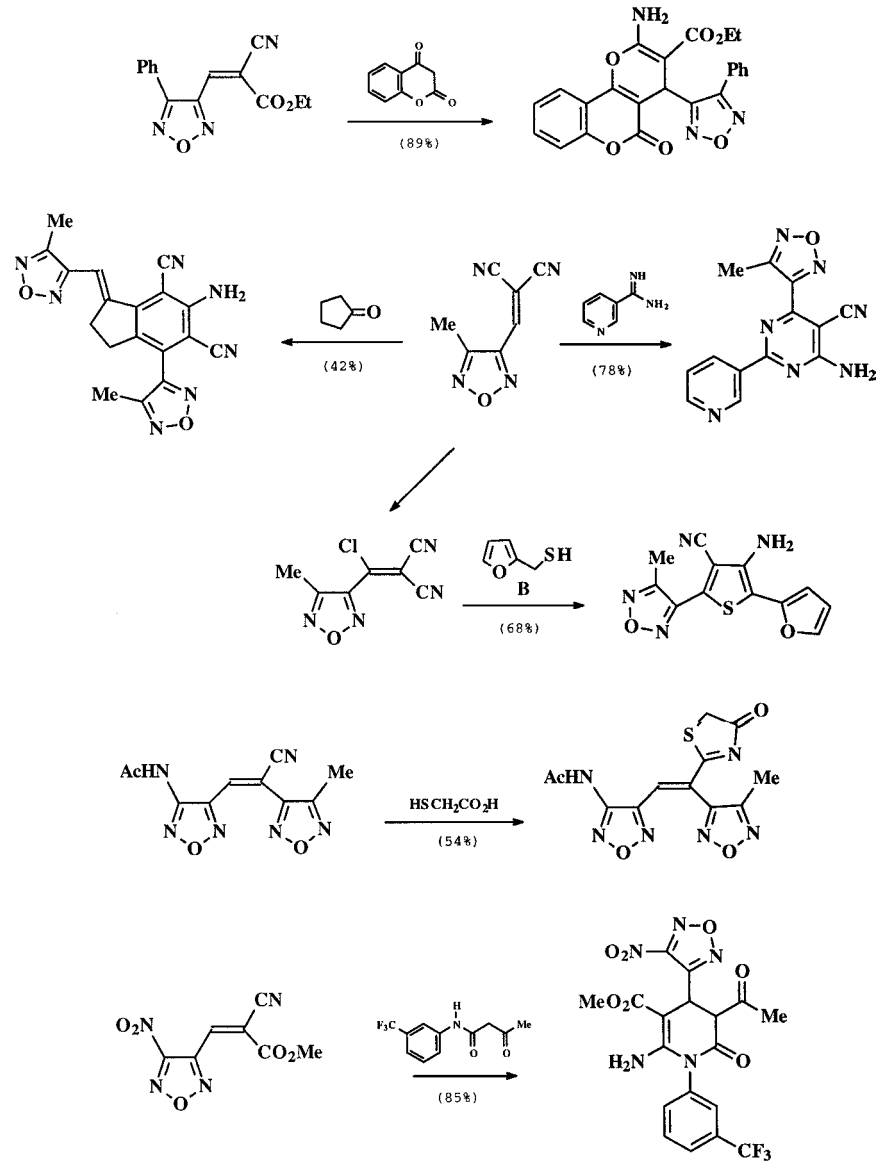
A method for the preparation of bis(furazanoyl)- and bis(furoxanoyl)furoxans has been developed utilizing the nitrosation of the corresponding bromoacetyl derivatives **121.** The resulting α-bromo-α-hydroximinoacetyl intermediates afforded the furoxans **122** on treatment with aqueous sodium carbonate (94IZV485, 94RCB445). An example is shown in Scheme 72.

The oxime of bromoacetylfurazan **123** was converted into the amine **125** by treatment with hexamethylenetetramine and subsequent acidic hydrolysis. Oxadiazine derivative **126** was made from the amine and formaldehyde in 57% yield (Scheme 73) (97ROC1760, 97ZOR1844).

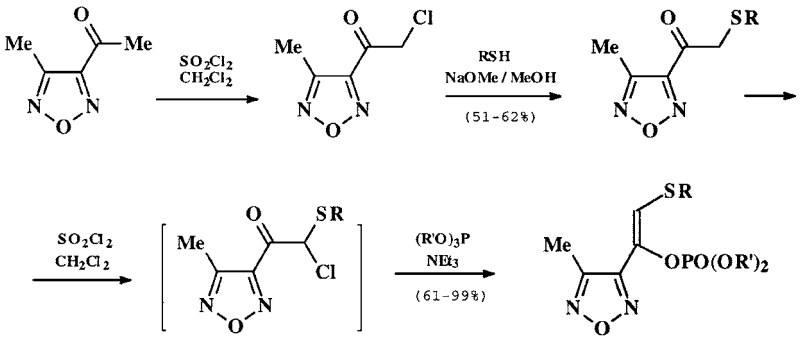
Treatment of 3-acetyl-4-methylfurazan with sulfur in morpholine resulted in a Willgerodt–Kindler transformation into the corresponding thioamide (Scheme 74). On further treatment with sulfuric acid 3-methylfurazan-4-acetic acid is obtained (96ROC734, 96ZOR766).

Only one of the two acetyl groups of diacetylfuroxans underwent a Schmidt reaction. A mixture of acetylamino- (**127**) and aminofuroxans **128** was obtained (95MC56) (Scheme 75). Under similar conditions 3-acetyl-4-nitrofuroxan afforded a mixture of tetrazole **129** and *N*-methylamide **130,** albeit in low yield.

Diaroylfuroxans react with an excess of diazomethane in diethyl ether at 20°C to form oxiranes **131** (Scheme 76). These compounds were reduced with $LiAlH_4$ (diethyl ether, reflux) to 1-amino-2-arylpropan-2-ols in moderate yields (67JOC4050). Treatment of diacylfuroxans with $LiAlH_4$ under similar conditions resulted in degradative reduction of the furoxan ring to arylethanolamines (67JOC1255).

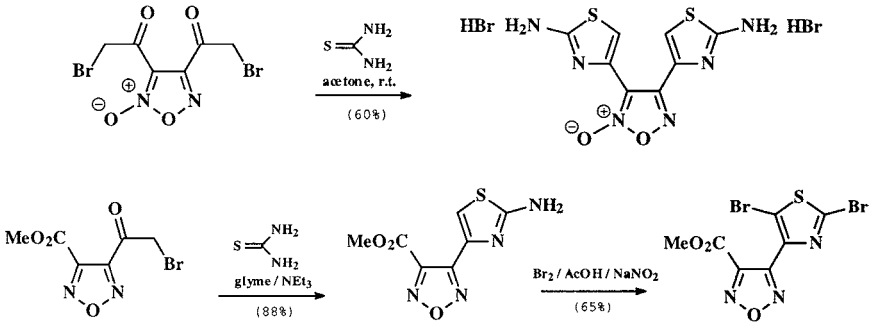


SCHEME 68

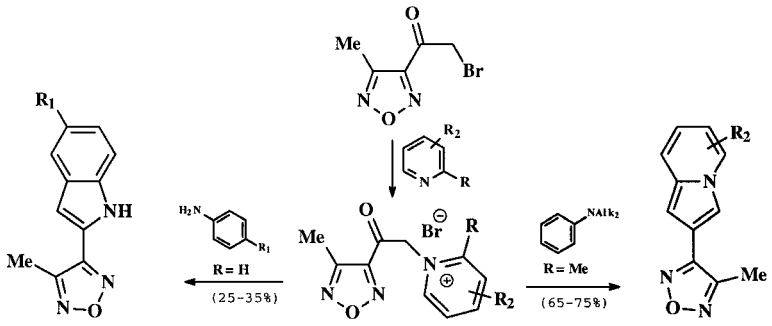


R, R′ = Me, Et

SCHEME 69



SCHEME 70

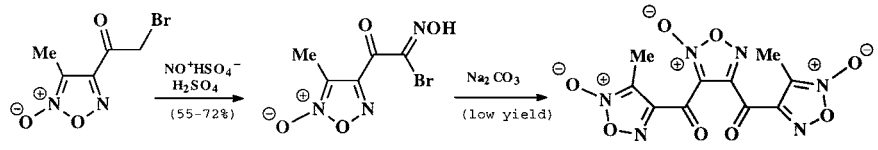


118 **119** **120**

R^1 = H, Me, F

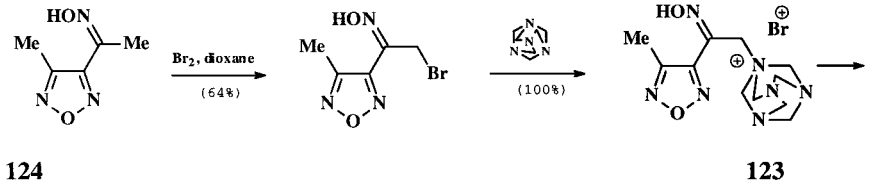
R^2 = H, 8-Me, 6-Et

SCHEME 71

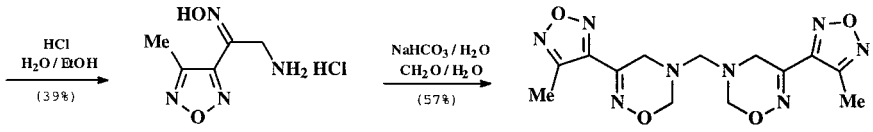


121 **122**

SCHEME 72

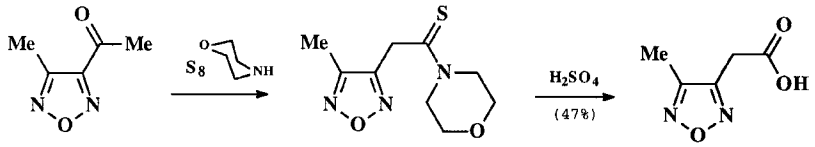


124 **123**

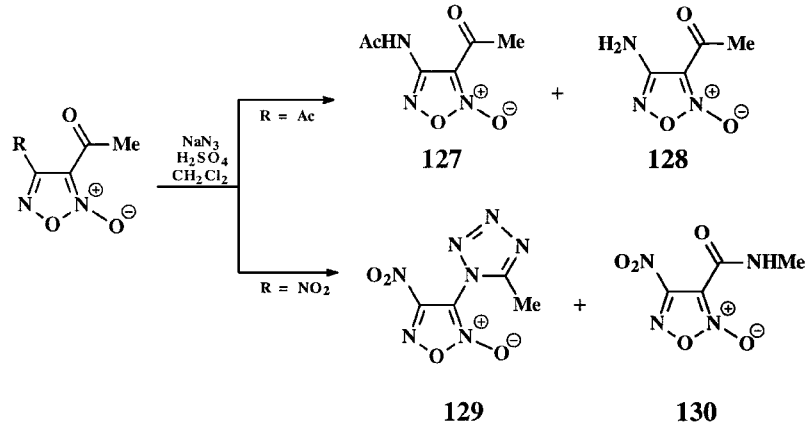


125 **126**

SCHEME 73



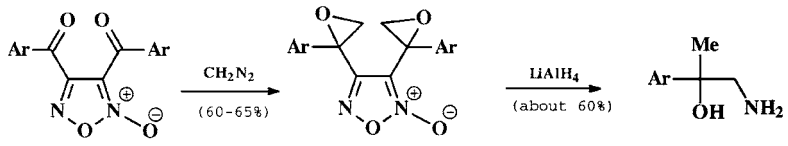
SCHEME 74



127 **128**

129 **130**

SCHEME 75



131

SCHEME 76

Although diaroylfuroxans were nitrated by nitrating mixture in the benzene ring (at the *meta* position) without destruction of the furoxan ring (55JA4233), an unusual result was obtained on nitration of dipyrazoloylfuroxan. Thus, treatment of this compound with a mixture of fuming nitric acid and oleum at 70°C afforded 52% dinitro- and 21% nitropyrazoles (Scheme 77) (91CHE656, 91KGS833).

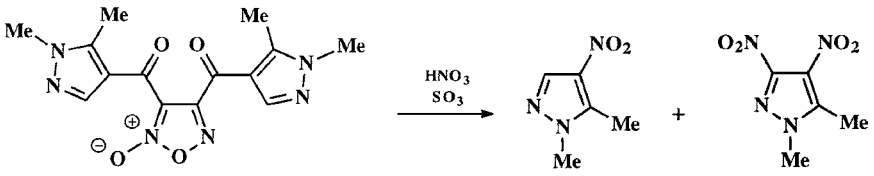
Various furazan and furoxan aldoximes were converted into nitrolic acids with dinitrogen tetroxide in CH_2Cl_2 at 20°C. Thus, from bisoxime **105** compound **132** was obtained and isolated as dioxane complex (Scheme 78) (93KGS117). Under reflux in $CHCl_3$ with dinitrogen tetroxide, terfuroxans **134** were obtained from aldoximes **133** in good yields (96HCA1803).

The dinitromethane derivatives **135** and **136** were obtained by nitration of oximes of monoacyl furazans and furoxans with dinitrogen tetroxide [36G819, 37G518, 63T(S)143] or nitric acid (37G388, 97MI11, 97ROC1760) (Scheme 79).

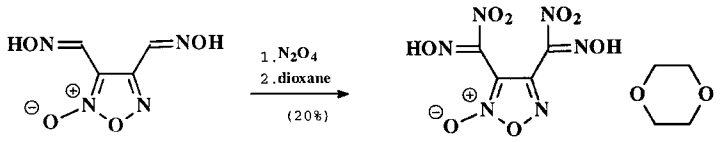
Dioximes of diacylfurazans and furoxans were cyclized under similar conditions to give the corresponding fused pyridazine di-*N*,*N*′-oxides (e.g., **137**) (25G67, 27G656, 88BAU2571, 88IZV2848, 97MI11, 97ROC1760). Nitration of the 3,6-dimethylpyridazino[4,5-*c*]furoxan 4,5-dioxide **137** using fuming nitric acid at room temprature occurred at the pyridazine ring to form the monocyclic furoxan **138** in 28% yield (Scheme 80) (96ROC925, 96ZOR957).

Prolonged reaction of 3,4-dihydroximinomethylfuroxan **105** with aqueous ammonia in the presence of pyridine resulted in a rearrangement to give isoxazole **139** and furazan **140** in approximately equimolar amounts. Short heating the same furoxan **105** in aqueous KOH produced the pyrazole derivative **141** (25LA7, 67JOC1255) (Scheme 81).

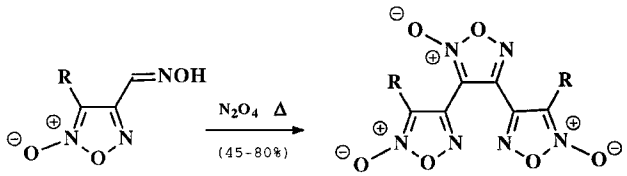
Nitroethylfurazan **143** has been synthesized by base-promoted mononuclear heterocyclic rearrangement (MHR) of oxime **142** (Scheme 82) (36G819, 82G181).



SCHEME 77



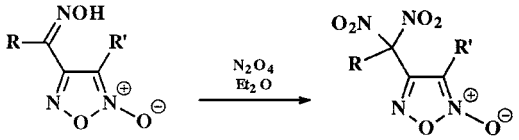
14 **132**



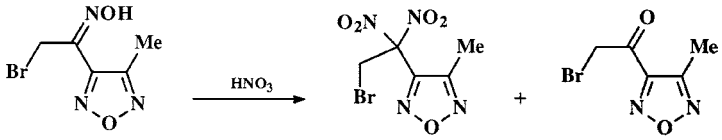
133 **134**

R = Me, Pr, Ph, CH_2Cl, CH_2OH, OEt, OPh

SCHEME 78

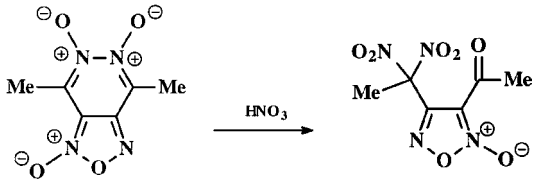


135



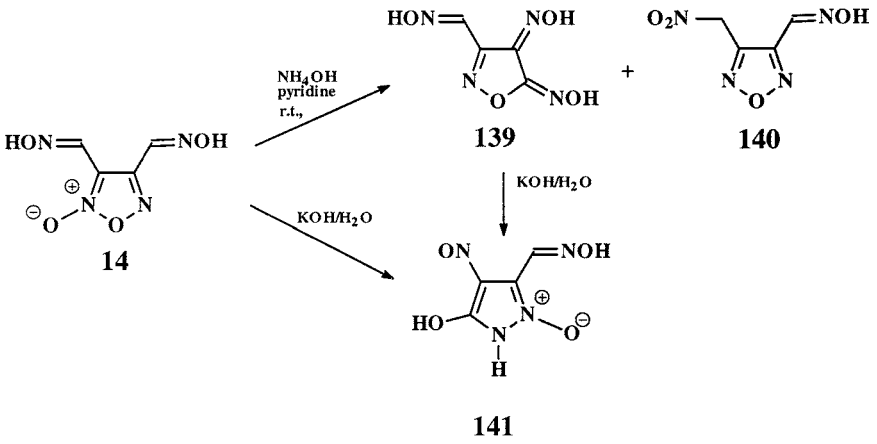
136

SCHEME 79



137 **138**

SCHEME 80



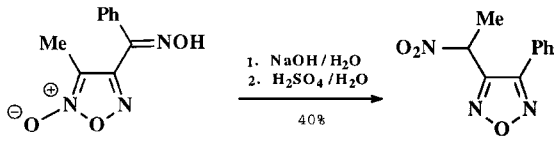
SCHEME 81

MHR of dioxime **144,** derived from dibenzoylfuroxan, with an acid catalyst afforded furazanylfuroxan **145** (Scheme 83) (33G159).

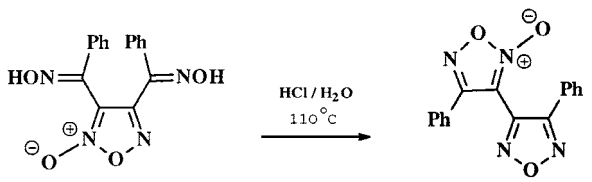
Another example of this rearrangement has been used to prepare 1,2,3-triazole **146** from furazanic phenylhydrazone **147** (Scheme 84) [93JCS(P1)2491]. Interestingly, furoxanic Z-phenylhydrazones **150** underwent thermal recyclization to 1,2,3-triazole *N*-oxides **152,** evidently through intermediate **151.** Treatment of the hydrazone 150 with *tert*-BuOK leads to the nitromethyl derivative **149** [000MI1] (Scheme 84). Lead tetraacetate oxidation of **147** with subsequent Lewis acid treatment of the initially formed intermediate afforded indazole **148** (Scheme 84) (85JHC29).

When heated in the presence of dipolarophiles, diacetyl- and dibenzoylfuroxan underwent ring opening with acyl group migration to give rearranged nitrile oxides that were trapped *in situ* to form adducts of type **153** (Scheme 85) (81JOC316, 85T727).

The type of the thermolysis process depends on the nature of the acyl group. Thus, other types of thermolysis processes involve reversible fragmentation of the furoxan ring to give two molecules of the corresponding nitrile oxide followed

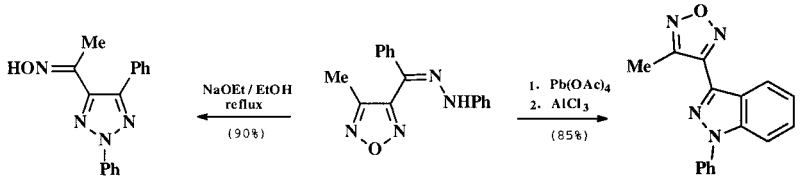


SCHEME 82

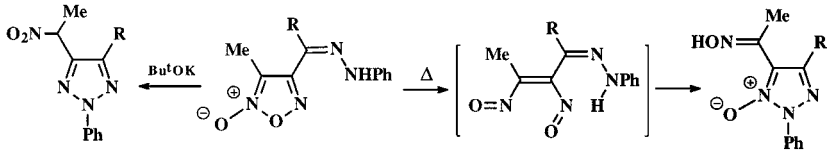


144 **145**

SCHEME 83

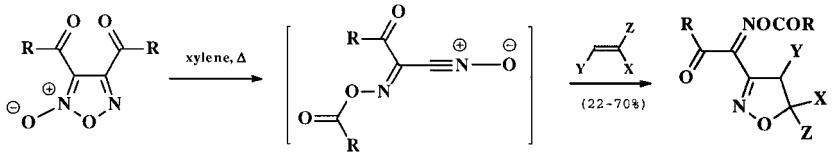


146 **147** **148**



149 **150** **151** **152**

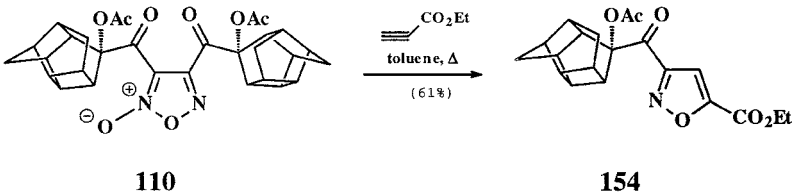
SCHEME 84



153

R = Me, Ph, $MeOC_6H_4$

SCHEME 85



110 **154**

SCHEME 86

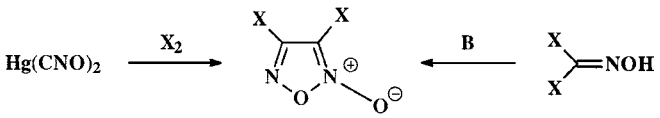
by irreversible [3 + 2]-dipolar cycloaddition with the appropriate dipolarophile. Thus, upon heating with ethyl propiolate in toluene at reflux for 36 hours, cage functionalized diacylfuroxan **110** was completely converted into isoxazole **154** in 61% yield (Scheme 86) (81JOC316, 98H271).

VI. Halofurazans and -Furoxans

A. Synthesis

3,4-Dihalofuroxans **155a,b** were first prepared in 1857 by Kekulé by treatment of mercury fulminate with chlorine or bromine (Scheme 87) (1857LA200, 1858LA279). Their structures were established in 1893 by Holleman (1893CB1403). During the first half of the last century several groups investigated these reactions in detail (09CB4192, 30G700, 31LA7, 32CB546, 50CB400). Yields up to 90–95% were achieved for the products. The reaction is dramatically affected by the conditions (solvent, reaction time and temperature, cation of fulminate).

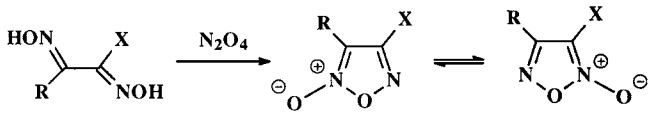
A simple and elegant synthesis of **155** from dihaloformaldoximes in quantitative yields was developed by De Paolini (30G700) and others (31LA7, 32CB546, 48BSF597, 61G47) (Scheme 87). Ponzio utilized the reaction of halo α-dioxime **156** with nitrogen oxides for one of the earliest synthesis of monohalofuroxans **157a** and **158a** (Scheme 88) (32G127). This method continues to be of use for the syntheses of other halo derivatives [63T(S)143, 82JHC427, 83JHC783, 90BAU909, 90IZV1020]. As a rule, a mixture of 3- and 4-halofuroxans is formed. A series of the individual isomers was prepared. Nitric acid [63T(S)143] and cerium ammonium nitrate (83JHC783) as well as electrochemical oxidation (27G124, 90BAU551, 90IZV630), were used to accomplish the reaction. Nikolaeva and coworkers utilized the reaction of 1-halopropenes with N_2O_3 for the syntheses of chloro- (**157b, 158b;** 40–45%) and 3(4)-bromo-4(3)-methylfuroxans (**159, 160;** 25–30%) (Scheme 89) (76MI1). A similar method was used for the synthesis of **157c, 158c** (24%), and their bromo analogues **161, 162** from haloalkynes (8%) (84AP695).



155a–c

a: X=Cl, **b**: X=Br, **c**: X=I

Scheme 87

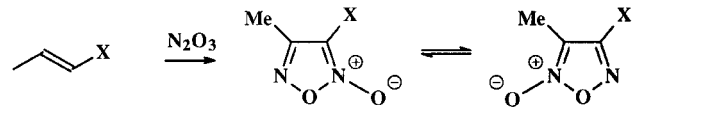


156a–d **157a–d** **158a–d**

	R	X	
a	H	Cl	49%
b	Me	Cl	42%
c	Ph	Cl	60%
d	NO_2	Cl	80%

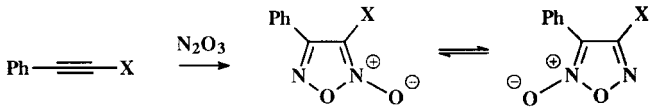
SCHEME 88

Relatively little is known about the synthesis of halofurazans. There are four approaches to prepare these derivatives: (i) deoxygenation of the corresponding furoxans; (ii) Sand-meyer reaction of furazanyl diazonium salts upon treatment with halogen acids; (iii) de-hydration of halo 1,2-dioximes; (iv) from nitrofurazans. The first halofurazan, 3-iodofurazan, was prepared in 60% yield by reaction of 3,4-diiodofuroxan **155c** with SO_2 in ethanol (Scheme 90) (31LA7). Chloro- (**158c**) (82JHC427) and bromophenylfuroxans (**161**) (84AP695) were reduced to furazans **163** (80%) and **164** (60%) by treatment with trimethyl phosphite (110°C, 4 hours) and $SnCl_2$/AcOH (95°C, 48 hours), respectively. There is one example of halo 1,2-dioxime transformation to halofurazan [69JCS(C)2794]. Thus, dehydration



158b **157b** (X = Cl)

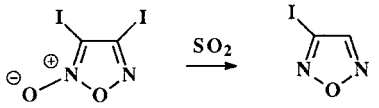
159 **160** (X = Br)



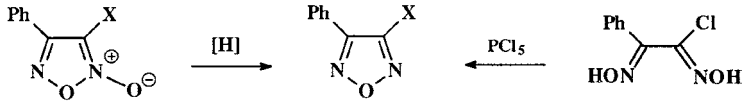
158c **157c** (X = Cl)

161 **162** (X = Br)

SCHEME 89



155c



158c **163** (X = Cl)

161 **164** (X = Br)

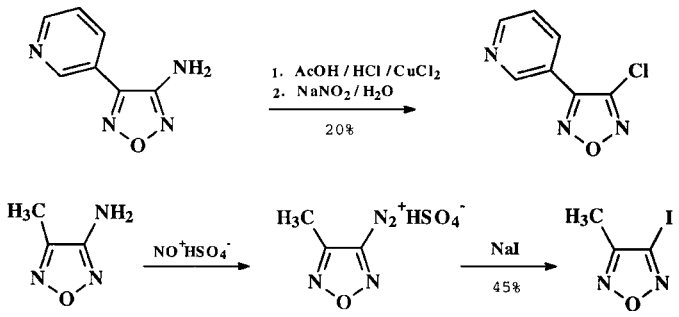
SCHEME 90

of ω-chlorophenylglyoxime with phosphorus pentachloride in dry ether at 3–5°C gave furazan **163** (14%) (Scheme 90).

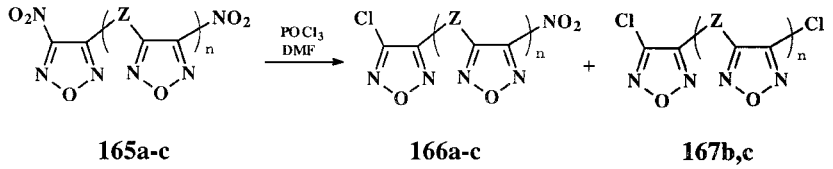
3-Chloro-4-(pyrid-3-yl)-furazan was obtained in moderate yield from the corresponding amine via the Sandmeyer reaction (92JMC2274, 92WO03430) (Scheme 91). The diazonium salt, prepared from 3-amino-4-methylfurazan and $NaNO_2$ in conc. sulfuric acid, on treatment with NaI gave 3-iodo-4-methylfurazan (45%) (93IZV1949, 93RCB1865).

In sharp contrast to this result, no halofurazans or -furoxans could be obtained when other aminofurazans and -furoxans were exposed to the same or to Sandmeyer reaction conditions (93IZV1949, 93RCB1865).

A new conversion of an activated nitro group at furazan ring into halogen was reported by Sheremetev *et al.* (000MC67) (Scheme 92). When dinitrofurazans **165a–c** were allowed to react with an excess of Vilsmeier reagent in $POCl_3$ on

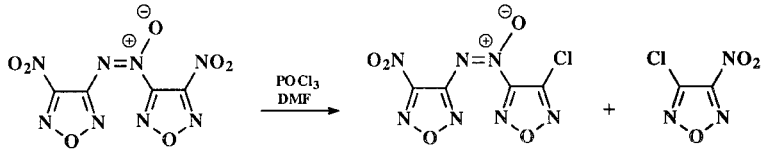


SCHEME 91



165a-c **166a-c** **167b,c**

a: n = 0; **b**: Z = single bond, n = 1; **c**: Z = -*N*=*N*-, n = 1



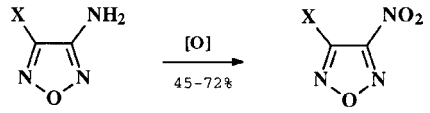
168 **169**

SCHEME 92

heating, the product obtained was a mixture of mono- (**166a–c**) and dichloro derivatives (**167b,c**) together with the starting material. Treatment of compound **168** with Vilsmeier reagent in the foregoing manner afforded about 50% yield of the 4-chloro-4′-nitroazoxyfurazan **169** and about 50% yield of the 3-chloro-4-nitrofurazan, which resulted from the nucleophilic displacement of the azoxyfurazanyl moiety (Scheme 92).

No 3,4-dichlorofurazan **167a** was isolated from 3,4-dinitrofurazan **165a** in this reaction. A modification of a substituent in halofurazan may be used for the synthesis of another halofurazan. Thus, oxidation of aminofurazans **170** with a mixture of $H_2O_2/H_2SO_4/Na_2WO_4$ gives the nitro compounds **171** (94MC138) (Scheme 93). 4,4′-Dichloroazoxyfurazan was prepared by oxidation of azo compound **167c** with Caro's acid in 67% yield (000MC67).

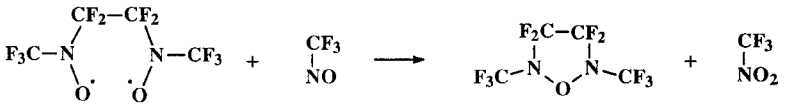
Nitration of the phenyl group in furazan **163** and furoxans **157c** and **158c** with 90% nitric acid yielded mixtures of the corresponding *o*-(31, 32, and 28%, respectively), *m*- (21, 23, and 3%, respectively), and *p*-nitro (48, 45, and 69%, respectively) products (84AP695).



170 **171**

X = F, Cl, Br

SCHEME 93



172 **173**

SCHEME 94

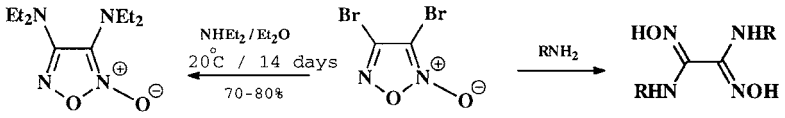
Surprisingly, trifluoronitrosomethane and perfluoro(2,5-diazahexane-2,5-dioxyl) **172** react together at 0°C in a sealed tube to form a mixture of products from which an unusual perfluoro furazan **173** was obtained in a moderate yield (76USP3965148) (Scheme 94).

B. REACTIVITY

Very few publications are available on the reactivity of halogens attached to the furazan ring. Nucleophilic displacement of bromine in **155b** by diethylamine led to product **174** (Scheme 95). However, nucleophilic attack followed by ring opening occurred when **155b** was treated with ammonia (16 mol, ethanol, 60–100°C, autoclave), aniline (8 mol, refluxing in ethanol for 1.5 h) or hydrazine (methanol, 0°C, 15 h), giving 1,2-dioxime derivatives **175** (09CB4192). All reactions of the chloro analog **155a** lead to 1,2-dioximes. However, the chlorine in **157c, 158c** is inert toward these nucleophilic reagents [32G127]. In contrast, nitrochlorofuroxans **157d, 158d** readily react with various nucleophiles to give nitro group displacement products (see Section VIII).

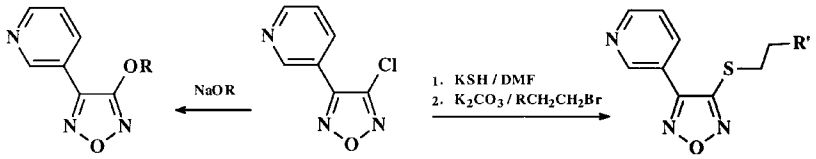
Furoxan **157c** (32G127) (but not furoxan **157b**) and furazan **163** [69JCS(C)2794] on treatment with sodium alkanoates give the corresponding ethers in good yields. A similar pathway was used for the preparation of 3-alkoxy-4-(pyrid-3-yl)furazans (Scheme 96) (90EUP384288, 92JMC2274). Nucleophilic replacement of halide by HS^- (with subsequent alkylation to compounds **176**) (92WO03430) occurs more readily than in the analogous benzene derivatives (Scheme 96).

Positional changes of the exocyclic oxygen atom in **157b** and **158b** discriminate between the reactivity of these compounds. Thus, **158b** readily reacts with the potassium salt of thiophenol to give sulfide **177** in 85% yield (83JHC783),



174 **155b** **175**

SCHEME 95



176

(R = Bu, 3-C_6H_{13}, 4-C_6H_{13}) (R′ = Ph, OPh)

SCHEME 96

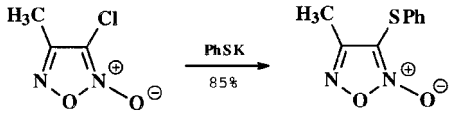
whereas a similar nucleophilic attack on **157b** leads to displacement of chlorine, giving **178** in only 2.5% yield with predominating ring opening of the furoxan ring (Scheme 97).

A metalated ester was generated from **179** at −78°C in THF. Treatment of this intermediate with a solution of a chlorofurazan in THF at the same temperature gave **180** (Scheme 98) (90EUP384288).

VII. Aminofurazans and -Furoxans, Azido Derivatives

A. SYNTHESIS

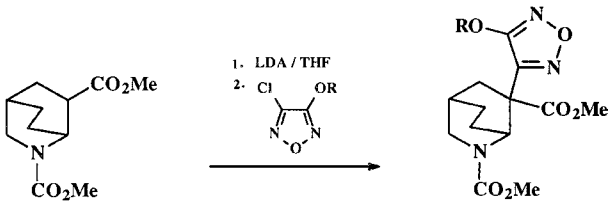
In their review on the syntheses of aminofurazans, Andrianov and Eremeev (84CHE937, 84KGS1155) identified two major approaches to the preparation of these compounds: (i) the preparation of aminoglyoximes, followed by dehydration, as a rule, with alkali, which is the more common methodology (Scheme 99); and (ii) transformations of other heterocycles.



158b **177**

157b **178**

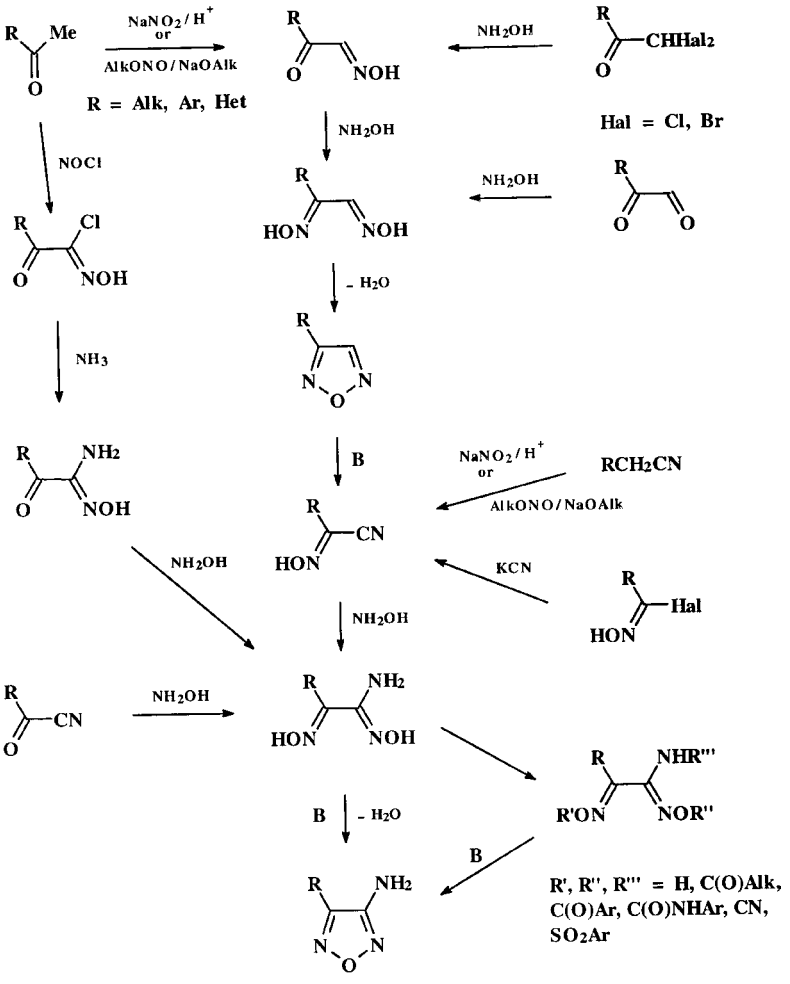
SCHEME 97



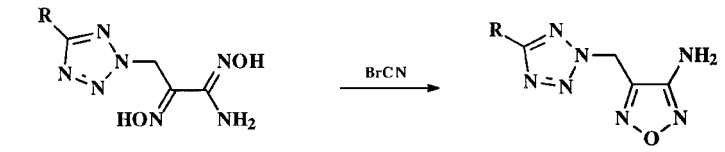
179 **180**

R = Bu, 4-C_6H_{13}

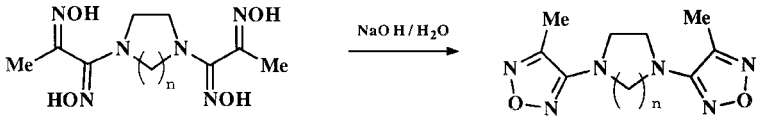
SCHEME 98



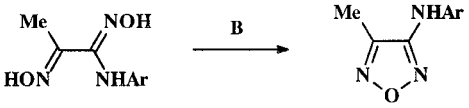
SCHEME 99



R = H, Me, NO_2



n = 2, 3

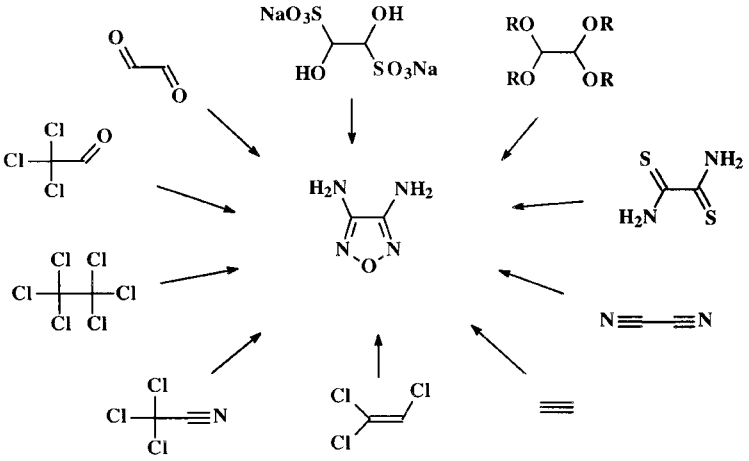


SCHEME 100

The dehydration of aminoglyoximes to aminofurazans is usually realized by heating with aqueous base. Under acidic conditions the glyoximes may undergo Beckmann rearrangement before cyclization giving 1,2,4-oxadiazoles. The success of the ring closure is usually strongly dependent on the aminoglyoxime configuration. Thus, *Z,Z*- and *E,E*-glyoximes showed different chemical reactivities; conditions employed in the cyclization of *Z,Z*-isomers were ineffective for the dehydration of *E,E*-glyoximes. However, acylation of an oxime or treatment with a base at an elevated temperature allows to prepare furazans from practically any aminoglyoxime. Some examples are shown in Scheme 100 (91BAU1915, 91IZV2159, 92KFZ56, 96MI5).

3,4-Diaminofurazan is among the most important compounds of this class (89AP579, 89MI1, 95MI1, 96IZV1250, 96MI3, 96RCB1189, 97JHC1057). Some approaches to this diamine from commercially available chemicals are outlined in Scheme 101 (96MI3). It should be noted that all these precursors can be transformed to this diamine under similar conditions (alkaline NH_2OH in solution of H_2O, DMSO, ethylene glycol, or dioxane, or in a mixture of these solvents in the presence of several additives, such as phase transfer catalysts, tertiary amines, or urethanes). Yields are in the region of 25–60%.

A simple and elegant one-pot synthesis of 3-amino-4-arylfurazans from the corresponding aroyl cyanides was developed by Lakhan and Singh (Scheme 102) [87IJC(B)690].

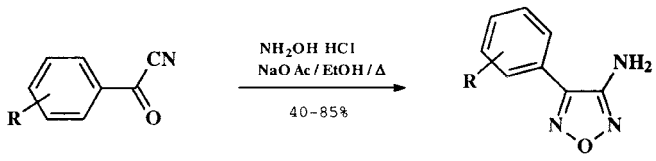


SCHEME 101

A number of examples of the transformation of various azoles with an α-oxime group in the side chain via MHR into furazans was discussed in earlier reviews (Scheme 103) (90CHE1199, 90KGS1443). The rearrangement has been achieved by melting or heating an oxime with alkali or acid. Only the *E*-isomer of the oxime underwent this process (92MC129, 94ZOR757). Some examples are given in Scheme 104 (88CHE707, 88KGS856, 91CHE102, 91CHE646, 91CHE651, 91CHE783, 91CHE785, 91CHE901, 91KGS122, 91KGS822, 91KGS827, 91KGS976, 91KGS979, 91KGS1121, 92CHE808, 92KGS969, 93ZOR1062, 96CHE1004, 96KGS1214).

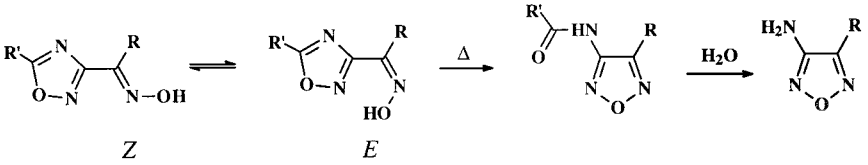
Good results were achieved by usage of a one-pot strategy combining the reaction of carbonyl compounds or their equivalents, with hydroxylamine being oximating, aminating, and redox reagent, and the ability of intermediate organic hydroxylamine derivatives to rearrange (Scheme 105). These one-pot transformations involved up to 10 steps (96MC246, 97MI5, 98MC135).

When aminofuroxans are treated with $P(OEt)_3$, PCl_3, $SnCl_2$, Sn/HCl, and Zn/AcOH, the corresponding aminofurazans are obtained (84CHE937, 84KGS1155,



R = H, *o*-Me, *m*-Me, *p*-Me, *p*-MeO, *p*-Cl, *p*-NO_2

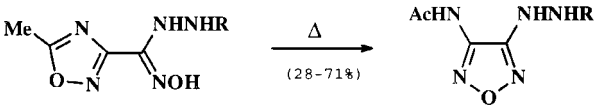
SCHEME 102



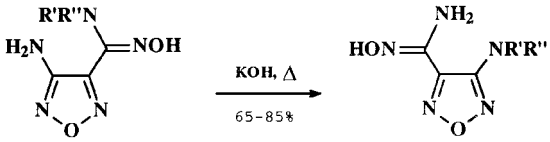
Z *E*

R = Me, Ar, NH_2; R′ = H, Alk, Ar

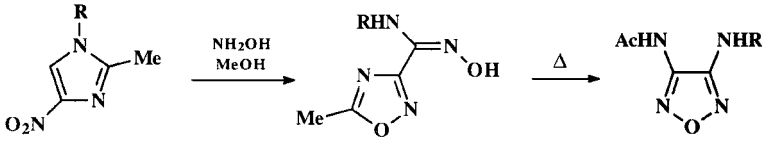
SCHEME 103



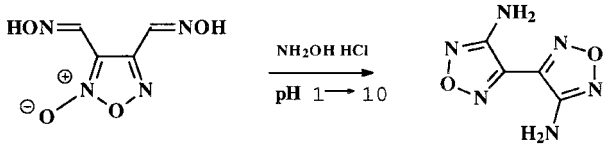
R = CO_2Et, *p*-$NO_2C_6H_4$



R′, R″ = H, Alk



SCHEME 104



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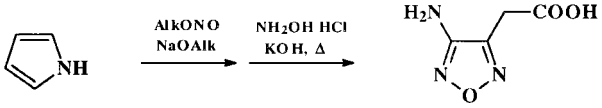
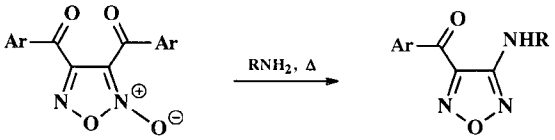


SCHEME 105

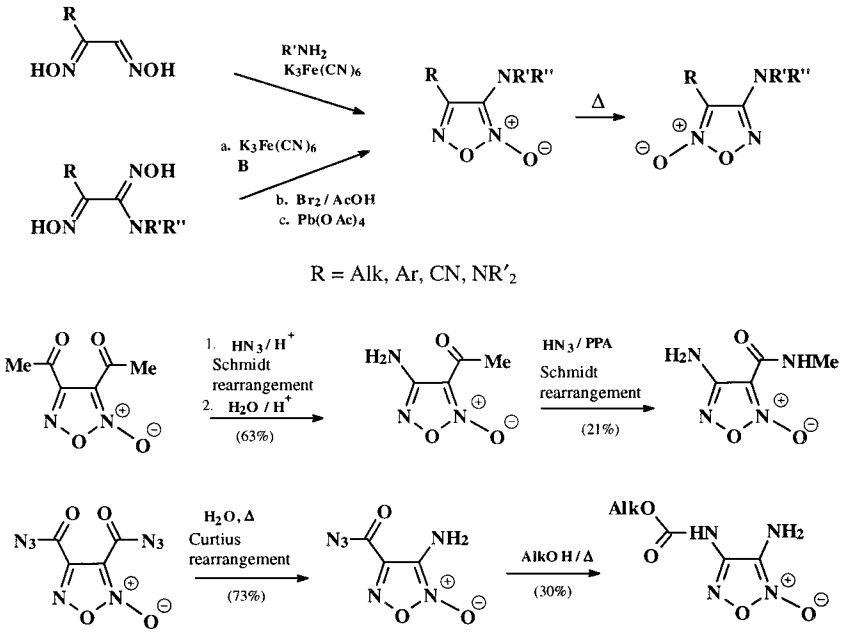


SCHEME 106

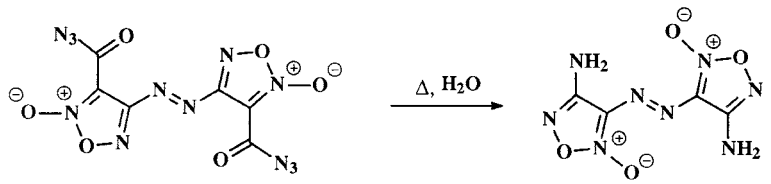
94IZV679, 94RCB630, 97MI3, 97MI4, 97MI14). Reactions of bis(aroyl)furoxans with amines also yield aminofurazans **181** (Scheme 106) (69JHC317).

There has been only minor progress in the chemistry of aminofuroxans since the review of Makhova and Godovikova (97MI3, 97MI4) and the comprehensive monographs of Khmelnitskii *et al.* (96MI1, 96MI2). The most commonly utilized methodologies are outlined in Scheme 107, although numerous other methods have been developed [88CHE927, 88KGS1124, 95MC56, 95MC58, 97CHE927, 97KGS1115].

In contrast to diamino*furazan*, diamino*furoxan* is probably unstable. All attempts to generate it from rearrangements shown in Scheme 107 failed. However, Curtius rearrangement of 3,3′-bis(azidocarbonyl)-4,4′-azofuroxan **182** with subsequent isomerization afforded 4,4′-diamino-3,3′-azofuroxan **183** in 69% yield (Scheme 108) (98DOK499, 98MI2, 98MI6).



SCHEME 107



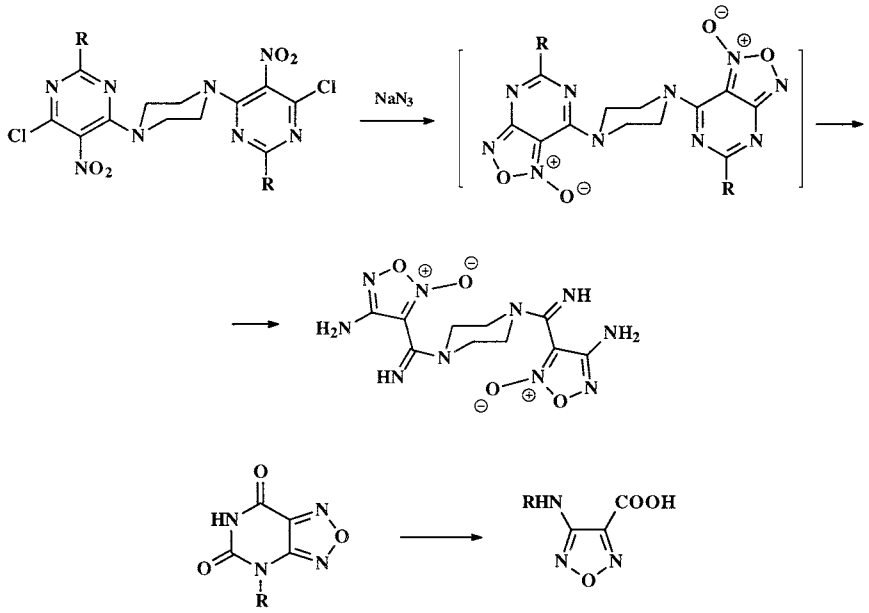
182 **183**

SCHEME 108

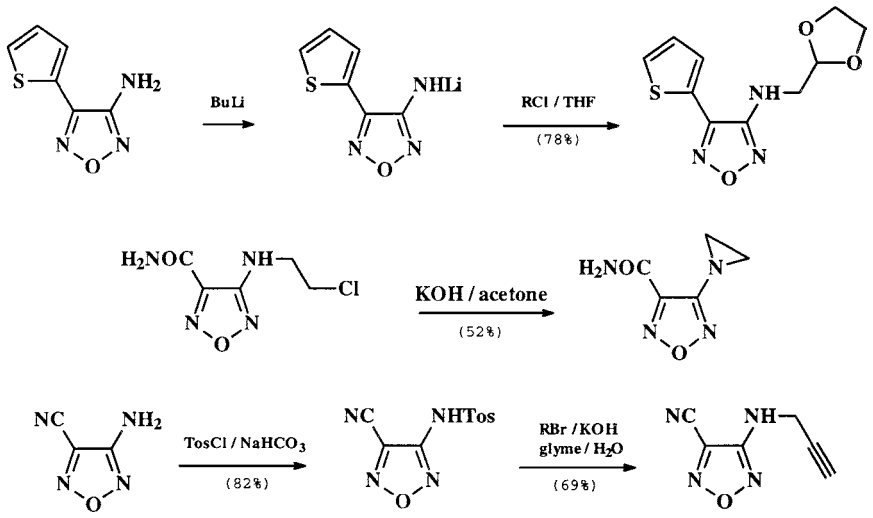
Ring-opening reactions, using fused furazans and furoxans as starting materials, have been used to prepare amino derivatives of monocyclic furazans and furoxans. This approach is most commonly applied to the synthesis of substituted aminofurazancarboxylic acids and their *N*-oxides (Scheme 109) (81CHE228, 81KGS321, 83H2351, 84T879, 92MI3, 92ZOR422).

B. REACTIVITY

Aminofurazans are weak bases ($-pK_{aBH}+$ for 3,4-diaminofurazan: 1.94 (81CHE228, 81KGS321), 3-amino-4-methylfurazan: −2.15 [81CHE27,



SCHEME 109



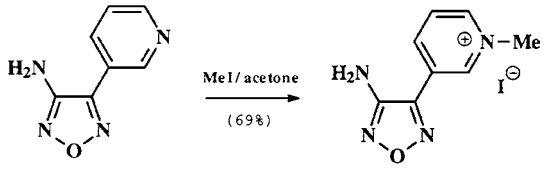
SCHEME 110

81KGS35]). They form salts only with anhydrous mineral acids (91CHE803, 91KGS998, 92ZSK54). Formation of similar amino*furoxan* salts ($-pK_{aBH}+$ for 4-amino-3-methylfuroxan: -3.01 [88AP77]) is virtually unknown. Aminofurazans give complexes with heavy metal salts (bonding the metal ion to the ring nitrogen atom) (91IC360, 94IZV2242, 94RCB2122, 97MI9, 97MI15) and crown ethers (95MI3). In some of its reactions amino groups in both furazans and furoxans resembles the amino groups of di- and trinitroanilines.

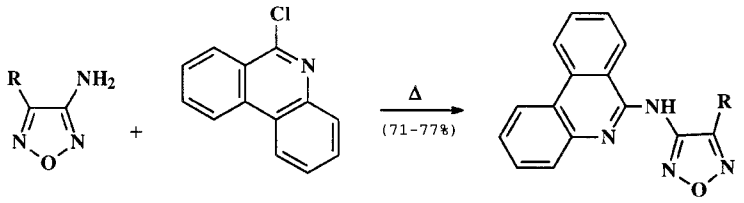
Aminofurazans are not alkylated under usual conditions, although the reaction may be effected by a modification of the amino group. Thus, the presence of metal (92ZOR422, 94UP1), sulfonyl (90MI1), or acyl (90MI1, 97JHC1057) groups at the amino substituent promotes attack on exocyclic nitrogen and good yields of the alkylation products are obtained (Scheme 110).

Alkylation of 3-amino-4-(pyrid-3-yl)furazan occurred at the pyridine ring (Scheme 111) (90EUP384288) (see also Scheme 187).

It has been shown that aminofurazans were *N*-arylated at the amino group on treatment with picryl *fluoride* in the presence of triethylamine. Use of the less



SCHEME 111



SCHEME 112

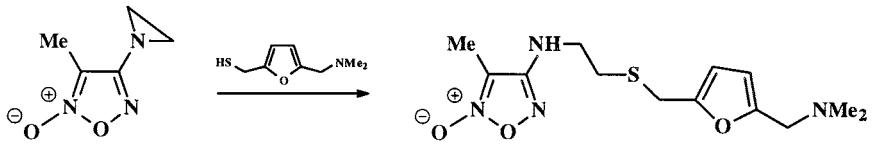
electrophilic picryl *chloride* failed (68JHC83). Heteroarylation of aminofurazans was carried out with phenanthridine chloride by fusion (Scheme 112) (90H869).

Alkylation and arylation of the aminofuroxans are unknown as yet, presumably because of their instability under harsh conditions. However, aziridino furoxans may be used as precursors for preparation of functionalized alkylamino derivatives (Scheme 113) (88AP77).

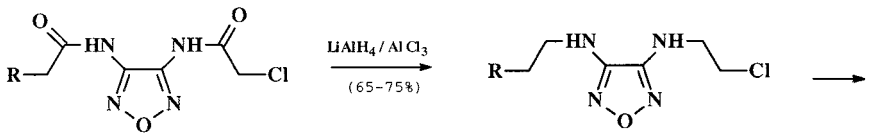
Alkylamino-substituted furazans can be obtained by reduction of acylamino derivatives. The chlorine atom at the side chain may be replaced with a nucleophile (Scheme 114) (85MI1, 88AP77, 89AP579, 89MI1, 92AP151).

In contrast to alkylation, the acylation and sulfonation of the amino group in furazans and furoxans have been extensively explored and a wide range of reagents has been used (84CHE937, 84FA265, 84KGS1155, 85MI1, 86CHE546, 86KGS666, 91JHC1677, 91ZOR1947, 92AP151, 95JOC4096, 96MI2, 97MI3, 97MI4, 97MI14, 99MC17). Treatment of aminofurazans with phosgene in the presence of pyridine under reflux in toluene led to good yields of isocyanates (Scheme 115) [85GEP(O)3409887, 86GEP(O)3501723]. Furazanyl isocyanates react with amines to give the corresponding ureas. Acylation of aminofurazans with isocyanates led to similar ureas [85GEP(O)3409887, 86GEP(O)3501723, 88GEP(O)3622862, 93EUP561250]. Furazanyl isocyanates were utilized for the synthesis of urethanes and tetrazolylfurazans (Scheme 115) (96EUP695748).

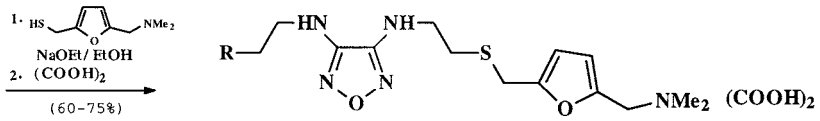
Treatment of aminofurazans with aryl isothiocyanates gave thioureas [89GEP(O) 3738946], whereas ethoxycarbonyl isothiocyanate yielded 1,2,4-thiadiazole derivatives that resulted from a rearrangement (86H3433). A similar rearrangement was observed in the reaction of isothiocyanates with borylated diaminofurazan **184** (Scheme 116) (92BAU140, 92IZV174). The synthesis of guanidinofurazans was achieved by treatment of borylated aminofurazans with carbodiimides (88BAU2128, 88IZV2363).



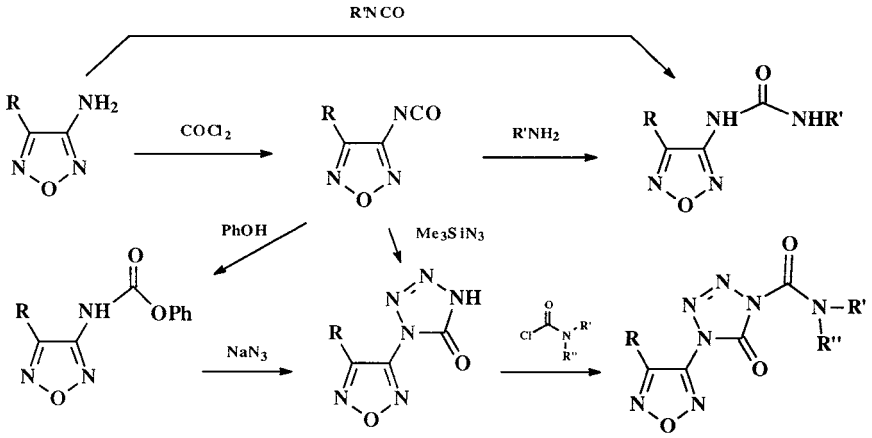
SCHEME 113



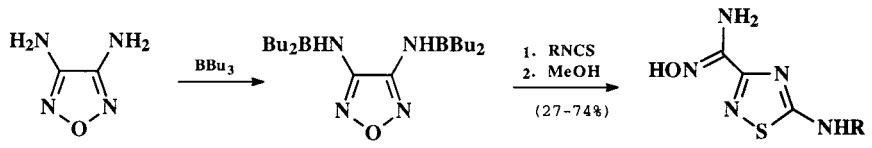
R = H, alkyl, cycloalkyl, Ar, Cl



SCHEME 114

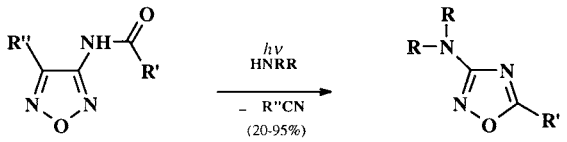


SCHEME 115



184

SCHEME 116



185 **186**

R′ = Me, Et, Pr, Bu, Bz, Ph, *p*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, *p*-NCC_6H_4 ; R″ = Me, Ph

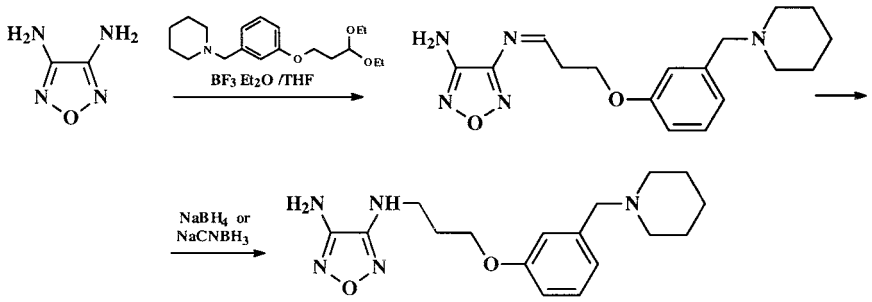
SCHEME 117

Irradiation of a methanolic solution of 3-acylaminofurazans **185** at $\lambda = 310$ nm in the presence of ammonia or primary or secondary amines produced excellent yields (70–95%) of 3-(R-amino)-5-R′-1,2,4-oxadiazoles **186** (Scheme 117) (95S917). Similar results were obtained by irradiation of 3-aroylaminofurazans in the presence of pyrrolidine at $\lambda = 254$ nm (92AP151).

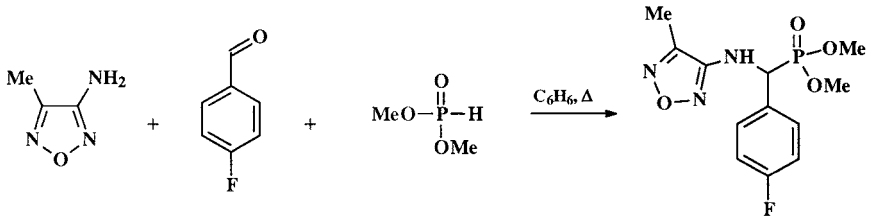
Condensation of aminofurazans with formaldehyde in the presence of H_2SO_4 afforded methylenebis(aminofurazans) (95ROC1125, 95ZOR1234). Reaction with formaldehyde and potassium sulfamate gave Mannich products involving the three building blocks (94CHE976, 94KGS1129, 95IZV719, 95RCB699). The amino group of furazans reacts with aldehydes or their counterparts in the presence of a catalyst, for example, a Lewis acid (85USP4507485) or *p*-toluenesulfonic acid (86JHC1519, 91JHC1677, 97JHC1057), to give Schiff bases in 50–95% yield. These compounds may be reduced by treatment with sodium borohydride to *N*-(R-methyl) derivatives (Scheme 118) (85USP4507485, 86JHC1519, 91JHC1677, 97JHC1057).

It has been reported that 3,4-diaminofurazan reacts with glyoxal to give 1,4,5,8-tetraazafurazano[3,4-*c*][3,4-*h*]decalin (85USP4503229) (a starting material for a tetranitro compound).

Furazanic amino phosphonates **187** are accessible by the Kabachnik–Filds reaction in the presence of dibenzo-24-*crown*-8 in 80–85% yields (Scheme 119) (92ZOB2708, 93ZOB1776).



SCHEME 118



187

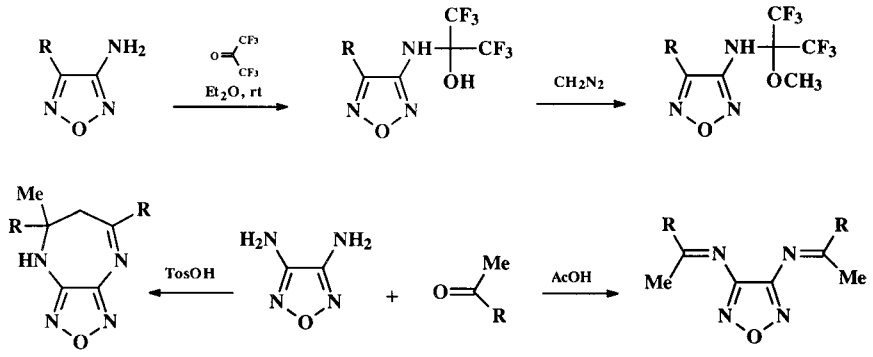
SCHEME 119

Aminofurazans underwent condensation with ketones to form either aminals [86MI2], Schiff bases (74JA7812, 91JHC1677), or fused furazans (86JHC1519), depending on the nature of reagents and reaction conditions (Scheme 120).

A traditional and widely used method for the synthesis of furazano[3,4-*b*]pyrazine derivatives is the reaction of α-dicarbonyl compounds or their analogs with 3,4-diaminofurazan (84CHE937, 84KGS1155, 96MI3, 97MI1, 97MI2, 97MI13). Some examples are given in Scheme 121 (88CHE1204, 88KGS1457, 97CHE1473, 97KGS1699, 98ZOR1078, 99KGS1002).

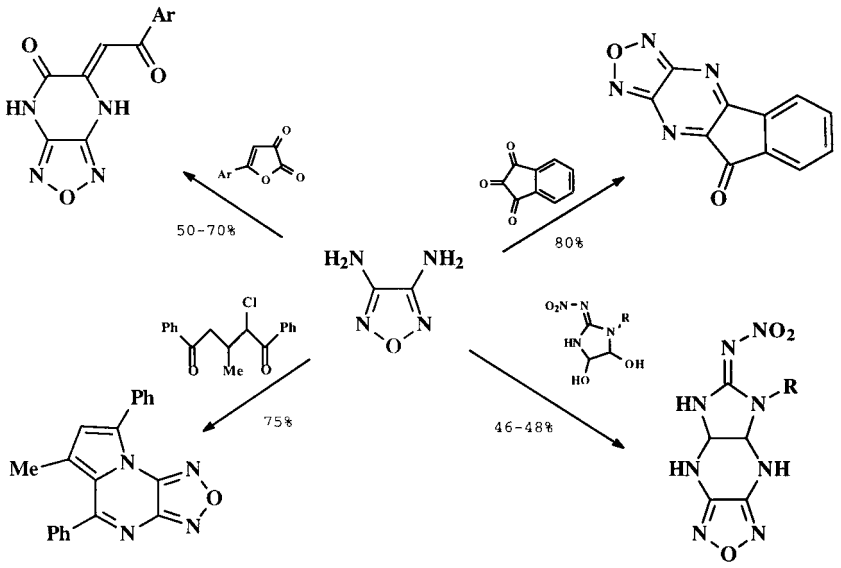
The result of condensation of β-dicarbonyl compounds with 3,4-diaminofurazan depends on the reaction conditions. With metal ions as templates, 14-membered rings **188** were formed exclusively (91MI2), whereas in the absence of these ions, only fused diazepines **189** were formed (Scheme 122) (89UKZ1064).

Monoamino derivatives react with β-dicarbonyl compounds in a different way. Thus, the synthesis of an unusual fused pyrimidine **190** has been achieved via condensation of 4-amino-3-phenylfuroxan with acetylacetone in the presence of



R = Alkyl, Aryl

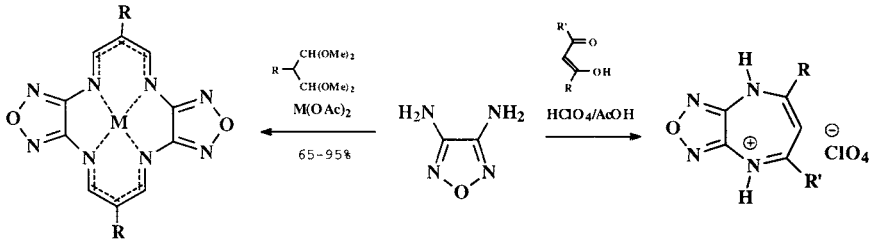
SCHEME 120



SCHEME 121

$HClO_4$ (Scheme 123) (92CHE193, 92KGS233). Monoamino furazans react similarly (80UKZ637).

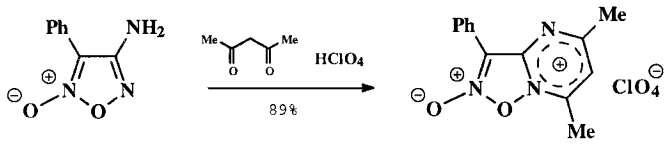
Aminofurazans and -furoxans react with hetero analogues of carbonyl compounds, such as nitrosobenzene (74BCJ1493, 81ZOR1123) and S—O or P—O reagents derived from DMSO (86S490, 90BAU1470, 90IZV1625, 92BAU1505, 92IZV1922) or $R_3P{=}O$ (89JHC1883, 91BAU455, 91IZV523) in the presence of dehydrating agents. The intermediates were utilized for further oxidation reactions (Scheme 124).



188 **189**

M = Cu, Ni, Co

SCHEME 122



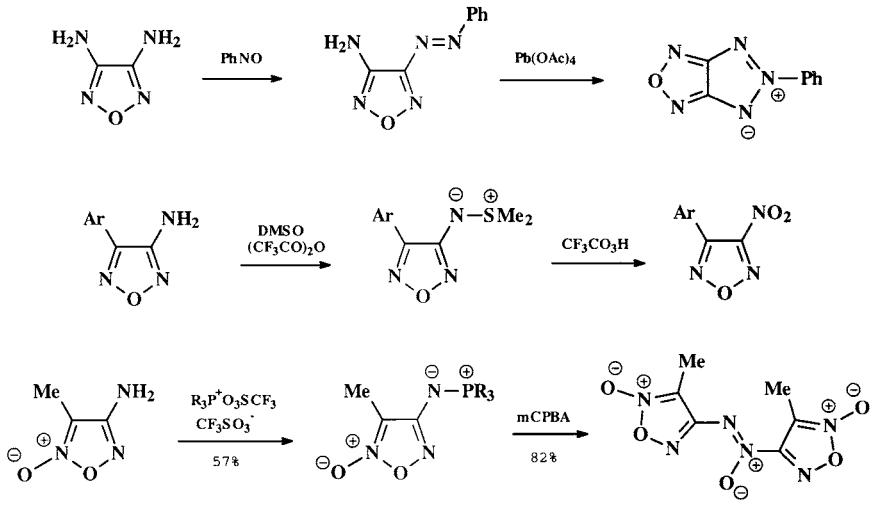
190

SCHEME 123

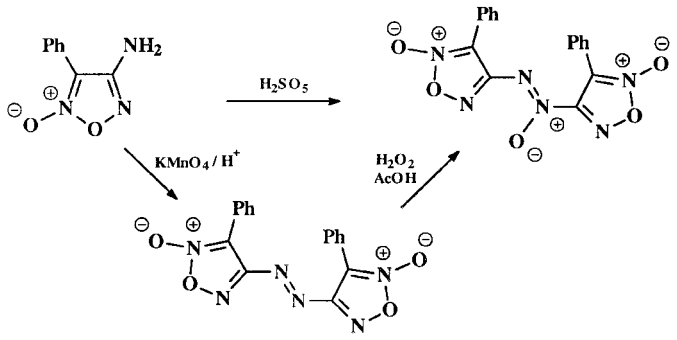
The oxidation of aminofurazans (97MI1, 97MI2, 97MI13) and -furoxans (97MI3, 97MI4, 97MI14) by peracids to the corresponding nitro derivatives was reviewed thoroughly in 1997 (see also the next sections). The same oxidants may be used for the synthesis of azoxy derivatives. Thus, azoxyfuroxans were formed by treatment of 4-aminofuroxans with a mixture of 85% H_2O_2 and sulfuric acid (Scheme 125) (99MC15). No successful similar reaction of 3-aminofuroxans has been achieved.

Azofurazans (91BAU1727, 91IZV1940, 94CHE629, 94CHE631, 94KGS714, 94KGS716, 95MI1, 96MI3, 96WO12711, 98JHC151, 98MI1) and azofuroxans (99MC15, 000UP1) were prepared from the corresponding amines by oxidation with $KMnO_4$/HCl, dibromoisocyanurate (DBI), and other one-electron oxidants.

Several novel chromophoric macrocycles have been reported that incorporate an azofurazan subunit as a key structural component (91MI3, 92MC157, 93MI2, 93URP1803407, 94MC102, 94MI1, 94MI2, 94MI3, 95MI4, 96CHE227, 96CHE352, 96IZV1250, 96KGS253, 96KGS406, 96MC66, 96MC193, 96MI3,



SCHEME 124



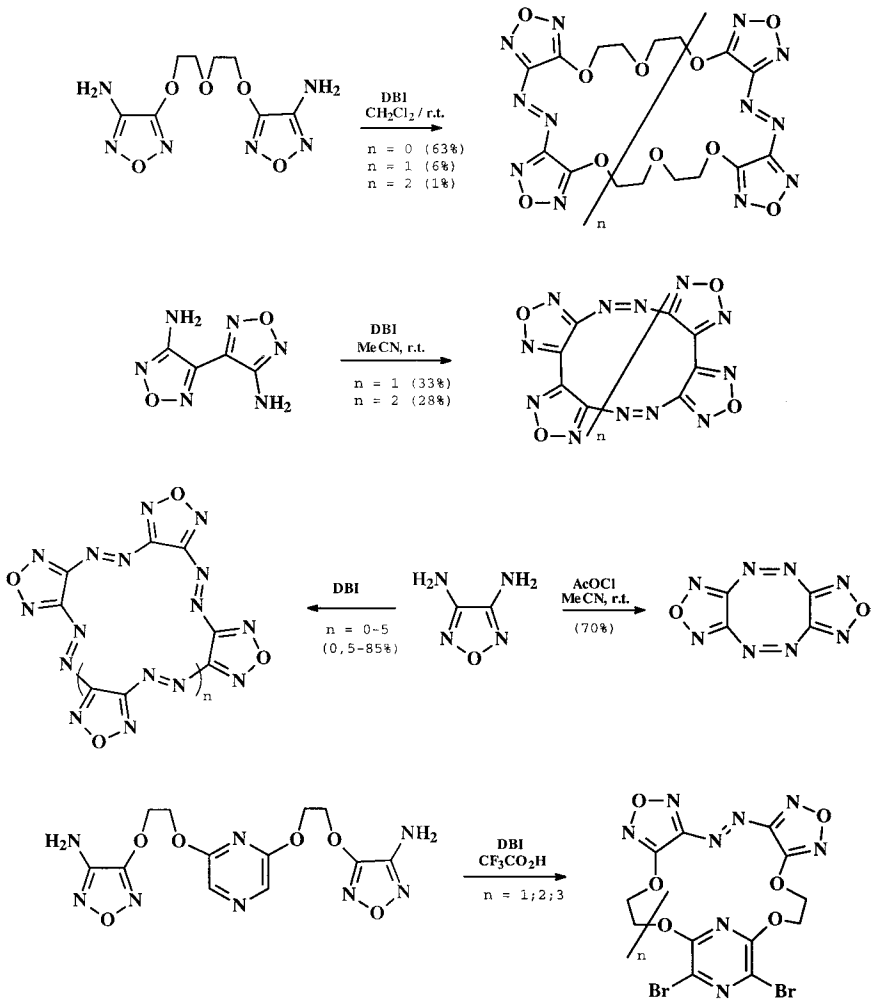
SCHEME 125

96RCB1189, 97MC5). Synthesis of the macrocycles was achieved by oxidative coupling of the bridged bis(amino) furazans. The ring closure is the result of N═N bond formation. Depending on the reaction conditions and the structural requirements of the bridge that links the aminofurazanyl moiety, the reaction may produce intramolecular coupling products as well as inter-molecular cyclic oligomers. Reagents such as DBI, AcOBr, and AcOCl were used as an oxidant. Some examples are given in Scheme 126. An intermediate in these reactions appears to be an N-halogenated product. The intermediate usually eliminates halogen to form the nitrene that dimerizes to an azo compound. However, *N*-chloro derivative **192** has been prepared from diaminoazofurazan **191** by the action of NaOCl in a mixture of CH_2Cl_2/H_2O in high yield (Scheme 127) [000UP7]. The synthesis of *N*,*N*-difluoroaminofurazan **193** also was accompanied by the formation of azo compound **194** (86BAU1901, 86IZV2086).

The thermal recyclization of 4,4′-bis(acetamido)-3,3′-azofuroxan **195** to (nitrotriazol-2-yl) furoxan **196** has been shown to involve two consecutive MHR (99MC17) (Scheme 128). Intramolecular nucleophilic attack initiated the process.

Other examples of nucleophilic attack on a furoxan ring leading to ring opening/recyclization are the formation of 1,2,3-triazole 1-oxides **198** from 4-alkylamino-3-nitrofuroxans **197** and alkylamines (Scheme 129). 3-Amino-4-nitrofurazan was observed as by-product (95MC194, 96CHE580, 96KGS675).

Only a small number of successful utilizations of furazan and furoxan diazonium salts was reported. A ring-cleavage reaction usually occurred when aminofurazans were diazotized under ordinary conditions. α-Hydroximinoacetonitriles were common products (Scheme 130) (79JHC689, 84CHE937, 84KGS1155, 93IZV1949, 93RCB1865). Diazonium salts can be prepared by diazotization of aminofurazans and furoxans at 0–5°C in conc. sulfuric acid or in mixtures with phosphoric or acetic acid (81ZOR1123, 88CHE1378, 88KGS1666, 93HAC521, 93IZV1949, 93RCB1865, 94CHE608, 94HAC441, 94KGS693, 95IZV1315, 95RCB1269, 96ROC734, 96ZOR766). Coupling with reactive aromatic

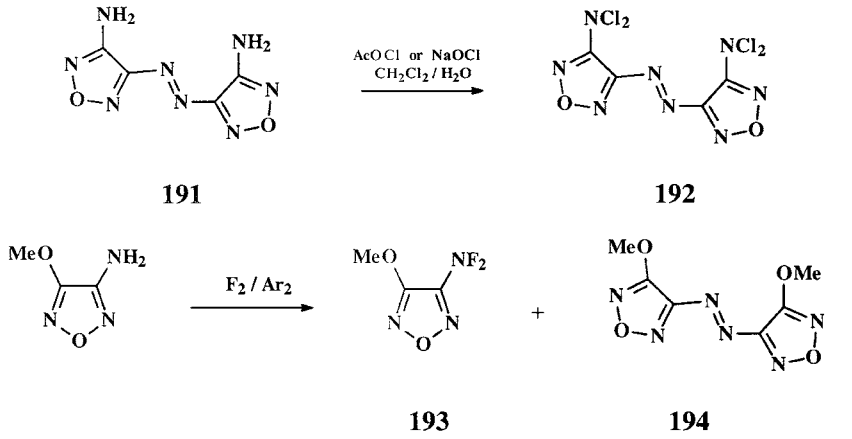


SCHEME 126

compounds gives moderate yields of diazo dyes (93IZV1949, 93RCB1865). A coupling reaction with a nitroalkane is the first step in the synthesis of [1,2,3]triazolo [4,5-*c*]furazans **199** (95IZV1315, 95RCB1269).

The sodium salt of 1-hydroxy-5-cyanotetrazole has been prepared in 51% yield by diazotization of 3-amino-4-azidofurazan in acetic acid (88CHE1378, 88KGS1666) (Scheme 130).

Treatment of the diazonium salts with sodium azide yields azido derivatives (93HAC521, 93IZV1949, 93RCB1865, 94HAC441, 96ROC734, 96ZOR766).



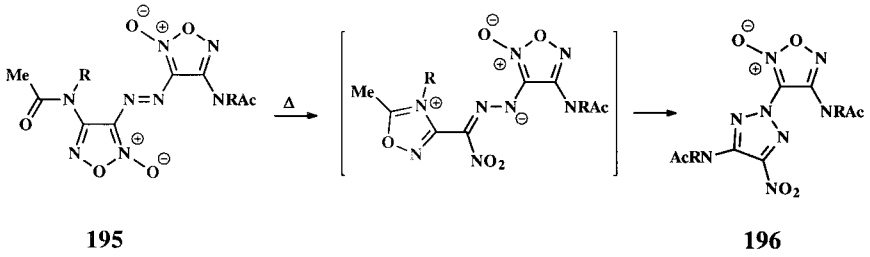
SCHEME 127

Diazotization of 3-amino-4-cyanofurazan using aqueous sodium nitrite and hydrochloric acid with subsequent ring opening gives chlorocyanoglyoxime (96ROC734, 96ZOR766) (Scheme 131).

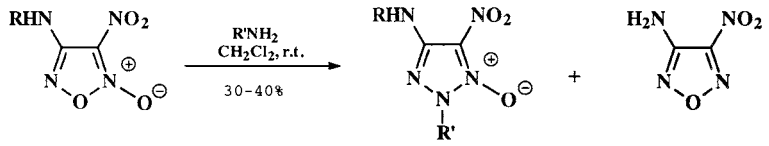
Dilution of a solution of diazonium salts in sulfuric acid with water affords triazene derivatives (95IZV1315, 95RCB1269). Treatment of a bridged bis(amino) furazans **200** with nitrous acid in acetic or hydrochloric acid gives macrocyclic triazene **201** (Scheme 132) (95MI4).

Alkylaminofurazans of type **202** were nitrosated to give the corresponding nitrosoamino derivatives, which were cyclized to fused 1,2,3-triazole 2-oxides **203** in 70–92% yields (96TL8577) (Scheme 133).

Azidofurazans and -furoxans undergo dipolar cycloaddition reactions with unsaturated compounds, in some cases regiospecifically. Thus, reaction of 3-amino-4-azidofurazan with 1-morpholinyl-2-nitroethene (toluene, reflux, 70 hours) gives 4-nitro-1,2,3-triazole **204** in 87% yield (99MI1, 000KGS406). Cycloaddition of the same azide to alkynes was accomplished by formation of a mixture of position isomers **205** and **206.** Regiospecific addition was observed only in singular cases

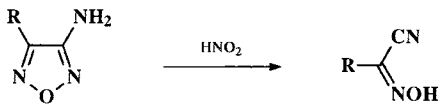


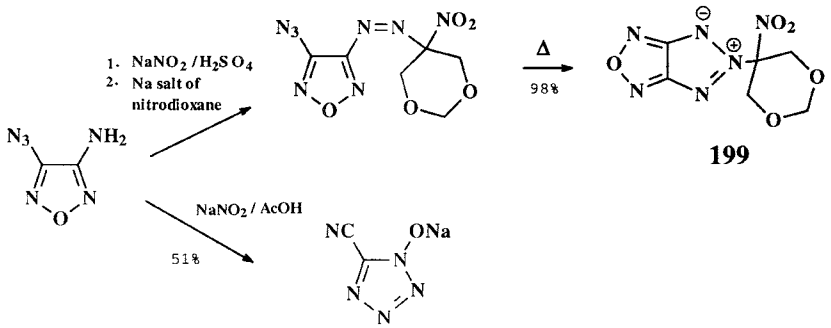
SCHEME 128



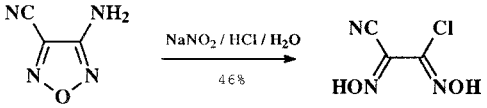
197 **198**

SCHEME 129

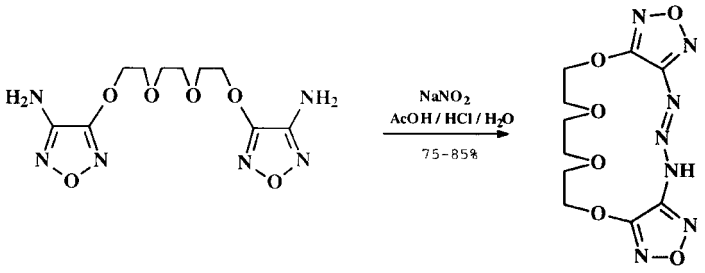




SCHEME 130

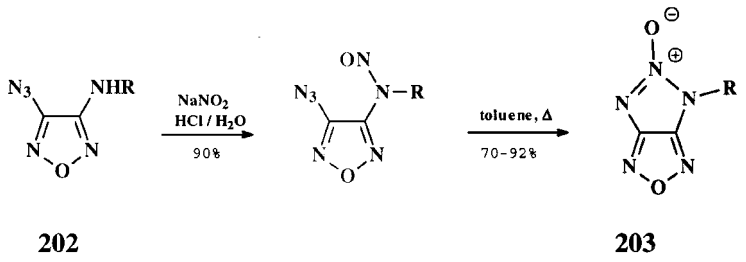


SCHEME 131



200 **201**

SCHEME 132



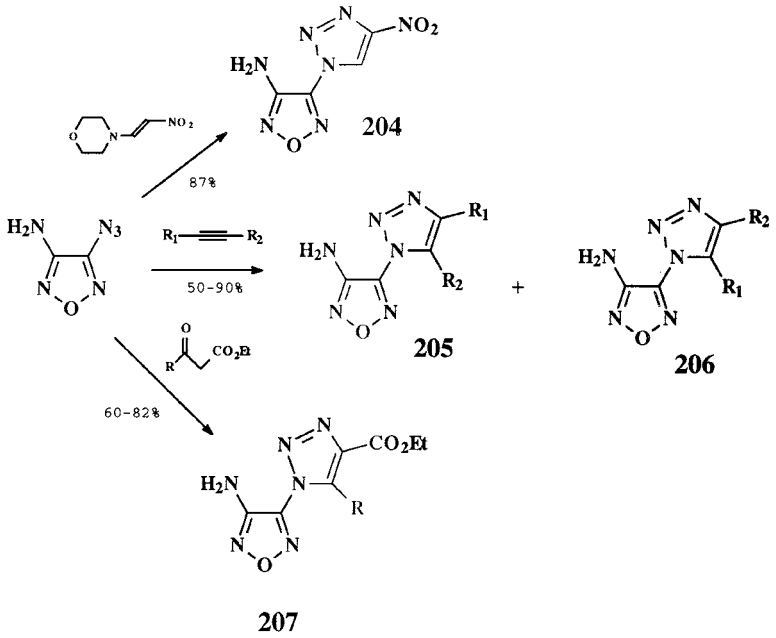
202 **203**

SCHEME 133

(000KGS100) (Scheme 134). Triazolylfurazans **207** were also prepared by condensation of azidofurazans with active methylene compounds in the presence of $MgCO_3$ (99MI1). A variety of azidofurazans and -furoxans reacted similarly to form the corresponding triazole derivatives.

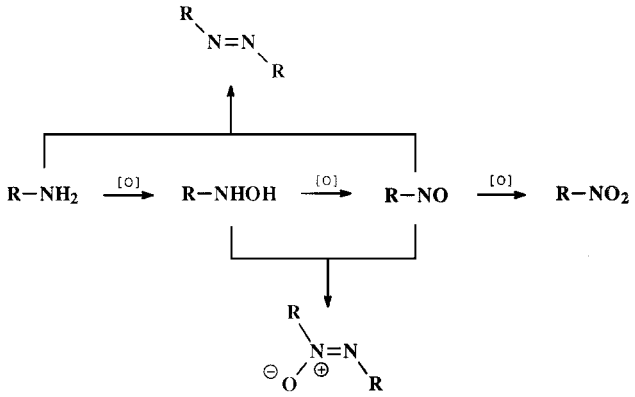
VIII. Nitrofurazans and -Furoxans

There have been very few publications on the chemistry of the nitro compounds since the comprehensive reviews of Sheremetev (97MI1, 97MI2) and Makhova and



204 **205** **206** **207**

SCHEME 134



SCHEME 135

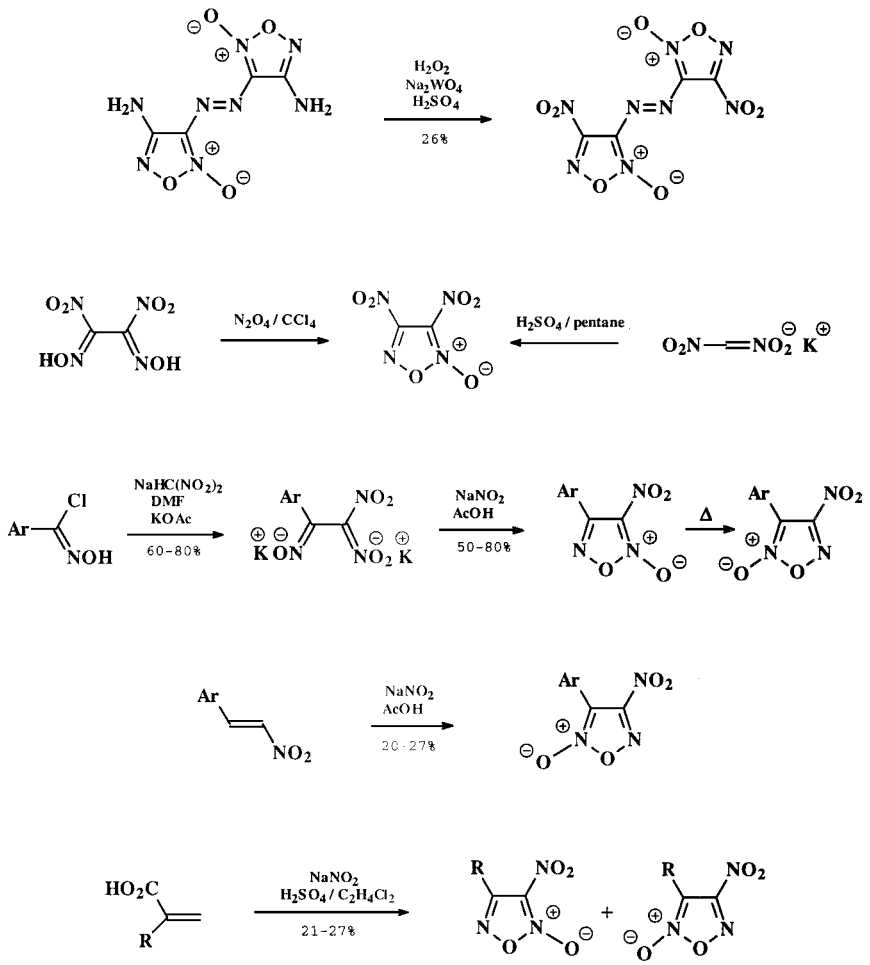
Godovikova (97MI3, 97MI4). This chapter concentrates on the more recent data, and references are made only to the more important previous papers, to illustrate the better-known aspects of the subject.

A. SYNTHESIS

Nitration of the parent furazan and its C-monosubstituted derivatives at the ring failed. The most common and convenient method of preparing nitrofurazans is the oxidation of the corresponding amines with a variety of oxidizing reagents, as illustrated in Scheme 135. The reagents commonly used for this purpose are 30–95% hydrogen peroxide and peracids, some of which are commercially available. A wide variety of nitrofurazans, bearing both electron-releasing and electron-withdrawing groups, has been prepared in this way (94MC138).

Nitroso- (90BAU1073, 90IZV1193, 99MI1) and azoxyfurazans (95MI1, 96MI3) can be the major products in similar oxidations, depending on the nature of the substrate and the oxidant, and on the experimental conditions employed.

There are five general approaches to synthesize nitrofuroxans: (i) similarly to nitrofurazans, by oxidation of aminofuroxans (97ROC1140, 97ZOR1216, 98DOK499, 98MI6, 99MI2); (ii) by oxidative cyclization of nitroglyoximes with N_2O_4 (94CHE465, 94KGS529); (iii) by dehydration of primary nitro compounds or their derivatives upon treatment with H_2SO_4 (95IZV722, 95RCB702); (iv) by nitrosation of α,α-dinitro-β-hydroximinoethane salts with a mixture of $NaNO_2$ and acetic acid (95MI2, 97IZV2232, 97RCB2117); (v) by nitrosation/nitration of alkenes with nitrogen oxides (96MI3, 97ZOR1216). Some examples are shown in Scheme 136.

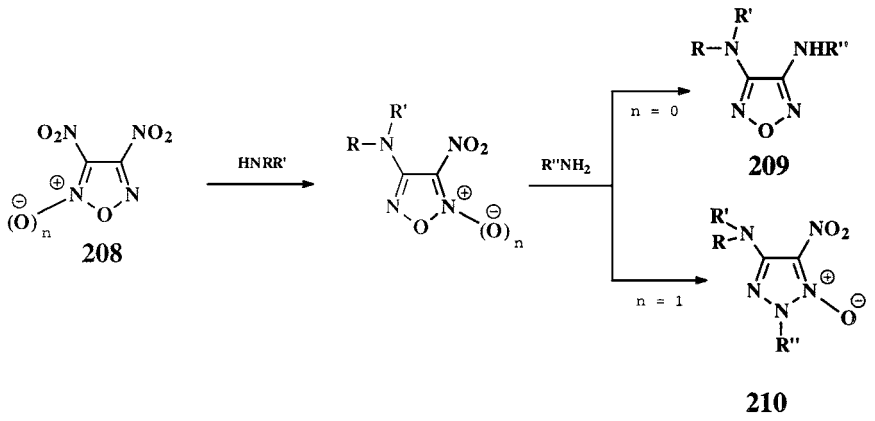


R = Et, CH_2CH_2OMe, CH_2CO_2Me

SCHEME 136

B. REACTIVITY

The nitrite anion is a good leaving group and it can be used in place of a chlorine substituent in many reactions. The nitro group at furazan and furoxan rings is readily replaced by a wide range of nitrogen, oxygen, sulfur, and carbon nucleophiles. The first nitro group in 3,4-dinitrofurazan **208** ($n = 0$) (000MI2) and 3,4-dinitrofuroxan **208** ($n = 1$) (94CHE465, 94KGS529) has been substituted by



SCHEME 137

amines in a similar way (Scheme 137). The second nitro group in these compounds shows different reactivities toward nucleophilic reagents. Thus, at the furazan ring the attack occurred at the carbon bearing the nitro group to give **209,** whereas at the furoxan ring the reaction is accomplished by transformation of the ring into 1,2,3-triazole-1-oxide **210** (96CHE580, 96KGS675).

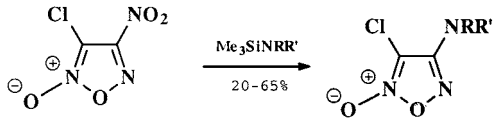
3-Chloro-4-nitro-furoxan **158d** reacts with nitrogen nucleophiles at C-4 (86BAU2198, 86IZV2398, 94CHE979, 94KGS1133, 94MC135) (Scheme 138).

The reaction of nitrofurazans with bases yields hydroxy derivatives or difurazanyl ethers, depending on the nature of the substrate, the base, and the solvent. Thus, hydroxyfurazans are readily obtained by the alkaline hydrolysis of mononitro derivatives (Scheme 139). Treatment of dinitrofurazans with an excess of the reagent gave the corresponding dihydroxyfurazans in good yields (99ZOR1555).

In an attempt to prepare monohydroxy derivatives from dinitrofurazans, a complex mixture of compounds was obtained (98MI1, 99ZOR1555).

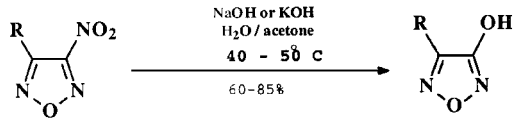
The nitro group at the furazan ring bearing another labile group can be displaced regioselectively by a hydroxy group on treatment with solid inorganic base *hydrates* in a dry solvent (98MC238) (Scheme 140).

Treatment of nitrofurazans bearing an electron-withdrawing group with an *anhydrous* solid inorganic base (Na_2CO_3, NaOAc, KCN, and other) in dry acetonitrile

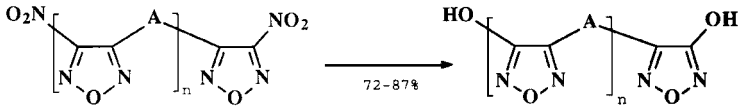


158d

SCHEME 138



R = Me, Ph, Het, NRR′



n = 0; 1

A = single bond, -N=N-

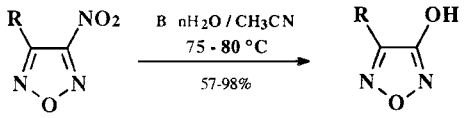
SCHEME 139

gave symmetrical difurazanyl ethers (96MC141, 98CEJ1023, 98MC238) (Scheme 141). The unusual formation of these ethers was suggested to occur via an initial intramolecular nitro–nitrite rearrangement.

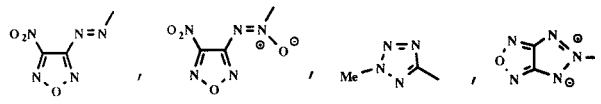
Under similar conditions bisnitrofurazans afforded oligomeric linear or macrocyclic ethers (96JOC1510, 99ZOR1555). An attempt to extend this reaction to nitrofuroxans failed.

Alkoxy-, aryloxy-, and heteroaryloxyfurazans (99ZOR143, 99ZOR1555, 000MI2) and -furoxans (94CHE465, 94KGS529) have been synthesized, in moderate to excellent yields, by treatment of the corresponding nitro derivatives with the sodium salts of alkanols or phenols. For example, the reaction of 3,4-dinitrofurazan and the sodium salt of 3,4-dihydroxyfurazan in glyme at 30°C afforded a mixture of monoether **211,** diether **212,** and a tricycle **213** in 10%, 43%, and 12% yield, respectively (98MI1) (Scheme 142).

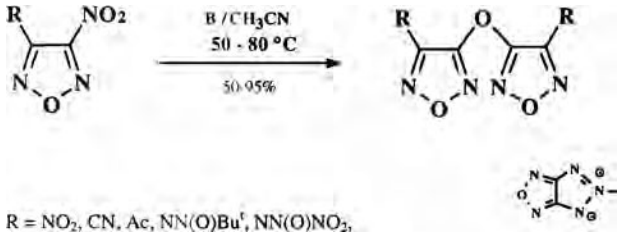
The reaction of 3,4-dinitrofurazan with pentaerythrol in polar aprotic solvents in the presence of a base gave the mono-, di-, tri-, and tetrafurazanyl ethers



R = NO_2, CN,



SCHEME 140



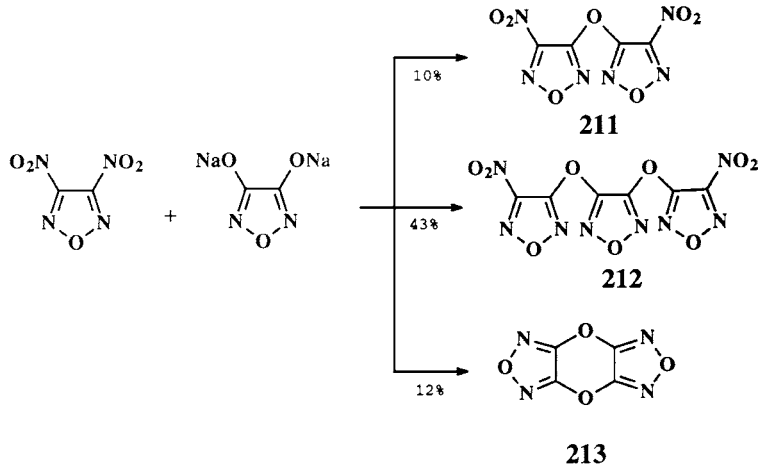
SCHEME 141

(Scheme 143). Other nitrofurazans reacted in a similar manner. Depending on the experimental conditions, different ratios of the ethers are produced. The yield of each of these ethers may amount to ∼70% (97MI7).

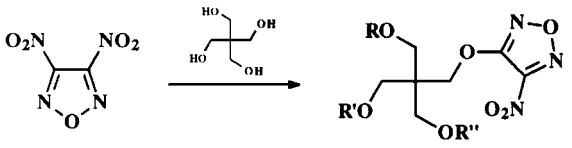
Functionalized thiols react with 3-amino-4-nitrofurazan in the presence of a base to form various thio derivatives (Scheme 144) (99MI3, 99MI4).

Treatment of 3,4-dinitrofurazan with potassium thiocyanate in acetic acid at 10–20°C led to the corresponding thiocyanate **214** in 83% yield along with a small amount of 3-mercapto-4-nitrofurazan, whereas at 70–75°C the precursor was converted into a mixture of the disulfide **215** (38%) and tricycle **216** (27%). Thioether **217** was prepared in 78% yield by reaction of 3,4-dinitrofurazan and sodium sulfide (95MC25) (Scheme 145).

Active methylene compounds also displace the nitro group at the furazan ring. Thus, 3,4-dinitrofurazan reacted with the sodium salt of ethyl β-oxo propionate or related compounds in the presence of a crown ether to give the corresponding ester, which was readily hydrolyzed and decarboxylated (92UP1) (Scheme 146).

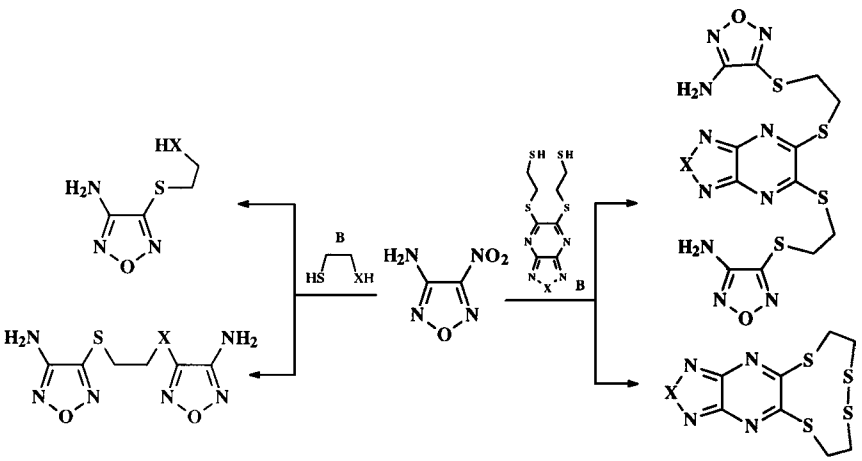


SCHEME 142



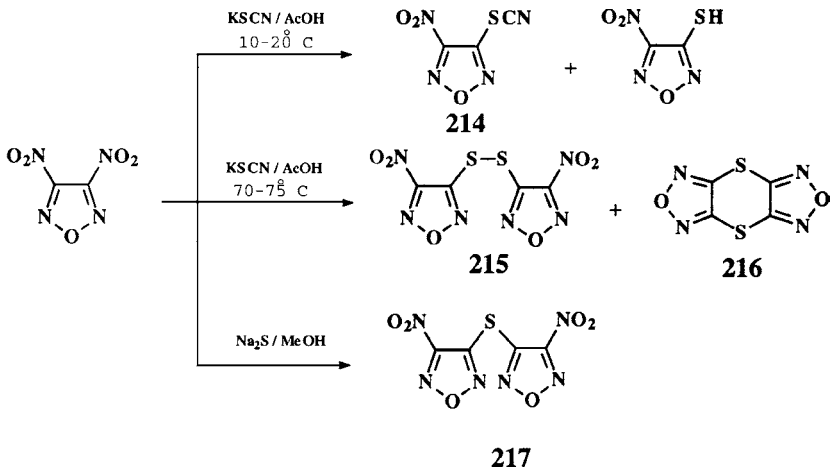
R, R′, R″ = H, nitrofurazanyl

SCHEME 143

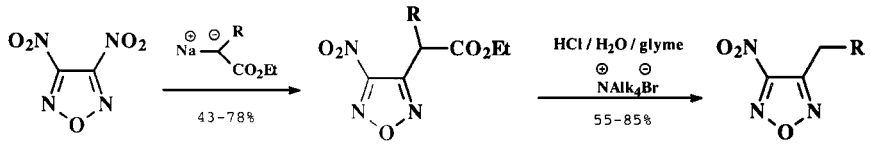


X = O; S; NR

SCHEME 144



SCHEME 145



R = CO_2Et, Ac, Bz, CN, nitrofurazanyl

SCHEME 146

Nitration of the phenyl group in phenylfurazans and furoxans with a mixture of nitric and sulfuric acid yielded mono- or dinitro derivatives (95MI2, 97ROC1140, 97ZOR1216, 99MI2). Nitroxymethyl derivatives (e.g., **218**) have been prepared in good yields by nitration of the corresponding hydroxymethyl compounds (Scheme 147) (94MC138, 97MI7, 97ROC1140, 97ZOR1216, 99MI2).

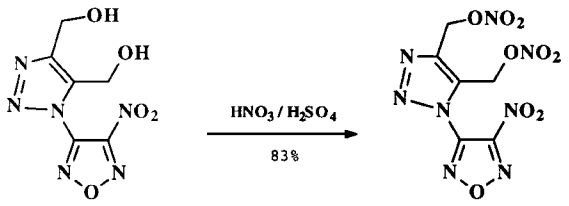
3,3′-Bis(3-nitrofurazanoxymethyl)oxetane **221** was synthesized in 52% yield by base-promoted ring closure of the corresponding 3-hydroxy-1-propyl triflate, **219,** which is readily available from the diol and triflic anhydride. Oxetane **221** can also be prepared in 74% yield by treatment of the trifurazanyl ether **220** with DBU. Polymerization and copolymerization reactions of oxetane **220** have also been investigated (97MI7) (Scheme 148).

In contrast to other furoxans, the cycloreversion of 3,4-dinitrofuroxan to nitroformonitrile oxide was observed even at room temperature. The nitrile oxide could be trapped *in situ* with electron-deficient nitriles (Scheme 149) (95MC231). Attempts to obtain cyclo adducts with styrene, phenylacetylene, *trans*-stilbene, and cyclohexene failed.

IX. Azoxyfurazans and -Furoxans

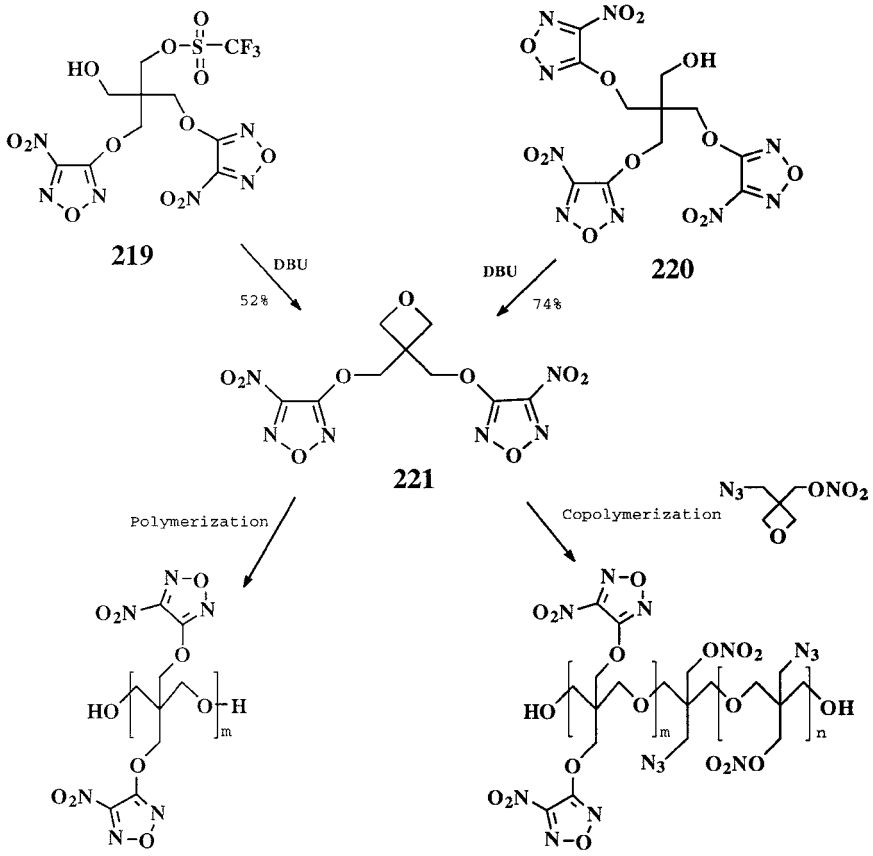
A. SYNTHESIS

The synthesis of the azoxy compounds has seen significant progress in the past decade. As already noted, compounds of this type may be prepared by



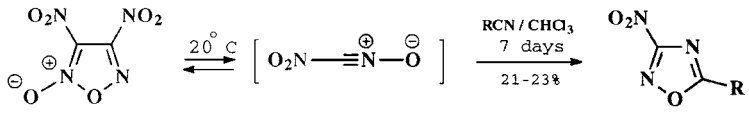
218

SCHEME 147



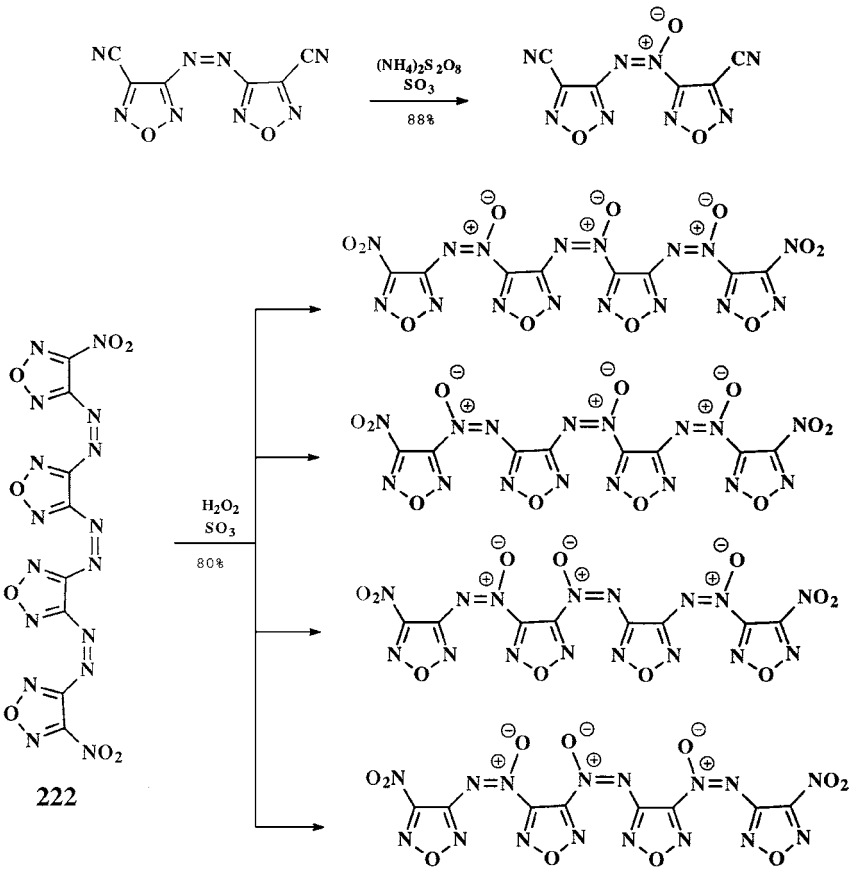
SCHEME 148

oxidative coupling of the corresponding amines. Oxidation of azofurazans is a more convenient way to azoxy derivatives (Scheme 150). Usually it involves treatment of the starting azo compound with an excess of an oxidant at 20–100°C (90BAU1073, 90IZV1193, 96MI3, 98MI2, 000MC67). A principal shortcoming of this method is the low regioselectivity in oxidation reactions of unsymmetrical and



R = CCl_3, CO_2Me

SCHEME 149



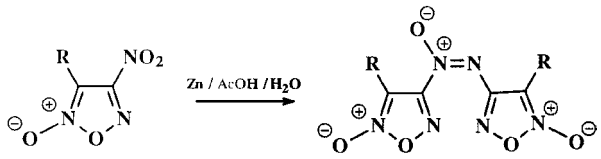
SCHEME 150

polyazo compounds (e.g., **222**) (94CHE629, 94CHE631, 94KGS714, 94KGS716, 94MC102, 97MC5, 98MI1).

Only a single example of azofuroxan oxidation to an azoxy derivative is known (99MC15). The most successful way to azoxyfuroxanes is reductive coupling of 4-nitrofuroxans with zinc dust in aqueous acetic acid (Scheme 151). 3-Nitrofuroxans do not form the expected 3,3′-azoxy derivatives; the starting compounds decompose under similar conditions (99MC15).

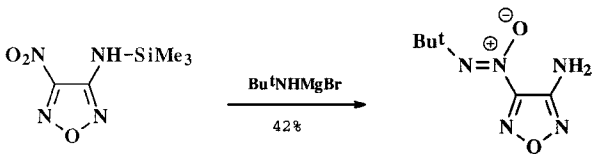
The reaction of nitrofurazans with *N*-magnesium derivatives of amines is a pathway to unsymmetrical azoxyfurazans (Scheme 152). Yields are in the region of 30–50% (92BAU1500, 92IZV1916).

Nitrosofurazans provide a regioselective access to unsymmetrical azoxyfurazans. Thus, oxidative coupling of 3-nitroso-4-methylfurazan with amines

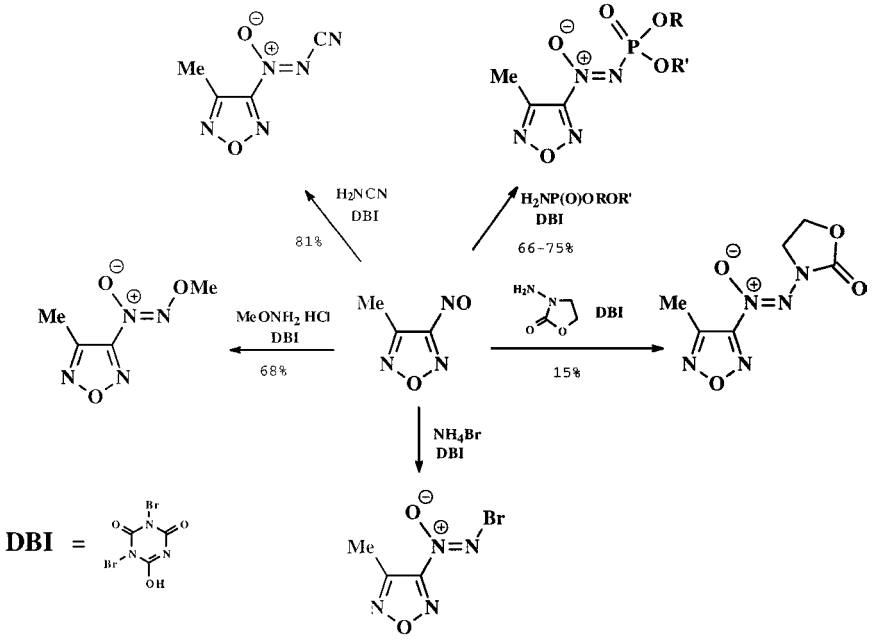


R = Ph, Me, Et, CH_2CH_2OMe

SCHEME 151

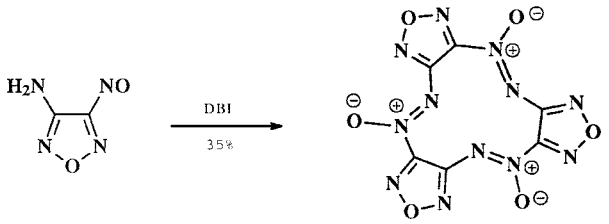


SCHEME 152

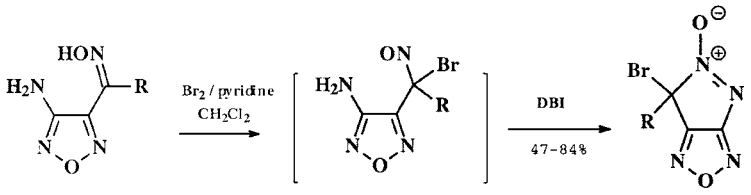


223

SCHEME 153

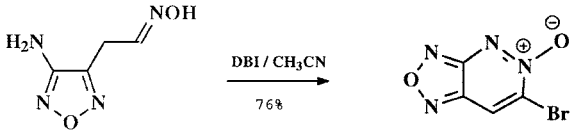


224



225

R = Me, Cl



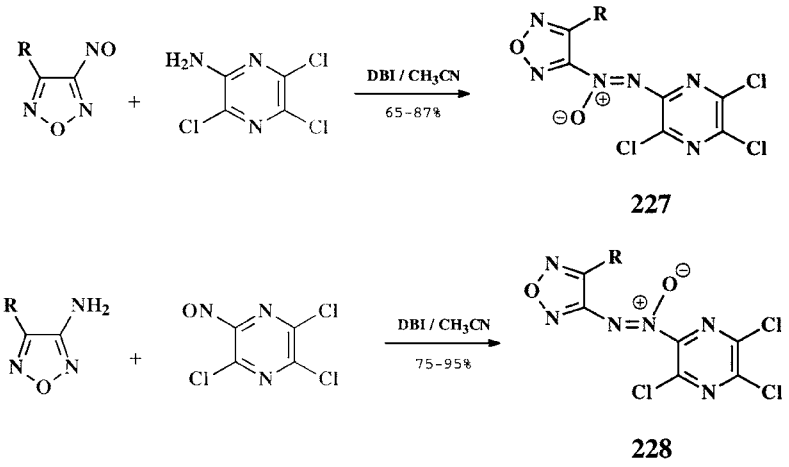
226

SCHEME 154

(90BAU2560, 90IZV2821, 91MC49, 92BAU902, 92IZV1148), hydroxylamines (90BAU1966, 90IZV2155), or hydrazines (92DISS1) in the presence of dibromoisocyanurate (DBI) afforded the corresponding azoxy derivatives in good yields. *N*-Bromoazoxyfurazan **223** was prepared from 3-nitroso-4-methylfurazan with DBI/NH_4Br (97DISS1) (Scheme 153).

The type of the oxidation product that may be prepared from precursors bearing both nitroso and amino groups depends on the number of atoms bridging them. Thus, on treatment of 3-amino-4-nitrosofurazan (two atoms between the reactive groups) with DBI, an intermolecular coupling product **224** (97MC7) was formed in 35% yield (Scheme 154). Similar reactions of precursors where three or four atoms were between nitroso and amino groups afforded pyrazolo[3,4-*c*]furazan-5-oxide **225** (93MC120) and furazano[3,4-*b*]pyridazine-5-oxide **226** (94UP1), respectively.

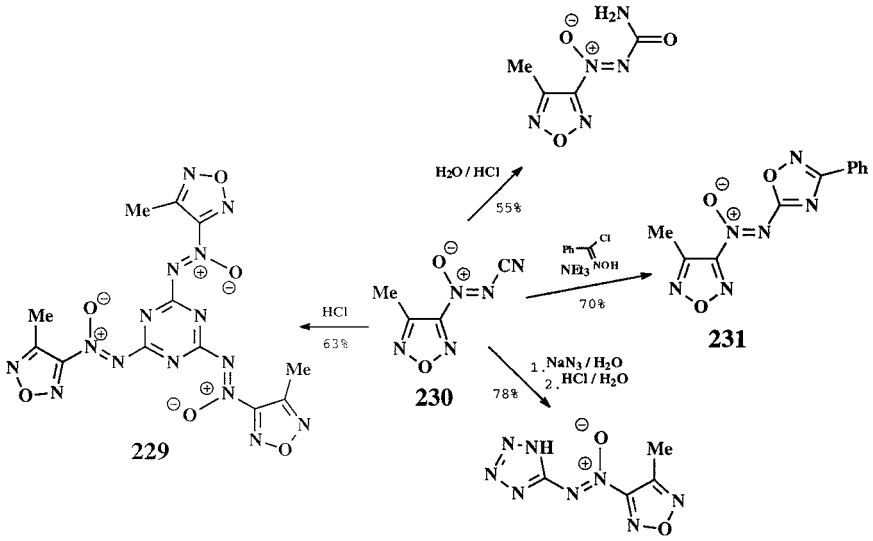
Isomeric azoxy derivatives **227** and **228** have been prepared by condensation of the corresponding amino and nitroso substrates (Scheme 155) (88UP1).



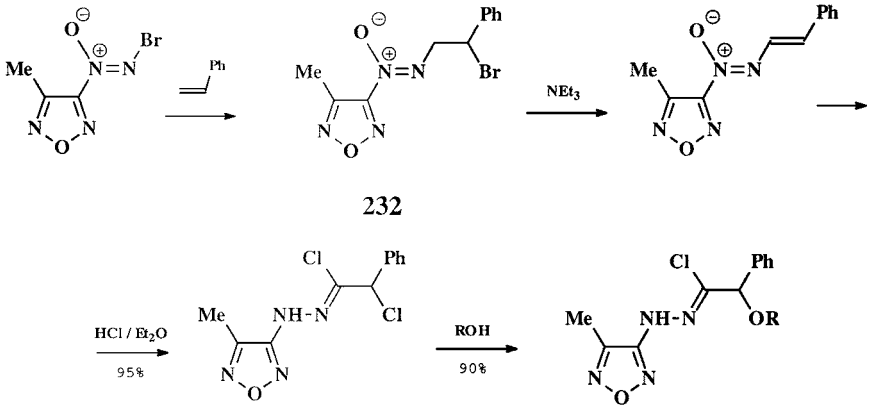
SCHEME 155

B. REACTIVITY

The *N*-nitrile group in cyanoazoxy-substituted furazans (e.g., **230**) is activated toward nucleophilic attack. It is an excellent substrate for dipolarophilic reactions. Thus, benzonitrile oxide adds to the nitrile group at 0°C to give a 1,2,4-oxadiazole **231** in good yield. Tetrazole formation was observed at room temperature. Cyanide **230** and hydrogen chloride react to give the 1,3,5-triazine **229** (Scheme 156) (91BAU1460, 91IZV1647).



SCHEME 156



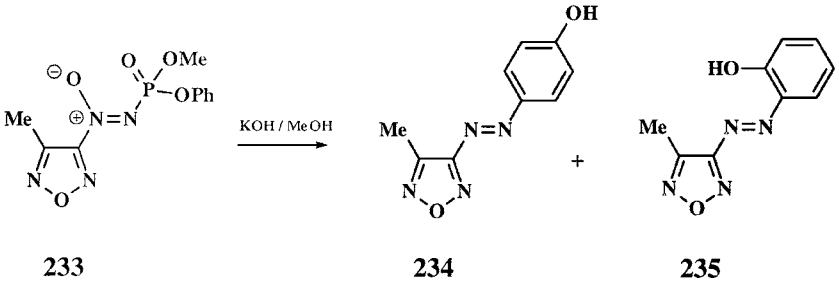
SCHEME 157

The *N*-bromine atom in bromoazoxy-substituted furazans has high electrophilicity. These compounds react with styrene to form α-bromo-β-azoxy derivatives, such as **232,** which upon treatment with triethylamine afforded β-azoxystyrenes. Subsequent reactions of the alkenylazoxy compounds may produce various functional hydrazones (Scheme 157) (94MC220, 95IZV924, 95IZV928, 95RCB897, 95RCB901, 97DISS1).

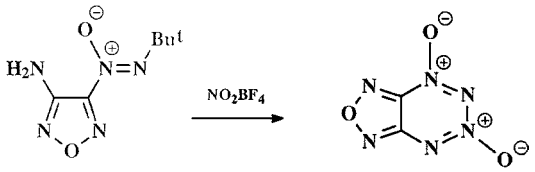
The *N*-phosphoryl group in azoxyfurazan **233** was removed under basic conditions (MeOH/KOH, −30°C) to give a mixture of azo compounds **234** and **235,** albeit in low yield (Scheme 158) (93IZV609, 93RCB577).

An unusual transformation was observed on treatment of 3-amino-4-*tert*-butylazoxyfurazan with an excess of nitronium tetrafluoroborate at −10°C in acetonitrile (Scheme 159). Furazano[3,4-*e*][1,2,3,4]tetrazine 4,6-dioxide **236** was obtained in 52% yield (95MC227).

An azoxy moiety on a furazan ring is a good leaving group. It can be used similarly to a nitro group in nucleophilic replacement reactions. Thus, the azoxyfurazanyl moiety in **237** is readily replaced by an *O*-nucleophile upon treatment with an alkoxide or phenoxide to give ether **238** (Scheme 160) (89BAU678, 89IZV749, 000HAC48).

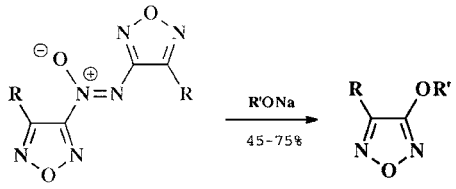


SCHEME 158



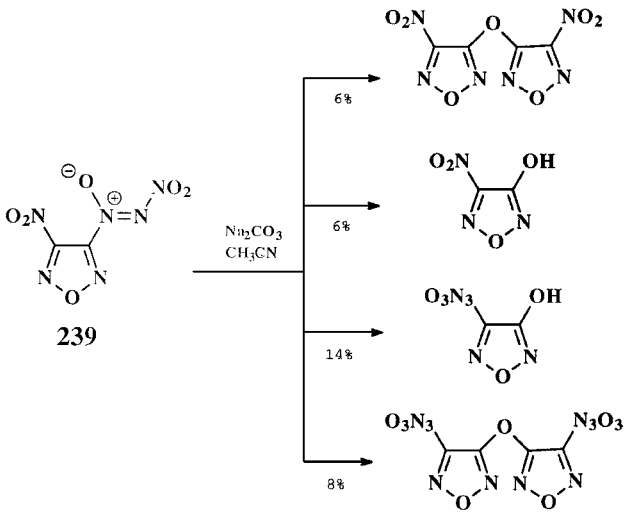
236

SCHEME 159



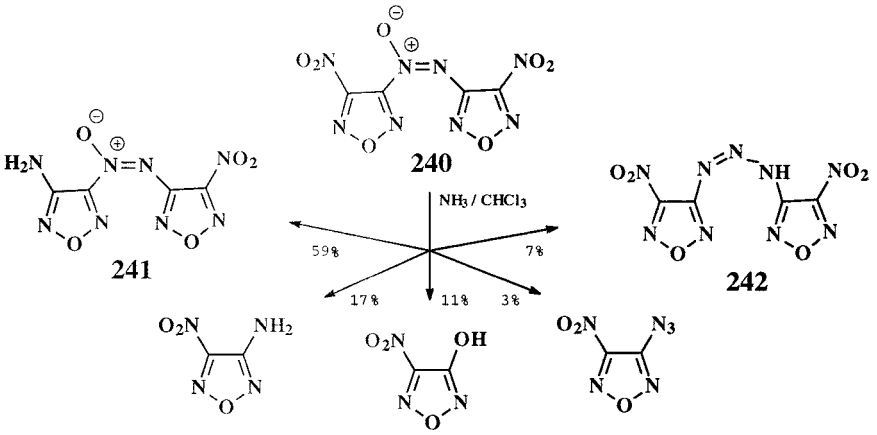
237 **238**

SCHEME 160



239

SCHEME 161



SCHEME 162

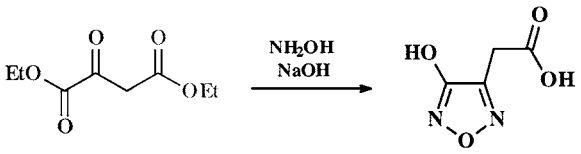
Nonselective attacks at carbon bonded with nitro group and carbon bonded with azoxy group were observed in reactions of **239** with bases in anhydrous acetonitrile (Scheme 161) (98CEJ1023). Reaction of 4,4′-dinitroazoxyfurazan occurred in a similar way (000HAC48).

When the 4,4′-dinitroazoxyfurazan **240** reacted with ammonia in anhydrous $CHCl_3$, a mixture of five compounds was formed (Scheme 162) (000HAC48). Compound **241** (59%) was the predominant product. However, the most interesting result of this reaction is the isolation of 3-azido-4-nitrofurazan (3%) and triazene **242** (13%). The formation of these compounds could be explained by reacting the intermediate diazotate generated from the leaving nitrofurazanazoxy moiety with ammonia and with 3-amino-4-nitrofurazan, respectively.

X. Hydroxy, Alkoxy, and Aryloxy Derivatives

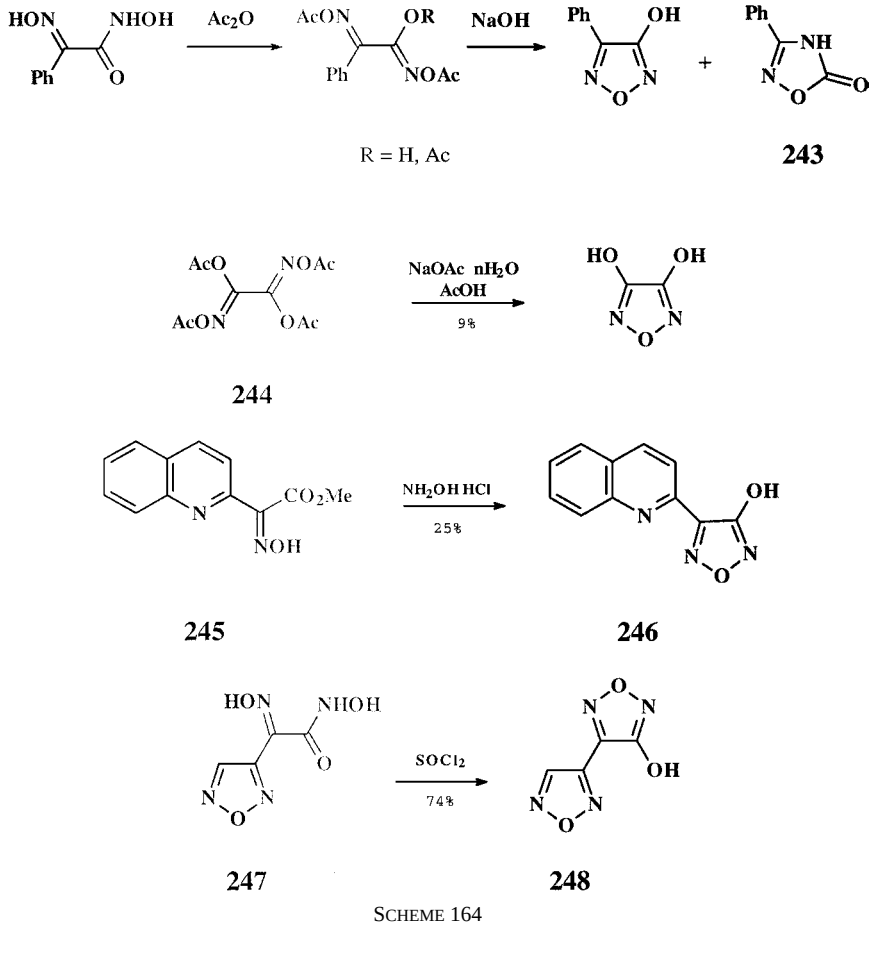
A. SYNTHESIS

The transformation of furazans and furoxans bearing at the ring a leaving group such as a halogen atom, a nitro group, or a sulfonyl moiety is the most common method for the synthesis of hydroxy, alkoxy, and aryloxy derivatives (see earlier discussion). An alternative synthesis of hydroxyfurazans is based on the construction of the ring. 3-Hydroxyfurazan-4-acetic acid, the first example of a furazan with a hydroxy substituent, was prepared by Hantzsch and Urbahn in 1895 by treatment of diethyl 3-oxosuccinate with hydroxylamine in aqueous NaOH (Scheme 163) (1895CB753). Others have used this method with minor modifications [65T1681, 67FRP1491583, 67USP3322750, 69GEP(O)1906194].

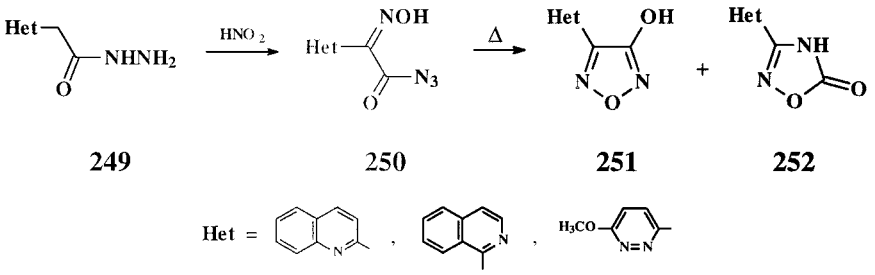


SCHEME 163

A mixture of 3-hydroxy-4-phenylfurazan and 1,2,4-oxadiazole **243** was prepared from α-phenyl-α-hydroximino hydroxamic acid by acylation and subsequent treatment with 15% aqueous NaOH (Scheme 164) (25G201). The reaction of tetraacetate **244** with sodium acetate hydrate in glacial acetic acid at 70°C gives 3,4-dihydroxyfurazan (9%) (92URP1752734). α-Hydroximino ester **245** reacts with hydroxylamine to form furazan **246** in 25% yield (Scheme 164) (79JHC689).



SCHEME 164



SCHEME 165

Treatment of pericyanil acid **247** with thionyl chloride affords hydroxyfurazan **248** in 74% yield (Scheme 164) (29LA54, 75LA1029). However, attempts to synthesize a hydroxyfurazan from α-R-α-hydroximino hydroxamic acids, with R = CH_3 or COOH, were unsuccessful (1895CB753).

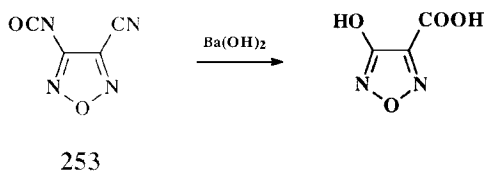
Nitrosation of hetaryl acetic hydrazide **249** gives azide **250,** which on thermolysis affords furazan **251** and 1,2,4-oxadiazole **252** (Scheme 165) (79JHC689). Depending on the solvent, different ratios of **251** and **252** were obtained. A higher proportion of furazan **251** (up to 70%) was formed in $CHCl_3$.

An interesting observation was reported concerning the hydrolysis of nitrile **253** with barium hydroxide (Scheme 166). It was stated that 3-hydroxyfurazancarboxylic acid was formed, although an adequate proof of the structure was not given (12LA196, 30LA43).

B. REACTIVITY

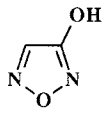
All hydroxyfurazans exhibit marked acidic properties. Compounds derived from furazans substituted with an electron-withdrawing group exhibit higher acidity than the corresponding 2,4-dinitro-6-R-phenol counterparts. Salts with sodium, ammonium, hydrazinium, and other cations are solids that are stable to store (1895CB753, 12G503, 97MI8, 98MC238, 98CEJ1023, 98MI4, 99ZOR1555); however, most of these salts explode on shock, friction, or ignition.

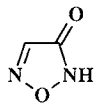
Hydroxyfurazans exist solely in the hydroxy form. This is in accord with quantum chemical calculations (Scheme 167). Density functional theoretical studies (B3LYP/6-311+G(2d,p)) indicate that 3-hydroxyfurazan is more stable than the



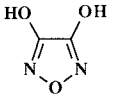
253

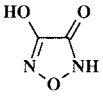
SCHEME 166

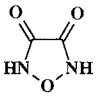




B3LYP/6-311+G(2d,p) (in hartrees) -337.37742 -337.36738

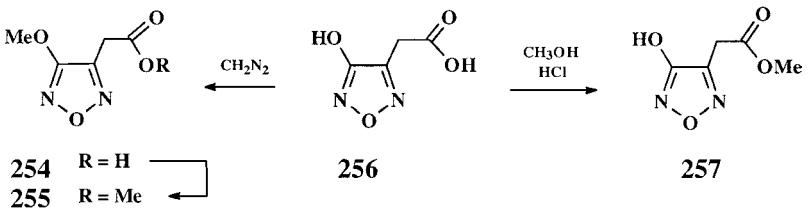




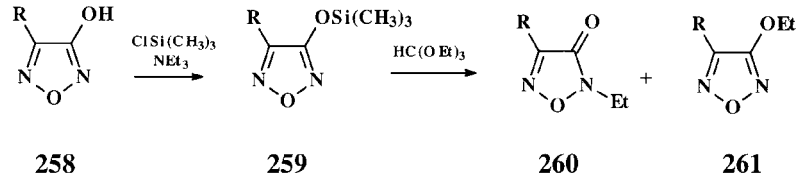


B3LYP/6-311+G(2d,p) (in hartrees) -412.62256 -412.62062 -412.60794

SCHEME 167

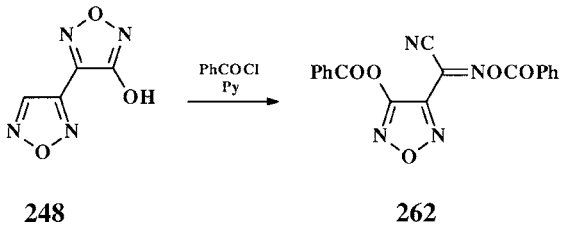


SCHEME 168



R = Ph, CN

SCHEME 169



SCHEME 170

corresponding 1,2,5-oxadiazolone-4 by 6.3 kcal/mol. The same holds for dihydroxyfurazan, although in this case the energy difference between the dihydroxy and the monohydroxy tautomer is quite small ($\Delta E = 1.2$ kcal/mol; basis set dependent). All calculations refer to the gas phase (000UP5).

Alkylation with electrophilic reagents occurs at the hydroxy oxygen giving ethers only (65T1681, 67USP3322750, 79JHC689). For instance, methoxy acid **254** was obtained from 3-hydroxyfurazan-4-acetic acid **256** and diazomethane in ether (67USP3322750). An excess of ethereal diazomethane afforded methoxy methoxycarbonyl derivative **255** (90%), whereas the hydroxy methoxycarbonyl derivative **257** (60%) was formed on refluxing the acid **256** in methanol saturated with dry HCl (Scheme 168) (65T1681).

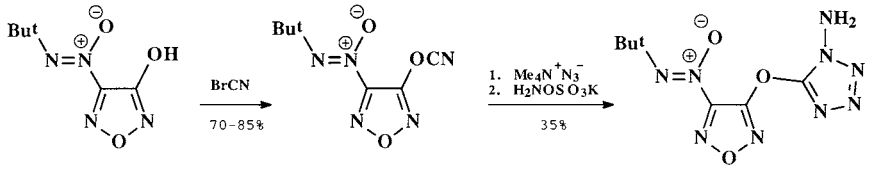
An electrophile can be introduced into the N-2 position of 3-hydroxyfurazans **258** via their *O*-trimethylsilyl intermediates (e.g., **259**). A 1:1 mixture of *N*- (**260**) and *O*-alkylation (**261**) products was formed on heating **259** with ethyl orthoformate (93T5905) (Scheme 169).

Boiling ethoxyfurazan **261** (R = Ph) in a sealed tube with hydriodic acid for 1.5 hours at 134–137°C afforded only 8% of the corresponding hydroxy derivative **258** (R = Ph), and 70% of the starting material was recovered. Treatment of **261** (R = Ph) with $LiAlH_4$ in THF under reflux did not afford the reduction product. Starting material was recovered quantitatively after 2.5 hours [69JCS(C)2794].

The hydroxy group undergoes *O*-acylation and deacylation (79JHC689). These reactions of functionalized hydroxyfurazans are valuable methods for modification of these compounds. Thus, hydroxybifurazan **248** was aroylated with benzoyl chloride in the presence of pyridine with concomitant cleavage of the unsubstituted furazan ring to give nitrile **262** (Scheme 170) (75LA1029).

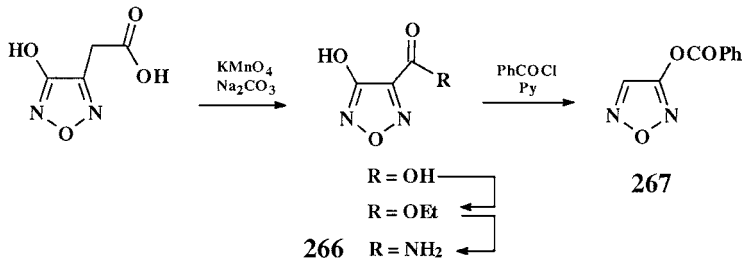
The hydroxy group of furazan **263** reacted with cyanogen bromide in glyme in the presence of Li_2CO_3 to give cyanate **264** in 70–85% yield (97MI8). Upon treatment with Me_4NN_3 and subsequently with a basic solution of hydroxylamine-*O*-sulfonic acid, *N*-aminotetrazole **265** was obtained in 35% yield (Scheme 171).

Oxidation of 3-hydroxyfurazan-4-acetic acid with potassium permanganate under alkaline conditions gave 3-hydroxy-4-furazancarboxylic acid (1895CB753). The acid yielded an ester when heated in ethanol saturated with dry HCl. The ester

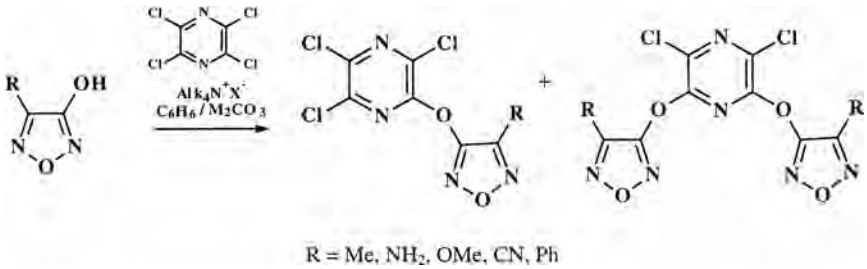


263 **264** **265**

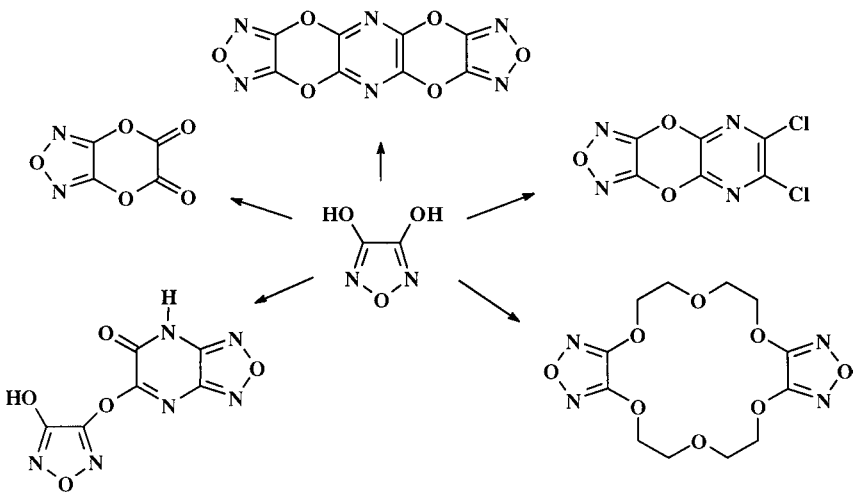
SCHEME 171



SCHEME 172



SCHEME 173



SCHEME 174

was converted to amide **266** by treatment with NH3 (Scheme 172) (12G503). This amide was also prepared by hydrolysis of hydroxybifurazan **248** (75LA1029).

There was some dispute over the product resulting from the benzoylation reaction of amide **266,** which, according to the original investigators, has the furazan structure **267** (Scheme 172) (29LA54).

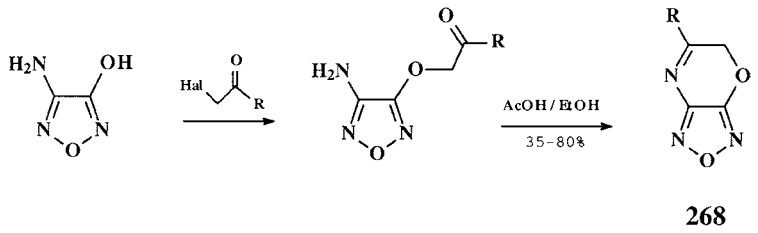
Phase transfer catalysts were used for nucleophilic displacement reactions of activated leaving groups by hydroxyfurazanyl anions. For example, tetrachloropyrazine was found to react with hydroxyfurazans in benzene/Na_2CO_3/tetraalkylammonium salts giving products of mono- or disubstitution (Scheme 173) (94MI1). The course of the reaction depends on the ratio of the reactants and the nature of the ammonium salt.

3,4-Dihydroxyfurazan reacts with bis-electrophiles in the presence of a base and a phase transfer catalyst to form furazano fused bicyclic or polycyclic systems (Scheme 174) (92URP1715808, 92URP1715809, 92URP1752734, 97MI8).

3-Amino-4-hydroxyfurazan reacts with α-haloacetyl compounds in the presence of NEt_3 to yield ethers which on heating in a mixture of acetic acid with ethanol gave annulated oxazines **268** in 35–80% yields (Scheme 175) (96UP1).

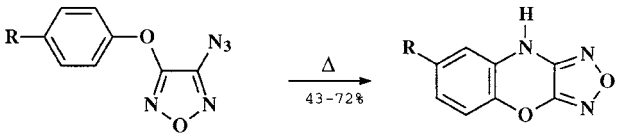
Phenoxazine analogues **270** were prepared by thermolysis of azides **269** in decalin in 43–72% yields (Scheme 175) (96UP1).

Quaternization of pyridine derivatives **271** with methyl iodide in acetone gave salts, which were reduced with sodium borohydride to tetrahydropyridines **272**



268

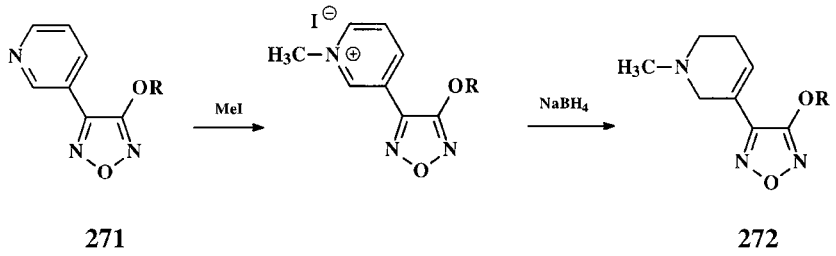
R = CH_3, CH_2Cl, Ar, Het



269 **270**

R = Cl, F, NMe_2, CH_3, OCH_3, Ph, Het

SCHEME 175



271 **272**

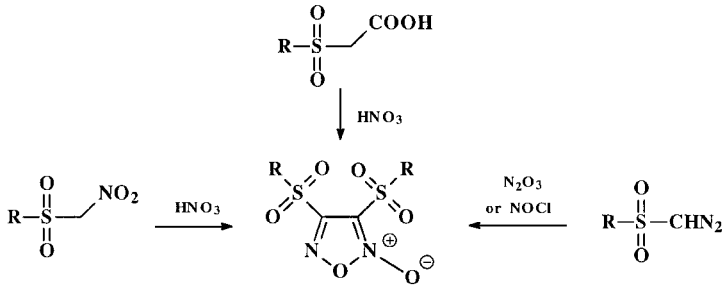
SCHEME 176

in 19–25% yields (Scheme 176) (90EUP384288, 92JMC2274). No reactions of hydroxyfuroxans have been reported.

XI. Thioderivatives of Furazans and Furoxans

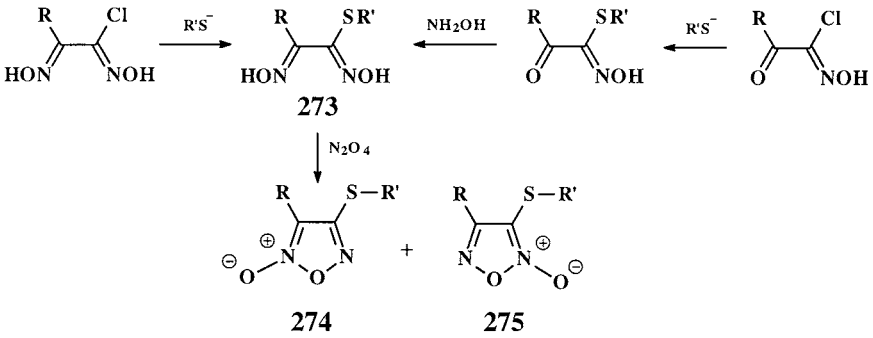
A. SYNTHESIS

Farrar utilized the reaction of arylsulfonylacetic acids with a mixture of nitric (d 1.5) and acetic acid under reflux for the first synthesis of a furoxan with S-linked substituents, such as 3,4-bis(arylsulfonyl)furoxans (50–65%) (64JCS904). Trifluoromethylsulfonyl analogues were prepared similarly (Scheme 177) (83BAU1016, 83IZV1125). 3,4-Bis(arylsulfonyl)furoxans have also been readily obtained in 24–87% yields from the corresponding arylsulfonylnitromethanes and a mixture of 90% nitric and acetic acids at 60–65°C (77JHC1415) or from arylsulfonyldiazomethane and N_2O_3 in CH_2Cl_2 at 0–5°C (75–100%) (71SC121). Nitrosyl chloride in CCl_4 at −5 to 5°C was also utilized for the synthesis of aryl- and alkylsulfonylfuroxans, but yields were low (74SC311).



R = Alkyl (CF_3, *tert*-Bu, $PhCH_2$), Aryl (Ph, *p*-MeC_6H_6, *p*-ClC_6H_4, *m*-ClC_6H_4, 4-Me-3-$NO_2C_6H_3$, *p*-FC_6H_4, *m*-$NO_2C_6H_4$)

SCHEME 177

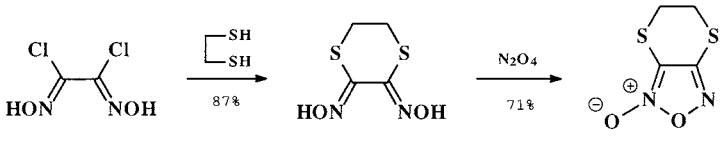


273

274 **275**

R = Me, CN, *tert*-Bu, CONHR″

R′ = Ar, Alk, CH_2CO_2R'', CH_2CH_2OH, $(CH_2)_2SCH_2CO_2Me$

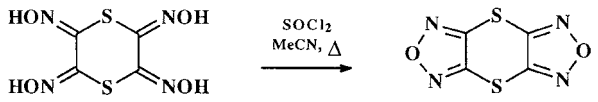


276

SCHEME 178

The reaction of haloglyoximes with suitable thiolates is a valuable method for the preparation of glyoxime sulfides **273.** Chloro oximes have also been used as starting materials for synthesis of sulfides. These latter compounds can react with N_2O_4 to afford a wide range of unsymmetrical furoxan sulfides in good yields, for example, a mixture of isomers **274** (major product) and **275** (Scheme 178) (92JMC3296, 95EUP683159).

Similar reaction sequences have also been used to prepare symmetrical furoxan sulfides and bicyclic compound **276** (95EUP683159). Other syntheses of furoxan sulfides and almost all those of furazan sulfides are based on the displacement of nitro and chloro groups by S-nucleophiles (see above). Furazan sulfides were also prepared by the reduction of the corresponding furoxans (73JHC587). The only synthesis of furazan sulfide **277** from the corresponding glyoxime was reported by Sheremetev *et al.* in 1991 (Scheme 179) (91URP1643546).

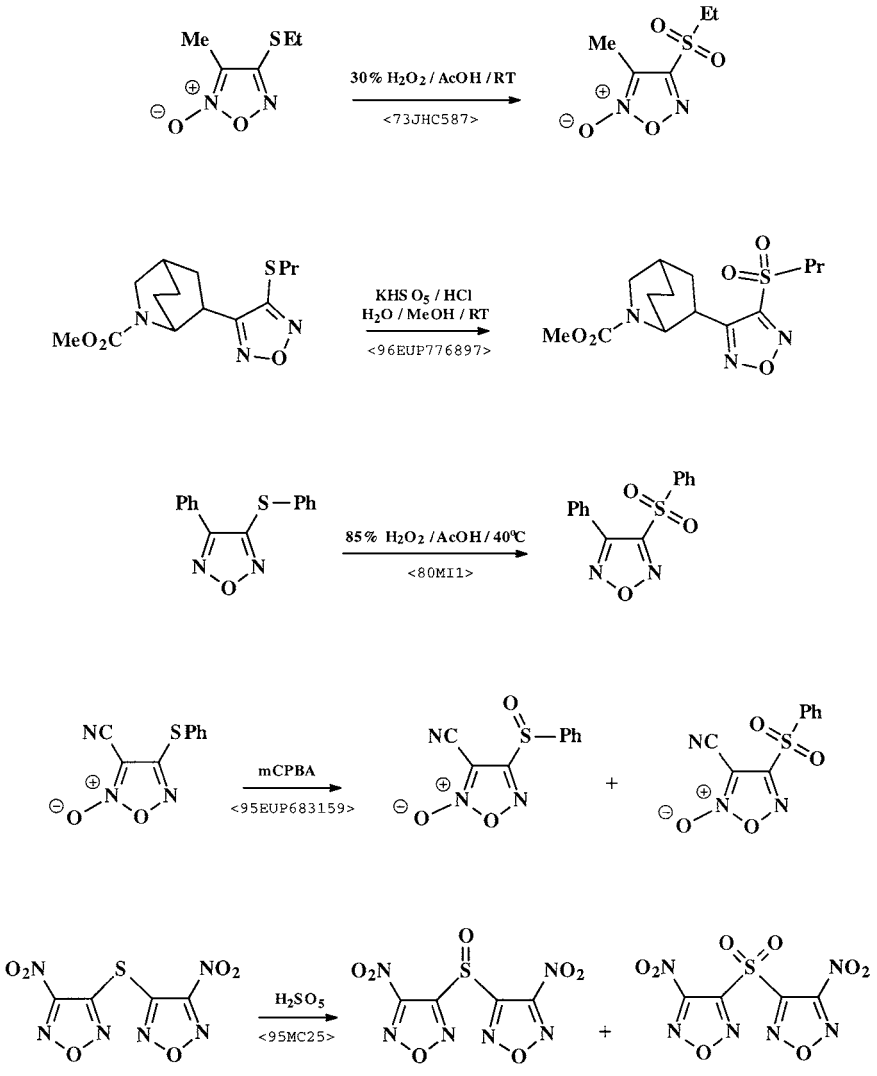


277

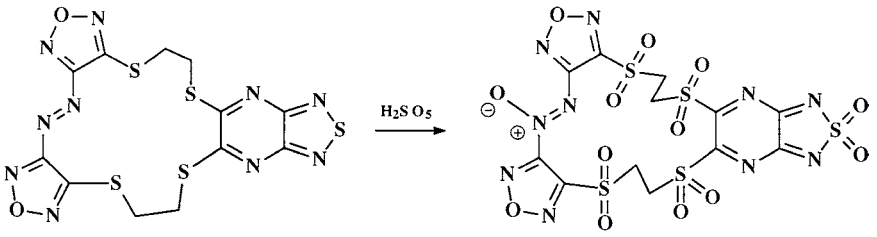
SCHEME 179

B. REACTIVITY

As a general rule, the furazan and furoxan sulfides are readily oxidized to the corresponding sulfoxides and sulfones. The ease of oxidation depends largely on the nature of second substituents in the ring. A number of examples are given in Scheme 180 (73JHC587, 77MI1, 80MI1, 92JMC3296, 95EUP683159, 95MC25, 96EUP776897).



SCHEME 180



278 **279**

SCHEME 181

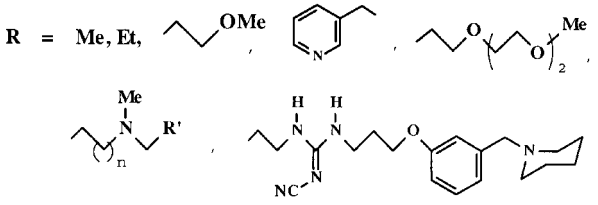
Treatment of macrocycle **278** with an excess of Caro's acid resulted in oxidation of all the sulfur atoms to sulfones and the azo group to an azoxy group (Scheme 181) (99MI4). The oxidation product **279** was formed in 42% yield. Products with smaller oxygen contents were obtained using weaker oxidizing agents.

The sulfonyl group in furazans and furoxans is readily displaced by various nucleophiles. Thus, reaction of 3,4-bis(arylsulfonyl)furoxans with alkoxides gave 4-alkoxy derivatives **280** in good yields (Scheme 182) (64JCS904, 95EUP683159, 97AF849, 97FA405, 97JMC463).

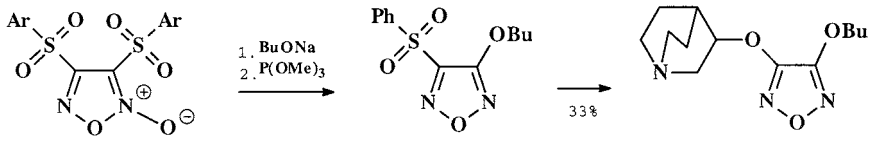
Heating 3,4-bis(phenylsulfonyl)furoxan with a solution of sodium butoxide in butanol followed by reduction with trimethyl phosphite gives furazan **281** (Scheme 183). Compound **281** was converted into dialkoxy derivative **282** with the lithium salt of (±)-1-azabicyclo[2.2.2]octan-3-ol in 33% overall yield (96WO12711, 97EUP773021, 98JMC379).

Nucleophilic displacements of alkylsulfonyl groups in furazans (Scheme 184) have also been reported (96EUP776897).

280

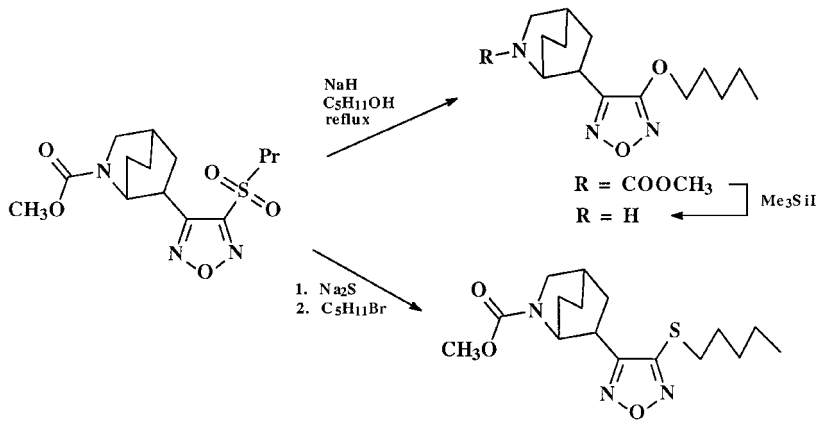


SCHEME 182

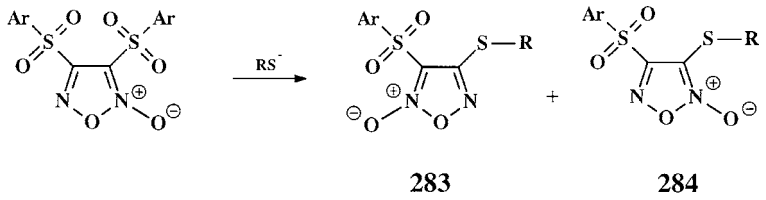


281 **282**

SCHEME 183



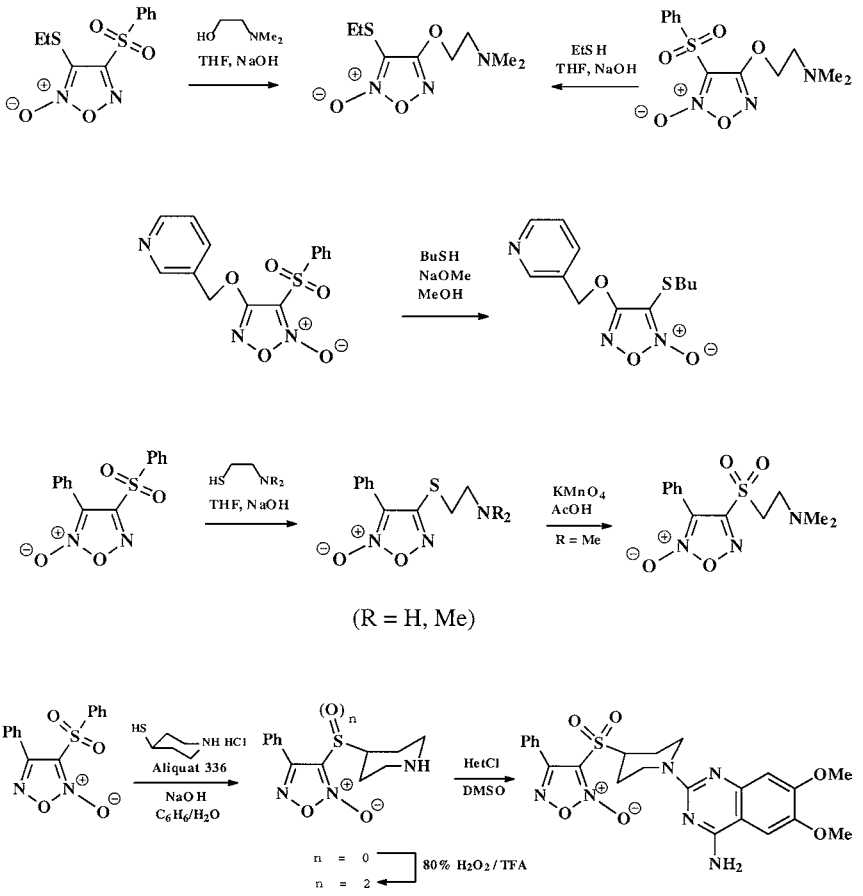
SCHEME 184



283 **284**

R = Et, $(CH_2)_nNMe_2$

SCHEME 185



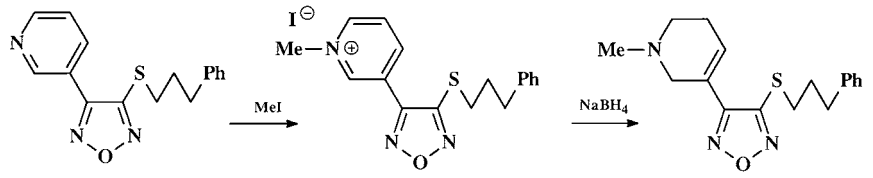
SCHEME 186

In contrast to alkoxides, thiolates react with 3,4-bis(arylsulfonyl)furoxans to give both isomeric products **283** and **284** (Scheme 185) (96JHC327, 97JMC463).

Some other examples of sulfonyl group nucleophilic displacements utilized in drug design are illustrated in Scheme 186 (95EUP683159, 97FA405, 97JMC463).

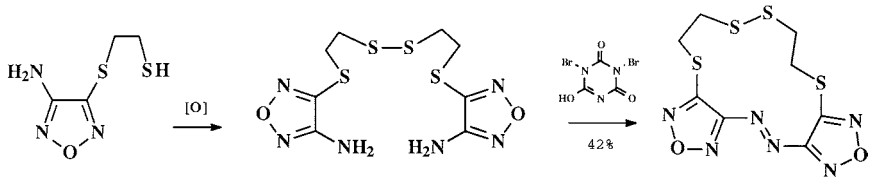
When the pyridinyl substituted furazan **285** was treated with methyl iodide in acetone, the quaternary salt was formed. Reduction with sodium borohydride affords tetrahydropyridine derivative **286** (Scheme 187; see also Scheme 176) (92WO03430).

Oxidation of thiol **287** with air in glyme gave disulfide **288,** which on intramolecular oxidative coupling with *N,N*-dibromoisocyanurate formed macrocycle **289** in 42% yield (Scheme 188) (99MI3).



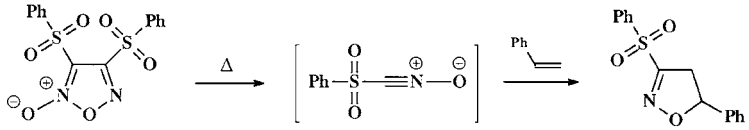
285 **286**

SCHEME 187



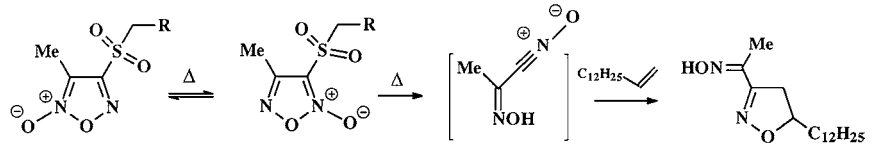
287 **288** **289**

SCHEME 188



290

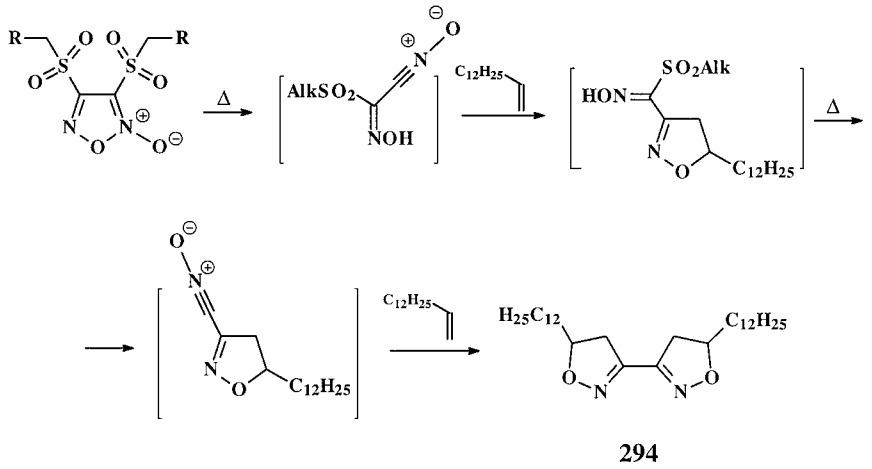
SCHEME 189



291 **292** **293**

R = H, Ph

SCHEME 190



294

SCHEME 191

Few reactions of sulfonylfuroxans with olefins have been reported. Depending on the substituents at the furoxan ring, nature of dipolarophile, and temperature, different types of products may be obtained. It is relatively simple to cyclorevert disulfonylfuroxans to α-sulfonyl nitrile oxides on thermolysis (81TL3371, 85T727). These nitrile oxides were trapped by dipolarophiles to yield sulfonyl-substituted isoxazole derivatives. For example, 3,4-bis(phenylsulfonyl)furoxan reacts with an excess of styrene in xylene under reflux to afford the corresponding isoxazoline **290** (Scheme 189).

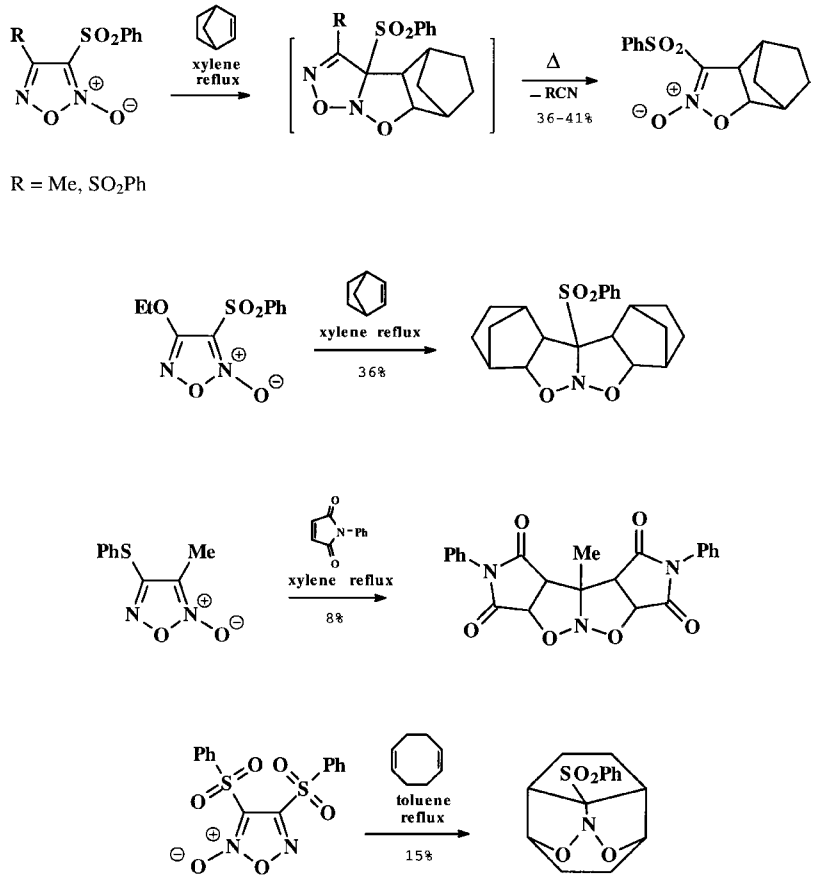
α-Hydroximino nitrile oxide **292** was formed from furoxans **291** in xylene–DMF (1:1) under reflux. It could be trapped with tetradecene to give isoxazoline **293** in 10–15% yield (Scheme 190) (86H889).

In a similar treatment of 3,4-bis(alkylsulfonyl)furoxans, both sulfonyl groups were eliminated (Scheme 191) (86H889). Bis(isoxazoline) **294** was isolated in 10–17% yield.

Furoxans bearing S-linked substituents may react with olefins as nitrones (85T727, 86H889). Some examples are given in Scheme 192.

XII. Conclusion

The chemistry of furazans and furoxans has been the subject of intensive investigations over the years. There has been been a substantial increase in synthetic manipulations of substituents attached to these ring systems. Additionally, there are a number of publications that deal with the incorporation of the heterocyclic rings into more complex molecules. It is the aim of this review to present new synthetic developments and to update reviews in the field of



SCHEME 192

monocyclic furazans and furoxans. Although there was also a remarkable progress in the application of theoretical methods (see, e.g., [86CHE214, 86KGS264, 92JCC177, 94JOC6431, 94JPC12933, 95JCR(M)0878, 95JCR(S)120, 95JST23, 96CHEC(II,4)229, 96HEC397, 96T743, 96JCS(P2)179, 96T743, 98JST263]) and in structural investigations (for furazans see, e.g., [85MI2, 85ZSK65, 88LA1017, 91ZSK45, 92AX(C)1092, 92JCS(P2)2179, 92JHC1835, 92KGS233, 93MI1, 93MI3, 93MI4, 95AX(C)666, 95MC25, 95MI3, 96CHEC(II,4)229, 96IZV1250, 96KGS406, 96MC141, 98CEJ1023]; for furoxans see, e.g., [71TL2907, 86AX(B)84, 87JCS(P2)523, 87K359, 87K1534, 88JCS(P2)661, 90IZV1625, 91ZSK148, 93LA441, 94JCS(P1)2841, 94MC7, 95ZK625, 96CHEC(II,4)229, 96JCS(P2)179, 96JHC327, 000UP2]), these topics have not been included, because a critical and more exhaustive treatment of these areas deserves a separate review.

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000UP2 The geometric data reported for 3,4-bis(*p*-chlorophenyl)furoxan (71TL2907) seem to be in error. A reinvestigation has shown that there are at least two polymorphic forms of this compound (monoclinic and orthorombic), which are both disordered: T. Traulsen, C. Näther, and W. Friedrichsen, unpublished results.

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 78

Tricyclic Azoloquinolines

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I. Introduction

Azoloquinolines are an interesting group of compounds. Some natural products contain a built-in azoloquinoline skeleton: Nybomycin (**1a**) is an antibiotic with fused oxazoloquinoline skeleton, isolated from *Streptomyces* cultures, and is quite active against Gram-positive bacteria, but insoluble. The degradation product—deoxynybomycin (**1b**)—produced by *Streptomyces hyalinum* n. sp. Hamada *et* Yakayama indicated somewhat higher activity compared with nybomycin itself. Isolation, structure elucidation, and synthesis of these two antibiotics were published in (70JA6994, 70JA6995, 73JA5003).

Thiazolopyridoacridine alkaloids obtained from marine sources, kuanoniamines (**2a–c**), bright yellow metabolites from the mollusk *Chelynotus semperi*, display only modest cytotoxicity. They strongly coordinate divalent ions (Fe^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}; $K_{eq} \approx 10^{10}\ M^{-2}$) and are pH indicators, their color changing from

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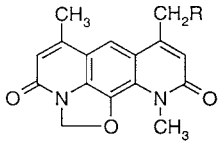
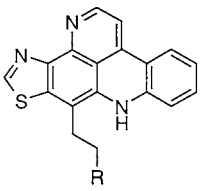


1a: R = OH

1b: R = H

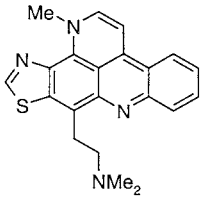


2a: R = i-BuCONH

2b: R = EtCONH

2c: R = MeCONH

2d: R = NMe_2



3

yellow ($\lambda_{max} = 430$ nm in basic or neutral media) to deep burgundy ($\lambda_{max} = 480-510$ nm) under acidic conditions. Indeed, their name is derived from the Hawaiian word *kuanoni,* which conveys the idea of changing color. In contrast to kuanoniamines, considerable bioactivity is found in dercitins (**2d, 3**), especially in **3.** These substances were obtained from deep-water sponges belonging to the *Stelletta* and *Dercitus* species (fam. Pachastrellidae). Compound **3** is a deep blue pigment ($\lambda_{max} = 590$ nm), whereas **2d** is bright yellow ($\lambda_{max} = 430$ nm); both change to deep burgundy ($\lambda_{max} = 480-510$ nm) in acidic media (95JA12460 and loc. cit.). Interestingly, the moderate potency observed for kuanoniamines is greatly enhanced in **3,** which exhibits not only strong antitumor activity *in vitro* and *in vivo,* but also immunosuppressive and antiviral properties and potential anti-HIV activity (92JA10081 and loc. cit.).

Another type of the naturally widespread azoloquinolines are 2-aminoimidazoquinolines. In the early 1980s, a large group of heterocyclic compounds was isolated from thermally processed meats and cooked food (broiled sun-dried sardines and fishes, fried beef, hamburgers, potatoes): pyrolysates of various amino acids and proteins, with strong mutagenic and carcinogenic activity, even higher than that of aflatoxin B_1. These compounds all sport a typical 2-aminoimidazole ring fused to other heterocycles (80MI2, 92MI2 and loc. cit.). From imidazoquinolines belonging to this group we mention 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ).

There exist many types of azoloquinolines, and therefore it is necessary to define the objects of interest to be described in this review. The tricyclic azoloquinolines reviewed in this article have an azole ring fused to the benzene ring of quinoline (not isoquinoline derivatives) in positions *f, g,* and *h.* This means that the benzene ring is between azole and pyridine rings, and all of them are *ortho–peri* condensed. The azole and benzene rings do not have a common heteroatom, and also a carbon

TABLE I
CITATIONS OF AZOLOQUINOLINES[a] IN *CHEMICAL ABSTRACTS*

	Vol. 1–85	Collective Volume 10	Collective Volume 11	Collective Volume 12	Collective Volume 13	Total
Years	Up to 1976	1977–81	1982–86	1987–91	1992–96	
Oxazoloquinolines	9	20	61	115	38	243
Thiazoloquinolines	28	171	177	161	77	614
Selenazoloquinolines	2	—	—	—	3	5
Oxadiazoloquinolines	5	—	1	1	—	7
Thiadiazoloquinolines	9	1	20	26	6	62
Selenadiazoloquinolines	—	9	—	7	—	16
Imidazoquinolines	[b]	347	400	738	652	2137
Triazoloquinolines	4	8	4	57	72	145
Total	57	556	663	1105	848	3229

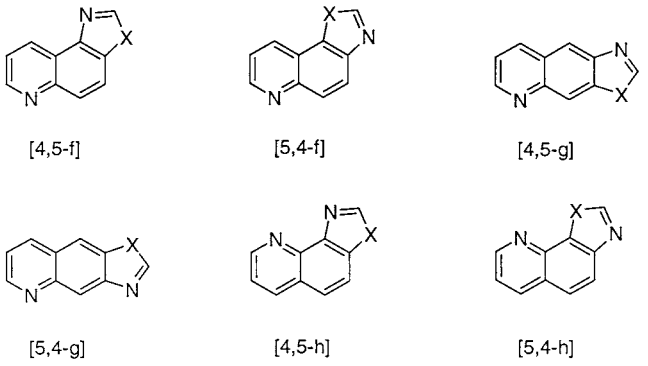
[a]Tellurazolo- and telluradiazoquinolines are not yet known.
[b]In review (81MI1).

atom is not attached to the benzene ring in the azole ring. This means that pyrrole condensed (indole), pyrazole condensed (indazole), and isoazole derivatives are excluded.

This review includes most of the published articles from the defined area and excludes only imidazoquinolines, which were reviewed in Weissberger–Taylor's series *The Chemistry of Heterocyclic Compounds* (81MI1). *Comprehensive Heterocyclic Chemistry II* (96MI1) mentioned only some of the azoloquinolines; in the first edition the authors omitted citations about this type of compounds. The trend toward interest in these compounds can be illustrated by the number of citations in *Chemical Abstract* as shown in Table I. Besides *Chemical Abstracts Substance/Subject (Collective) Indexes*, the MDL database search has been used.

Because of the number of citations, only selected imidazoquinolines are described, and biological activity is mentioned only briefly. The largest increase in the number of citations was caused by the discovery of the antibacterial properties of nalidixic acid type drugs. Efforts to prepare the bioisosters, for example of oxolinic acid, intensified in the early 1970s, and the discovery of the carcinogenic properties of 2-aminoimidazoquinolines followed in the early 1980s. These azoloquinolines can be considered as benzene-separated deazapurines.

There exist two main strategies for the preparation of azoloquinolines. The first one exploits the pyridine ring closure starting from the appropriately substituted aminoethylene derivatives. Angularly annelated heterocycles are produced regioselectively as main products in accord with Clar's theorem (72MI1), extended to heterocycles by Hajos (83JOC3199). The annelation effect can be explained by different heteroaromatic stability of the isomer pairs due to the higher degree of



SCHEME 1

aromatic stability expected. This type of syntheses is partially covered by a review published in *Advances in Heterocyclic Chemistry,* Vol. 54 [92AHC(54)]; the volume has also indexes to search according to the amine used to react with dialkyl alkoxymethylenemalonates and according to ring systems obtained by ring closure of dialkyl aminomethylenemalonates.

The second strategy involves cyclization of the corresponding *ortho*-disubstituted quinolines, giving a single product. This is the best method for preparing linearly annelated azoloquinolines.

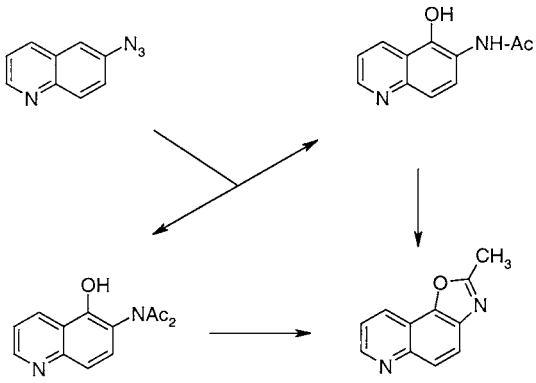
Each section has the following structure: synthesis of target structures, properties including spectral properties (meaning anomalous or confirming structure), reactions on ring atoms, reactions on substituents, partially saturated heterocycles, applications, and biological properties.

II. Azoloquinolines

Many tautomeric structures for azoloquinolines without a bridgehead hetero atom can be drawn, the most likely of them for X = O, S, Se, NH: oxazoloquinolines, thiazoloquinolines, selenazoloquinolines and imidazoquinolines are shown in Scheme 1.

A. OXAZOLOQUINOLINES

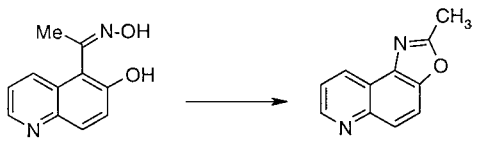
Thermal decomposition of 6-azidoquinoline in a mixture of acetic and polyphosphoric acid at 140–145°C for 2 hours produced 6-diacetamido- and 6-acetamido-5-hydroxyquinoline. Both compounds sublimed at 220°C (0.1 mm) to give 2-methyloxazolo [5,4-*f*]quinoline **5** (68JCS(C)1937) (Scheme 2). [4,5-*f*]-Fused



5

SCHEME 2

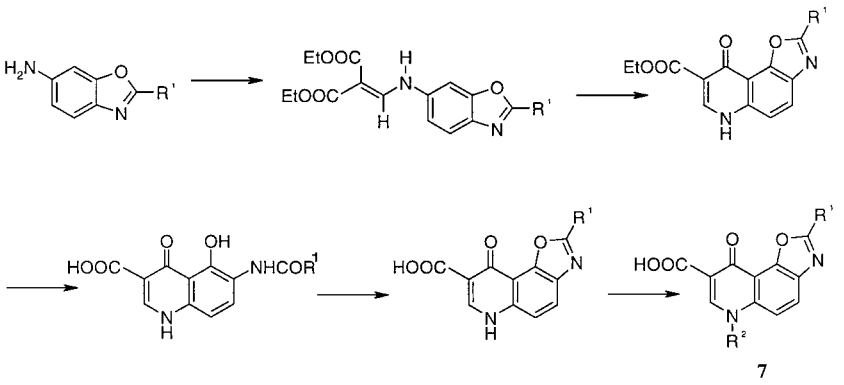
isomer **6** originated after rearrangement when 5-acetyl-6-hydroxyquinoline oxime was heated in conc. sulfuric acid at 100–120°C for 2 hours (68YZ1412).



6

2,4,7-Trimethyloxazolo[4,5-*f*]quinoline prepared from 2,7-dimethyl-6-methoxyquinoline using nitration, demethylation (or reversed), reduction, and cyclization with acetic anhydride confirms unambigously the structure of the aromatic part of the antibiotic X-537A after nitration and alkaline degradation (71JOC3621).

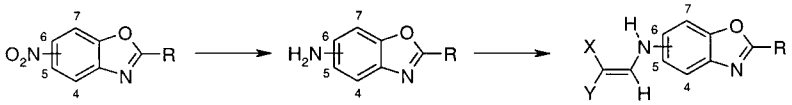
Gould–Jacobs reaction has been applied to the synthesis of oxazolo[5,4-*f*]quinolines by Japanese authors (74JAP(K)2): 2-Alkyl- or aryl-6-aminobenzoxazole with diethyl ethoxymethylenemalonate refluxed in ethanol gave the corresponding aminomethylene malonate, which after thermal cyclization in Ph_2O afforded only angularly annelated ethyl 9-oxo-6,9-dihydrooxazolo[5, 4-*f*]quinoline-8-carboxylates. When hydrolyzed in KOH–ethanol such carboxylates not only produced the appropriate acids, but simultaneously the oxazole ring has been opened. Dehydration with polyphosphoric acid caused ring closure of the oxazole ring, and subsequent pyridine nitrogen atom alkylation with alkyl iodides in ethanol in the presence of K_2CO_3 gave analogues of nalidixic acid **7**—bactericides against Gram-positive and Gram-negative bacteria (no data) (Scheme 3).



7

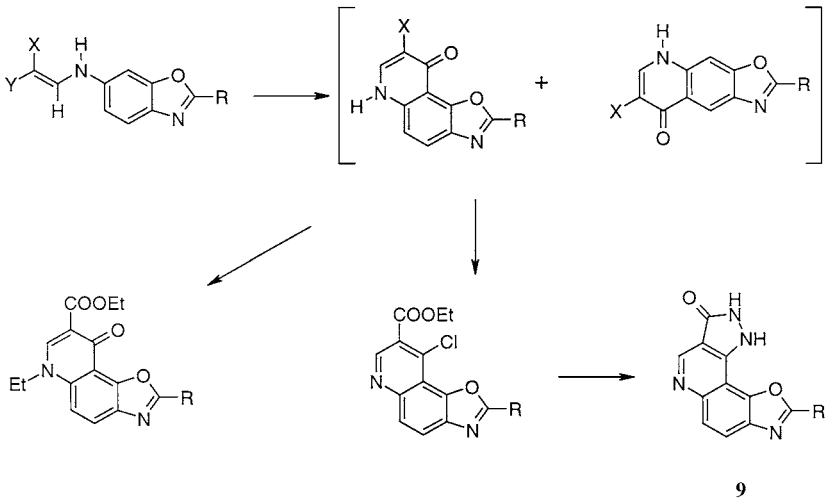
SCHEME 3

Comprehensive work in this field has been done by Slovak authors (98MI1, 95M1359, 96CCC269, 96CCC371, 97CCC99). They prepared 2-substituted (H, Me, Ph) 4-, 5-, 6-, and 7-nitrobenzoxazoles, which were then reduced to amines (not isolated) and subjected to subsequent nucleophilic substitution with activated enol ethers such as alkoxymethylene derivatives of malonic acid esters and nitrile, 3-oxobutanoic acid esters, pentanedione, or cyanoacetic acid esters to yield aminoethylenes **8.**



R = H, Me, Ph; X, Y = COOEt, COOMe, COMe, CN **8**

Thermal cyclization of the derivatives **8** carrying an aminoethylene substituent in position 6 is generally relatively slower than that of 5-substituted ones and not influenced by substituent in position 2. Only 6-benzoxazolyl derivatives yielded regioselectively angularly annelated oxazazolo[5,4-*f*]quinolines, while other (2-methyl- and 2-phenylbenzoxazolyl) derivatives with an aminoethylene substituent in position 6 afforded a mixture of angularly and linearly annelated products (oxazolo[5,4-*f*]/[4,5-*g*]quinolines). Ethylation of these mixtures in DMF with K_2CO_3 resulted in the 6-ethyl derivatives (N-ethylation), compounds derived from the more stable angularly annelated products, due to the decomposition of linearly annelated oxazoloquinolines. Aromatization of the mixtures of cyclization products with $POCl_3$ led to the same results as described above and the corresponding 4-chlorooxazoloquinolines were formed (95M1359). The chlorine atom of chlorooxazoloquinole carboxylic acid esters can be replaced with hydrazine and cyclized to pyrazoloquinolineoxazoles **9** (Scheme 4).



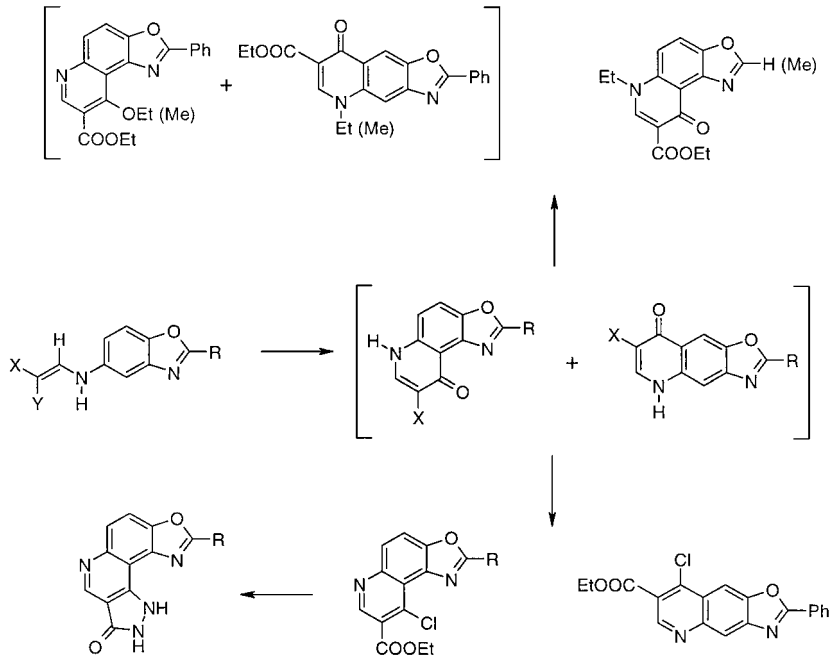
9

SCHEME 4

5-Substituted benzoxazole derivatives also gave mixtures of oxazolo[4,5-*f*]/[5,4-*g*]quinolines. Ethylation of these mixtures afforded only products derived from angularly annelated oxazoloquinolines excepting 2-phenyl derivatives giving mixture of 5-ethyl-2-phenyl-8-oxo-5,8-dihydro-oxazolo [5,4-*g*]quinoline-7-carboxylic acid ethyl ester (N-ethylation of the linearly annelated product) and 9-ethoxy-2-phenyloxazolo[4,5-*f*]quinoline-8-carboxylic acid ethyl ester (O-ethylation of the angularly annelated product—the same as those obtained from chloroxazoloquinoline and sodium ethoxide). The same results were obtained from methylation. Chlorination with $POCl_3$ (95M1359) also gave only angularly annelated product except for the 2-phenyl derivatives, where (as in the case of ethylation) the linearly annelated product could also be isolated—first linearly annelated azoloquinoline resulting from the Gould-Jacobs reaction. Reactions of chloroxazoloquinolines with hydrazine led also to analogous pyrazoloquinolineoxazoles **10** (Scheme 5).

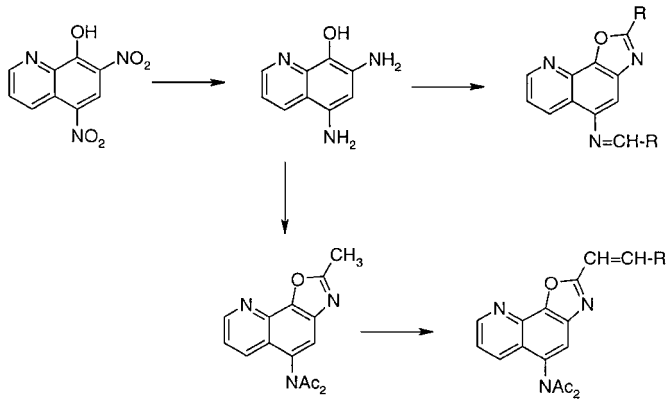
A series of 2-aryloxazolo[4,5-*h*]quinoline-5-arylidines was prepared by the reaction of 5,7-diamino-8-hydroxyquinoline with aromatic or aliphatic aldehydes in the presence of a basic catalyst such as piperidine. On the other hand, 2-styryl-5-diacetylamino-oxazolo[4,5-*h*]quinolines were prepared by interaction of 2-methyl-5-diacetylamino-oxazolo[4,5-*h*]quinoline with aromatic aldehydes (77MI1, 82MI2) (Scheme 6).

These compounds showed a remarkable activity toward Gram-positive (e.g., *Bacillus cereus, Staphylococcus aureus, Sarcina lutea*) and Gram-negative bacteria (e.g., *Pseudomonas* sp.); the activity was somewhat lower in the styryl derivatives (82MI2).



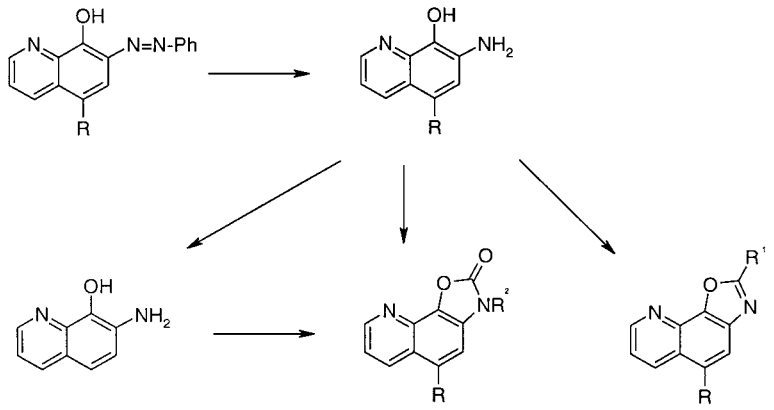
10

SCHEME 5



R = Me-, Et-, C_6H_5-, 2-HOC_6H_4-, 4-HOC_6H_4-, 2-HOC_6H_4-, 4-$MeOC_6H_4$-, 4-HO-3-$MeOC_6H_4$-, 4-ClC_6H_4-, 4-$Me_2NC_6H_4$-, 4-$O_2NC_6H_4$-, 3-$O_2NC_6H_4$-, PhCH=CH-, 2-furyl-

SCHEME 6



11 **12**

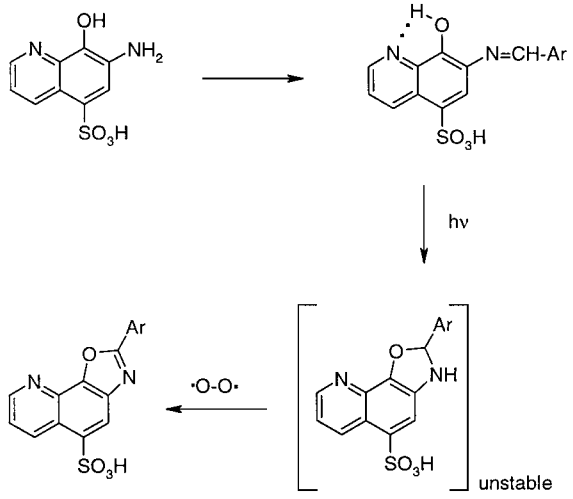
X = O, N-Ph; R = H, Cl, SO_3H; R^1 = H, Me, CCl_3, Ph, CH_2COOEt, COOMe, COOEt, COONa, $COONH_3C(CH_2OH)_3$; R^2 = H, Ac, COOEt, CH_3, $CONMe_2$, 2-$MeOC_6H_4CO$, PhCH=CHCO

SCHEME 7

Starting from 8-hydroxyquinoline and subsequent sulfonation, coupling, or nitrosation and reduction, one obtains the 8-hydroxy-7-aminoquinoline-5-sulfonic acid, which can be desulfonated to the 8-hydroxy-7-aminoquinoline. The last two products were cyclized to the corresponding 2-oxo-1,2-dihydrooxazolo[4,5-*h*] quinolines **11** using urea or phosgene, respectively (82MI1, 85JMC1255). When an aromatic or aliphatic aldehyde had been used the 2-alkyl- or 2-aryl-substituted oxazoloquinolines **12** were prepared. 2-Methyl-substituted oxazoloquinolines can serve for preparation of 2-styryl derivative (87JIC218). Another simple one-step synthesis employed ethyl triethoxyacetate for the preparation of ethyl 5-chloro-oxazolo[4,5-*h*]quinoline-2-carboxylate **12** ($R = Cl$, $R^1 = COOEt$) (84SC947) (Scheme 7).

5-Chloro-oxazolo[4,5-*h*]quinoline-2-carboxylic acid methyl ester was the most active compound in tests for inhibitors of antigen-induced release of histamine *in vitro* from rat peritoneal mast cells (IC_{50} of 0.3 μM) and as inhibitors of IgE-mediated passive cutaneous anaphylaxis in the rat (ED_{50} (intraperitoneal) of 0.1 mg/kg in dose 0.5 mg/kg as an inhibitor of the test)—10 times and 60 times more potent, respectively, than the disodium salt of cromoglycic acid (85JMC1255).

The 8-hydroxy-7-aminoquinoline-5-sulfonic acid was used to clarify the role of intramolecular hydrogen bonding on the cyclization rate of hydroxy Schiff bases in the preparation of 2-aryloxazolo[4,5-*h*]quinoline-5-sulfonic acids **13.** Irradiation



13

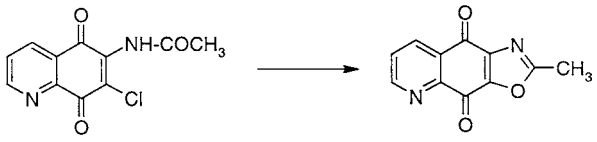
Ar = C_6H_5, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

SCHEME 8

of 7-arylideneamino-8-hydroxyquinoline-5-sulfonic acids in dioxan under aerobic conditions by 365 nm light effected a photocyclodehydrogenation reaction to give the products. The possible reaction pathway was thought to proceed through the formation of the thermally unstable 2-aryloxazolino[4,5-*h*]quinoline-5-sulfonic acids by a singlet mechanism followed by the formation of product (91MI1) (Scheme 8).

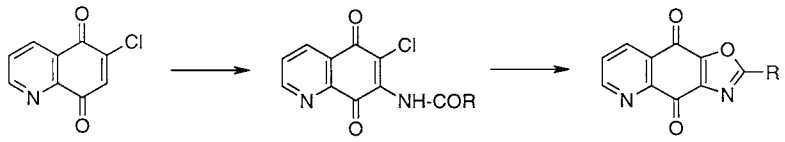
The rate of the corresponding reaction of naphthole derivatives was greater than that of quinoline derivatives.

Linearly annelated 2-methyl-4,9-dioxo-4,9-dihydrooxazolo[4,5-*g*]quinoline **14** was prepared in 31% yield by cyclization of 6-acetamido-7-chloro-5,8-dioxo-5,8-dihydroquinoline in acetic anhydride and sulfuric acid (59LA108).



14

The isomeric 2-substituted 4,9-dioxo-4,9-dihydrooxazolo[5,4-*g*]quinolines **15** were prepared in the same way starting from corresponding 6-chloro derivative (91CCC1919).



15

Biological testing of these compounds against some Gram-positive and Gram-negative bacteria species showed that all prepared substances had a remarkable bacterial activity against *Bacillus cereus.*

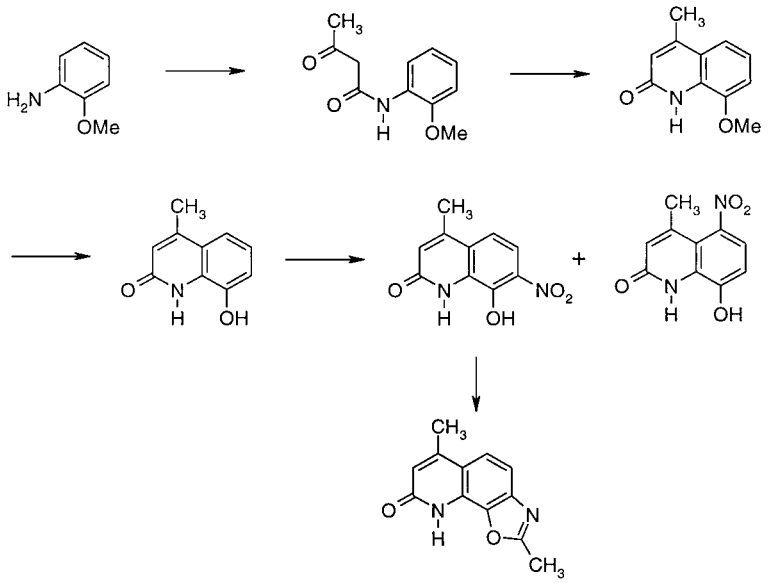
Oxazoloquinolone **16** helped to elucidate the structure of two nitroquinolones (with a nitro group in position 5 or 7, respectively). Treating 2-anisidine with diketene gave 2-methoxyacetoacetanilide, which cyclized in PPA to a product that, after demethylation with refluxing 48% HBr gave 8-hydroxy-4-methyl-2-oxo-1,2-dihydroquinoline. Nitration of the later one gave a mixture of two isomers, from which the 7-isomer was separated and after reduction afforded the corresponding 2-methyloxazoloquinolone. After ring closure and reduction it can serve as starting material for the synthesis of nybomycin and deoxynybomycin (70JA6994, 70JA6995, 73JA5003) (Scheme 9).

Five oxazoloquinolone carboxylic acids and their esters (4,5/5,4-*f*,*g*, or *h* fused) with ethyl substituent on the pyridine nitrogen were studied with ^{1}H NMR. A comparison with benzene proton shifts in relation to diamagnetic anisotropy of the neighboring carbonyl group or nitrogen atom of oxazole ring allows one to distinguish the type of oxazoloquinolone skeleton without the need for supplementary techniques (92RRC267). Similar fluorosubstituted derivatives with a cyclopropyl substituent on nitrogen atom exhibit minimum inhibiting concentrations of 0.025 to 12.5 μg/ml against *Staphylococcus aureus*, *Escherichia coli*, etc.

Acids, esters, and salts were used as medical and agrochemical bactericides (89JPP1, 89JPP2).

Interaction of 6,7-dichloroquinoline-5,8-dione with amides in ethylene glycol afforded oxazolo[4,5-*g*]quinoline-4,9-dione, a compound with activity against Gram-positive bacteria (no data) (90MI2).

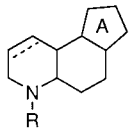
Deca/octahydro 6-alkyloxazolo *f*-fused quinolines **17** were prepared and evaluated as dopaminergics (87EUP1). A series of linearly annelated 8-alkyl-deca/octahydrooxazoloquinolines **18** and their salts were prepared for use as dopamine D_2-agonists and hypertensive agents. The *trans*-(±)-1-propyl-6-oxodecahydroquinoline was brominated, then treated with urea in methanol to give the 2-amino



16

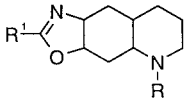
SCHEME 9

derivative; the product inhibited secretion of prolactin, lowered blood pressure by 39.0% at a dose of 100 μg/kg, and slowed the heart rate by 17.5% (86EUP1, 87USP2).



17

A = (un)substituted oxazole ring



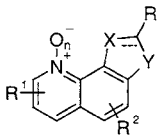
18

R = H, $PhCH_2$, alkyl,alyl; R = alkyl

R^1 = H, Cl, Br, alkyl, alkyloxy, hydroxy, (di)alkylamino, 1-pyrrolidinyl; 4*a*,8*a*-*trans*

1-Hydroxy-*N*,*N*-bis(hydroxymethyl)-*N*-methylmethanaminium salts and related types of compounds **19** for prevention and treatment of peptic ulcers and

stomach ulcer healing response to ranitidine or allergy inhibitors have been prepared (89USP1).



19

R, R^1, R^2 = H, lower alkyl, halogen, CF_3, aryl, alkylaryl, amino, alkylamino, AcNH, CN; X, Y = O, S, N; n = 0,1

Several 7-substituted (H, halogen, alkoxy, alkylthio, halogen, alkyl, carboxyl) oxazolo[5,4-*h*]quinolines were found to be very effective against broadleaf weeds (90EUP1, 90GEP1).

B. THIAZOLOQUINOLINES

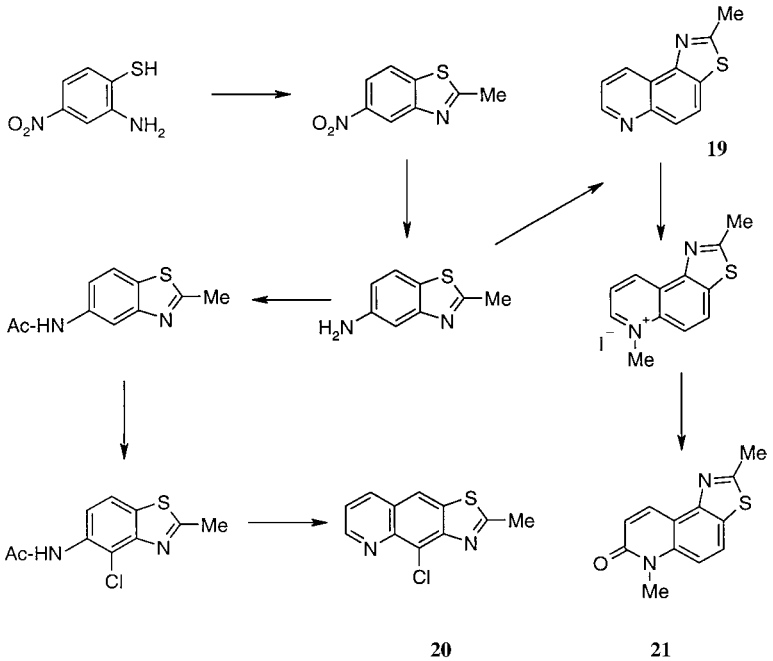
The chemistry of thiazoles is interesting in view of their propensity for biological activity. For that reason thiazoloquinolines have also been a widely studied group of compounds. A preferred route to thiazoles exploits α-halogeno ketones in a reaction with thioamides to give the fused 2-substituted thiazole derivatives.

The first thiazoloquinolines, namely angularly annelated 2-methyl-thiazolo [4,5-*f*]quinoline **19** and linearly annelated 2-methyl-thiazolo[4,5-*g*]quinoline **20,** were prepared in 1937 in poor yield using the Skraup reaction and exploiting the blockage of position 4 in 5-amino-2-methylbenzothiazole with a chlorine atom, as shown in Scheme 10 (37LA60).

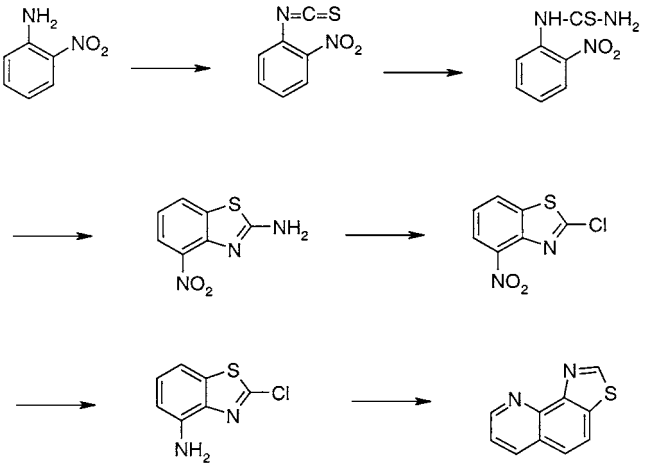
2-Methyl-thiazolo[4,5-*f*]quinoline **19** was methylated by methyl iodide on the nitrogen atom of pyridine giving the appropriate methodide. A subsequent oxidation with potassium hexacyanoferrate in alkaline media gave the 2,6-dimethyl-7-oxo-6,7-dihydrothiazolo[4,5-*f*]quinoline **21** (37LA60).

Thiazolo[5,4-*h*]quinoline **22** was prepared 2 years later starting from 4-aminobenzothiazole, also by the Skraup procedure. The 4-aminobenzothiazole was prepared in six steps from 2-nitroaniline (40HCA328) (Scheme 11).

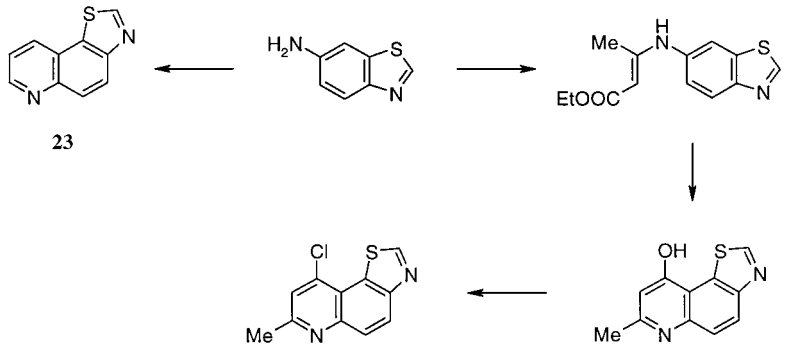
Thiazolo[5,4-*f*]quinoline **23** was prepared in 1949 starting from 6-aminobenzothiazole using Skraup reaction conditions: glycerol, sodium 3-nitrobenzenesulfonate, and 78% sulfuric acid and heating at 110°C for 12 hours. Angular ring fusion



SCHEME 10



SCHEME 11

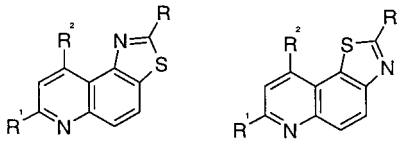


23

SCHEME 12

was established on the basis of comparison of its UV spectra with angular and linear naphthothiazoles (50JCS680). The same amine with ethyl acetoacetate afforded the corresponding crotonate, which cyclized in paraffin preheated to 270°C to give the 7-methyl-9-hydroxythiazolo[5,4-*f*]quinoline. A subsequent chlorination with phosphorus oxychloride converted the quinoline to 9-chloro compounds (49JCS355) (Scheme 12).

When 2,6-diaminobenzothiazole is subjected to the Skraup reaction, the 2-aminothiazolo[5,4-*f*]quinoline **25** ($R^1 = R^2 = H$, $R = NH_2$) originates (67JCS(C)2212). Starting from 2-methyl-5-aminobenzothiazole, 6-aminobenzothiazole, or 2-methyl-6-aminobenzothiazole condensing with methyl vinyl ketone or crotonaldehyde, the corresponding thiazololepidines **24, 25** ($R^1 = H$, $R^2 = Me$, $R = H$, Me) or thiazoloquinaldines **24, 25** ($R^1 = Me$, $R^2 = H$, $R = H$, Me) originated, respectively. Their structure was established using UV and ^1H NMR spectra due to the large coupling constant of *ortho*-protons H_4 and H_5 (64AC(R)530, 65JHC242).

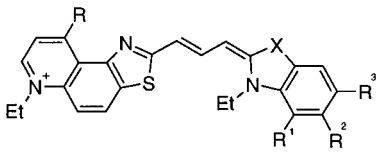


24 **25**

Sixteen non- to trimethyl-substituted thiazoloquinolines of these types were investigated under electron impact mass spectra; thiazoloquinolines lose carbon monosulfide (CS) from the thiazole and HCN from both heterocyclic nuclei. When 2-methylthiazoloquinolines fragment, the hydrogen radical and a loss of a neutral

molecule of acetonitrile gives thiirene-type ionradicals. Compounds with a 7-methyl substituent undergo the direct loss of a methyl radical from the parent ion; this behavior is not unexpected, being typical for 2-methylquinolines instead of 9-methyl substituted compounds (72JHC501).

9-Methylthiazolo[4,5-*f*]- and [5,4-*f*]quinolines were quarternized with methyl iodide for 100 hours to give a monomethiodide on the nitrogen atom of quinoline. The assignment of the site of quarternization was made using magnetic resonance spectroscopy (66TL3867). Activation of the 2-methyl group after quarternization with ethyl iodide allows the preparation of trimethine dyes in the reaction with appropriate aldehydes, whereas the methyl group on the thiazole ring is more reactive than the methyl group on the pyridine ring (64AC(R)530).

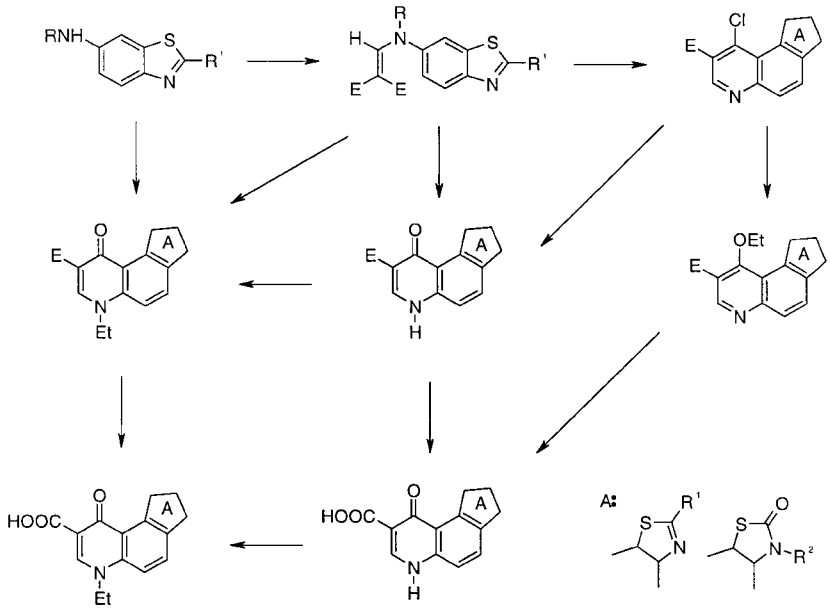


R = H, Me; X = S, Se; R^1,R^2 = H, Me, MeO, (–CH=CH–)$_2$; R^3 = H, Me

7- and 9-methyl-substituted thiazolo[5,4-*f*]- and [4,5-*f*]quinolines quarternized with methyl iodide could condense with 4-dimethylaminobenzaldehyde, aryldiazonium salts, and phthalic anhydride, and gave respectively the corresponding styryl-, diazamethine-, or phthaloic dyes, the UV spectra of which were studied. A bathochromic shift was also observed when the thiazole nucleus was replaced by thiadiazole (72MI2). 7-Methylthiazolo[4,5-*f*]quinoline was quarternized analogously with ethyl iodide and the activated methyl group was condensed to form cyanine dyes having λ_{max} between 535 and 597 nm (67MI1).

The relative ease of preparation of condensed thiazole derivatives is a consequence of facile thiazole ring closure, and therefore also benzothiazole amines with an amino group on the benzene ring (except for the weakly regioselective nitration of benzothiazoles) are very easily accessible and useful substrates for the Gould–Jacobs reaction.

2-Substituted 6-amino- or 6-ethylaminobenzothiazoles were converted with diethyl ethoxymethylenemalonate to enamines. The latter can be thermally or catalytically (acids) cyclocondensed, alkylated, and hydrolyzed exclusively to a series of angularly annelated 2-substituted 6-*H*/ethyl-6,9-dihydro-9-oxothiazolo[5,4-*f*] quinoline-8-carboxylic acids (76CPB130, 76CPB136, 76CPB147). Cyclization can also take place in the presence of phosphorus halides—$POCl_3$, PCl_3, PCl_5 (75JAP(K)2) (Scheme 13).



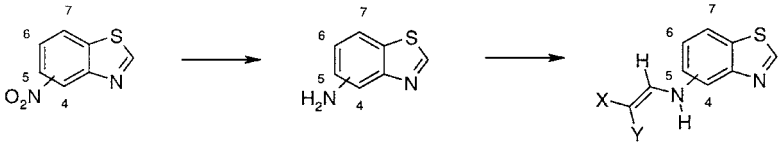
R = H, Et; E = COOEt; R^1 = H, Cl, MeS, Me, EtO, HS, $MeSO_2$, CH=CH-2-(5-nitrofuryl) (76CPB130); R^1 = NC, MeSO, MeO, EtO, *n*-BuO, $PhCH_2O$, $R^3{}_2N$, HOOC, EtOOC, $R^3{}_2NC(=NH)$, $R^3R^4NC(=NH)$, $EtOC(=NH)$, H_2NOC, H_2NSC, R^4NHOC; R^2 = H; R^3 = H, Me, Et, $Et_2NCH_2CH_2$, $HOCH_2CH_2$, $O(CH_2CH_2)_2$; R^4 = different (76CPB136); R^1 = MeS, $MeSO_2$; R^2 = H, Me, *n*-Pr, *n*-Bu, $CH_2{=}CHCH_2$, $PhCH_2$, $MeCOCH_2$, $BrC_6H_4COCH_2$, CH_2COOEt, CH_2COOH, CH_2CH_2Cl, $CH{=}CH_2$; substituent in position 6: Me, *n*-Pr, *n*-Bu, $PhCH_2$, CH_2COOEt, $CH_2{=}CHCH_2$ (76CPB147)

SCHEME 13

The 3,6-bis(2-fluoroethyl) derivative (R^2 = substituent in position 6 = CH_2CH_2F) was also prepared as an antibacterial compound (no data) (77JAP(K)2). The 2-ethoxy derivative shows antibacterial effects in Mueller–Minton medium during 48 hours at the following minimum inhibiting concentrations: *Staphylococcus preumoniae* (12.5 μg/ml), *Diplococcus pneumoniae* DP-2 (25 μg/ml), and *Erysipelothirix rhusiopathiae* (*E. insidiosa*) (25 μg/ml) (71GEP(O)1). 2-Oxothiazolo[5,4-*f*]quinoline-8-carboxylic acids were converted to the halides (73JAP(K)1, 74JAP(K)3) and later to corresponding amides (73JAP(K)1). Pyridine *N*-oxides derived from the aromatized 2-oxochlorothiazoloquinoline carboxylic acid

derivatives were synthesized using 3-chloroperbenzoic acid (75JAP(K)1). 2-Oxo-3-methyl-6-ethyl carboxylic acid (tioxacin) give a soluble complex with aliphatic amines (79YZ476) and had the highest activities against G(+) and G(−) bacteria, including *Escherichia coli* resistant to nalidixic acid and *Pseudomonas aeruginosa* from 98 acids of this type. In the series of 2,6-disubstituted derivatives, 2-alkoxy compounds were active only against G(+) bacteria, whereas 2-OH, -SO_2Me, and -CN derivatives were active only against G(−) bacteria. 2-Amino and 2-carbamoyl compounds had no activities. In the 3,6-dialkyl-2-oxo derivatives, the most effective alkyl substituent was a Me or Et group. Replacement of the 2-oxo group by a thioxo, imino, or hydrazino group lowered the activities (79YZ483).

In order to study the regioselectivity of thermal cyclocondesation, all four possible nitrobezothiazoles with nitrogroup in positions 4, 5, 6, and 7 were prepared, further reduced, and ultimately converted into aminoethylene of type **26.**



26

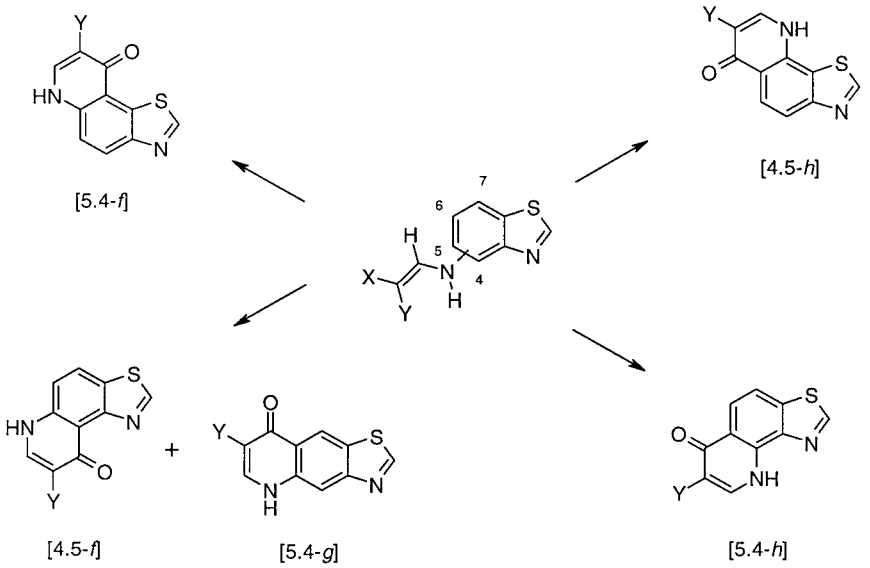
X, Y = COOEt, COOEt; COOEt, CN; COOEt, COMe; COMe, COMe; CN, CN;

$COOCMe_2OCO$

4-, 6-, and 7-substituted aminoethylenes with least one alkoxycarbonyl group yielded regioselectively only angularly annelated thiazoloquinolines; Thus, 4-substituted produced thiazolo[5,4-*h*]quinolines, 6-substituted gave thiazolo[5,4-*f*]quinolines, and 7-substituted afforded thiazolo[4,5-*h*]quinolines. In contrast, 5-substituted aminoethylenes cyclized to afford both possible products: angularly annelated thiazolo[4,5-*f*]quinolines and linearly annelated thiazolo[5,4-*g*]quinolines (Scheme 14).

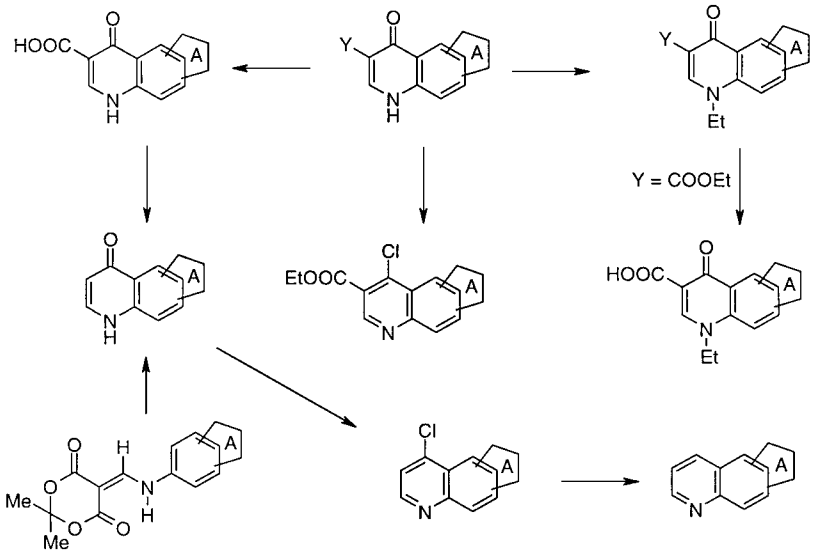
Because of the extremely low solubility of the cyclized products, only the 8-acetyl-9-X oxo-6,9-dihydrothiazolo[5,4-*g*]quinoline was isolated. On the other hand, 6-substituted derivatives having the same possibility to produce linearly or angularly annelated thiazoloquinolines cyclize regioselectively.

Products of the thermal cyclocondensation were ethylated using ethyl iodide with K_2CO_3 in DMF, and the esters were hydrolyzed to analogues of nalidixic acid; the starting compounds (Y = COOEt) were also hydrolyzed to the corresponding acids. No antibacterial activity was found for the compounds prepared. Decarboxylation of the nonalkylated acids was attempted, but because of low yields the target compounds were prepared using thermal cyclocondensation of Meldrum's acid (losing carbon dioxide and acetone) (Scheme 15).



Y = H, COOEt, COMe, CN

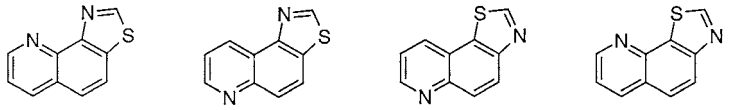
SCHEME 14



Y = COOEt, COMe, CN

SCHEME 15

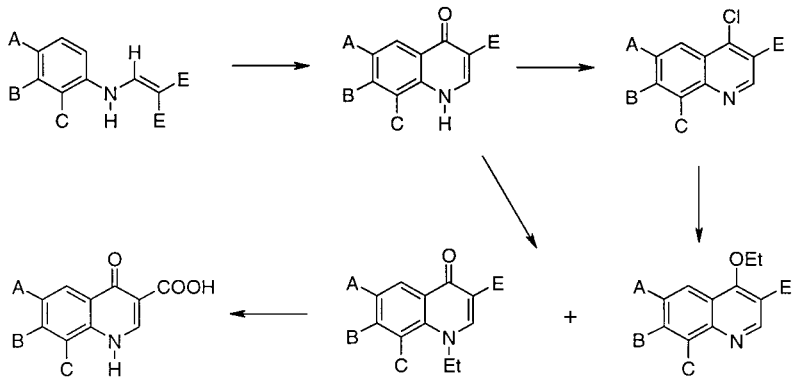
Aromatization of thiazoloquinolones and of the corresponding ethoxycarbonyl derivatives using $POCl_3$ in DMF affords the corresponding chlorothiazoloquinolines. Removal of the chlorine atom using hydrogenation with Pd on carbon gave the parent heterocycles shown hereafter (96MI2).



[5,4-*h*] [4,5-*f*] [5,4-*f*] [4,5-*h*]

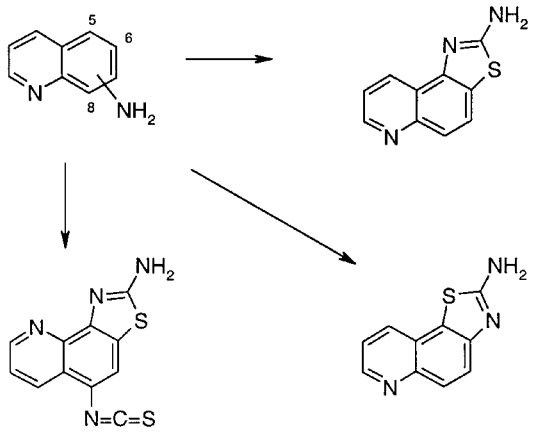
The possibility to prepare linearly annelated thiazoloquinolines using the Gould–Jacobs reaction is based on the fact that the more preferred *ortho*-position for origination of the angularly annelated tricycle must be occupied, for example, with a chlorine atom. Thus, the 2-substituted 4-chlorobenzothiazoles (substituent in position 2: H, Cl, SMe, NMe_2) with activated aminoethylene substituent in position 5, or 7-chlorobenzothiazoles with substituent in position 6, gave the linearly annelated product. When the aminoethylene substituent is in positions 4 and 7, the only possible angularly annelated product is formed (Scheme 16) (77JAP(K)1, 77JAP(K)3, 79CPB1).

The cyclization products can be ethylated using ethyl iodide with K_2CO_3 in DMF to give in the case of thiazolo[4,5-*g*]- or [4,5-*h*]quinolones a mixture of O- and N-ethylated products, whereas in the case of thiazolo[5,4-*g*]- or -[5,4-*h*] quinolones only *N*-ethyl products arise. Products of O-ethylation were prepared by



A, B, C = fused (2-substituted) thiazole ring, Cl; E = COOEt

SCHEME 16



27

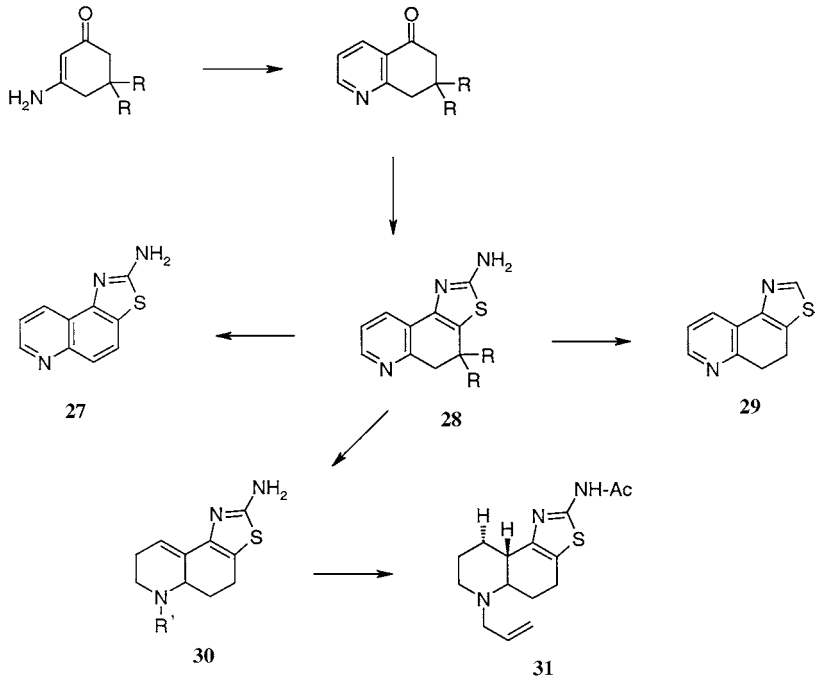
SCHEME 17

an unambigous method exploiting the corresponding chloro derivative. Hydrolysis of the N-ethylated thiazoloquinolones afforded the target analogues of nalidixic acid.

Another possibility for preparing the linearly annelated thiazoloquinolines is the ring closure of the thiazole ring to the starting quinoline. Thiocyanation of 5-, 6-, and 8-aminoquinoline was studied in (51JPJ553). Thus, reaction of KSCN and bromine in glacial acetic acid with 5-aminoquinoline afforded 2-aminothiazolo[4,5-*f*]quinoline, whereas 8-aminoquinoline formed the isomeric 2-amino-5-thiocyanothiazolo[5,4-*h*]quinoline. 6-Aminoquinoline leads under the same conditions to 2-aminothiazolo[5,4-*f*]quinoline **27** (Scheme 17). The corresponding acetyl and stearyl derivatives were also prepared.

2-Aminothiazolo[5,4-*f*]quinoline **27** and its acetyl derivative are effective as inhibitors of fogging in the preparation of photographic emulsions by both the acid and the NH_4OH processes (51JPJ553).

2-Amino-4,5-dihydrothiazolo[4,5-*f*]quinoline **28a** was deaminated with hypophosphorous acid to 4,5-dihydrothiazolo[4,5-*f*]quinoline **29;** DDQ oxidized **29** to 2-aminothiazolo[4,5-*f*]quinoline **27.** An alkylation at the nitrogen atom of pyridine and subsuquent partial reduction gave the 6-alkyl-4,5,5*a*,6,7,8-hexahydro- **(30**) and *trans*-4,5,5*a*,6,7,8,9,9*a*-octahydro analogues **31.** 2-Amino-4,4-dimethyl-4,5-dihydrothiazolo[4,5-*f*]quinoline **28b** was prepared starting from 1-amino-5, 5-dimethyl-cyclohexe-3-one. The substances prepared were considered to be related to the known mutagenic IQ (*see* Section III.D, Imidazoquinolines), where the N(3)-Me moiety of IQ has been replaced by a sulfur atom; they were tested and found to be potent mutagens: A fully aromatic tricyclic structure is required



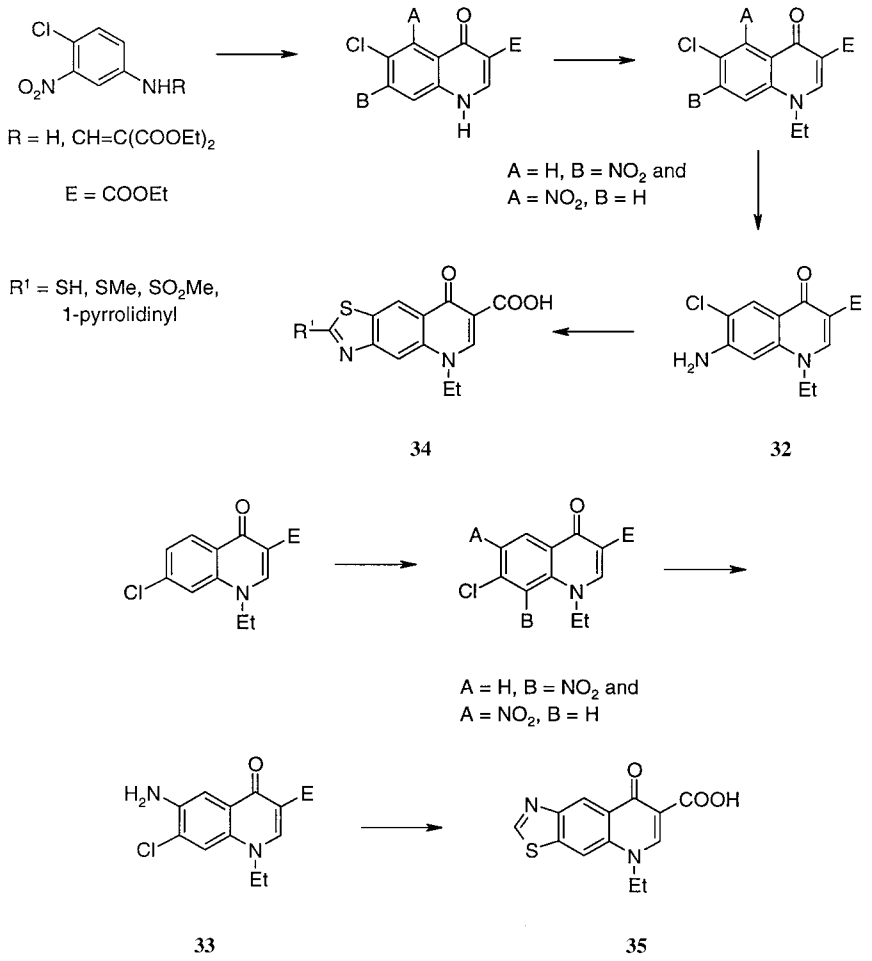
a: R = H; b: R = Me; R´ = different

SCHEME 18

for mutagenicity. Enzymatic oxidation can provide the required aromaticity to partially reduced analogues, but more extensively reduced compounds where the central ring cannot be oxidized, are not mutagenic (Scheme 18) (93EJM547).

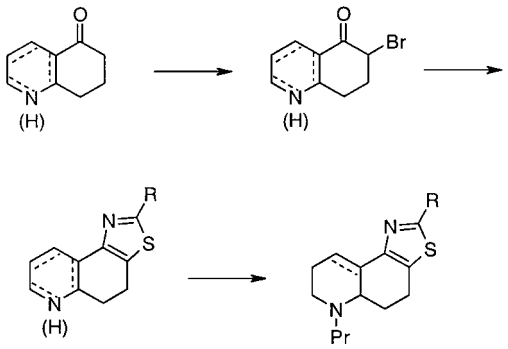
The same methodology was also used starting from the ethyl 6-amino-7-chloro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate, prepared by reduction of the nitro derivative. The requisite nitro derivative was prepared by nitration of ethyl 7-chloro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate. A second isomer was prepared from 4-chloro-3-nitroaniline by reaction with diethyl ethoxymethylene-malonate, subsequent thermal cyclization, and further ethylation because of low solubility of the formed quinolone. After separation and reduction, the ethyl 7-amino-6-chloro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **32** was obtained. The *ortho*-chloroaminoquinolones **32, 33** were cyclized to the corresponding 2-substituted thiazoloquinolines **34** and **35,** and the latter were derivatized (Scheme 19) (74JAP(K)4, 79CPB1).

All of the acids prepared in (74JAP(K)4, 79CPB1) were tested for their antimicrobial activities *in vitro*: 2-Thiazolone derivatives showed far higher activity



SCHEME 19

than thiazoles in a series of [5,4-*f*]-type thiazoloquinolines. The 2-chloro derivative (76CPB130, 77JMC791) showed nearly the same activity, and 2-cyano, 2-carbamoyl, 2-diethylaminoethylcarbamoyl, and some other derivatives (76CPB136) showed higher activities than the nalidixic acid. The 2-diethylamino-ethylcarbamoyl derivative and 2-oxo-3-methyl derivative (76CPB136, 76CPB147, 77JMC791) exhibited activity against *Escherichia coli*, resistant to nalidixic acid, and unequal activities against *Pseudomonas aeruginosa.* With respect to the [4,5-*g*]-type compounds, the thiazolones exhibited unsatisfactory activity, whereas thiazoles possessed exceptional activity against tested bacteria. It can be concluded



30

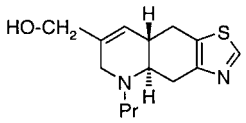
R = Ph, NH_2, $NHCOCHMe_2$

SCHEME 20

that activities of condensed quinoline carboxylic acids are closely affected by the bulkiness of substituents and the condensing position of the fused ring.

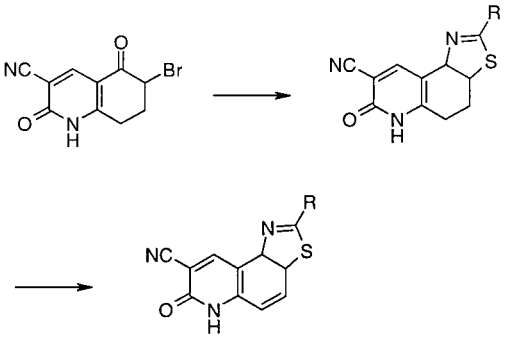
trans-2-Amino-5-propyl-4,4*a*,5,6,7,8,8*a*,9-octahydrothiazolo[4,5-*g*]quinoline **30** and its enantiomers have been reported to possess dopaminergic activity (prolactin inhibition and turning behavior in rat lesions) (84MI2). A series of rigid tricyclic analogues was synthesized via an α-bromoketone (prepared itself by cyclocondensation of propinal with 3-amino-2-cyclohexen-1-one and subsequent bromination), ring closure of thiazole ring with thiourea, and then reduction (Scheme 20) (87EUP1, 91JMC2736, 95JHC177). It was evaluated for dopaminergic activity and dopamine autoreceptor selectivity, which resides in (+) enantiomers of title compounds, whereas (−) seems to be a weak partial dopamine agonist. The efficacy of the (+) enantiomer in the Sidman avoidance test in squirrel monkeys and its lack of EPS liability in the same species qualify this compound as a potencial antipsychotic with perhaps an improved profile over currently available agents.

Linearly annelated 7-(5-propyl-*trans*-4,4*a*,5,6,8*a*,9-hexahydrothiazolo[4,5-*g*] quinoline)methanol **36** at 0.1, 1.0, 10, 100, and 1000 μg/kg in spontaneously hypertensive rats gave 5.7, 24.2, 36.8, 43.0, and 48.3% lowering of blood pressure, respectively.



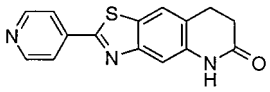
36

When, aiming at its cardiotonic activity (stimulant), the 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-cyano-6-bromoquinoline is made to react with different thioamides, the appropriate 6-substituted 8,9-dihydro- (R = cyanomethyl-, 2-oxopyrrolidinylmethyl-, 2-oxohexahydroazepinomethyl-, and thioxopyrrolidinylmethyl-) (94KFZ43) or (R = H, Me, NH_2, $NH_4{}^+S^-$) (86JAP(K)1, 89H1517) thiazolo[4,5-*f*]quinolines **37** or oxidized products (89H1517) are produced.



Four tested compounds at 10^{-10} M concentration increased the contraction of guinea pig heart more effectively than amrinone (86JAP(K)1).

2-Pyridyl-4-bromo-6-oxo-5,6,7,8-tetrahydrothiazolo[5,4-*g*]quinolones and analogues were prepared and tested as potential inotropic agents for treatment of heart failure. For example, the 2-(4-pyridyl) substituted thiazoloquinolone **38** gave a 122% increase in contractility of guinea pig papillary muscle (89EUP1).

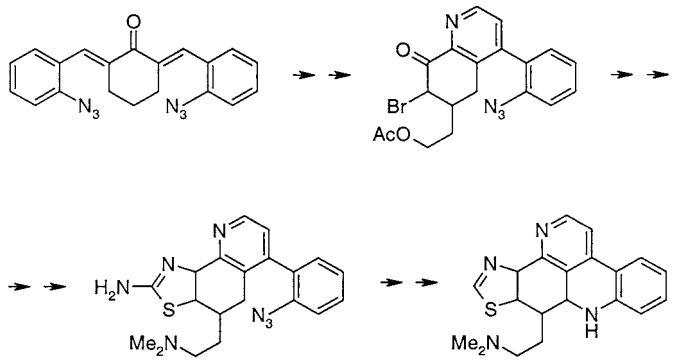


38

Dihydrothiazoloquinoline is a key intermediate in the synthesis of natural sulfur-containing pyridoacridine alkaloids—kuanoniamines and derdercitins, where the starting dienone is converted after a multistep reaction sequence to an α-bromoketone, which in turn was cyclized with thiourea to the desired dihydrothiazoloquinoline, photochemically convertible to the final alkaloid derivatives **39** (Scheme 21) (92JA10081, 95TL4709, 95JA12460).

Acetylation of 6-amino-7-chloro-5,8-quinolinedione and subsequent replacement of the chlorine atom to a -SH and then a -SMe group gave the final linear 2-methyl-4,9-dioxo-4,9-dihydrothiazolo[4,5-*g*]quinoline **40** (59LA108).

When in position 2 on a 2-pyridyl or 2-furyl ring, 4,9-oxo groups can be reduced and acylated; the obtained compounds were active against streptococci and staphylococci (62GEP1).



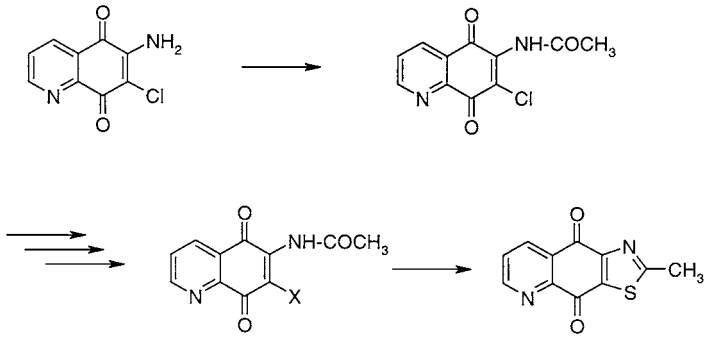
39

SCHEME 21

The 2-methyl-4,9-dioxo-4,9-dihydrothiazolo[4,5-*g*]quinoline was first quarternized with methyl iodide on pyridine nitrogen and then treated with *N*-methylquinolinium-4-yl salt, affording monomethine cyanine dyes **41** to study solvatochromism, acid–base properties, and antimicrobial activities (95MI1).

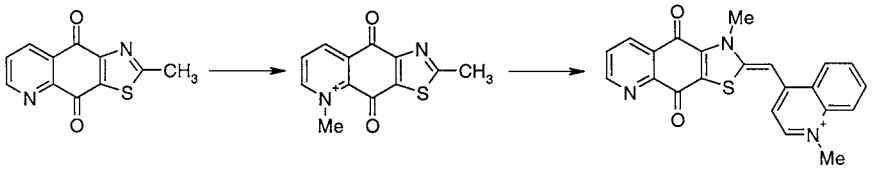
The isomeric thiazolo[5,4-*g*]quinoline skeleton was prepared from 6-chloroquinoline-5,8-dione hydrochloride by reaction with thiourea, resulting in the 2-amino-4,9-dioxo-4,9-dihydroderivative **42** (91CCC1919).

Some quinolinoquinone heterocyclic dimethine cyanine dyes have been prepared, and their solvatochromic and spectral behavior in buffer solutions has been



40

SCHEME 22



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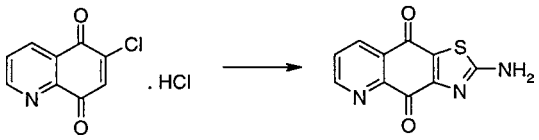
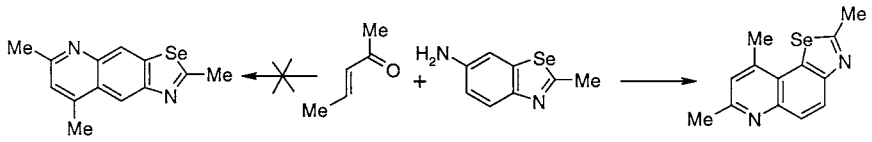


42

utilized to select an optimum solvent and pH value so that they might be applied as photosensitizers. Some have been tested for their antimicrobial activity (96DP89).

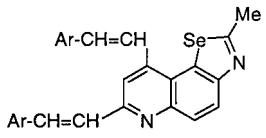
C. SELENAZOLOQUINOLINES

2-Methyl-6-aminobenzoselenazole when treated with 3-penten-2-one gave by a simple Doebner–Miller type reaction the 2,7,8-trimethylselenazoloquinoline **43** in 18.6% yield, that is the angular product and not the linearly annelated one was formed. Its structure was confirmed by the $^3J_{4,5}$ coupling constant in proton NMR (71JHC693). Selenazoloquinoline **43** can be converted via the 6-methylpyridium salt in the reaction with 4-dimethylaminobenzaldehyde to 2,6-dimethyl-7,9-bis(1-(4-dimethylaminophenyl)-2-ethenyl)selenazolo[5,4-*f*]quinolinium iodide **44** (Ar = 4-dimethylaminophenyl). This dye exhibited two absorption maxima between 500 and 600 nm (72MI2).



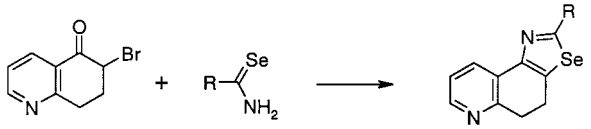
43

2-Substituted 4,5-dihydroselenazolo[4,5-*f*]quinolines originated from an α-bromoketone and substances bearing a $-C(=Se)-NH_2$ substituent. Thus,



44

selenourea afforded 2-amino- and substituted selenobenzamides afforded 2-aryl-4,5-dihydroselenazolo[4,5-*f*]quinolines **45** (95JHC177).



45

Reaction of **45** with an excess of methyl iodide afforded the 6-monomethiodide. The strong deshielding effect observed for protons and methyl protons in the pyridine ring indicates that quaternization took place on the pyridine nitrogen atom (71JHC693). Enhanced reactivity of the 7- and 9-methyl groups in the pyridine ring of the methiodide against 4-dimethylaminobenzaldehyde enable one to obtain the corresponding tricyclic styryl derivative, a compound characterized by a broad UV absorption band with two main peaks in the green region of the spectrum ($\lambda_{max} \approx 510$ and 570 nm) and used as a dye (71JHC693).

III. Diazoloquinolines

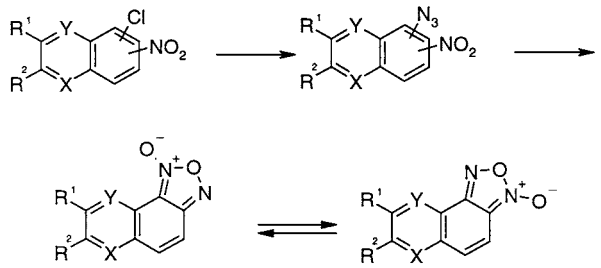
1,2,3-Diazoloquinolines are often prepared using the Hurd–Mori reaction starting from ketones after reaction with the corresponding hydrazine-containing reagent, whereas 1,2,5-diazoloquinolines arise from *ortho*-diamines. These latter possess an *o*-quinoid structure and their stability depends on their ability to share a lone electron pair in conjugation, that is, the most stable are 1,2,5-selenadiazoles and the least stable are 1,2,5-oxadiazoles. For the synthesis of pyridine-substituted diazoloquinolines, the Gould–Jacobs reaction is preferred.

A. Oxadiazoloquinolines

1. *1,2,5-Oxadiazoloquinolines*

The of study furoxanes, for example, condensed 2,1,5-oxadiazole *N*-oxides, also involves consideration of the oxadiazole nucleus. Thus, a series of 6,

8-dimethyl/nonsubstituted 1,2,5-oxadiazolo[3,4-*f*] or [3,4-*h*]quinolines **46** were prepared by heating *ortho*-azidonitroquinolines in dimethylsulfoxide or acetic acid in yields ranging from 13 to 63%. A synthesis based on the nucleophilic substitution of a chlorine atom in the appropriate chloronitroquinoline (prepared from chloronitroanilines via Skraup reaction or reaction with acetone and paraldehyde) is shown.



46a **46b**

In the *N*-oxides **46** the tautomerism of the oxygen atom attached to the oxadiazole nucleus was determined as $\Delta G^* \approx 20$ kcal mol^{-1}. The steric effect of the 9-methyl group of 7,9-dimethyl 1,2,5-oxadiazolo[3,4-*f*]quinoline *N*-oxide **46,** (Y = C—CH_3; X = N; R^1 = H; $R^2 = CH_3$) would not be expected to favor the presence of an appreciable proportion of the 1-oxide form (**46a**) (Table II). Both the 1,2,5-oxadiazolo[3,4-*h*]quinoline *N*-oxides **46** (Y = N; X = CH, C—CH_3; R^1 = H, CH_3; R^2 = H) showed a small but marked preference for the 3-oxide form (**46b**). The preference for the 3-oxide form in these compounds is as expected; the lone pair of electrons on the quinoline nitrogen atom repels the polar *N*-oxide group in the 1-oxide form. It is about 6 kcal mol^{-1} easier to cyclize the corresponding *o*-dinitrosoquinolines, a fact that was interpreted as being due to an increase in the aromaticity of the fused ring (68JCS(B)1516).

Kinetic studies of pyrolysis of azides, giving oxadiazole *N*-oxides in near-quantitative yields, showed that the 5-azido-6-nitroquinoline pyrolyzed in acetic acid 27.6 times faster than did 5-azidoquinolines, because of the −M effect of the group adjacent to the azide group (85AJC1045).

Various reactions of nitroquinolines with hydroxylamine in potassium hydroxide alkalinity afforded oxadiazoloquinolines besides the known aminonitroquinolines. 1,2,5-Oxadiazolo[3,4-*f*]quinolines were obtained from the 5- or 6-nitroquinolines. The 7- and 8-nitroquinolines gave the appropriate 1,2,5-oxadiazolo[3,4-*h*]quinolines.

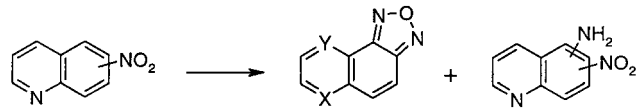
The proportion of oxadiazoloquinolines compared to aminonitroquinolines decreases from the 5-, to the 8-, to the 7-nitro series; it is smallest for 6-nitroquinolines (73YZ1019, 73YZ1024).

TABLE II

FREE-ENERGY VALUES (ΔG°, ± 0.1 kcal mol^{-1}) FOR THE TAUTOMERISM OF SOME SUBSTITUTED OXADIAZOLO[3,4-*f*] OR [3,4-*h*]QUINOLINE *N*-OXIDES **46**

	Position of exocyclic oxygen	ΔG°	ΔG^*	Solvent[a]
Oxadiazolo[3,4-*f*]quinoline	1	0.38		
	3	—	19.7	TMU
7,9-Dimethyloxadiazolo	1	—		
[3,4-*f*]quinoline	3	>1.5	Not determined	$AsCl_3$
Oxadiazolo[3,4-*h*]quinoline	1	—		
	3	0.20	20.2	TMU
6,8-Dimethyloxadiazolo	1	—		
[3,4-*h*]quinoline	3	0.28	20.0	NMP

[a]TMU, tetramethylurea; NMP, 1-methylpyrrolidin-2-one.

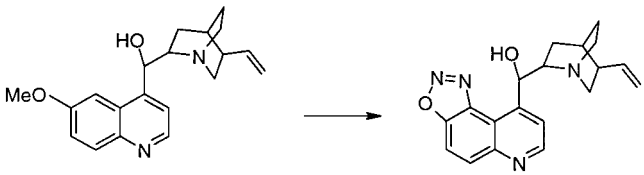


X = CH, Y = N; X = N, Y = CH

The electron impact positive ion spectrum of 1,2,5-oxadiazolo[3,4-*f*]quinoline *N*-oxide **46** shows the loss of N_2O_2 from the molecular ion, a process that must be followed by a substantial rearrangement to enable the observed loss of propynenitrile. This remarkable result apparently arises through a series of H-atom shifts which relocate the dehydroaromatic moiety in the heteroring (89OMS465).

2. *1,2,3-Oxadiazoloquinolines*

4-Substituted-1,2,3-oxadiazolo[4,5-*f*]quinoline **47** originated after nitration, reduction, and diazotization of alkaloid quinine during the study of its structure and reactions (53RZC495, 54RZC61).

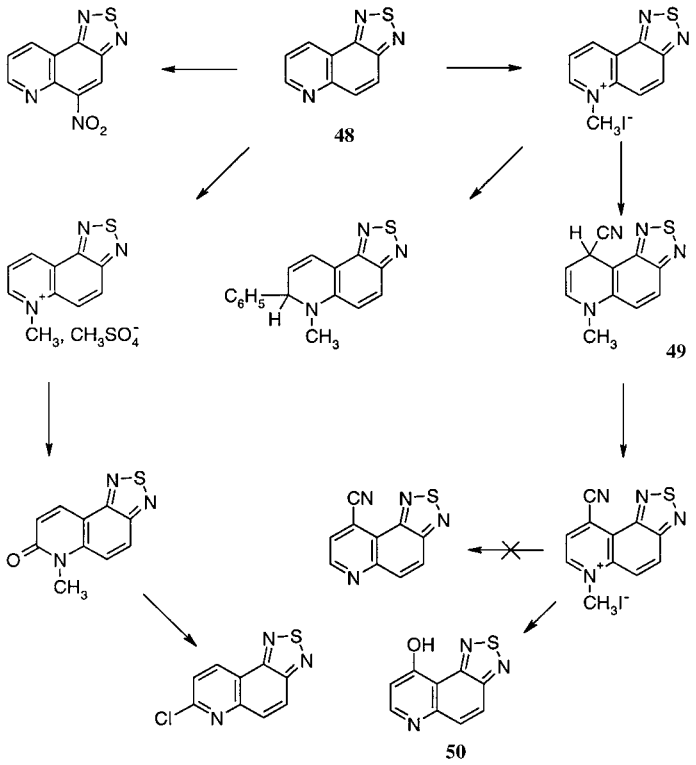


47

B. THIADIAZOLOQUINOLINES

1. *1,2,5-Thiadiazoloquinolines*

Angularly annelated thiadiazoloquinolines and their reactions with electrophiles and nucleophiles have been studied intensively by Italian and Indian authors (63MI1, 67MI1, 81IJC744). 1,2,5-Thiadiazolo[3,4-*f*]quinoline **48** was prepared by a multistep reaction starting from 6-nitroquinoline, through 5-amino-6-nitroquinoline and 5,6-diaminoquinoline. The final cyclization was effected with thionyl chloride in dry benzene to give the product in 26.9% yield (81IJC744) or in toluene in 82% yield (63MI1). The same product was obtained from a Skraup reaction using glycerol and sulfuric and arsenic acid, starting from 5-amino-2,1,3-benzothiadiazole, and the UV spectrum was studied (63MI1). Subsequent methylation of **48** with dimethyl sulfate in dry benzene provided the methosulfate. The latter can be oxidized with potassium hexacyanoferrate in alkaline conditions to give the 6,7-dihydro-6-methyl-1,2,5-thiadiazolo[3,4-*f*]quinol-7-one (Scheme 23).

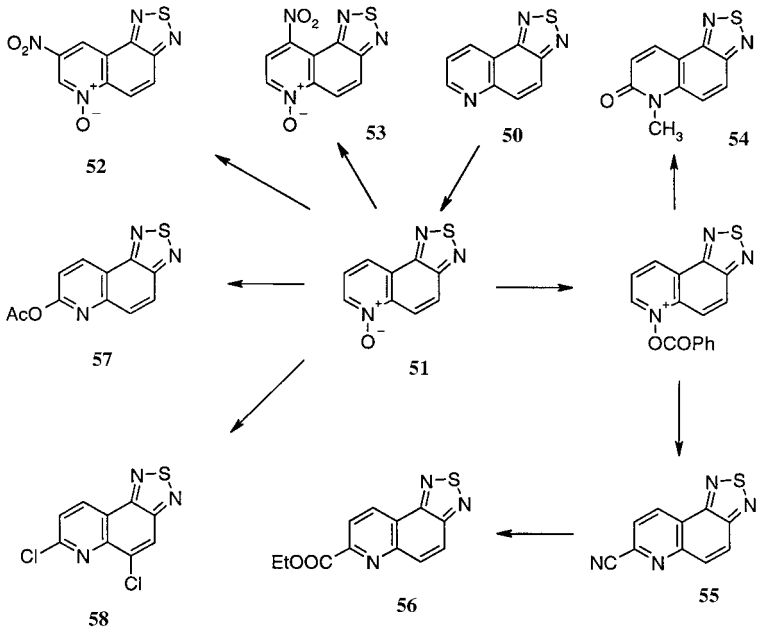


SCHEME 23

When treated with phosphorus pentachloride in *p*-dichlorobenzene in a sealed tube, the quinol-7-one gave the 7-chloro-1,2,5-thiadiazolo[3,4-*f*]quinoline. Its methylation with methyl iodide afforded the methiodide, and the latter on reaction with aqueous potassium cyanide gave the 6,9-dihydro-9-cyano-1,2,5-thiadiazolo[3,4-*f*]quinoline **49.** The dihydro compound smoothly oxidizes by the action of iodine in methanol in the presence of pyridine to give the methiodide of 9-cyano-1,2,5-thiadiazolo[3,4-*f*]quinoline, which on refluxing with ethyl benzoate gave 1,2,5-thiadiazolo[3,4-*f*]quinol **50** instead of 9-cyano-1,2,5-thiadiazolo[3,4-*f*]quinoline as expected. The addition product of the methiodide with phenylmagnesium bromide has been assigned the structure of 6,7-dihydro-6-methyl-7-phenyl-1,2,5-thiadiazolo[3,4-*f*]quinoline. Nitration of 1,2,5-thiadiazolo[3,4-*f*]quinoline with fuming nitric acid in the presence of concentrated sulfuric acid occurs at position 5 (81IJC744).

The 6-*N*-oxide **51** is an important intermediate for preparing many derivatives of 1,2,5-thiadiazolo[3,4-*f*]quinoline **48** substituted at the pyridine ring. Compound **51** arises from 1,2,5-thiadiazolo[3,4-*f*]quinoline **48** by oxidation with *m*-chloroperbenzoic acid. *N*-Oxide **51,** on treatment with benzoyl nitrate, afforded the 8-nitro-1,2,5-thiadiazolo[3,4-*f*]quinoline-6-*N*-oxide **52,** whereas nitration with a mixture of fuming nitric acid and sulfuric acid gave the corresponding 9-nitro-1,2,5-thiadiazolo[3,4-*f*]quinoline **53** instead of selena analogues, which extruded elemental selenium. Reissert's reaction of 1,2,5-thiadiazolo[3,4-*f*]quinoline-6-*N*-oxide **51** with benzoyl chloride and sodium hydroxide gave, surprisingly, the 6-methyl-7-oxo-6,7-dihydro-1,2,5-thiadiazolo[3,4-*f*]quinoline **54;** with potassium cyanide it afforded the 7-cyano-1,2,5-thiadiazolo[3,4-*f*]quinoline **55** in 60% yield, and the cyano group could be hydrolyzed with ethanol to an ethyl ester **56.** The 7-acetoxy derivative **57** originated when 6-*N*-oxide **51** was heated under reflux with acetic anhydride in 40% yield, whereas reaction of **51** with an excess of phosphorus oxychloride gave, surprisingly, the 5,7-dichloro-1,2,5-thiadiazolo[3,4-*f*]quinoline **58** (Scheme 24) (86IJC271).

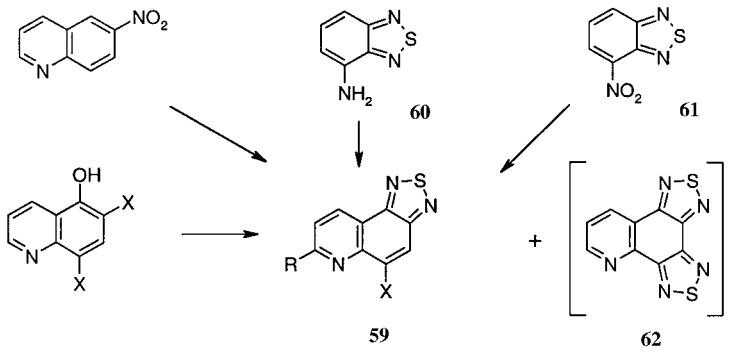
Using the same reaction conditions for preparation of the [3,4-*f*] isomer **48,** the isomeric 7,8-diaminoquinoline gave 1,2,5-thiadiazolo[3,4-*h*]quinoline **59** in only 26% yield in benzene (81S316) or toluene (63MI1). The formation of product **59** was also observed in the Skraup reaction starting from 4-amino-2,1,3-benzothiadiazole **60** (63MI1) or in 15% yield in a one-step Skraup reaction starting from the 4-nitro-2,1,3-benzothiadiazole **61.** The yields of **59** (R = X = H) are comparable in both the presence and the absence of arsenic pentoxide (81IJC922). When crotonaldehyde diacetate reacts with 4-amino-2,1,3-benzothiadiazole **60,** the 7-methyl derivative **59** is formed (R = Me) and also gave the cyanine dyes. Both were studied using the UV spectra (67MI1). Hydroxy-substituted benzoheterocycles with tetrasulfur tetranitride afforded condensed thiadiazoles **59** and bisthiadiazoles **62.** Thus, reaction of 8-hydroxyquinoline gave the mono and bis condensed products in ratio 27:7, whereas 5,7-dibromo-8-hydroxyquinoline



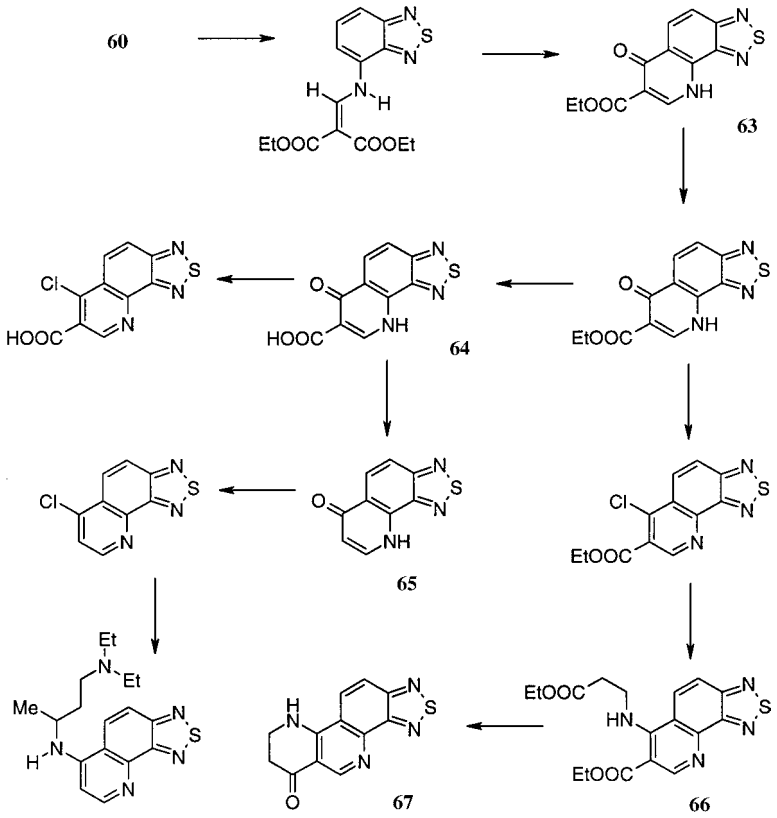
SCHEME 24

gave only a bis[1,2,5]thiadiazolo[3,4-*f*:3′,4′-*h*]quinoline **62** (Scheme 25) (91BCJ68).

Another approach involves utilization of the amines for addition of a fused pyridine ring to the benzothiadiazole skeleton. The Gould–Jacobs reaction of 4-amino-2,1,3-benzothiadiazole **60** with diethyl ethoxymethylenemalonate gave the substitution product, and, after thermal cyclization in diphenyl ether, afforded the



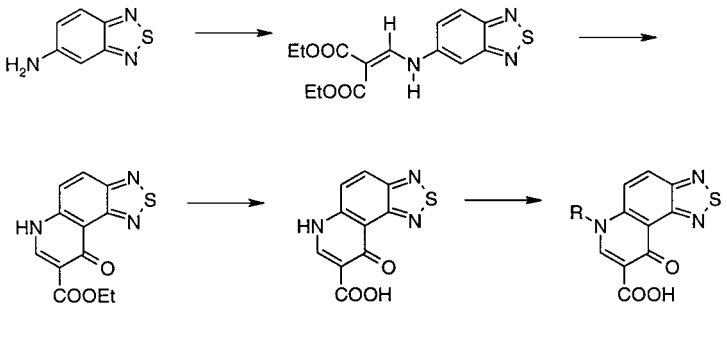
SCHEME 25



SCHEME 26

potentially antiparsitic ethyl 6-oxo-6,9-dihydro-1,2,5-thiadiazolo[3,4-*h*]quinoline-7-carboxylate **63,** which could be hydrolyzed to the corresponding acid **64.** After decarboxylation, the acid afforded the 6-oxy-6,9-dihydro-1,2,5-thiadiazolo[3,4-*h*]quinoline **65.** These three products were chlorinated using either phosphorous oxytrichloride or thionyl chloride to produce the corresponding chloro compounds. The reactive chlorine atom could be substituted with nucleophiles such as 1-diethylamino-4-aminopentane or β-alanine. The product of the reaction with β-alanine product **66** was hydrolyzed to a diacid and subsequently cyclized with acetic anhydride in the presence of potassium acetate to give the 6-oxo-6,7,8,9-tetrahydro-2,1,3-tiadiazolo[4,5-*h*]-1,6-naphtyridine **67** (Scheme 26). The naphtyridine **67,** however, showed no activity against *P. berghei* (76KGS61).

5-Amino-2,1,3-benzothiadiazole treated under similar conditions afforded, regioselectively, an analogous angularly annelated ester **68** and acid **69,** both to be tested for inhibition of the DNA synthesis (74MI1). Subsequent alkylation of the



68 **69** **70**

SCHEME 27

acid in ethanol with methyl iodide or ethyl iodide gave, in the presence of aqueous potassium carbonate, the 6-methyl or ethyl substituted acids **70,** respectively (Scheme 27) (74JAP(K)1).

1,2,5-Thiadiazolo[3,4-*f*]-,[3,4-*g*]-, and [3,4-*h*]quinolines with an α-methyl group attached to the nitrogen atom of pyridine were converted with ethyl 4-toluenesulfonate or ethyl iodide to the corresponding quarternary salts, which afforded, when treated with 2-[2-(ethylthio)vinyl]benzazole (2-benzoxazolyl, 2-benzthiazolyl, 2-benzselenazolyl, or 2-quinolinyl), the corresponding trimethincyanine dyes having λ_{max} between 546 and 620 nm. The wavelength increased in going from the benzoxazolyl to the quinolinyl derivative. Analogous styryl derivatives have been prepared using 4-dimethylaminobenzaldehyde to have λ_{max} 533 or 538 nm, respectively (67MI1).

1,2,5-Thiadiazolo[3,4-*f*]quinoline monoamine oxidase inhibitory activities were examined in (91YZ499), but the values were too high to compare with other pentanthrene type of heterocycles.

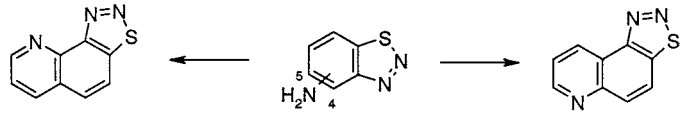
Forty-eight quinolones were tested against 23 strains of bacteria. One of them, 9-ethyl-6-oxo-6,9-dihydro-thiadiazolo[4,5-*h*]quinoline-7-carboxylic acid, had the strongest antibacterial effect. Upon esterification the activity decreased, and amidization stopped it altogether (90MI1). Nonethylated acid **64** itself has a minimum inhibitory activity of 6.25 μg/ml against *Staphylococcus aureus* Smith (84MI1).

2. *1,2,3-Thiadiazoloquinolines*

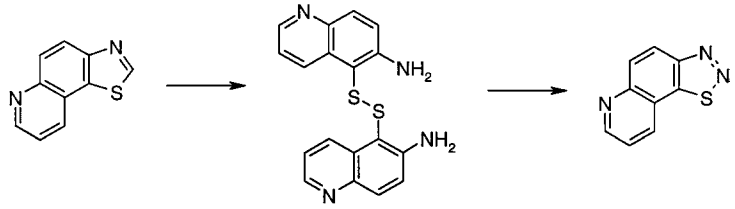
Skraup synthesis starting from 4- and 5-aminobenzothiadiazole afforded only angularly annelated products: thiadiazolo[5,4-*h*]- and [4,5-*f*]quinoline, respectively. Attempts to cyclize 4-chloro-5-aminobenzothiadiazole failed (37LA38).

The parent skeleton of 1,2,3-thiadiazolo[5,4-*f*]quinoline was accessed by hydrazinolysis of thiazolo[5,4-*f*]quinoline to obtain first the corresponding

disulfide as intermediate **71,** which was then diazotized to give the target compound (49JCS355).



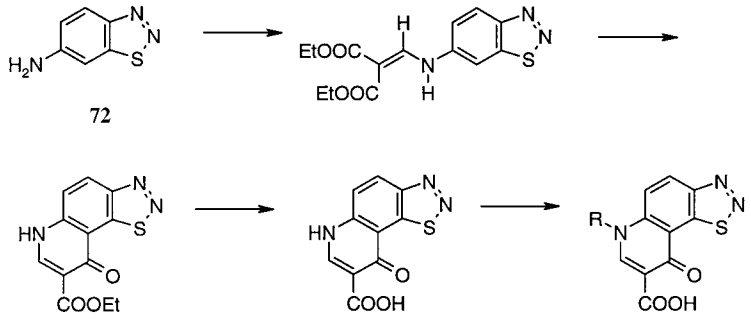
Under similar conditions, as in the case of 5-amino-2,1,3-benzothiadiazole, and starting from 6-amino-1,2,3-benzothiadiazole **72,** the 1,2,3-thiadiazolo[5,4-*f*]quinoline derivatives **73** resulted (Scheme 28) and were tested for antibacterial properties (74JAP(K)1).



71

The same amine **72,** and its 5-isomer, were condensed with 2-butenaldehyde or 3-oxo-2-butene, respectively, and cyclized and quarternized with methyl iodide to give the quinolinium compounds **74** and **75.**

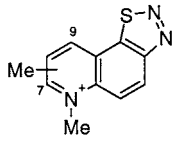
When treated with 4-dimethylaminobenzaldehyde, diazonium salts, or phthalic anhydride, these salts produced the corresponding styryl or azamethine dyes derived from 1,2,3-thiadiazolo[4,5-*f*] or [5,4-*f*]quinolines. The λ_{max} of azamethine



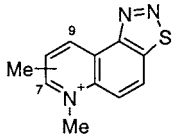
72

73

SCHEME 28



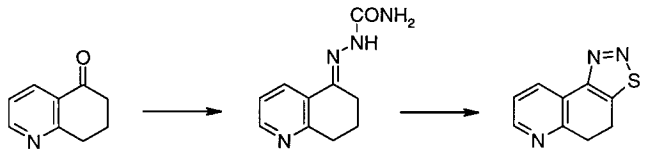
74



75

and styryl dyes prepared from 9-methyl substituted heterocycles were higher than those of dyes from the 7-methyl isomer; a bathochromic shift was also observed when the thiazole nucleus was replaced by thiadiazole. The azamethine's λ_{max} was also influenced by the substituent(s), increasing through the series 2,5-dichloro- > 4-nitro- > 2-methyl- > 4-nitro-. The λ_{max} of the quinophthalones were slightly higher for those containing the thiadiazole nucleus.

Isomeric 4,5-dihydro[4,5-*f*]derivative **76** has been prepared from 7,8-dihydro-5(6*H*)-quinolinone via a semicarbazone and its subsequent reaction with thionyl chloride (95JHC177).



76

6-[4-(4-Alkylpiperazin-1-yl)phenylamino]-1,2,5-thiadiazolo[3,4-*h*]quinolines showing antihelmintic activity against alveolar echinococcosis and hymenolepidis (94RUP1), including methyl derivative (Drug 6-1574) and especially methyl derivative and ethylderivative (Drug 6-1569), are as effective as mebendazole against the larval stage of *Echinococcus multilocularis* infection.

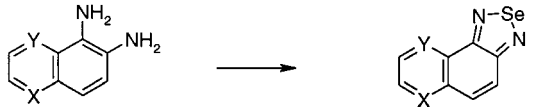
Drug 6-1574 has been demonstrated to ensure a 100% recovery of spontaneously *Hymenolepis nana*-infected albino mice given doses 2.5–5 times lower than the ED of phenasal (niclosamide) (94MI1).

C. SELENADIAZOLOQUINOLINES

1. *1,2,5-Selenadiazoloquinolines*

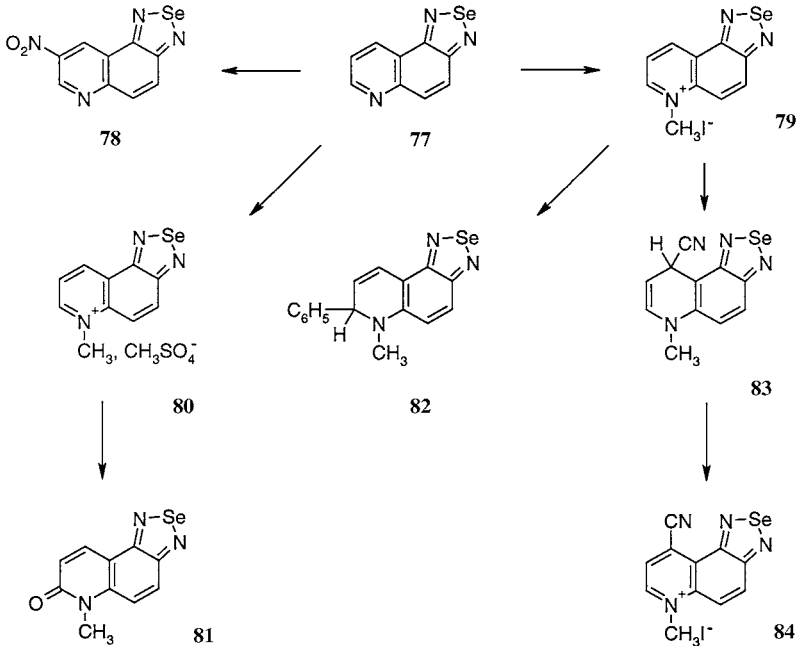
In 1981 the first the preparation of 1,2,5-selenadiazolo[3,4-*f*]quinoline **77** was published, starting from the 5,6-diaminoquinoline (81IJC648, 99MI1), while its

isomer, 1,2,5-selenadiazolo[3,4-*h*]quinoline **94,** could be made from 7,8-diamino-quinoline (81S316, 99MI1) by treatment with selenium dioxide.



77: X = N, Y = CH; **75**: X = CH, Y = N

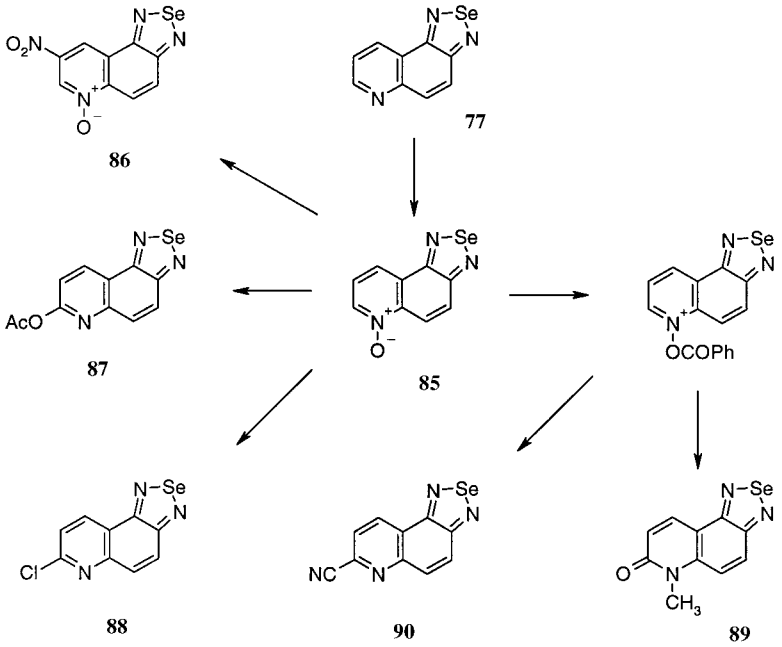
The nitration of 1,2,5-selenadiazolo[3,4-*f*] quinoline **77** with benzoyl nitrate affords the 8-nitro derivative **78,** whereas methylation with methyl iodide or methyl sulfate afforded the corresponding 6-pyridinium methiodide **79** or methosulfate **80,** respectively (Scheme 29). The pyridinium salt **80** was submitted to oxidation with potassium hexacyanoferrate and provided 7-oxo-6,7-dihydro derivative **81** or, by reaction of pyridinium salt **79** with phenylmagnesium bromide, the 7-phenyl-6,7-dihydro derivative **82.** Nucleophilic substitution of the methiodide **79** with potassium cyanide resulted in the formation of 9-cyano-6,9-dihydroderivative **83,** which can be oxidized by iodine to 9-cyano-1,2,5-selenadiazolo [3,4-*f*]quinoline methiodide **84.** All the reactions proceeded in moderate yields (81IJC648).



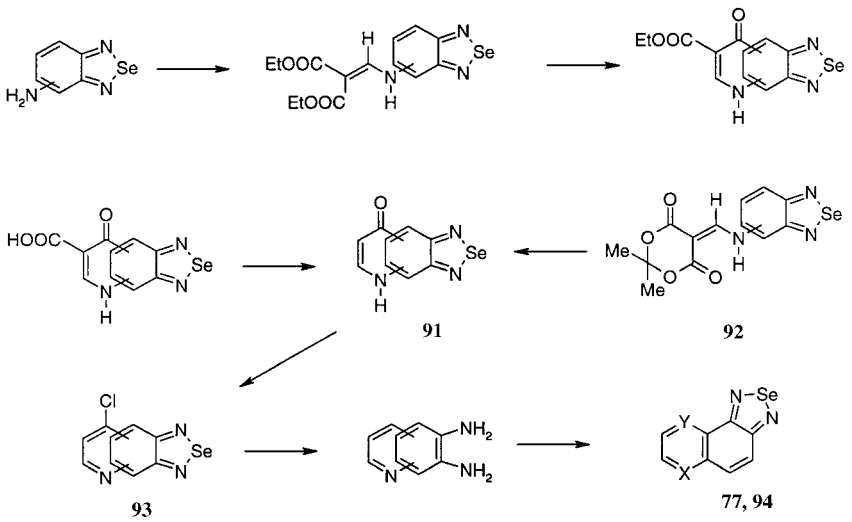
SCHEME 29

1,2,5-Selenadiazolo[3,4-*f*]quinoline **77** reacts with *m*-chloroperbenzoic acid to give the 6-*N*-oxide **85.** Nitration of this *N*-oxide with benzoyl nitrate afforded a 8-nitro derivative **86,** but in sulfuric acid with fuming nitric acid it resulted in ring fission, giving the selenium metal. Acetylation of the same *N*-oxide **85** with acetic anhydride gave the 2-acetoxy derivative **87;** with phosphorus oxychloride it gave the 7-chloro-1,2,5-selenadiazolo[3,4-*f*]quinoline **88.** The value of the coupling constant is too high for *ortho* protons at the pyridine ring. Benzoylation of starting benzoselenadiazoloquinoline *N*-oxide **85** takes place on the same nitrogen atom. Therefore, a Reissert's reaction with sodium hydroxide afforded the 6-methyl-6,7-dihydro-1,2,5-selenadiazolo[3,4-*f*]quinoline-7-one **89,** whereas with potassium cyanide it gave the 7-cyano derivative **90** (Scheme 30) (86IJC271).

9-Oxo-6,9-dihydro-1,2,5-selenadiazolo[3,4-*f*] quinoline-8-carboxylic acid and its ethyl ester were prepared (74MI1) to evaluate its bioactivity. These and isomeric 1,2,5-selenadiazolo[3,4-*h*]quinolines were prepared using a Gould–Jacobs reaction starting from 4- or 5-amino[2,1,5]benzoselenadiazoles, respectively. Subsequent decarboxylation gave the same products **91** as a thermal cyclization of the corresponding N-substituted aminomethylene Meldrum's acids **92** (Scheme 31). After aromatization of selenadiazoloquinolones with phosphorous oxychloride, the corresponding 6- or 9-chloroselenadiazoloquinolines **93** were produced. These



SCHEME 30

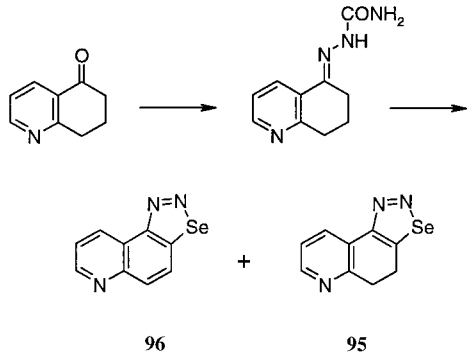


SCHEME 31

can be reduced to the 5,6- or 7,8-diaminoquinolines, respectively. The conversion to 1,2,5-selenadiazolo[3,4-*f*]quinoline **77** and 1,2,5-selenadiazolo[3,4-*h*]quinoline **94** was carried out with selenious acid (99MI1).

2. *1,2,3-Selenadiazoloquinolines*

Selenium dioxide oxidation of 7,8-dihydro-5(6*H*)-quinolinone semicarbazone gave, in addition to the expected 4,5-dihydro selenadiazoloquinoline **95** (analogous to sulfur derivative **76**), the oxidized 1,2,3-selenadiazolo[4,5-*f*]quinoline **96,** which, when heated to 210°C for 30 min, gave the dimeric [1,4]diselenino [2,3-*f*:5,6-*f*′]diquinoline (95JHC177).



D. IMIDAZOQUINOLINES

Imidazoquinolines can be considered benzene separated deazapurines, and together with the discovery of mutagenic activity of the fused 2-aminoimidazole nucleus, this field of research received a strong impetus in the early 1980s. A review concerning imidazoquinolines has been included in Weissberger's *Chemistry of Heterocyclic Compounds*, Vol. 40, in chapter entitled "Tricyclic 6-6-5 Fused Benzimidazoles and Congeneric Tricyclic Compounds" (81MI1), covering this area up to 1980. The current review has been designed as a continuation of this earlier work.

Most frequently the synthetic routes to imidazoquinolines involve the ring closure of pyridine ring starting from aminobenzimidazoles. Ring closure of the imidazole ring is preferred when starting from *o*-diaminoquinolines.

Many theoretical studies were published about this interesting group of compounds up to 1980 and were sumarized in (81MI1). Only protonation, tautomerization, and valence tautomerization of selected imidazo[4,5-*f*]quinolines were studied in a theoretical study of gas and liquid basicity of imidazo[4,5-*f*]quinolines in the past few years (93MI1). The theoretical calculations have shown that the first protonation (Fig. 1) takes place at the pyridine nitrogen atom rather than at the imidazole nitrogen atom (the energy difference between the alternative protonated forms was found to be 8.75 kcal mol^{-1}). The preferred tautomeric form was found to be the 3*H* tautomer. However, the value of the former proton tautomerization (27 ± 3 kcal mol^{-1}) should include a simultaneous valence tautomerism (Fig. 4) that was estimated to be on the order of 6 kcal mol^{-1}. A satisfactory correlation (Fig. 2) between experimentally obtained pK_a values and computed electron densities and energies was found (Tables III, IV; Fig. 3).

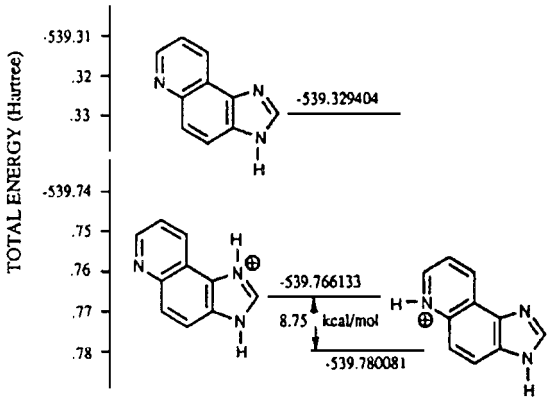


FIG. 1. Energy values for the neutral and two alternative protonated forms of imidazo[4,5-*f*]-quinoline.

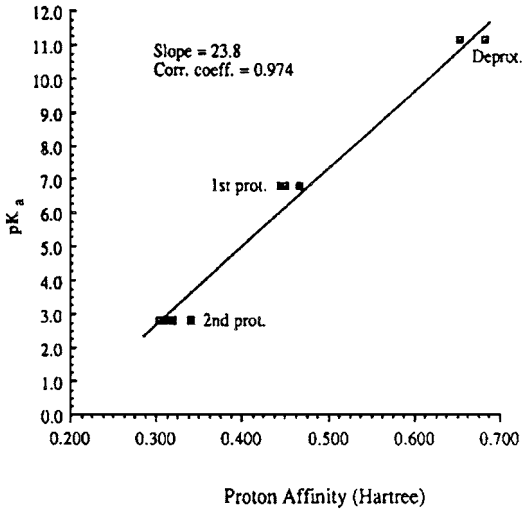


FIG. 2. Proton affinities and pK_a values for imidazo[4,5-*f*]quinolines.

In the early 1980s large group of heterocyclic compounds was isolated from thermally processed meats and cooked food: broiled sun-dried sardines and fishes; fried beef; hamburgers; and potatoes—pyrolysates of various amino acids and proteins, with strong mutagenic and carcinogenic properties, even higher than those of aflatoxin B_1. The structures of these compounds typically possess a fused 2-aminoimidazole ring (80MI2, 92MI2, and loc. cit.). From the imidazoquinolines belonging to this group we mention the 2-amino-3-methylimidazo[4,5-*f*]quinoline **97** (IQ) and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline **98** (MeIQ). Methods of their separation and detection were based especially on chromatography (HPLC; 83MI2) and extraction methods (96MI3 and loc. cit.). Methylated 2-aminoimidazo[4,5-*f*]quinolines (compounds having a methyl group at position N-1 or N-3) were strong mutagens. The 1,5-dimethyl derivative was more mutagenic than the 3,5-dimethyl derivative, and the introduction of a methyl group at position 4 and position 5 enhanced and reduced the mutagenicity, respectively (81MI2). Also, the metabolism of ^{14}C-labeled IQ and MeIQ (83ACS157) was studied in suspensions of hepatocytes isolated from PCB-pretreated rats. The 3-trideuterio analogue of **97** was prepared in 41% overall yield (88SC973). The scheme for the main metabolic pathways of **97** and **98** in the rat was suggested (89MI1). The mechanism involved in the metabolic activation of **97** to a mutagenic intermediate was studied *in vitro* in (83MI3).

^{3}H labeling of IQ and MeIQ was achieved by bromination of **97** in acetic acid to give the 5-bromo derivative. After hydrogenolysis with $^3H_2$/Pd in THF, the 5-bromo derivative gave the 5-^{3}H derivative in >97% radiochemical purity.

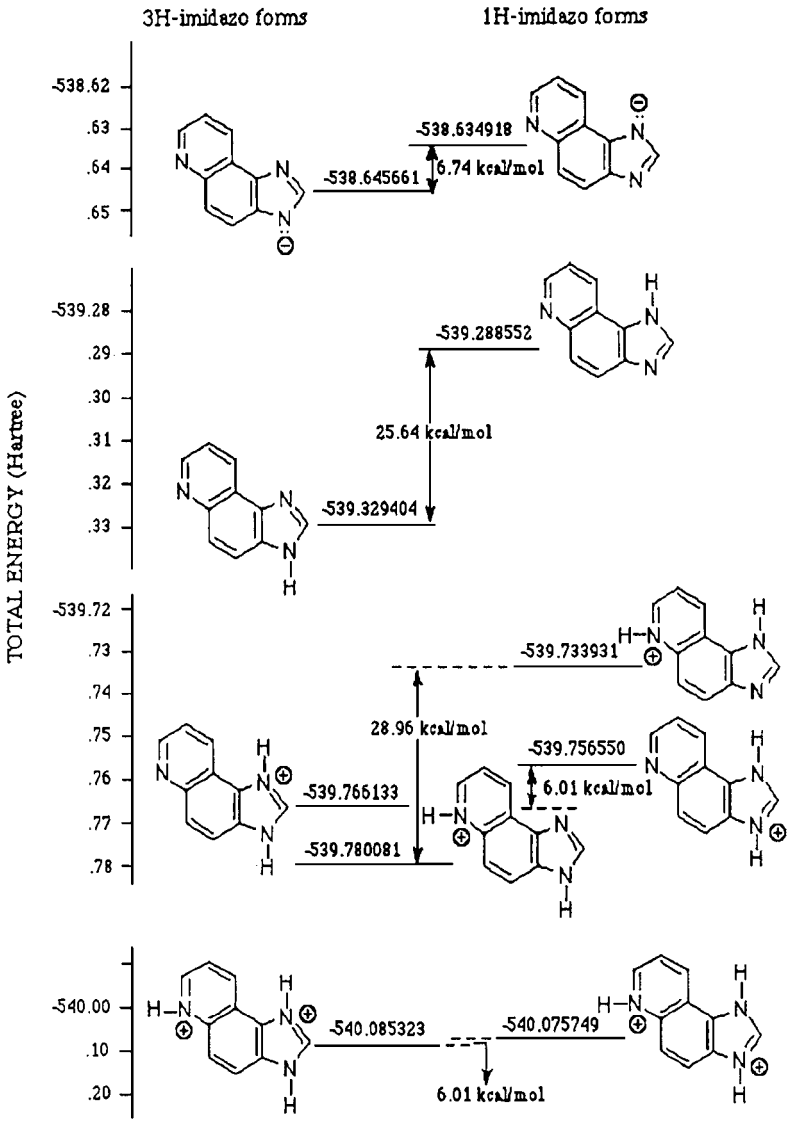


FIG. 3. Energies and structures for the 3*H*-imidazo and 1*H*-imidazo forms, tautomers, and their deprotonated and protonated forms.

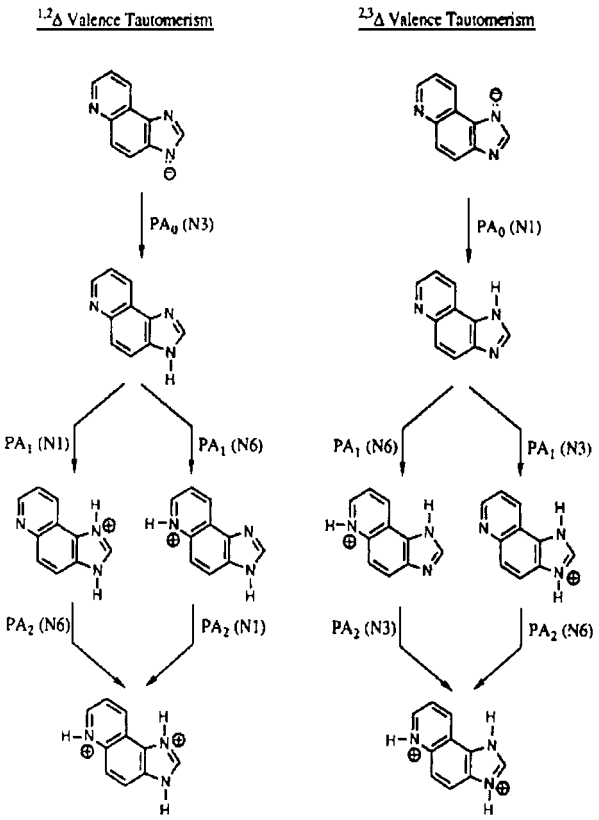


FIG. 4. Valence tautomerism of protonated imidazo[4,5-*f*]quinoline.

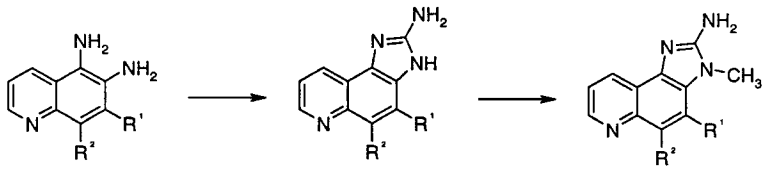
8-Bromo-7-methyl-6-methylaminoquinoline was nitrated with $AcONO_2$ to give the 6-N(NO_2)Me derivative, which rearranged in diluted sulfuric acid to the 5-nitro derivative. Reduction of the latter compound, followed by condensation with BrCN and final hydrogenolysis using $^3H_2$, led to a product of >99% radiochemical purity (85MI1).

The proposed structure of **97** isolated from broiled sardines was confirmed by straightforward synthesis starting from 5,6-diaminoquinolines. After reaction with cyanogen bromide it afforded the 2-amino-imidazo[4,5-*f*]quinolines **99** (R^1, R^2 = H, Me), which was then converted into its 3-*N*-methyl derivative **100** by lyophilization and subsequent heating under reduced pressure of the corresponding tetramethylammonium salt (R^1 = H, R^2 = H, Me) (80MI3, 81JCS(P1)2290). Regioselectivity of the methylation was elucidated on the basis of nuclear Overhauser effect of the irradiated methyl signal, and only H-4 intensity increased 13% (R^1 = R^2 = H) (81JCS(P1)2290).

TABLE III

CALCULATED PROTON AFFINITIES AND pK_a VALUES FOR IMIDAZO [4,5-*f*]QUINOLINES

$E_{prot} - E_{unprot}$		PA0 (deprotonated)	PA1 (first protonation)	PA2 (second protonation)
	N1	—	—	0.309190
$^{1,2}\Delta$ or 3*H*	N3	0.683740	—	—
	N6	—	0.450677	0.305240
	N1	0.653630	—	—
$^{2,3}\Delta$ or 1*H*	N3	—	0.467998	0.341810
	N6	—	0.445379	0.319190
pK_a		11.17	6.83	2.83



99 100

When 2-amino-4-methylimidazo[4,5-*f*]quinoline ($R^1 = Me$, $R^2 = H$) was alkylated with methyl iodide in K_2CO_3–DMSO, a mixture of both 1*H*-1,4-dimethyl- and 3*H*-3,4-dimethyl derivatives was obtained (80CL1391). In the case of DMF–DMA or its bis-trideuterio analogue, methylation in the ratio 8:1 in favor of the 3*H*-isomer is preferred (88SC973).

The 6-6-5 membered ring of the IQ system assumes a planar conformation: All carbon or nitrogen atoms deviate from the plane, but no more than 0.028 Å, from the

TABLE IV

TOTAL ENERGY VALUES OF 3*H* AND 1*H* FORMS OF IMIDAZO[4,5-*f*]QUINOLINES FOR NEUTRAL, CATIONIC AND ANIONIC FORMS

	Total energy (Hartree)	
Type of process	3*H*-Imidazo form	1*H*-Imidazo form
Deprotonated	−538.645661	−538.634918
Neutral	−539.327404	−539.288552
N1 protonated	−539.776133	—
N3 protonated	—	539.756550
N6 protonated	−539.780081	−539.733931
N1 and N6 protonated	−540.085323	—
N3 and N6 protonated	—	−540.075749

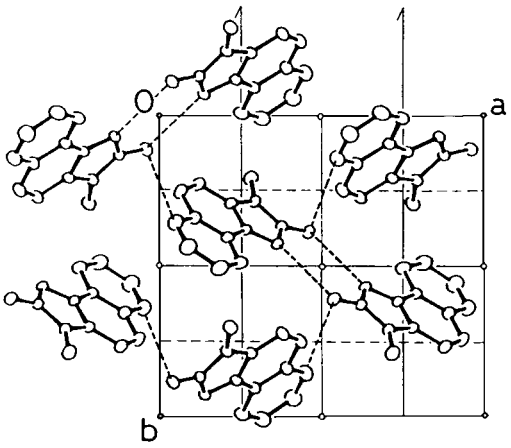
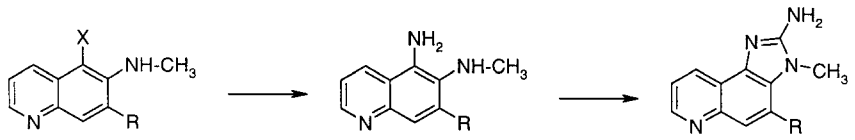


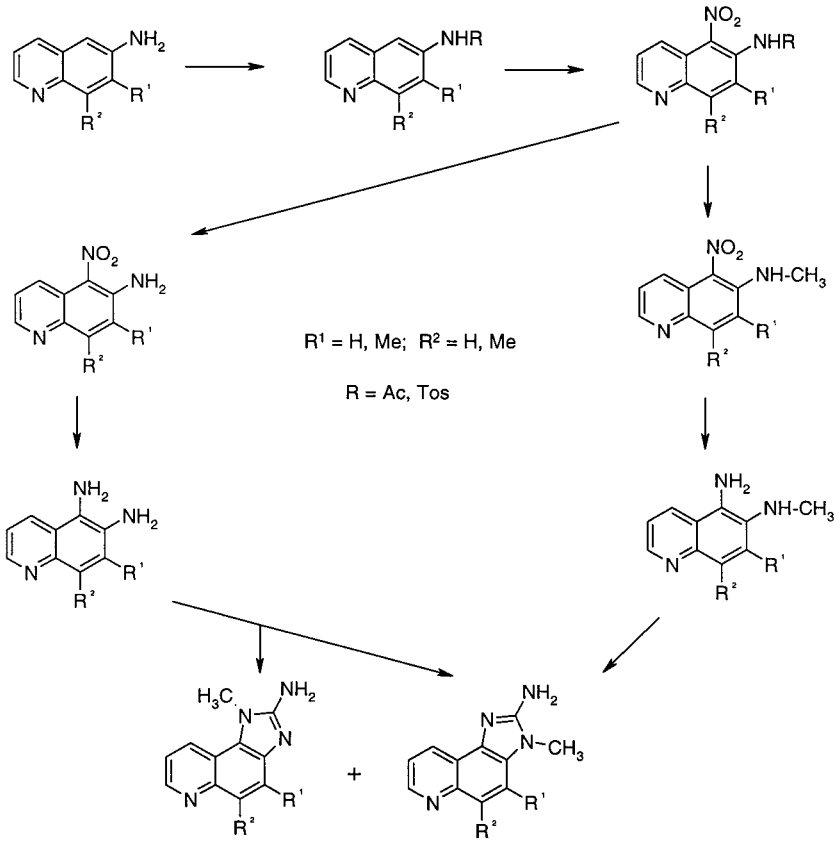
FIG. 5. The projection of crystal structure of **97** (IQ) along the *c*-axis (hydrogen bonds are shown with heavy broken lines).

best-fit plane of 13 ring atoms. As for the quinoline moiety of IQ, the bond lengths and bond angles are much the same as those of quinoline and quinoline derivatives. The crystal structure of IQ is shown in Fig. 5. Within a monoclinic unit cell, a pair of IQ molecules are nearly coplanar and form two intermolecular hydrogen bonds, N(2)–H(2B) · · · N(1). The $N(2)H_2$ group is also involved in another intermolecular hydrogen bond, N(2)–H(2A) · · · N(6). Only partial stacking is observed around the C(7)–N(6)–C(11) moiety of the two adjacent IQ molecules (80MI1).

Independent synthesis of IQ, eliminating the alkylating reaction step, involved the cyclizations of 7-R-5-amino-6-methylaminoquinolines with cyanogen bromide. When ^{14}C-labeled BrCN was used, the corresponding 2-^{14}C-labeled analogues of IQ and MeIQ were synthesized (83ACS157). The diamines are available from 5-nitroderivatives, which in turn have been prepared by nitration of methylaminoderivatives (82CPB1857).



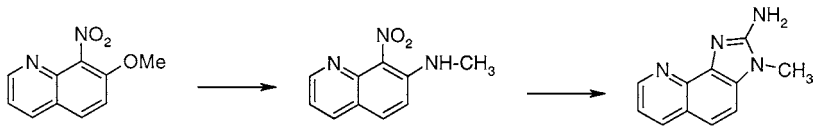
6-Aminoquinolines bearing a methyl group in position 7 or 8 are building blocks for the synthesis of homologues of IQ, such as MeIQ and its 5-methyl isomer. After



SCHEME 32

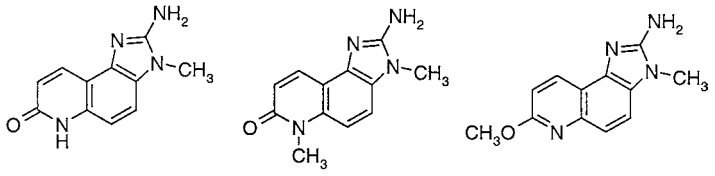
protection (acetylation or tosylation), nitration, reduction, and cyclization with cyanogen bromide, the target product was prepared, accompanied by its isomer (because of prototropy), by heating the tetramethylammonium salts under vacuum (Scheme 32) (82BCJ2233).

The requisite 6-methylaminoquinolines were prepared from 3-R-4-chloroanilines using the Skraup reaction, followed by nitration and methylammonolysis (83ACS157) or from 7-R-6-aminoquinolines using a sequence of formylation, reduction, and nitration (82CPB1857). For the preparation of 7-, 8-, and 9-methyl or 7,9-dimethyl IQ homologues, radical methylation instead of ammonolysis of the chloronitroquinolines and the corresponding 6-methoxyquinolines were used (94ACS823). By this methodology the isomer of IQ, 2-amino-3-methyl-3*H*-imidazo[4,5-*h*]quinoline **101,** was prepared (93H101).



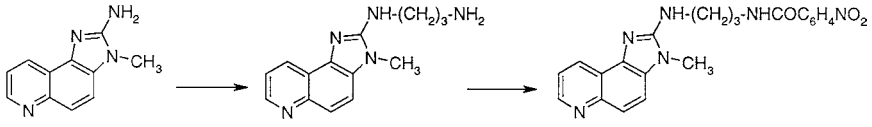
101

The major detectable anaerobic metabolites of IQ and MeIQ are the 7-hydroxy derivatives. 7-HO-IQ **102** is itself a powerful direct-acting mutagen. The *O*-methyl **103** and *N*-methyl **104** derivatives of 7-HO-IQ have been prepared from suitably substituted 5-amino-6-methylaminoquinolines in order to determine whether the tautomeric form of 7-HO-IQ plays any role in its bioactivity. Both methyl derivatives show comparable mutagenicity when tested directly against the T98 strain of *Salmonella typhimurium*, indicating that the quinolone structure does not play a major role in the mutagenicity of 7-HO-IQ. Neither 7-HO-IQ nor the methylated derivatives cleaved DNA in the presence of metal cations (87H2877, 89H1127, 89H1915).



102 **104** **103**

IQ was derived using propylenediamine to the appropriate propylamino derivative and acylated with 4-nitrobenzoyl chloride to nitrobenzamides **105;** the nitrobenzamides were used as haptens to generate the anti-IQ specific monoclonal antibodies (87H2069).

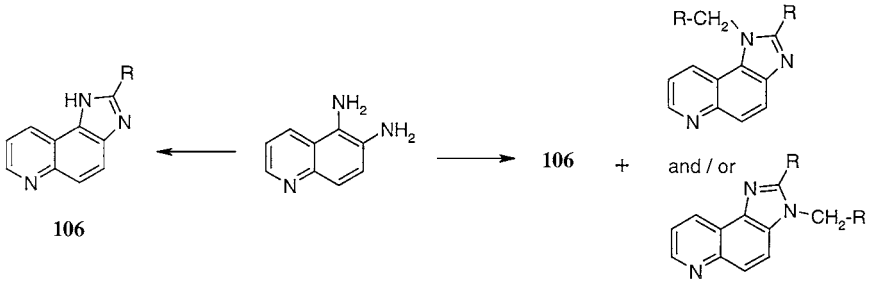


105

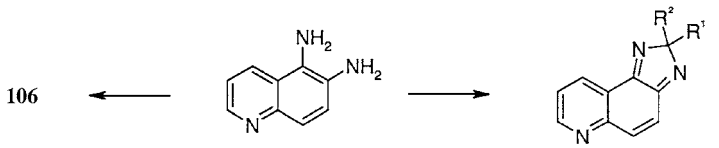
Diamines formed upon photolysis of 6-quinolyl azide in isopropyl-, *n*-butyl-, and *n*-hexylamines are very unstable, so they were cyclized to the corresponding 1-substituted imidazo[4,5-*f*]quinolines by heating the residue obtained after evaporation of the photolysis solvent with formic acid at reflux (82JCS(P1)421). Instead

of acids (84IJC673), the imidoyl ethers were used to cyclize 5,6- and 7,8-diaminoquinoline to form 2-substituted imidazo[4,5-*f*] and [4,5-*h*]quinolines, respectively. The activity of copper and FAD-dependent amine oxidases was tested, and K_i was calculated. The 2-methyl-3*H*-imidazo[4,5-*f*]quinoline was found to activate the copper bovine serum enzyme, but it inhibited the FAD mitochondrial enzyme (87FA513).

5,6-Diaminoquinoline also reacts with aldehydes in nitromethane. In a molar ratio of 1:1 it gave 2-substituted **106,** and in a molar ratio of 1 : 2, 1,2-disubstituted imidazo[4,5-*f*]quinolines **107** were formed (85IJC372, 82MI4).

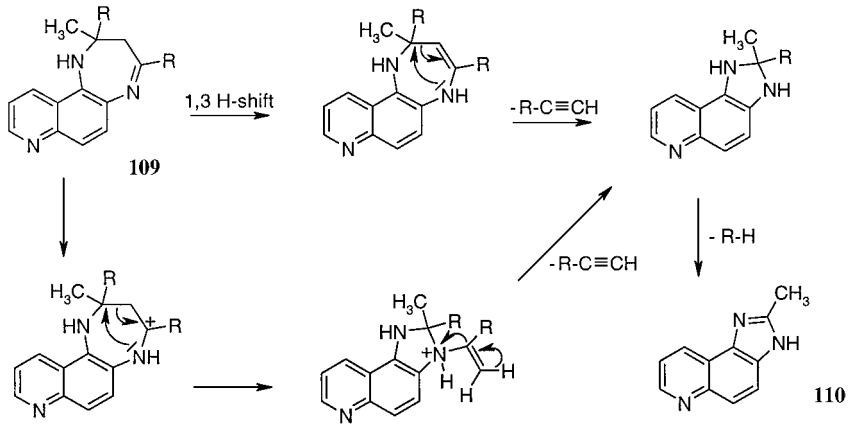


Using different mono- and diketones in acetic acid (at room temperature) afforded the following products: from benzophenone, 2,2-diphenyl-2*H*-imidazo[4,5-*f*]quinoline; from dibenzylketone, the 2-benzyl-imidazo[4,5-*f*]quinoline; and from 2,4-pentanedione, 2-methyl-imidazo[4,5-*f*]quinoline. Cyclohexanone under reflux gave 2-*n*-pentyl-, whereas at room temperature it afforded the *spiro*[cyclohexane-1,2′]-(2*H*)-imidazo[4,5-*f*]quinoline **108** (R^1R^2=$(CH_2)_5$) (86IJC527).



R^1, R^2 = Ph, Ph; $-(CH_2)_5-$; R (in **106**) = Me, Pe, CH_2Ph **108**

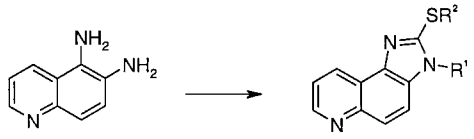
2,2,4-Trialkyl-2,3-dihydro-1*H*[1,4]diazepino[2,3-*f*]quinolines **109,** obtained from the reaction of 5,6-diaminoquinoline with ketones, on treatment with acid or under thermal conditions afforded solely the 2-methyl-3*H*-imidazo[4,5-*f*]quinoline **110.** However, no change was observed when diazepinoquinolines were treated



SCHEME 33

with a base under similar conditions. A plausible mechanism for the formation product has been suggested (Scheme 33) (89IJC272).

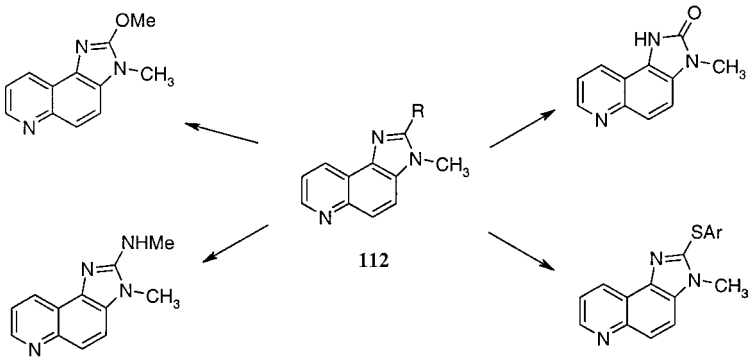
The same diamine, when treated with carbon disulfide in alkaline medium, yielded 2-mercapto-1*H*-imidazo[4,5-*f*]quinoline (88PS267, 88SC973, 86IJC264), which, on treatment with alkyl, aralkyl, and acid halides, gave the corresponding thioethers and thioesters **111,** respectively (88PS267, 86IJC264).



111

R^1 = H, Me; R^2 = H, Pr, Bu, $C_6H_5COCH_2$, 4-$ClC_6H_4COCH_2$, 4-$BrC_6H_4COCH_2$, 4-$MeOC_6H_4COCH_2$, 4-$O_2NC_6H_4COCH_2$, 3-$MeC_6H_4COCH_2$, Ac, COPh, CH_2COOH

3-Methyl-3*H*-2-mercapto- or methylthio-imidazo[4,5-*f*]quinoline was oxidized with 30% hydrogen peroxide in alkaline medium or with potassium permanganate in acidic medium to the corresponding 2-sulfonic acid or sulfone, whereas desulfurization occurred when hydrogen peroxide in acetic acid was used (95ACS225). 2-Sulfonic acid and (see Scheme 34) the methylsulfonyl derivative obtained from the methylthio derivative **112** or the 2-chloroderivative obtained from the 2-mercapto derivative can, under pressure, exchange the substituent in position 2 for a 2-amino group when sodium amide in liquid ammonia is used (88SC973, 94ACS823).



112

$R = SO_2Me, SO_3H$; $Ar = 4\text{-}C_6H_4CH_3$

SCHEME 34

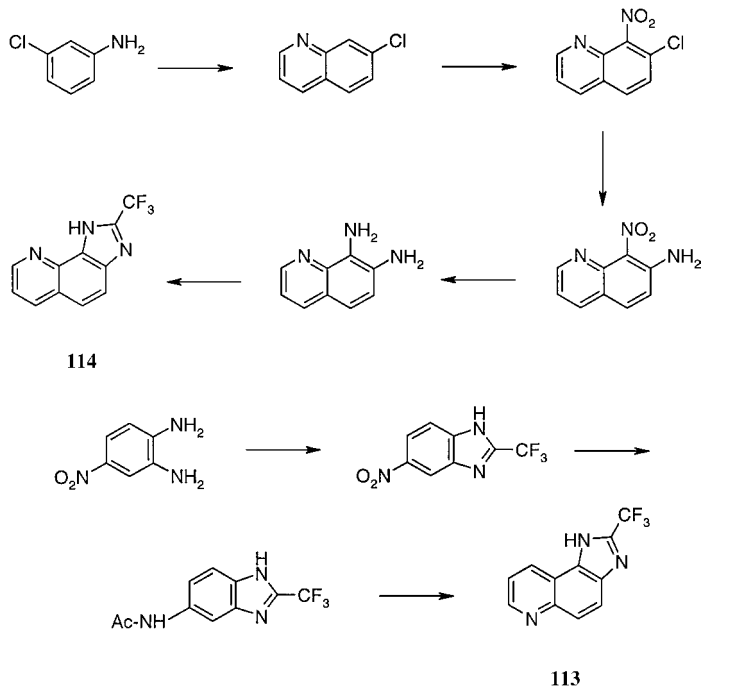
Substituents in position 2 easily undergo a nucleophilic substitution with MeONa, NaOH, $MeNH_2$, or ArSNa, respectively (94ACS823).

Angularly annelated 2-trifluoromethylimidazo[4,5-*f*] and [4,5-*h*]quinoline have been prepared from 5(6)-acetamido-2-trifluromethylbenzimidazole and 7,8-diaminoquinoline, respectively. They undergo hydrolysis in dilute sodium hydroxide to give parent skeletons imidazo[4,5-*f*] and [4,5-*h*]quinoline **113, 114** (Scheme 35) (81JFC573).

The hydrolysis proceeds via a diazafulvene intermediate, which in these systems can be formed without a total loss of aromatic character of the tricycle. It is tempting to suggest that, using this reasoning, linearly annelated 2-trifluoromethylimidazo[4,5-*g*]quinoline should be inert toward alkaline hydrolysis, as formation of the diazafulvene intermediate will again involve total dearomatization of the heterocyclic system (Scheme 36).

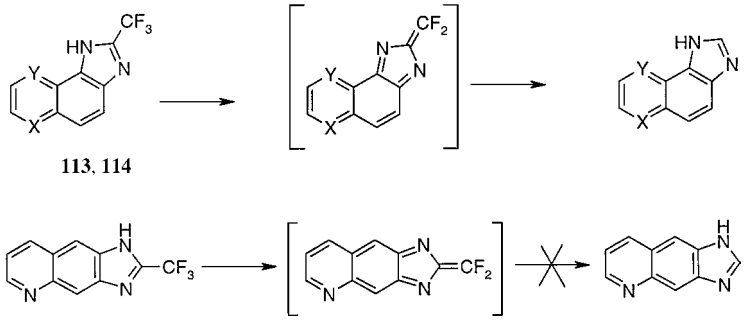
Absorption and emission spectra of six 2-substituted imidazo[4,5-*f*]quinolines ($R = H$, Me, CH_2Ph, Ph, 2-Py, $R^3 = H$; CH_2Ph, $R^3 = Ph$) were studied in various solvents. These studies revealed a solvent-independent, substituent-dependent character of the title compounds. They also exhibited bathochromic shifts in acidic and basic solutions. The phenyl group in the 2-position is in complete conjugation with the imidazoquinoline moiety. The fluorescence spectra of the compounds exhibited a solvent dependency, and, on changing to polar solvents, bathochromic shifts occur. Anomalous bathochromic shifts in water, acidic solution, and a new emission band in methanol are attributed to the protonated imidazoquinoline in the excited state. Basic solutions quench fluorescence (87IJC187).

The association of the excited state derived from four 2-substituted imidazo [4,5-*f*]quinolines with 2-propanol in cyclohexane has been studied. The unusual bathochromic shift and the bandwidth of the fluorescence spectra of these heterocyclic compounds in 2-propanol–cyclohexane solutions, compared with those

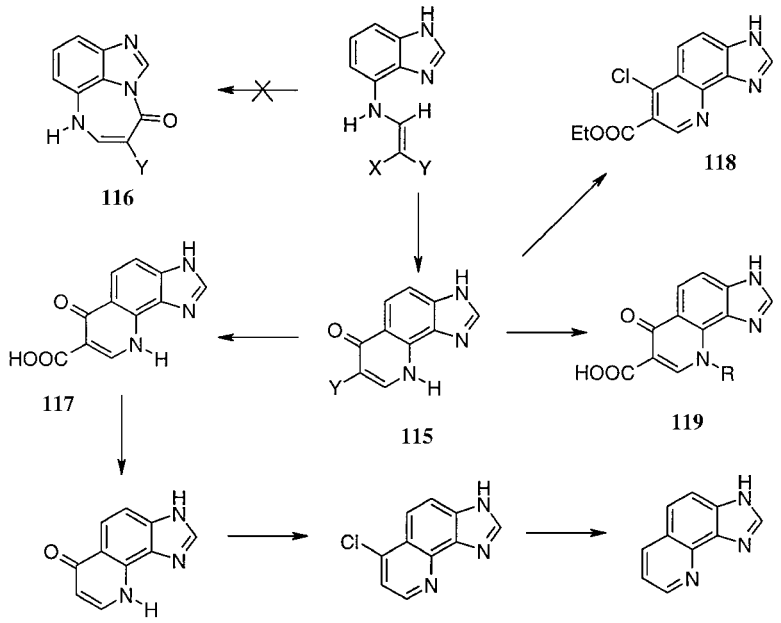


SCHEME 35

obtained in cyclohexane solutions, have been attributed to the association of the excited state imidazoquinolines with the 2-propanol molecules. Hydrogen bonding between the imidazole >N–H moiety of the excited state imidazoquinolines and the 2-propanol is shown to be responsible for the association (87MI1).



SCHEME 36



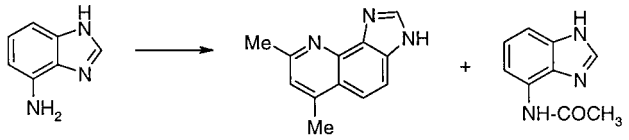
SCHEME 37

The applied Gould–Jacobs reaction is very often used to prepare angularly annelated pyridine-ring-substituted imidazoquinolines in inert media under conditions of thermal cyclocondensation, for example; at temperatures above 250°C.

4-Substituted benzimidazole derivatives with activated aminoethylene substituent cyclize in Dowtherm to afford angularly annelated 7-substituted 6-oxo-6, 9-dihydroimidazo[4,5-*h*]quinolines **115** (Y = CN, COOEt) and not the tricyclic diazepinobenzimidazole system **116.** The product can be hydrolyzed in alkaline media to the corresponding carboxylic acid **117** or aromatized using $POCl_3$ in DMF to a chloroester **118** (87CCC2918). The acid was decarboxylated, aromatized with $POCl_3$ in DMF, and dechlorinated by reduction on Raney nickel to give the parent heterocyclic skeleton of imidazo[4,5-*h*]quinoline (Scheme 37) (88CCC1068).

Alkylation of the cyclization product **115** and the following hydrolysis gave 9-alkyl substituted 6-oxo-6,9-dihydroimidazo[4,5-*h*]quinoline-7-carboxylic acid derivatives **119,** compounds useful as antibacterials (no data) [80JAP(K)1].

4(7)-Aminobenzimidazole can react with 1,3-diketones as a bidentate nucleophile, but with 2,4-pentanedione in glacial acetic acid it gives a Combes product, 1*H*-6,8-dimethylimidazo[4,5-*h*]quinoline **120,** accompanied by 4(7)-acetamidobenzimidazole (91T7459).



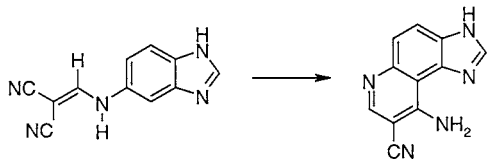
120

In the search for new fluorometric reagents for trace metal determinations, ferroin-type compounds, namely 2-(2-pyridyl)-2*H*- and 2-(3-isoquinolyl)-3*H*-imidazo[4,5-*h*]quinolines, and their silver, lead, and zinc chelates were tested for luminiscence in aqueous ethanol solutions at various pH values (80TAL1021).

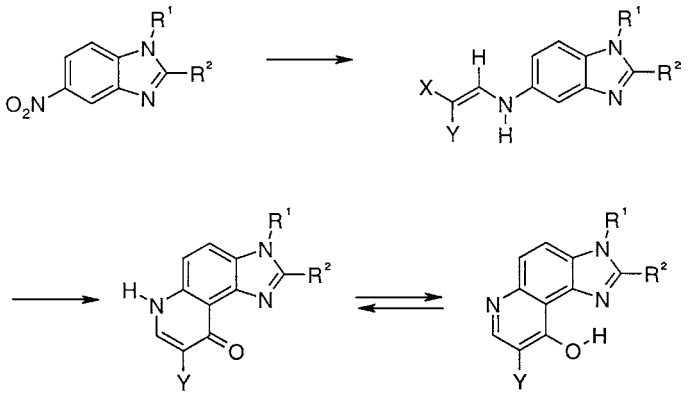
1- and 2-(un)substituted 5-nitrobenzimidazoles (R^1, R^2 = H, Me; Me, H; Me, Me in 82MI3; H, H in 87CCC2918; H, 4-ClC_6H_4; H, 4-MeC_6H_4 in 92CCC397; Me, H in 94CCC1145) were reduced to the corresponding amines. The amines were not isolated and subjected to the reaction with diethyl ethoxymethylenemalonate (X = Y = COOEt in 82MI3 and 94CCC1145) or to all other possible types of enolethers (X, Y = COOEt, COOMe, COMe, CN in 87CCC2918, 92CCC397). The isolated aminoethylenes were thermally cyclized to angularly annelated to 1,2,8-trisubstituted 9-oxo-6,9-dihydroimidazo[4,5-*f*]quinolones **121** (82MI3, 87CCC2918, 92CCC397). Quinolones **121** exist predominantly in the oxo form **121a,** but there can exist three tautomeric forms (the oxo form of the pyridone nucleus with a 1*H* tautomer on the imidazole nucleus, the oxo form of the pyridone nucleus with a 1*H* tautomer on the imidazole nucleus, and finally a hydroxy form of the pyridone nucleus with a 3*H* tautomer on the imidazole nucleus **121b**) (Scheme 38).

In cyclization of 6-aminoethylene substituted 1-methylbenzimidazole, an angularly annelated 1*H*-1-methyl-8-ethoxycarbonyl-9-oxo-6,9-dihydroimidazo[5,4-*f*] quinolone **122** prevails over the sterically less hindered (9-oxo group vs 1-methyl group) linearly annelated imidazo[4,5-*g*]quinoline **123.** Hydrolysis of the cyclization product produced the corresponding acid **124** (Scheme 39) (94CCC1145).

The 5(6)-aminomethylenepropanedinitrile derivative was cyclized smoothly in very good yield (93%) with $AlCl_3$ to the almost insoluble 9-amino-8-cyanoimidazo[5,4-*f*]quinolone **125** (87CCC2918).



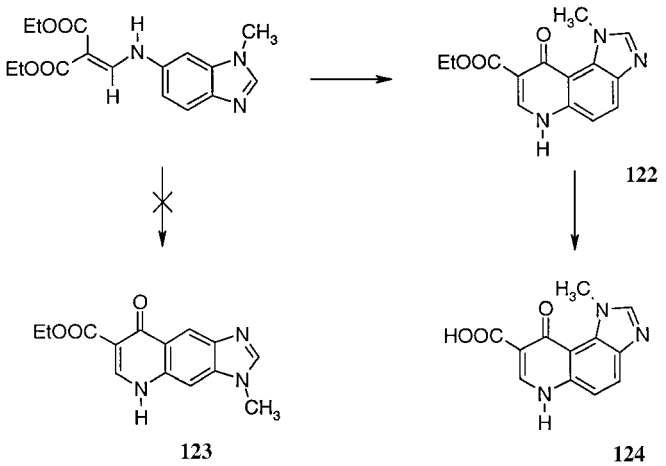
125



121a **121b**

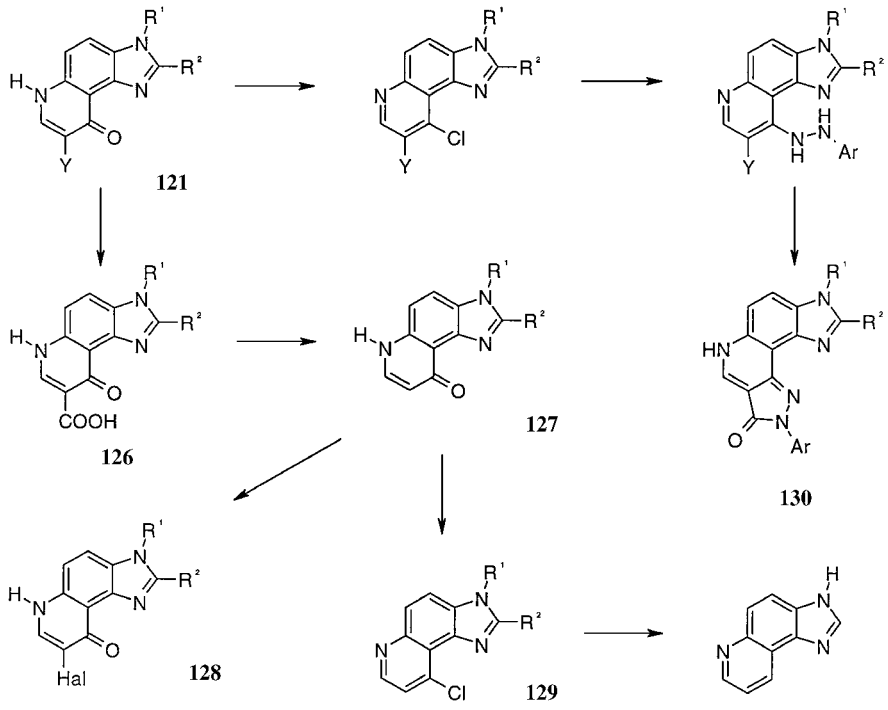
SCHEME 38

Products of cyclization of the 5-aminoethylene benzimidazole derivatives **121** can be modified by hydrolysis and decarboxylation of the resulting acid **126** to 9-oxo-6,9-dihydroimidazo[4,5-*f*]quinolines **127** (82MI3, 87CCC2918, 88CCC1068, 90JMC2640). These quinolines were brominated or iodinated in alkaline media to yield derivatives halogenated in position 8 **128** (82MI3) or aromatized with $POCl_3$ to appropriate 9-chloroderivatives **129** (88CCC1068), such as analogous 8-ethoxycarbonyl derivatives (87CCC2918, 90JMC2640). The 8-ethoxycarbonyl derivatives were converted to arylhydrazines and, after cyclization in basic media,



122 **123** **124**

SCHEME 39



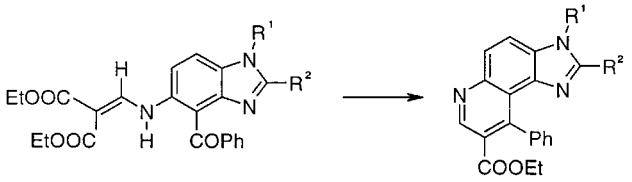
SCHEME 40

to the corresponding pyrrazolo condensed heterocyclic systems **130** (Scheme 40) (90JMC2640).

The anti-parasitic activity *in vitro* against *Entamoeba histolytica* and *Trichomonas vaginalis* and *in vivo* against *Syphacia obvelata* and *Hymenolepis nana* of 8-halogeno-9-oxo-6,9-dihydroimidazo[4,5-*f*]quinolines **128** was studied. Only derivatives monomethylated in position 3 showed an *in vitro* amoebicidial activity similar to that of metronidazole, but these derivatives were found to be toxic in mice (82MI3). The MIC values of 7-/8-substituted (CN, COOH, COOEt) 6-/9-oxo-6,9-dihydroimidazo[4,5-*f*/*h*]quinolines documented a slight antibacterial activity of this type of quinolone analogue (97MI1). When the chloro derivatives of these types, and those derived from other β-ketoesters, were treated with alkyl, cycloalkyl, aryl, or heteroarylamines or 2-methoxythiophenol, the corresponding amino derivatives (arylthio) were prepared (162 examples) aiming at enhancement of the immune system response in mice challenged with *Pseudomonas aeruginosa* (86EUP2, 87USP1). The 7-methyl-9-arylaminoimidazo[4,5-*f*]quinolines, prepared from the corresponding chloroderivatives with anilines, provided potent protective effects in this model with minimum effective doses ranging from

1 to 6 mg/kg. Importantly, these compounds were also able to provide complete protection at only slightly higher doses. Replacement of the N—H with either sulfur or N—Me significantly reduced activity (92JMC4595).

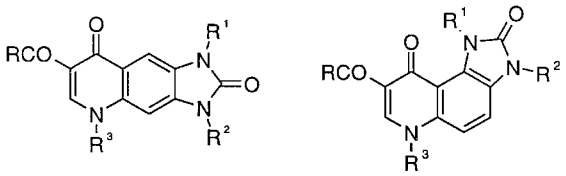
A substituent in the *ortho*-position to the aminoethylene propanedioate group caused a change in orientation of the cyclization reaction: In the case of the *ortho*-benzoyl group this took part in the cyclization reaction in PPA to yield angularly annelated 2,3-disubstituted-3*H*-9-phenyl-8-ethoxycarbonyl-imidazo [4,5-*f*]quinolines **131** (86KGS857, 89KGS692), but in the mixture of PPA and $POCl_3$ linearly annelated ethylesters of 2-substituted 1-phenyl-4-benzoyl-8-oxo-5,8-dihydroimidazo[5,4-*g*]quinoline-7-carboxylic acid originated and were subsequently converted to the corresponding chloro derivatives using $POCl_3$ or to a mixture of the corresponding N- and O-ethylated products (89KGS692).



131

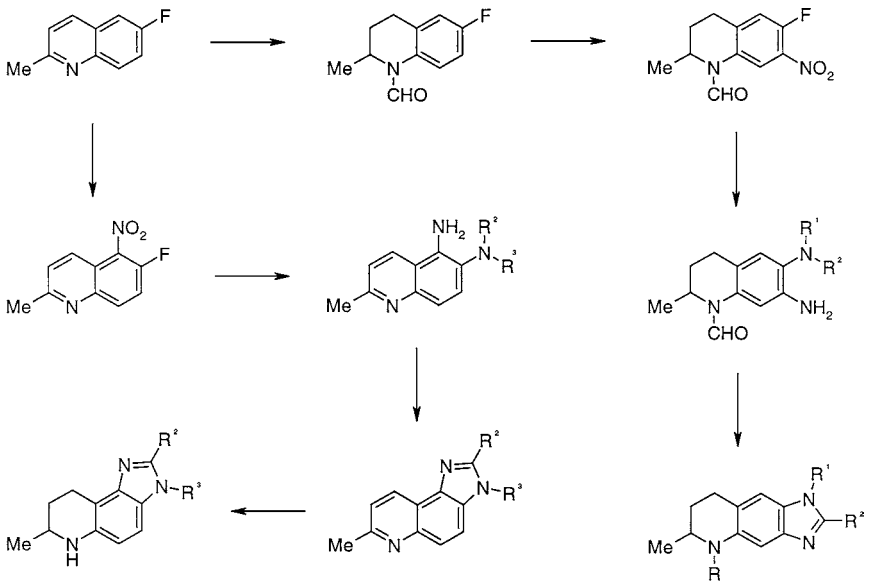
R^1 = Ph; R^2 = H, Et

Linearly annelated esters, acids, and hydroxamic acids **132** showed antibacterial and anticarcinogenic activities (doses 0.2–2.0 g/day) [80JAP(K)2, 81JAP(K)1], whereas angularly annelated **133** has demonstrated MIC against *Staphyloccocus aureus*, *Streptococcus biogenes*, and *Sarcina lutea* (79JAP(K)1).



132 **133**

Polyhydrogenated imidazoquinolines are served through their pyridine ring for preparation of tetracyclic fused heterocylic compounds with a quinolone substructure unit. Both strategies, final constitution of pyridine or imidazole ring, respectively, have been published (94JHC153). Starting from 6-fluoro-2-methylquinoline,



134 **135**

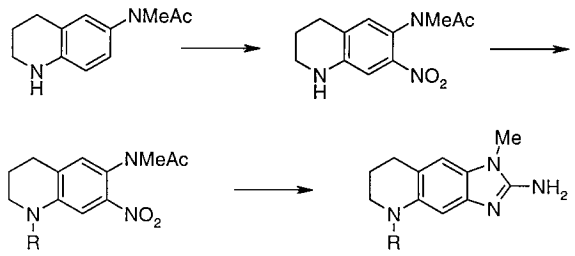
R = H, CHO; R^1, R^2, R^3 = H, Me, Et, Pr, Ph, $(CH_2)_{3\text{-}5}$

SCHEME 41

a sequence of nitration, amination, reduction, imidazole ring cyclization, and pyridine ring reduction was used to prepare the angularly annelated 3*H*-2,3-disubstituted 7-methyl-6,7,8,9-tetrahydroimidazo[4,5-*f*]quinolines **134** (Scheme 41). After partial reduction of the pyridine ring followed by nitration, amination, reduction, imidazole ring closure, and final deprotection, the linearly annelated 1*H*-1,2-disubstituted 6-methyl-5,6,7,8-tetrahydroimidazo[4,5-*f*]quinolines **135** were also prepared and used in the Gould–Jacobs reaction with diethyl ethoxymethylenemalonate.

The 6-methylacetylamino-1,2,3,4-tetrahydroquinoline, after nitration and separation of isomers, following reduction and deprotection, gave the 7-amino-6-methylamino derivative, which cyclized with cyanogen bromide. Alkylation of the cyclization products afforded inhibitors of thymidylate synthase, 5-substituted 2-amino-1*H*-1-methyl-5,6,7,8-tetrahydroimidazo[4,5-g]quinolines 136, designed for use in iterative protein crystal analysis (Scheme 42) (92JMC847).

Derivatives of 1-ethyl-7-alkylamino-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **137** have been reduced to corresponding diamines **138** and afterwards converted exclusively to linearly annelated imidazo[4,5-*g*]quinoline-7-carboxylic acid derivatives **139** (Scheme 43) (88KFZ33).

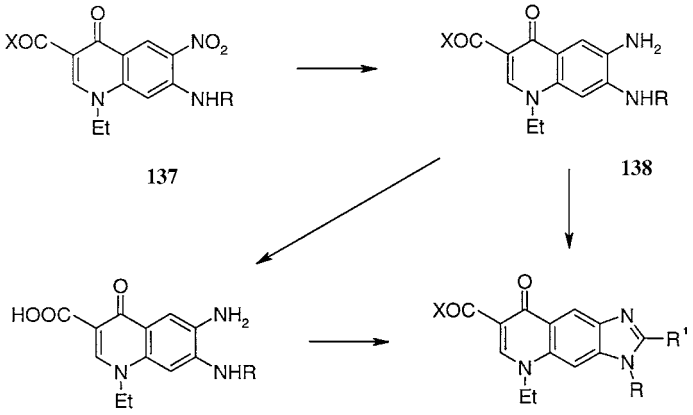


136

SCHEME 42

4-Substituted 6-cyclopropyl-6,9-dihydro-5-methoxy-9-oxo-1*H*-imidazo[4,5-*f*] quinoline-8-carboxylic acids **140** were prepared as potential antibacterial quinolone derivatives (Scheme 44). Among them, 5-methoxyderivatives (X = OMe, Y = F) were superior to the corresponding ofloxacin type analogues in *in vitro* antibacterial activity. 4-Amino derivatives with X = OMe were equipotent against *Staphylococcus aureus*, but 2 to 16 times less potent against *Escherichia coli* and *Pseudomonas aeruginosa* compared to the 5-fluoro analogue (X = F) (96CPB987).

Polysubstituted imidazo[4,5-*f*]quinolines were prepared and evaluated by Spencer and Alaimo, but also by other authors for possible antihelmintic activity

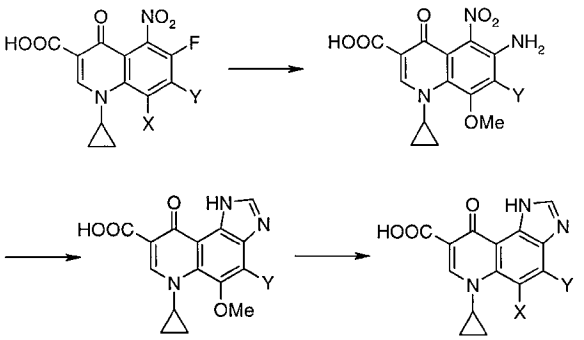


137 **138** **139**

X = NH_2, OEt, OH; R = H, CH_2CH_2OH, $CH_2CH_2NEt_2$, Me;

R^1 = H, $CH_2CH_2NEt_2$, CH_2CH_2OCHO, CH_2CH_2OAc, CH_2CH_2OH

SCHEME 43



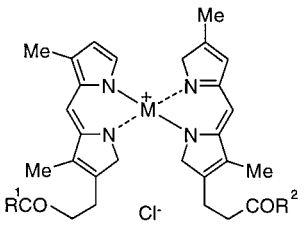
140

X = H, F, Cl, OMe Y = F, Cl, 1-piperazinyl, 4-methyl-1-piperazinyl, 3-aminopyrrolidinyl, 3-aminomethylpyrrolidinyl

SCHEME 44

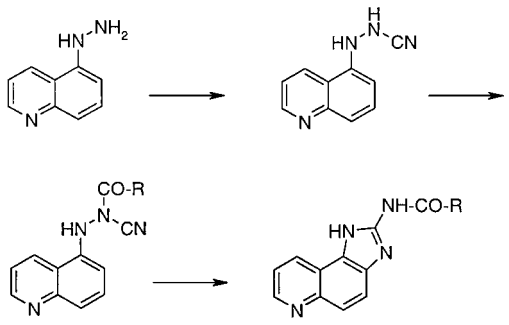
(81MI1), and also for microsomal (83MI1), antiparasitic (83EJM(CT)535), antimicrobial (83EJM(CT)535], and antihistaminic activities (74AP894). They were also tested as immunomodulating agents (162 examples) (86EUP2).

Diamines such as ethylenediamine, 1,4-phenylenediamine, or 2,5-toluenediamine were condensed with 9-chloro-7-methyl-imidazo[4,5-*f*]quinoline, and these products with deuterioporphyrin monomethyl ester or deuterioporphyrin, respectively. When the latest products were refluxed with $MnCl_2$ or $CoCl_2$ in DMF they gave metalloporhyrins **141,** designed as intercalator-linked porphyrins and related metalloporphyrin derivatives such as cellular DNA targeted agents, with K_{assoc} values for interactive binding of these compounds to calf thymus DNA in the range $1.9–3.0 \times 10^6$ L mol^{-1} (92BCJ579).



141

R^1, R^2 = OMe, -NH-$(CH_2)_2$-NH-R, -NH-  -NH-R, -NH-  -NH-R ; R = 7-methyl-9-imidazo[4,5-*f*]quinolinyl; M = Co, Mn



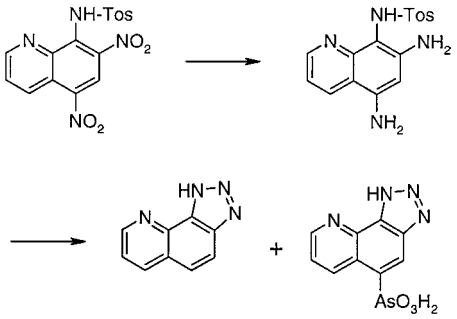
142

SCHEME 45

There are but a few methods for preparing an imidazole nucleus using mono-substituted derivatives. One of them, a smooth thermal 1-aza-1′,3′-diaza-3, 3′-sigmatropic rearrangement, was applied to 1-(5-quinolyl)-2-cyano-2-acylhydrazine to provide the 2-acylamino-imidazo[4,5-*f*]quinoline **142** in high yield (83%) (Scheme 45). The starting 5-quinolylhydrazine was made to react with BrCN to give the cyanamide, which, in turn, was acylated in the presence of triethylamine (97TL3115).

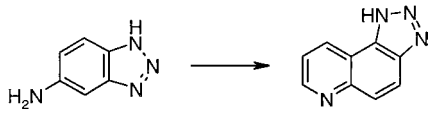
IV. Triazoloquinolines

Triazolo[4,5-*h*]quinoline **143** and triazolo[4,5-*h*]quinoline-5-arsonic acid **144** were isolated from mother liquors after reduction and bis-diazotization of 5,7-dinitro-8-(4-toluenesulfone)aminoquinoline in the presence of cupric sulfate with trisodium arsenite (32JCS2196).



143 **144**

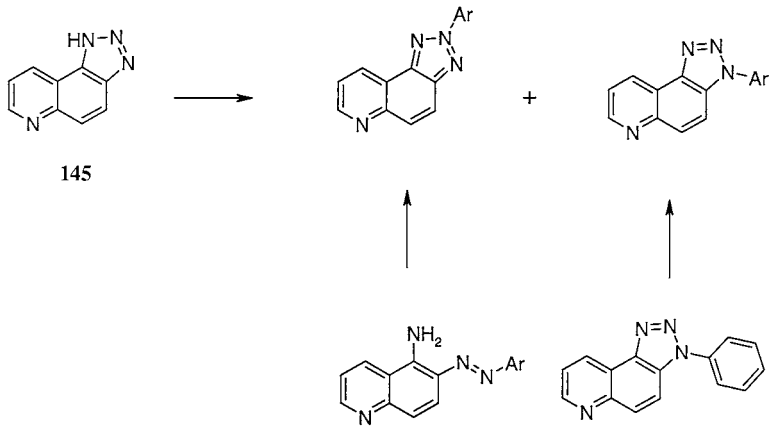
The isomeric triazolo[4,5-*f*]quinoline **145** was synthetized by the Skraup reaction from 5(6)-aminobenzotriazole (34CB213).



145

Oxidation of 5-arylazo-6-aminoquinoline **146** with copper sulfate in pyridine gave the corresponding 2-aryltriazolo[4,5-*f*]quinolines **147.** Condensation of halogenated nitrobenzenes with triazolo[4,5-*f*]quinoline **145** yielded the appropriate 2*H*- and 3*H*-aryl derivatives. The nitration of 3-phenyl-3*H*-triazolo[4,5-*f*]quinoline **147** occurred at position 4 of the phenyl ring (Scheme 46) (73T221).

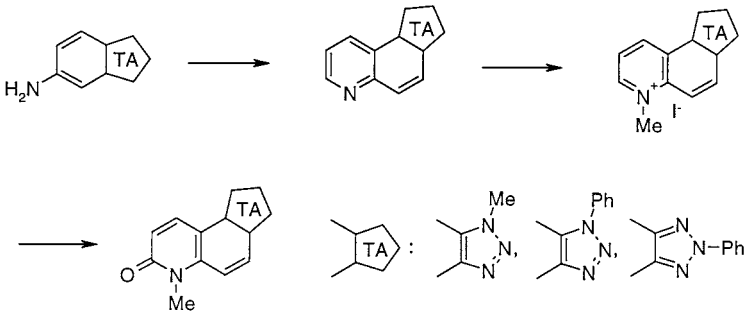
1- and 2-substituted 5-aminobenzotriazoles afforded, in the Skraup reaction, triazolo[4,5-*f*]quinolines (1899JPR72, 27LA121, 27G179, 52CJC711), compounds that upon treatment with methyl iodide yielded the 6-methylquinolium iodides (27LA121) and other salts (with hydrochloric, nitric, sulfuric, dichromic, acetic, dihydroplatinic acids; mercuric chloride; methyl, ethyl iodide, chloride, and ethyl bromide) (1899JPR72, 27G179). Methylquinolinium iodide could be



145 **146** **147**

Ar = Ph, 4-$O_2NC_6H_4$, 4-MeC_6H_4 , 2,4-$(O_2N)_2C_6H_3$, 5-indazolyl, 1,2-dimethyl-5-benzimidazolyl, 1-methyl-5-benzotriazolyl, 5-benzothiophenyl, 6-quinolyl

SCHEME 46

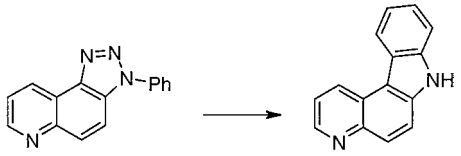


148

SCHEME 47

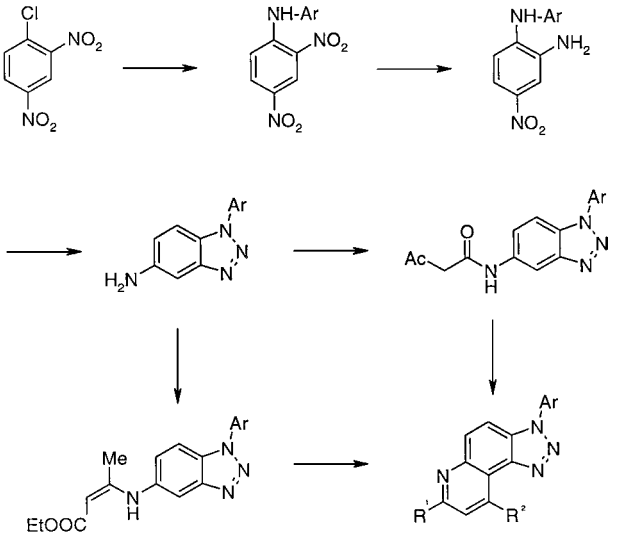
oxidized with silver oxide or potassium ferricyanide in sodium hydroxide to the corresponding 6-methyl-7-oxo-6,7-dihydro analogues **148** (Scheme 47). (1899JPR72, 27LA121). Attempts to prepare the linearly annelated triazoloquinoline starting from 1-methyl-4-chloro-5-aminobenzotriazole failed (27LA121).

When 3-phenyl-3*H*-triazolo[4,5-*f*]quinoline was heated at 390–400°C, 7*H*-pyrido[2,3-*c*]carbazole **149** originated. Its structure could be confirmed by unambiguous synthesis from the 8,9,10,11-tetrahydro-7*H*-pyrido[2,3-*c*]carbazole (52CJC711).



149

1-Arylsubstituted 5-aminobenzotriazoles, resulting from condensation of the appropriately substituted aniline with 2,4-dinitrochlorobenzene, subsequent reduction with sodium sulfide in hot ethanol to the corresponding derivative of 2-amino-4-nitrodiphenylamine, conversion into the 5-nitro-1-arylbenzotriazole, and another reduction with zinc dust and aqueous ethanolic calcium chloride, were treated with ethyl acetoacetate to give the 5-acetoacetamido derivative. Under the conditions of Knorr reaction, the acetamido derivative failed to cyclize to the corresponding 2-quinolone derivative, and only the starting amine was isolated, whereas action of phosphorus oxychloride afforded the 7-chloro-9-methyl-3-phenyl-3*H*-triazolo[4,5-*f*]quinoline **150** ($R^1 = Cl$, $R^2 = Me$) (Scheme 48). The same starting compounds, when given the crotonate **151** and under Conrad–Limpach reaction

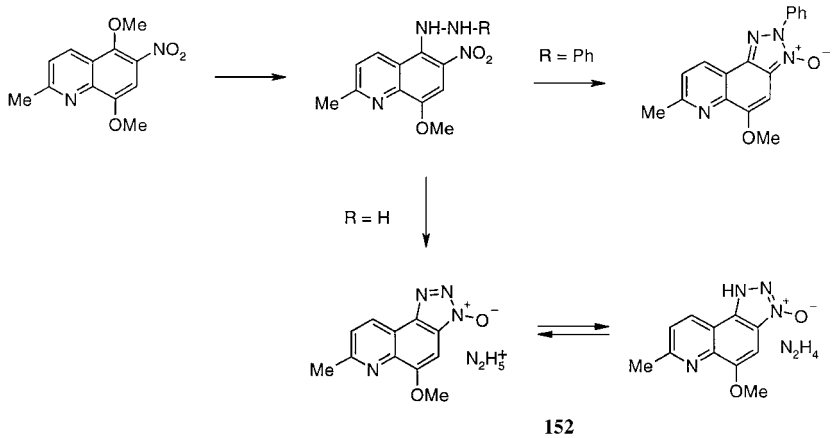


151 **150**

SCHEME 48

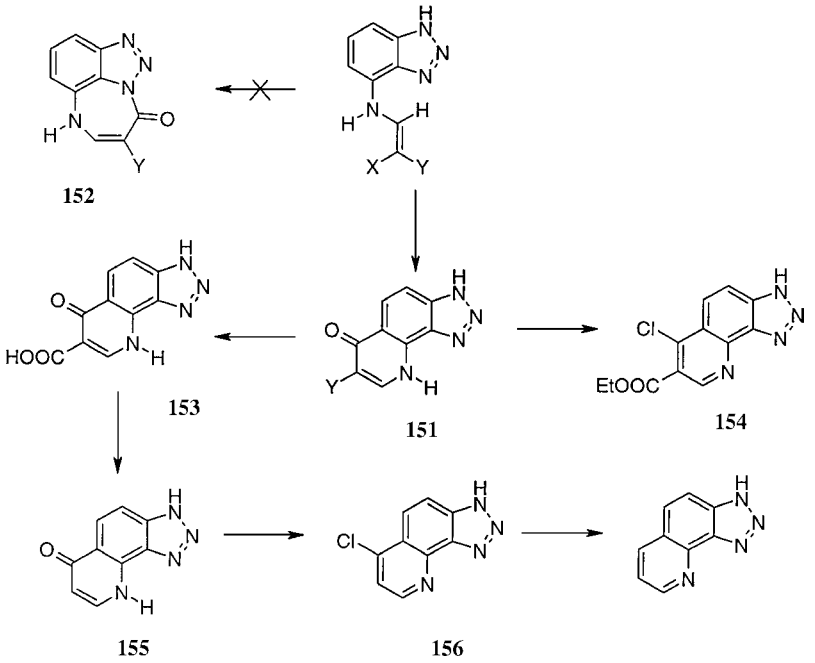
conditions, yield 7-methyl-3-phenyl-3*H*-9-oxo-6,9-dihydro-triazolo[4,5-*f*]quinoline **150** ($R^1 = Me$, $R^2 = OH$ as in the oxo form) (55JCS337).

Triazoloquinoline *N*-oxides **152** (R = H, Ph) were prepared in 71% yield by treating the 6-nitro-5,8-dimethoxyquinaldine with an excess of appropriate hydrazine (Scheme 49) (74OPP295).



152

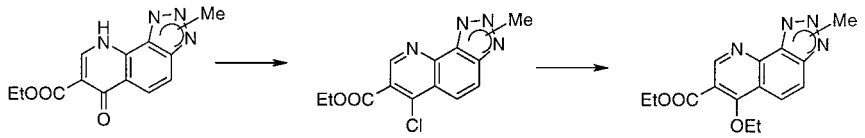
SCHEME 49



SCHEME 50

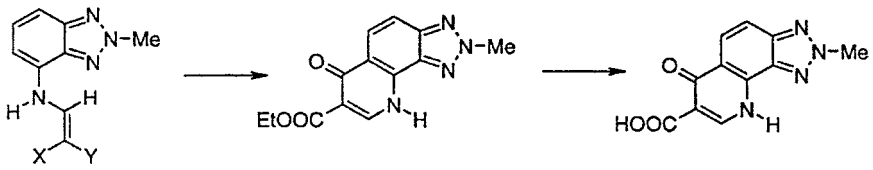
4-Substituted benztriazole derivatives with activated aminoethylene substituent cyclized in Dowtherm to angularly annelated 7-substituted 6-oxo-6,9-dihydrotriazolo[4,5-*h*]quinolines **151** (Y = CN, COOEt) and not to the tricyclic diazepinobenzotriazole system **152.** The product **151** (Y = COOEt) can be hydrolyzed in alkaline media to the corresponding carboxylic acid **153** or aromatized using $POCl_3$ in DMF to a chloroester **154** (87CCC2918). The acid **153** was decarboxylated to **155; 155** was aromatized with $POCl_3$ in DMF to **156** and dechlorinated by reduction on Raney nickel to give the parent heterocyclic skeleton of imidazo[4,5-*h*]quinoline **143** (Scheme 50) (88CCC1068).

Italian authors published the use of additional amines, such as 1-methyl-4-aminobenzotriazole and its 4-ethylamino homologues, for preparation of the corresponding ethyl-substituted aminoethylene and the subsequent thermal cyclization using Dowtherm (92FA1001), but, according to the proposed mechanism of the Gould–Jacobs reaction, the alkylated aminoethylene cannot be thermally cyclized [71JHC357, 92AHC(54), 00MI1], and therefore by-products resulting from decarboxylation and alkylation arise (92FA1001). N-nonsubstituted quinolones **157** have also been chlorinated in the case of 1-methyl-1*H* and 2-methyl-2*H* derivatives, and the latter was also ethoxylated (92FA1001).



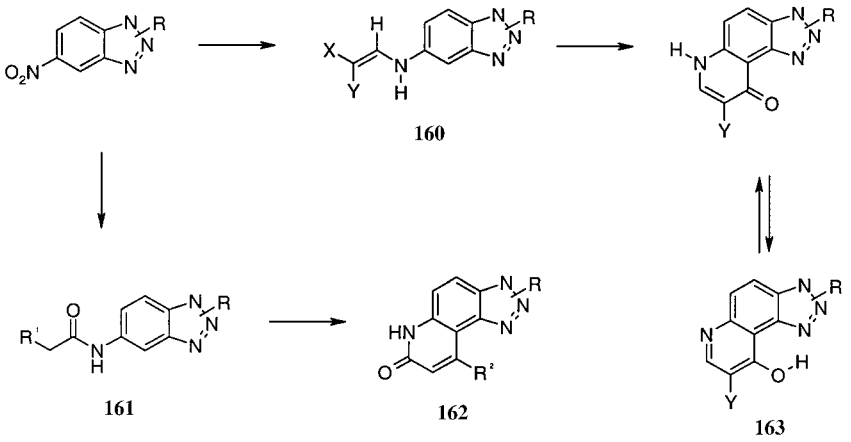
157

2-Methylbenzotriazole derivatives with an aminoethylene substituent in position 4 also regioselectively produce only the angularly annelated 7-ethoxycarbonyl-6-oxo-6,9-dihydro-2-methyl-2*H*-triazolo[4,5-*h*]quinoline **158.** Under alkaline hydrolysis the ester **158** yielded the corresponding acid **159** (90CCC1038, 92FA1001).



158 159

5-Nitrobenzotriazoles with a substituent in position 1 or 2 (R = H in 82MI5, 87CCC2918, 89FA609, 89FA619; 1-Me in 89FA619, 94CCC1145; 2-Me in 82MI5, 89FA609, 89FA619, 94CCC1145; 4-ClC_6H_4, 4-MeC_6H_4 in 92CCC397) were reduced to the corresponding amines. The amines were not isolated and were subjected to further reactions with diethyl ethoxymethylenemalonate (**160,** X = Y = COOEt in 82MI5, 89FA609, 89FA619, 94CCC1145), ethyl acetoacetate, and ethyl benzoylacetate (**161,** in 82MI5, 89FA609), respectively, or with all other possible types of enolethers (**160,** X, Y = COOEt, COOMe, COMe, CN in 87CCC2918, 92CCC397). β-Ketoesters were treated with the amines at 135–140°C, and the intermediate amides were cyclized with PPA to 9-R^2-2-methyl-7-oxo-6,7-dihydro-2*H*-triazolo[4,5-*f*]quinoline **162** (R^2 = Me, Ph). The isolated aminoethylenes were thermally cyclized to the angularly annelated 1,2,8-trisubstituted 9-oxo-6,9-dihydrotriazolo[4,5-*f*]quinolones **163** (Scheme 51) (82MI5, 87CCC2918, 89FA609, 89FA619, 92CCC397, 94CCC1145). Such quinolones exist prediminantly in the oxo form, but there are three other possible tautomeric forms (the oxo form of the pyridone nucleus with a 1*H* tautomer on the triazole nucleus; the oxo form of the pyridone nucleus with a 1*H* tautomer on the triazole nucleus; and finally, the hydroxy form of the pyridone nucleus with a



R = H, 1-Me, 2-Me, 1-(4-ClC_6H_4), 1-(4-MeC_6H_4); R^2 = Me, Ph;

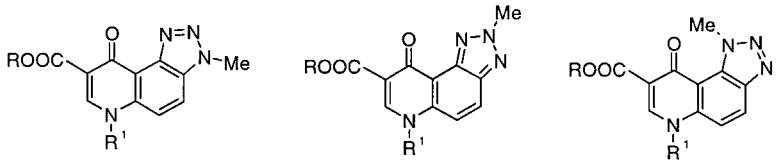
X,Y = COOEt, COOMe, COMe, CN

SCHEME 51

3*H* tautomer on the triazole nucleus). Only some of this type of compound exhibited slight antibacterial activity (89FA619, 97MI1).

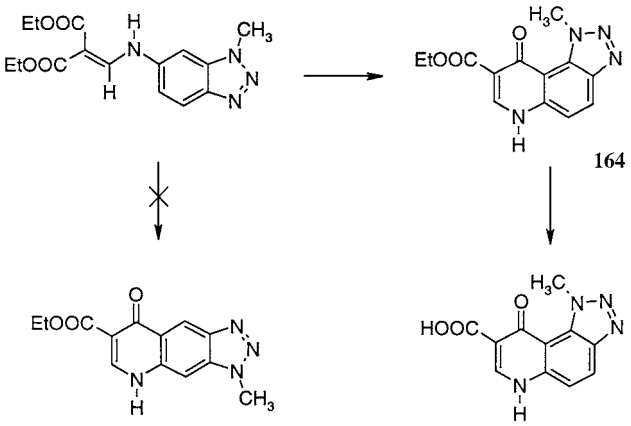
Angularly annelated 1*H*-1-methyl-8-ethoxycarbonyl-9-oxo-6,9-dihydrotriazolo [5,4-*f*]quinolone is formed preferably **164** over the sterically less hindered (9-oxo group vs 1-methyl group) linearly annelated triazolo[4,5-*g*]quinoline **165** in a reaction starting from 6-aminoethylene substituted 1-methylbenzotriazole. Hydrolysis of the cyclization product produced the corresponding acid **166** (Scheme 52) (94CCC1145).

Products of cyclization of 5-aminoethylene benzotriazole derivatives with eliminated prototropy of the azole ring can be alkylated on the nitrogen atom of the pyridone and then hydrolyzed to the corresponding acids (76JAP(K)1, 89FA619). The prepared compounds **167–169** and their salts were tested against bacteria (no data) (76JAP(K)1).



167 **168** **169**

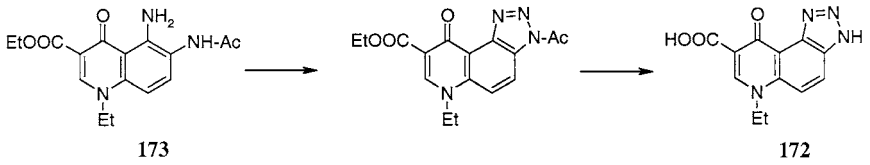
R = H, Et; R^1 = Me, Et



SCHEME 52

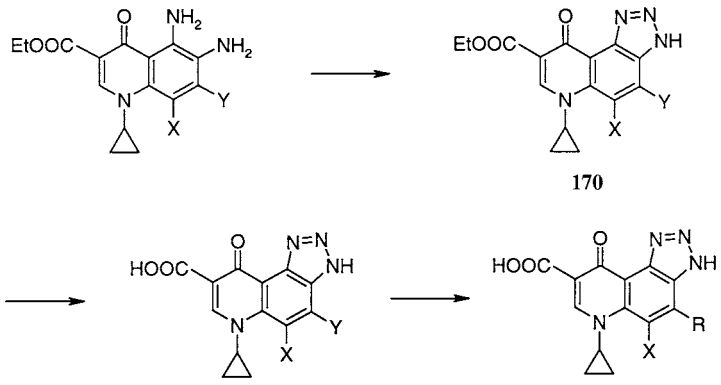
When there is no substituent at the triazole ring, the prototropism of the azole ring causes a nonregioselective alkylation (95MI2). Therefore, suitable precursors are used for regioselectively alkylated products. Thus, substituted 5,6-diamino-1-cyclopropylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid esters **170** were diazotized and converted to the corresponding triazolo[4,5-*f*]quinolines **171** having a prototropic nonsubstituted triazole ring attached to the quinolone nucleus (Scheme 53) (95CPB2123).

Using similar methodology, the 6-ethylated 9-oxo-6,9-dihydro-triazolo[4,5-*f*] quinoline-8-carboxylic acid **172** was prepared starting from ethyl 1-ethyl-4-oxo-5-amino-6-acetylamino-1,4-dihydroquinoline-3-carboxylate **173,** using first diazotization and then hydrolysis. Such alkylation is impossible to achieve by direct alkylation (89FA619, 95MI2). *In vitro* tests showed a good and selective activity against *Escherichia coli* (MIC 12.5 μg/ml (89FA619)).



Methylation using dimethylsulfate in alkaline media of acid **172** led to the corresponding 2-methyl-2*H* derivative (89FA619).

Linearly annelated 3-phenyl-3*H*-5-ethyl-8-oxo-5,8-dihydrotriazolo[4,5-*g*]quinoline-7-carboxylic acid and ester **173** were prepared starting from ethyl 7-chloro-6-



170

171

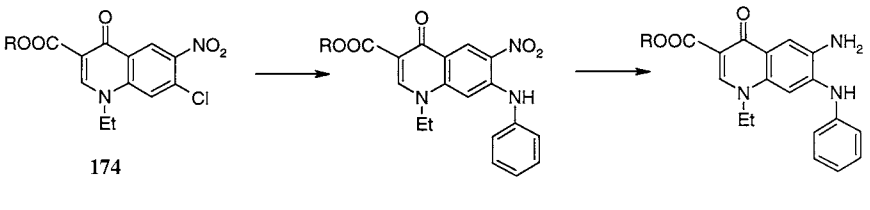
X = H, F, Cl, OMe Y = F, Cl R = 1-piperazinyl, 4-methyl-1-piperazinyl,

3-aminopyrrolidinyl, 3-aminomethylpyrrolidinyl

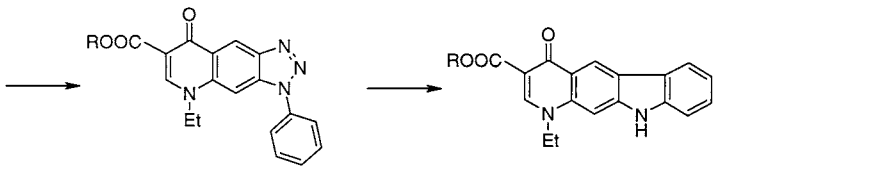
SCHEME 53

nitro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **174.** Thermal decomposition of the title compound **173** led to the indolo[3,2-*g*]quinolinone **175** (Scheme 54) (93H2753).

Esters of 9-oxo-6,9-dihydro-triazolo[4,5-*f*]quinoline-8-carboxylic acids **176** can be hydrolyzed and decarboxylated to afford the 9-oxo-6,9-dihydrotriazolo[4,5-*f*]quinolines **177** (Scheme 55) (87CCC2918, 88CCC1068, 90JMC2640). These in turn were aromatized with $POCl_3$ to the appropriate 9-chloroderivatives **178,**

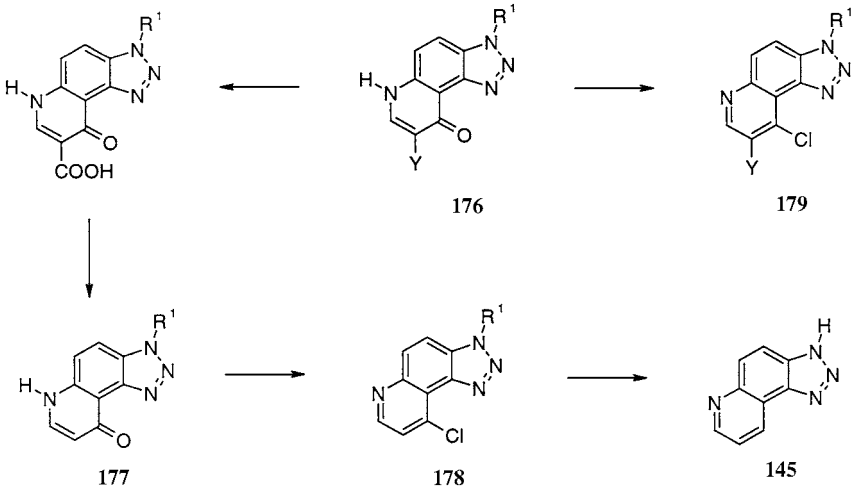


174



173 175

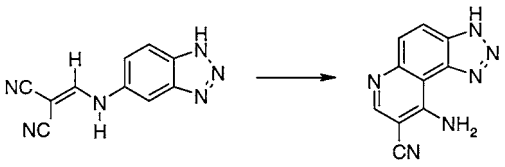
SCHEME 54



SCHEME 55

such as the analogous 8-ethoxycarbonyl derivatives **179** (87CCC2918, 89FA619). The latter hydrolyze to the corresponding chloro acids (89FA619).

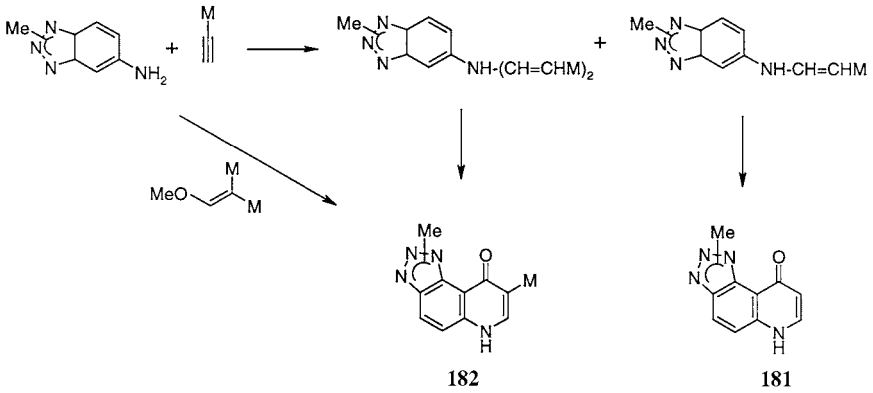
The 5(6)-aminomethylenepropanedinitrile derivative was cyclized smoothly in good yield (72%) by the action of $AlCl_3$ to the very poorly soluble 9-amino-8-cyanotriazolo[5,4-*f*]quinolone **180** (87CCC2918).



180

Reactions of 5(6)-aminobenzotriazole and all three of its methylated homologues on the azole ring were investigated by Italian authors, who took different activated ethylenes and acetylenes, such as methyl propiolate (95H2459), dimethyl acetylenedicarboxylate (93H259), and dialkyl alkoxymethylene propanedioate (95H2459, 89FA609, 89FA619), as mentioned earlier.

These amines gave, with methyl propiolate, products of Michael mono- and bis-addition. Adducts underwent further reaction leading to triazolo[4,5-*f*]quinolones **181,** after retro Diels–Alder reaction and acetylene elimination to its methoxycar-



SCHEME 56

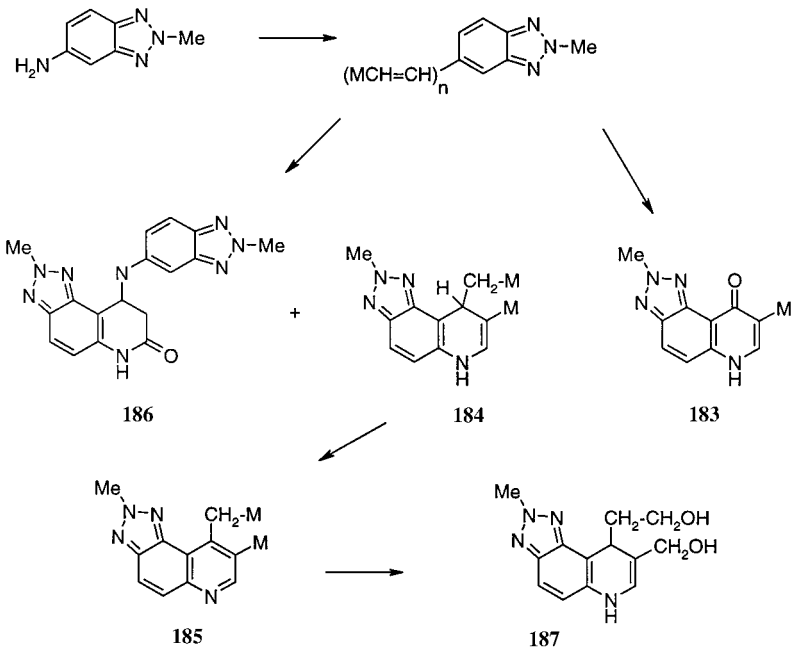
bonyl derivative **182** (Scheme 56)—the same product that originated after reaction of the amine with dimethyl methoxymethylene propanedioate.

5-Amino-2-methylbenzotriazole, the amine with a nonaromatic structure, gave accordingly the 6,9-dihydro-triazolo[4,5-*f*]quinolone **183,** similar to **182;** derivative **184,** which could be smoothly oxidized to diester **185;** and traces (1%) of the 7-oxo-6,7-dihydro-9-(2-methyl-5-benzotriazolylamino)-2-methyl-2*H*-triazolo [4,5-*f*]quinoline **186.** The ester groups were reduced using lithium aluminum hydride to the corresponding alcohols **187** (Scheme 57) (95H2459).

When reacted with dimethyl acetylenedicarboxylate, the amines produced benzotriazolylaminobutendioates **188** accompanied by *N*-benzotriazolyl substituted 2-pyridones; only in the case of 5-amino-2-methyl-2*H*-benzotriazole, the triazolo-9,10-dihydrobenzo[*b*]azepine and an unusual cyclization product, triazolo-2-oxindole (convertible into 2-methyltriazolo[4,5-*f*]carbostyril-9-carboxylate) were formed. The quinolones **189** were aromatized to chloroesters **190;** these in turn were hydrolyzed to chloroacids **191** and decarboxylated to 9-chlorotriazolo[4, 5-*f*]quinolines **192** (Scheme 58) (93H259). The chlorine atom could be replaced with 17 various secondary amines to give the corresponding 9-aminoalkyl(aryl) derivatives **193,** some of which exhibit both cell selectivity and tumor growth inhibition activity at concentrations between 10^{-8} and 10^{-4} M (95FA47).

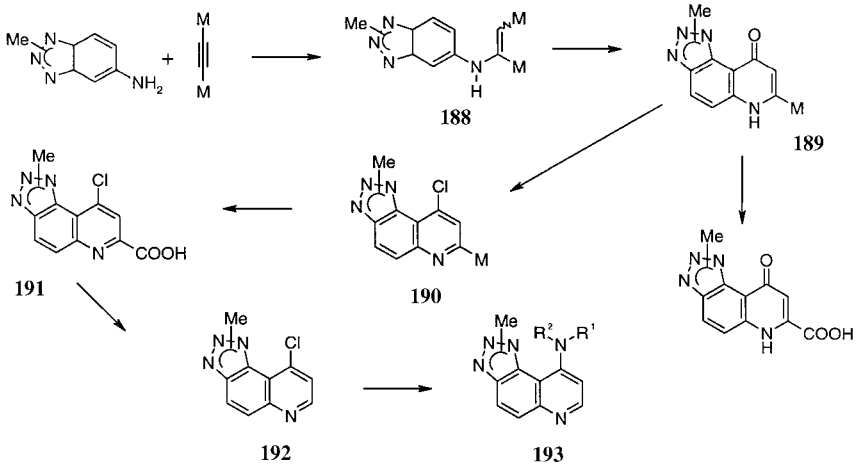
5-Amino-2-phenyl-2*H*-benzotriazole reacted with epichlorhydrin in chlorobenzene at 140–145°C to give the *N*-benzyl-7-hydroxy-6,7,8,9-tetrahydrotriazoloquinoline derivative **194.** This was benzylated and rearranged by heating in DMSO to give the isomeric 7-benzyloxy derivative **195** (Scheme 59) (77MI2).

2-Phenyl-2*H*-triazolo[4,5-*f*]quinoline was prepared and used as optical brightener, light, and drug stabilizer (86GEP1), whereas 3,5,7-3*H*-trimethyl-triazolo[4, 5-*f*]quinoline was identified by gas chromatography/mass spectrometry as a water pollutant of the Shinano River (Japan) (82MI6).



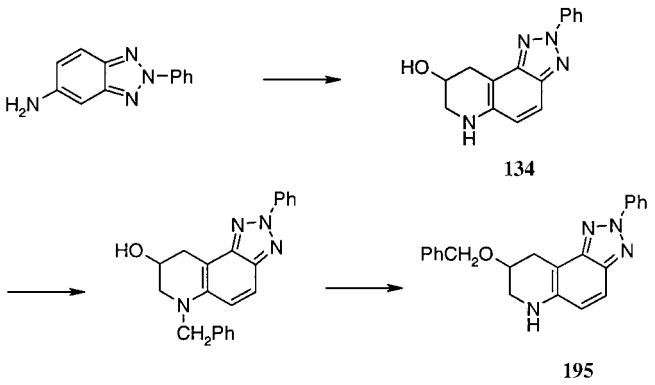
M = COOMe throughout

SCHEME 57



R^1, R^2 = various substituent

SCHEME 58



SCHEME 59

7-Methyl-*N*-(3-methoxyphenyl)-1*H*-1,2,3-triazolo[5,4-*f*]quinoline-9-amine was prepared and tested as an immunostimulant (93MI2).

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 78

Stereocontrolled Additions to Dihydropyridines and Tetrahydropyridines: Access to N-Heterocyclic Compounds Related to Natural Products

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I. Introduction

The first synthesis of a 1,4-dihydropyridine, which is known as the Hantzsch ester, is attributed to Arthur Hantzsch (1882LA1, 1885CB1744). Since then,

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many methods for the synthesis (82CRV223, 88AHC199, 91AGE1559, 94TL707) of dihydropyridines have been developed and their characterization, structure, and chemical reactivity have been thoroughly studied. Reactivity studies of dihydropyridines have involved mainly selective reductions, cycloaddition reactions, electrophilic additions to the ring carbons, N-alkylations, substitution reactions, and their use in the synthesis of natural products. Various pharmacological properties (81AGE762, 85JOC2427, 96JOC223) of dihydropyridines have been noted. Several dihydropyridines have been synthesized worldwide as commercial products, including nimodipine (81BJP582), nisoldipine (80AF2144), nifedipine (71N578, 72AF1), nitredipine (81AF2056), amlodipine (85MI1), felodipine (84MI2), isradipine (84MI1), and nivadipine (83MI1). Dihydropyridines, acting as a NADH (reduced nicotinamide adenine dinucleotide) model compound (65JOC1914, 90BCJ2683, 92JA9755, 97JOC3582) have the unique ability to reduce unsaturated functionalities [75TL2437, 77CI(L)277, 77CL391, 78TL4281, 99JOC8980] (such as ketones and aldehydes) and diaryl disulfides (82TL3189, 83TL5231). A property that severely restricts their use in organic synthesis is their easy oxidation (89JOC3721) to the corresponding pyridinium salts [NADH is converted to NAD in many metabolic reductions (76JA5689, 88MI2)]. Thus, reaction of NBS with N-substituted 1,4-dihydropyridines yielded the corresponding pyridinium salts (89KGS1083). However, the past several years have seen the emergence of new methods for the transformation of dihydropyridines to polysubstituted piperidines involving alternative dihydropyridine oxidations (nonbiomimetic) that overcome this problem. Electrophilic additions to dihydropyridines and tetrahydropyridines, followed by trapping of the resulting iminium salts with nucleophiles, give rise to substituted piperidines or azasugars in a straightforward and highly stereoselective fashion. Many hydroxylated piperidines (azasugars) are commonly found in nature, and some of them are interesting candidates for the inhibition of various glycosidases (96CRV1195, 97TL8009). Several reviews [72CRV1, 77H(7)593, 82CRV223, 88AHC199, 88H(27)291, 91AGE1559] have been published describing the synthesis, reactions, utilities, and pharmacology of dihydropyridines. This review particularly emphasizes recent developments in the area of the stereoselective transformation of dihydropyridines to piperidine derivatives and their use as a starting material or intermediate in the synthesis of alkaloids and azasugars.

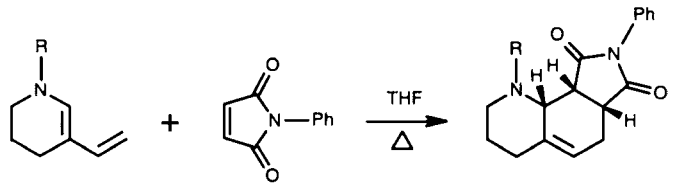
II. Addition Reactions

A. Cycloaddition Reactions

A number of dihydropyridines and tetrahydropyridines undergo cycloaddition reactions.

1. *[4 + 2] Cycloaddition Reactions (Diels–Alder Type Reactions)*

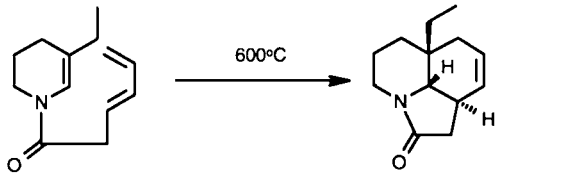
1,2,3,4-Tetrahydropyridines **1** having a vinyl group at the 5-position act as electron-rich 1,3-dienes and conveniently undergo [4 + 2] cycloaddition reactions with *N*-phenylmaleimide (**2**) or with maleic anhydride to give octahydro-1*H*-pyrrolo[3,4-*h*]quinoline-1,3-diones **3** or their oxygen analogues, respectively (82JA6697, 98T2563). The reaction stereoselectively gives the Diels–Alder *endo*-cycloadducts (established by ^{1}H–^{1}H coupling constants and NOE experiments) in 42–57% overall yield.



(1) (2) (3)

R = *t*-Bu, *i*-Pr

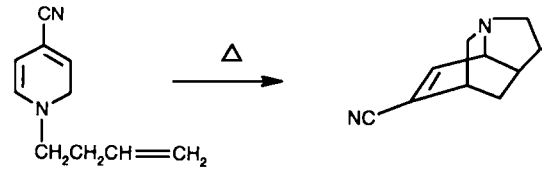
The intramolecular cycloaddition reaction of enamides has been exploited in alkaloid synthesis (81JOC3763). One successful application is provided by the total synthesis of the fused indolizidine **5** from **4** as a 1:1 mixture of epimers in 43% total yield; **5** is a key intermediate in aspidosperma alkaloid synthesis (79JA3294).



(4) (5)

1:1 Mixture of epimers (43%)

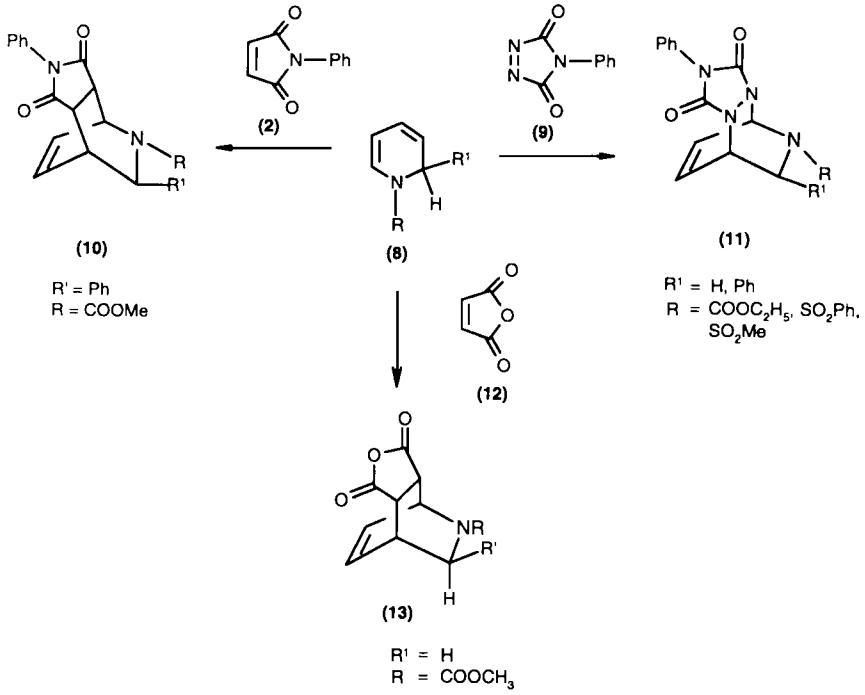
The 1,2-dihydropyridine ring system is capable of behaving as a diene component in Diels–Alder reactions (39LA195). For instance, *N*-alkenyl-1,2-dihydropyridines **6,** derived either from *N*-alkenylpyridinium salts (77M929) or by heating the dihydropyridine dimers in toluene (74HCA1204), undergo an intramolecular Diels–Alder reaction to give tricyclic amines **7.**



(6) (7)

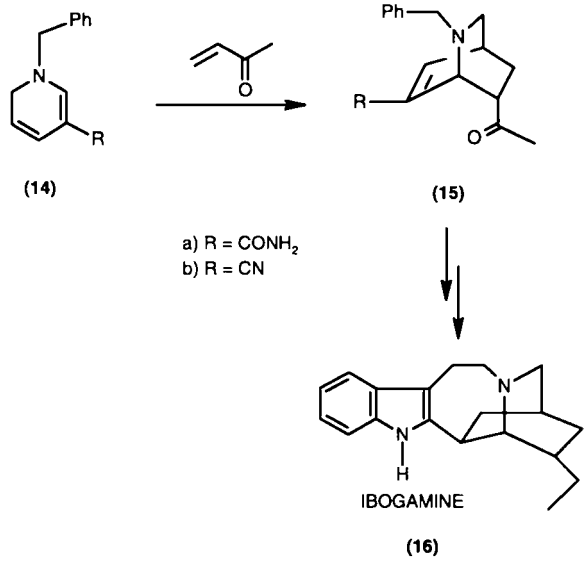
1,2-Dihydropyridines **8** react with dienophiles such as *N*-phenyl maleimide **(2)** and 1,2,4-triazoline-3,5-dione **9** to give the Diels–Alder adducts **10** and **11,** respectively (76JHC481). Fowler observed that when a mixture of 1,2- and 1,4-dihydropyridines was treated with maleic anhydride (**12**), only 1,2-dihydropyridines yielded the Diels–Alder adducts **13,** whereas the 1,4-dihydropyridines showed no reactivity with **12** (72JOC1321) (Scheme 1).

The ability of 1,2 (or 1,6)-dihydropyridines to undergo a Diels–Alder reaction with dienophiles such as methyl vinyl ketone, methyl acrylate, and acrylonitrile has been utilized in the synthesis of polyfunctional isoquinuclidine as a key intermediate in the synthesis of aspidosperma- and iboga-type alkaloids (66JA3099).

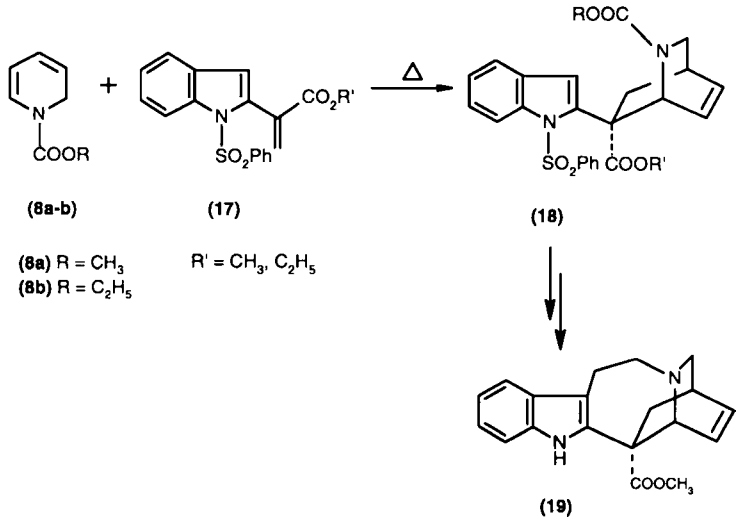


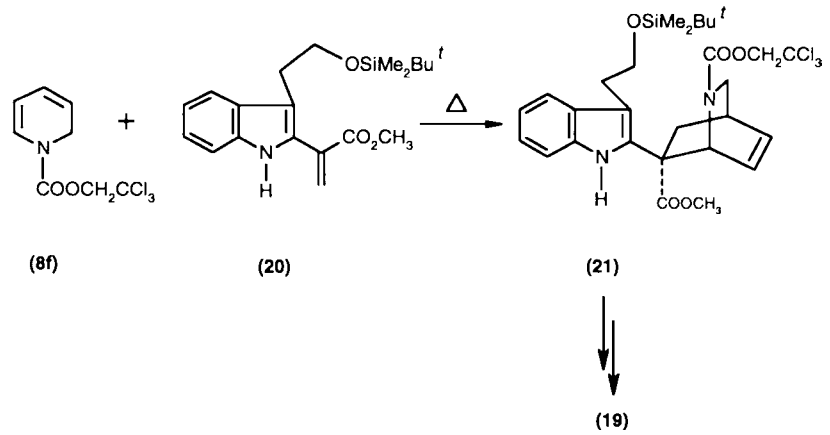
SCHEME 1

For example, the Diels–Alder reaction of *N*-benzyl-3-carboxamido-1,6-dihydropyridine (**14a**) and *N*-benzyl-3-cyano-1,6-dihydropyridine (**14b**) with methyl vinyl ketone yielded isoquinuclidines **15a** and **15b,** respectively, which can be converted into ibogamine alkaloid (**16**).



Sundberg and Bloom reported that methyl or ethyl 2-(1-benzenesulfonylindol-2-yl)acrylate (**17**) on heating with both 1-methoxycarbonyl-1,2-dihydropyridine



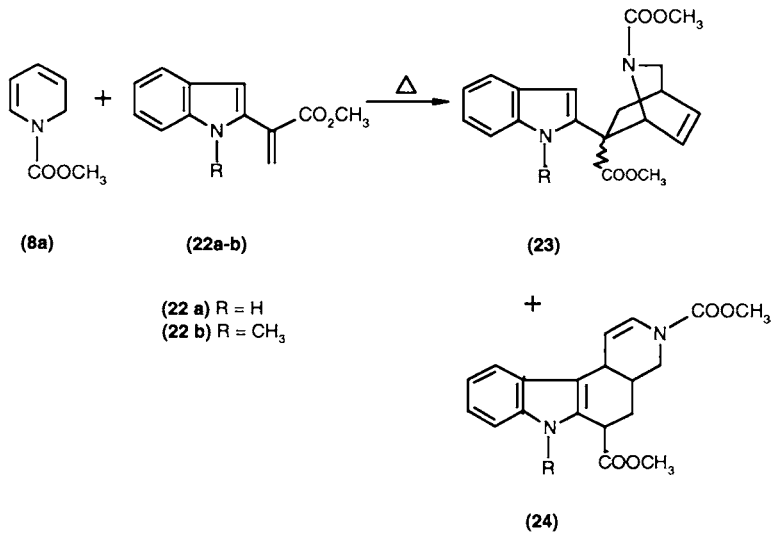


(**8a**) and 1-ethoxycarbonyl-1,2-dihydropyridine (**8b**) gave the 7-methoxy(ethoxy) carbonyl-7-(2-indolyl)isoquinuclidine skeleton **18** regiospecifically and with stereoselectivity ∼10:1. These adducts can be elaborated to the iboga alkaloids such as 20-desethylcatharanthine (**19**) (78TL5157, 80JOC3382).

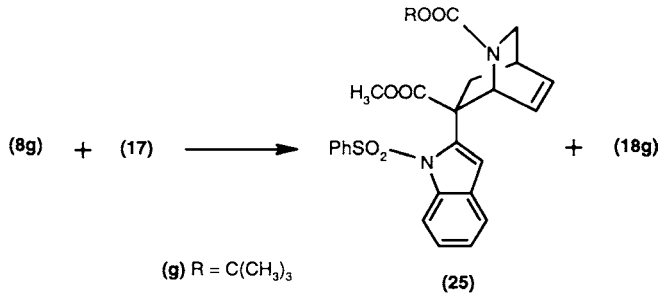
Alternatively, the desethylcatharanthine can be obtained from the adduct **21** in the reaction of 2-(indol-2-yl)acrylate **20** and *N*-alkoxycarbonyl-1,2-dihydropyridine **8f** (81CC37).

When methyl 2-(indol-2-yl)acrylate derivative (**22a**) reacted with *N*-methoxycarbonyl-1,2-dihydropyridine (**8a**) in refluxing toluene, in addition to the dimer of **22a** (25%), a mixture of the expected isoquinculidine **23a** and the product **24a** (two isomers) was obtained in 7% and 45% yields, respectively (81CC37). The formation of **24a** indicates the involvement of the 3,4-double bond of dihydropyridine. Similarly, Diels–Alder reaction of methyl 1-methyl-2-(indol-2-yl)acrylate (**22b**) with **8a** gave, in addition to dimer of **22b,** a mixture of adducts **23b** and **24b.** However, in this case, product **23b** was obtained as a major product in a 3:2 mixture of two isomers (with α- and β-COOMe). The major isomer shows an α-configuration. The yields of the dimer, **23b,** and **24b** were 25%, 30%, and 6%, respectively. Thus, a substituent on the nitrogen atom or at the 3-position of indole favors the formation of the isoquinuclidine adduct **23.**

The Diels–Alder reactions of the methyl or ethyl ester of benzenesulfonylindole-2-acrylic acid with several 1-alkoxycarbonyl-1,2-dihydropyridines are reported and only a single stereoisomer was obtained, as in the case of 1-methoxy(ethoxy)-carbonyl-1,2-dihydropyridines. However, when the Diels–Alder reaction of **17** was carried out with **8g** [R = $(CH_3)_3C$], a mixture of two stereoisomers **18g** and **25** were obtained in a 1:1 ratio (65% total yield). The bulky *tert*-butyl group creates sufficient steric interference with the indole ring to cause the loss of stereochemistry;



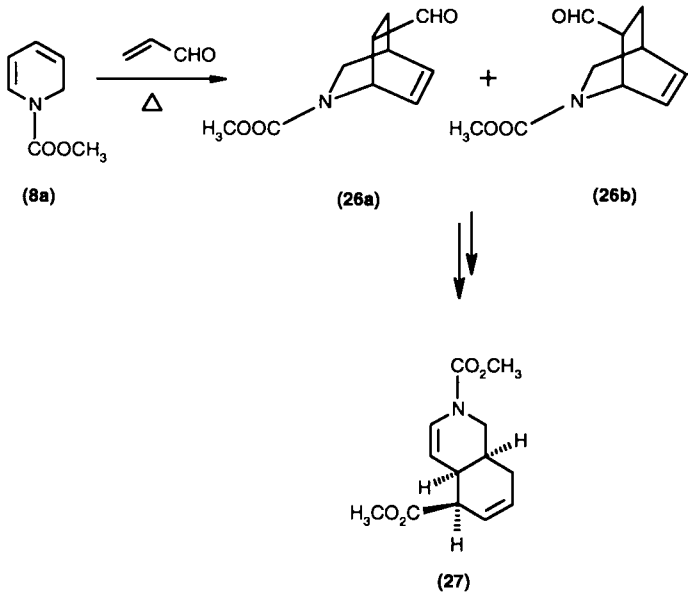
hence the mixture (81JOC4836). The **18g** provided access to the 6-nor analogue of 20-desethylcantharanthine.



1-Methoxycarbonyl-1,2-dihydropyridine (**8a**), prepared from pyridine according to the procedure given by Fowler, and acrolein on heating under reflux in toluene gave aldehydes **26a** and **26b** in the ratio of 7:3 (70% total yield). These aldehydes were converted into *cis*-hydroisoquinoline **27** in 79% yield (79TL2485).

2. *[2 + 2] Cycloaddition Reactions*

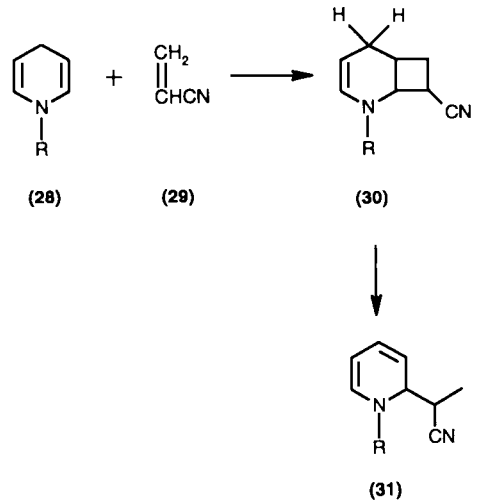
1,4-Dihydropyridines **28** behave as enamines and undergo [2 + 2] cycloaddition reactions with dienophiles such as acrylonitrile (**29**) and dimethyl acetylenedicarboxylate (**32**). For instance, *N*-alkyl-1,4-dihydropyridine **28** reacts with **29** to give



(8a) (26a) (26b)

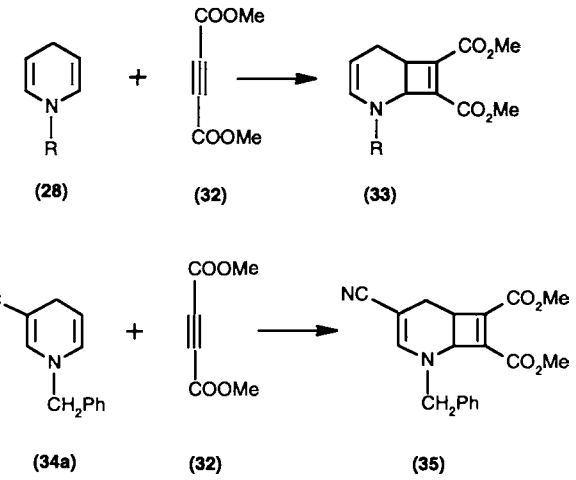
(27)

cyclobutapyridine **30,** which then undergoes ring opening with proton abstraction to yield 2-substituted-1,2-dihydropyridine **31** [71AGE733, 97JCR(S)34]. However, with dimethyl acetylenedicarboxylate (**32**), 1,4-dihydropyridines **28** and **34a** gave cyclobutene derivatives **33** and **35,** respectively (71CC1421).

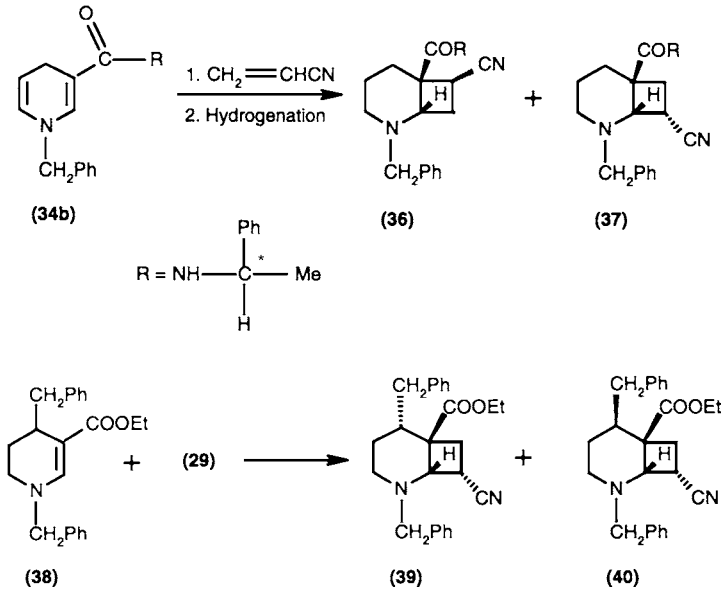


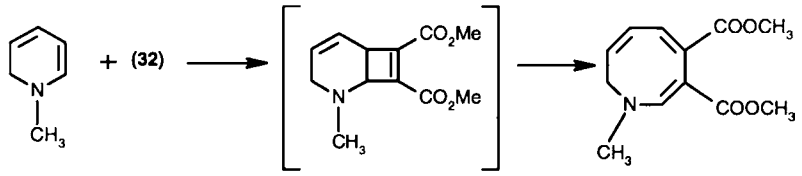
(28) (29) (30)

(31)



The [2 + 2] cycloaddition reaction of *N*-benzyl-1,4-dihydropyridine **34b** with acrylonitrile, followed by catalytic reduction gave two pairs of diastereoisomeric amides **36** and **37** with a low diastereomeric excess, probably due to the large distance between the asymmetric center and the site of acrylonitrile attack. Compounds **36** and **37** were resolved into the four individual diastereoisomers (ca 5% for compound **36** and 15% for **37**) [97JCR(M)321]. Irradiation of 1,4-dibenzyl-1,4,5,6-tetrahydropyridine **38** in the presence of **29** gave two stereoisomers,



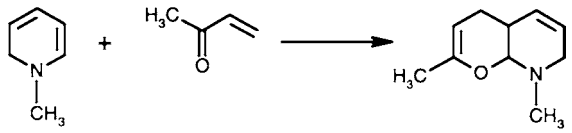


(41a) (42) (43)

ethyl 2-*trans*-5-benzyl-*trans*-8-cyano-*cis*-2-azabicyclo[4.2.0]octane-6-carboxylate (**39**) and ethyl 2-*cis*-5-benzyl-*trans*-8-cyano-*cis*-2-azabicyclo[4.2.0]octane-6-carboxylate (**40**), in 15% and 38% yields, respectively.

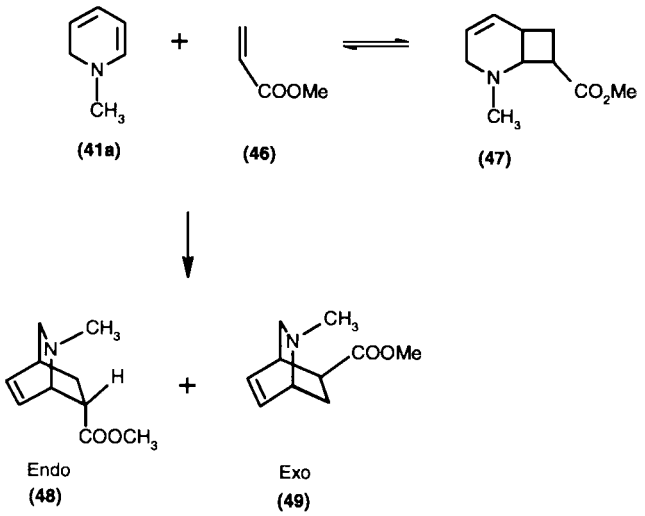
N-Alkyl-1,2-dihydropyridines that are not stabilized by electron-withdrawing groups on the ring could behave as dienophiles towards alkynes. For example, *N*-methyl-1,2-dihydropyridine **41a** reacts with dimethyl acetylenedicarboxylate (**32**) to give [2 + 2] cycloaddition product **42,** which rearranges to give the azocine derivative **43** [74JCS(P1)2496].

Another example in which *N*-methyl-1,2-dihydropyridine (**41a**) behaves as an enamine rather than a diene is its reaction with methyl vinyl ketone (**44**) (64JCS2165). The product is a pyran **45,** which is obtained in 100% yield, rather than an isoquinuclidine derivative (80JOC1657).



(41a) (44) (45)

Fowler and co-workers reinvestigated the reaction of *N*-methyl-1,2-dihydropyridine (**41a**) and methyl acrylate (**46**) at a low temperature (−10°C) and detected the cyclobutane **47** as the major product (80JOC1657). In this reaction *N*-methyl-1,2-dihydropyridine behaves as an enamine (64JOC801).The structure of **47** is supported by spectral data, which show the presence of a 1,2,5,6-tetrahydropyridine ring. However, at high temperature, cyclobutane **47** exists in equilibrium with the starting materials, which react again to give the thermodynamically more stable isomeric Diels–Alder adducts **48** and **49.** The structures of **48** and **49** were found to be different from those reported earlier by Wiley *et al.* (72JMC374) and were assigned (on the basis of ^{1}H NMR and mass spectra) as *endo*-*N*-methyl-2-aza-7-(carbomethoxy)bicyclo[2.2.2]oct-5-ene and *exo*-*N*-methyl-2-aza-8-(carbomethoxy)bicyclo[2.2.2]oct-5-ene, respectively (Scheme 2).

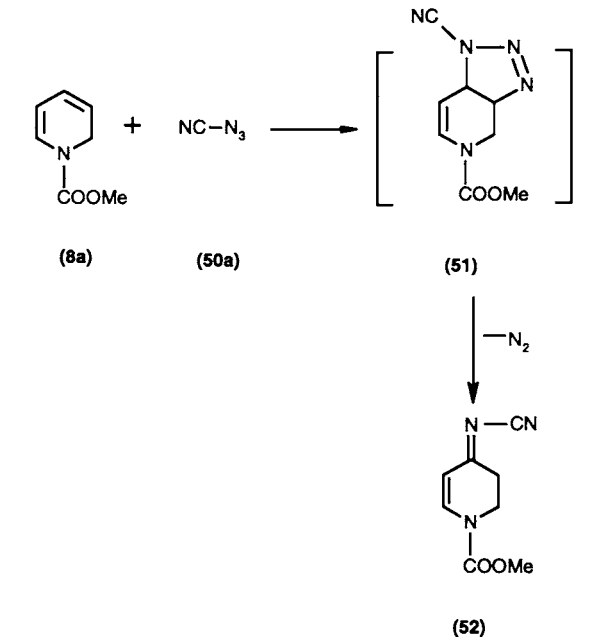


SCHEME 2

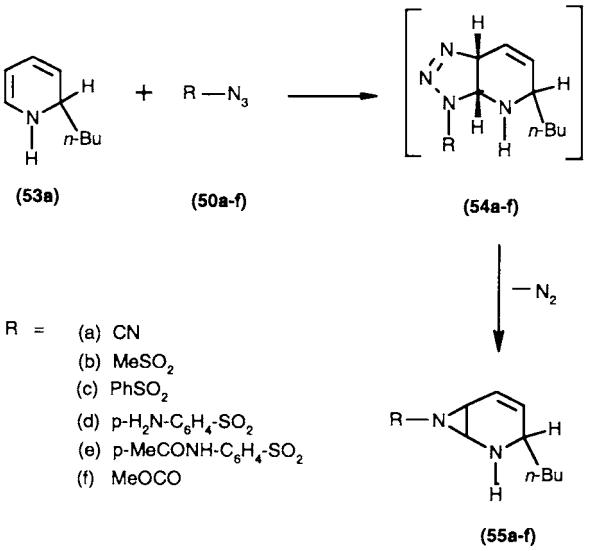
3. *1,3-Dipolar Cycloaddition Reactions*

1,2-Dihydropyridines undergo 1,3-dipolar addition reactions, involving either a 3,4-double bond of the dihydropyridine or an enamine double bond; the path depends upon nature and position of substituents on dihydropyridine ring. Thus, 1-methoxycarbonyl-1,2-dihydropyridines (**8a**) without any substituent on ring reacted with cyanogen azide (**50a**) to yield cyanamide **52** in 52% yield (78CJC10, 78JHC401). In this reaction the 3,4-double bond of dihydropyridine is involved in a 1,3-dipolar addition to afford initially **51,** which on hydrogen shift and loss of nitrogen gave **52.** However, Knaus and co-workers reported that 2-*n*-butyl-1,2-dihydropyridine (**53a**), without any substituent at nitrogen, behaves as an enamine and undergoes a regiospecific 1,3-dipolar addition reaction with azides **50a–f** on the enamine double bond to give ultimately pharmacologically interesting bicyclic aziridines **55a–f** in quantitative yields via triazoline intermediates **54a–f** (79CJC2342). These bicyclics exhibited significant analgesic, antibacterial, and antifungal activities (79MI1). Under similar conditions, reaction of **53b** with **50a** gave the pharmacologically interesting 7-cyano-2,7-diazabicyclo[4.1.0]hept-4-ene **56** in 100% yield (79JHC409).

Similarly, the regiospecific 1,3-dipolar cycloaddition reaction of 1-methyl-1,2-dihydropyridines **41** with cyanogen azide (**50a**) and selected organic azides **50c** and **50g** afforded 2-methyl-2,7-diazabicyclo[4.1.0]hept-4-enes **57,** which can be elaborated to 1-methyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (**58**) and 1-methyl-2-piperidylidenes **59a–d** (85CJC2362).

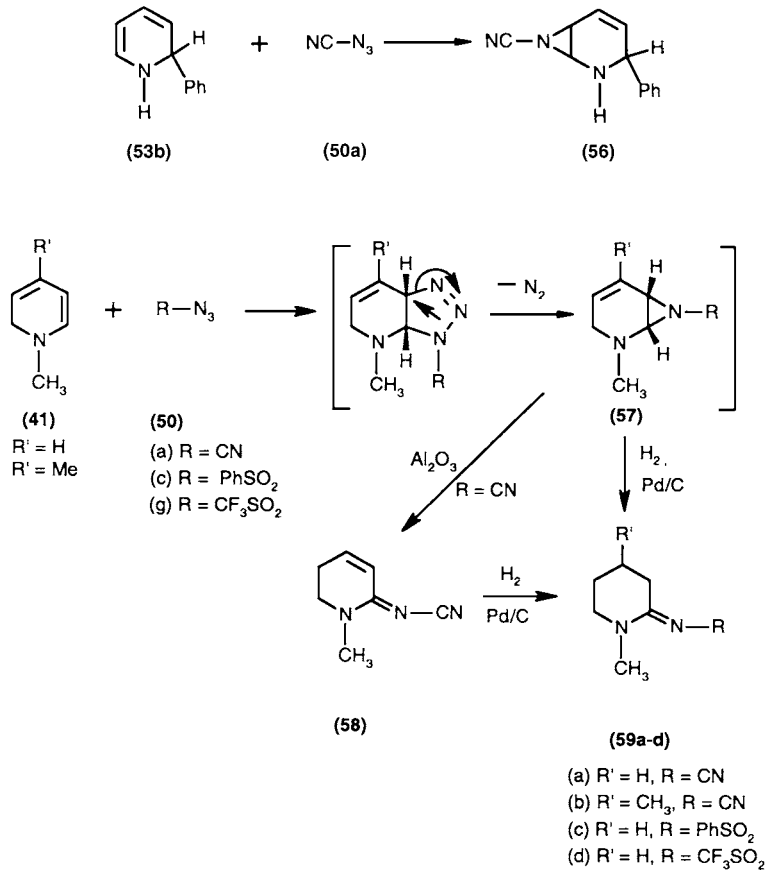


(8a) (50a) (51) (52)



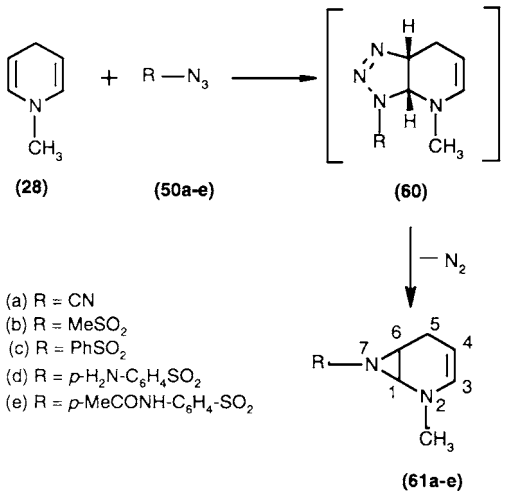
(53a) (50a-f) (54a-f) (55a-f)

R = (a) CN
(b) $MeSO_2$
(c) $PhSO_2$
(d) p-H_2N-C_6H_4-SO_2
(e) p-MeCONH-C_6H_4-SO_2
(f) MeOCO



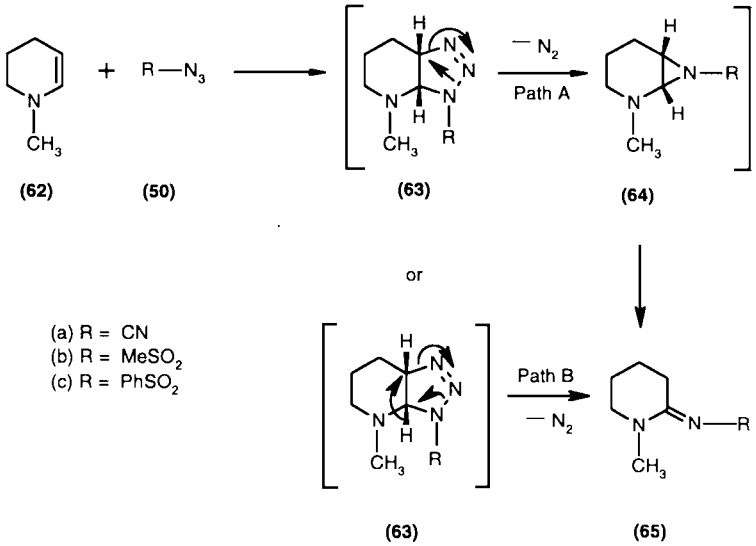
The 1,3-cycloaddition reaction of 1,4-dihydropyridines **28** with azides **50a–e** afforded in 94–98% yield 7-substituted-2,7-diazabicyclo[4.1.0]hept-3-enes **61a–e** possessing analgesic, antiprotozoal, antiinflammatory, antidepressant, and antihistaminic activities (81JMC462). The reaction proceeds via triazoline intermediates **60,** which immediately lose nitrogen to afford **61.** The analgesic activity of **61** was evaluated by the phenylquinone writhing test (68BJP295), and antiprotozoal activity was determined by the method of Diamond and Burtgius (71MI1).

The reaction of 1-methyl-1,2,3,4-tetrahydropyridine **62** and azides **50a–c** in dry ether at 25°C afforded the 1-methylpiperidylidene-2-sulfon(cyan)amides **65a–c** in good yield (82JHC1259). The reaction proceeds via a triazoline intermediate **63,** which loses nitrogen to afford **65.** The elimination of nitrogen from triazoline intermediate **63** occurs by two possible mechanisms [68JCS(C)277]. In path A, the **63** could eliminate nitrogen to give first an unstable 2,7-diazabicyclo[4.1.0]heptane



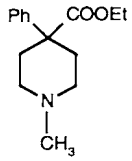
(28) (50a-e) (60) (61a-e)

64, which rearranges to afford the product **65;** or (in path B) **63** loses nitrogen and undergoes a rearrangement in one step to yield **65** (Scheme 3). The 1-methylpiperidylidene-2-benzenesulfonamide (**65c**) bears some structural similarity to the analgesic drug meperidine (**66**) (91MI1). Thus, several derivatives of *N*-alkylpiperidylidene-2-sulfonamides (87JHC1413) were prepared and tested for analgesic activity using the phenylquinone writhing test (68BJP295).



(62) (50) (63) (64) (63) (65)

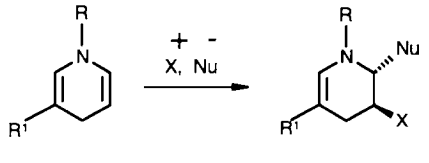
SCHEME 3



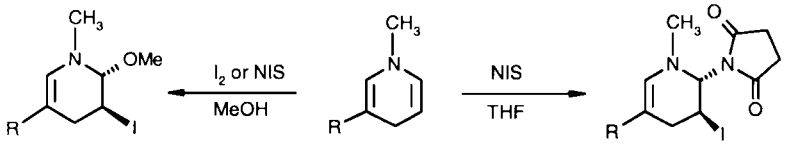
(66)

B. Alkoxy Halogenation and Addition of *N*-Halosuccinimide

Lavilla *et al.* have reported several stereocontrolled oxidative electrophilic additions to *N*-alkyl-1,4-dihydropyridines **34** leading to the synthesis of 3-halo-2-substituted-1,2,3,4-tetrahydropyridines **67** (98JOC2728). Adding a stoichiometric amount of iodine or NIS (*N*-iodosuccinimide) to a methanolic solution of 1-methyl-1,4-dihydropyridine **34c** gave the *trans* 3-iodo-2-methoxy-1-methyl-1,2,3,4-tetrahydropyridines **68** (R = CN) in 90% yield. Spectroscopic analysis (^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, and ^{1}H–^{13}C correlation) confirmed that the only stereoisomer results from *anti* addition. However, when the reactions of **34c, d** with NIS were carried out in the presence of THF, *trans*-3-iodo-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridines **69** were formed in 74–77% yields. These transformations take place by electrophilic additions to the more reactive enamine double bond, thus bypassing the most common oxidation to pyridinium salts (90T8117, 94MI1). It is also possible to introduce bromine, chlorine, and fluorine at the 3-position of the tetrahydropyridine ring by this procedure, using NBS (*N*-bromosuccinimide),



(34) (67)



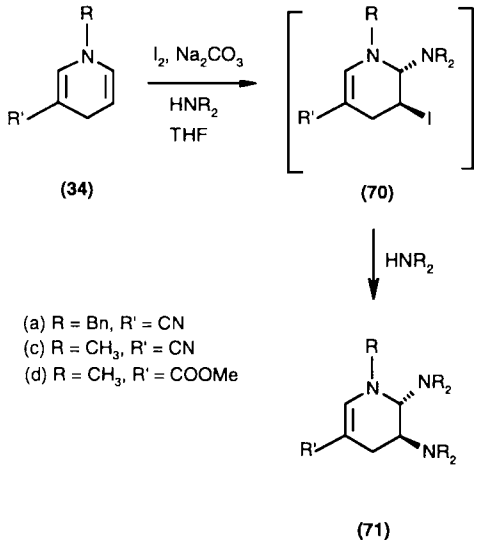
(68) (34c-d) (69)

(c) R = CN
(d) R = COOMe

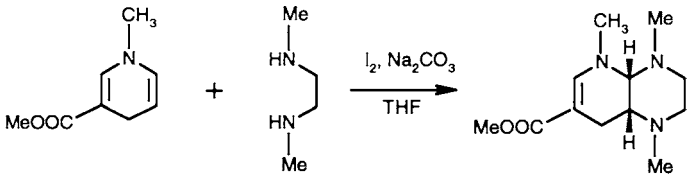
NCS (*N*-chlorosuccinimide), and *N*-fluoropyridinium triflate (90JA8563), [or *N*-fluorodibenzenesulfonimide (91SL187)], respectively.

C. DIAMINATION

N-Methyl(benzyl)-1,4-dihydropyridines **34** undergo vicinal diamination in the presence of iodine and secondary amines to give *trans*-2,3-diamino-1,2,3,4-tetrahydropyridines **71** in yields ranging from 80 to 95% (98CC2715). The secondary amines used in this reaction are piperidine, pyrrolidine, morpholine, and 1-methylpiperazine. The reaction proceeds by the initial formation of *trans*-2-amino-3-iodotetrahydropyridine **70,** which undergoes an internal nucleophilic substitution reaction followed by a stereoselective ring opening of the resulting aziridinium ion promoted by a second equivalent of the secondary amine. The spectroscopic analysis (including ^{1}H–^{1}H COSY and ^{1}H–^{13}C correlation experiments) of the products suggests a *trans* relationship between the two amino groups and a major conformation in which these substituents are axial. When *N,N′*-dimethylethylenediamine (**72**) was reacted with **34d,** the bicyclic adduct **73** was obtained in 80% yield as a mixture of two isomers. The major isomer has *cis*-decaline type fusion (confirmed by NOE and NOESY) due to intramolecular nucleophilic attack in the initially formed *trans*-2-amino-3-iodotetrahydropyridine, which occurs faster from the remaining secondary amino group to form the more stable six-membered ring. The initially formed aziridinium intermediate also can be intramolecularly opened by the remaining amino group to give bicyclic adduct **73.**



(34) (70) (71)

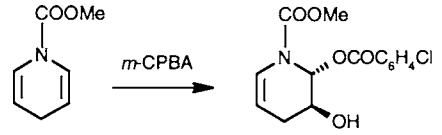


(34d) (72) (73)

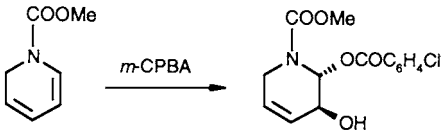
D. Oxidation with Peracids

N-Alkyl-1,4-dihydropyridines on reaction with peracids undergo either extensive decomposition or biomimetic oxidation to *N*-alkylpyridinum salts (98JOC10001). However, *N*-methoxycarbonyl derivatives of 1,4- and 1,2-dihydropyridines (**74**) and (**8a**) react with *m*-CPBA to give the methyl *trans*-2-(3-chlorobenzoyloxy)-3-hydroxy-1,2,3,4-tetrahydropyridine-1-carboxylate (**75**) and methyl *trans*-2-(3-chlorobenzoyloxy)-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**76**) in 65% and 66% yield, respectively (nonbiomimetic oxidation). The reaction is related to the interaction of peracids with enol ethers and involves the initial formation of an aminoepoxide, which is opened *in situ* by *m*-chlorobenzoic acid regio- and stereoselectively (57JA3234, 93JA7593).

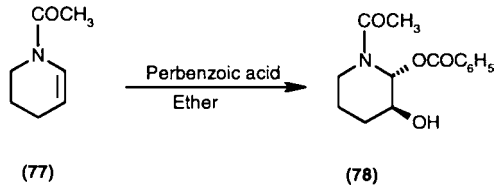
Treatment of *N*-acetyl-1,2,3,4-tetrahydropyridine (**77**) with perbenzoic acid gave the addition product 1-acetyl-2-benzoyloxy-3-hydroxypiperidine (**78**) in 50% yield (72JOC2343).



(74) (75)



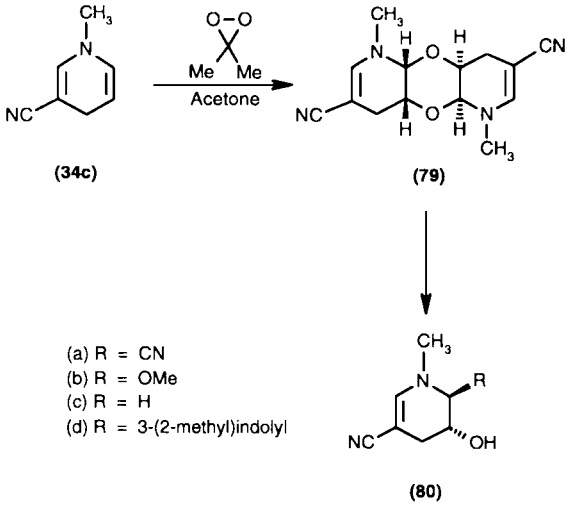
(8a) (76)



(77) (78)

E. Oxidation with Dimethyldioxirane

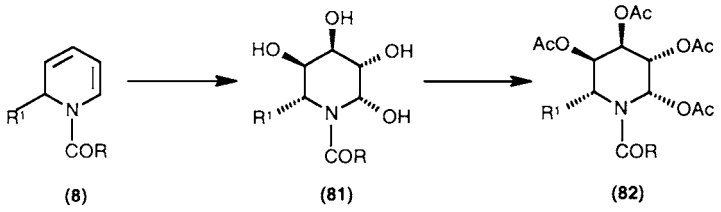
N-Methyl-1,4-dihydropyridine **34c** was transformed into tricyclic dioxane **79** on oxidation with dimethyldioxirane (DMD) (89ACR205, 89CRV1187, 91CB2377) in 72% yield (97CC213, 98JOC10001). The reaction is believed to proceed through the initial epoxidation of the unsubstituted enamine double bond followed by ring opening of the oxirane ring to give an iminium ion that undergoes dimerization. The oxygen atoms at C2–C3 in tricyclic dioxane **79** are *cis*. Tricyclic dioxanes act as highly functionalized iminium ion precursors and on reaction with various nucleophiles such as $Me_3SiCN–TiCl_4$, MeOH–TFA, $Et_3SiH–TiCl_4$, and 2-methylindole-TFA gave 2,3-disubstituted tetrahydropyridines, **80a, 80b, 80c,** and **80d,** respectively. The spectral data (^{1}H NMR, COSY, HMQC, and NOESY) of tricyclic dioxane **79** showed an *anti* relationship between the two tetrahydropyridine rings (a small amount of the other isomer with *syn* stereochemistry was also detected) and the *cis*-position of oxygens at C2–C3. The reaction seems to be quite general and works well with *N*-benzyl- or *N*-methyl-1,4-dihydropyridines having different electron-withdrawing groups, such as CN or COOMe, at the 3-position.



(34c) (79) (80)

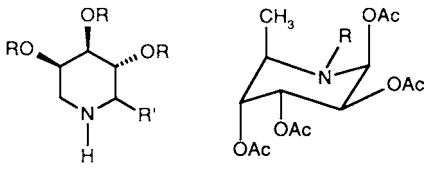
F. Catalytic Double Osmylation

Stereospecific catalytic double osmylation of 1,2-dihydropyridines **8a, 8i,** and **8h** with a catalytic amount of OsO_4 in acetone/water (9:1 v/v) in the presence of an excess of *N*-methylmorpholine oxide (NMO) directly gave piperidinoses, aminoarabinoses **81a** and **81i,** and aminoaltrose **81h,** respectively (90TL2139, 95TL1767). These are characterized by their tetraacetates **82,** which are prepared by treating **81** with acetic anhydride in pyridine. The second osmylation step occurs *anti* with respect to the first one. When there is an alkyl group at the 2-position of 1,2-dihydropyridine **81h,** it plays the dominant role and orients the attack of OsO_4 so that osmylation at the double bond between C3−C4 occurs *anti* with respect to the alkyl group, whereas the osmylation of the second double bond (between C5 and C6) occurs *syn* with respect to the alkyl group. These aminosugars can be converted into 1-deoxyaminosugars **83,** which are analogous to some well-known 1-deoxypiperidinose derivatives (94T1135, 97TL8009), such as deoxynojirimycin (DNJ) (94NPR135) and deoxymannojirimycin (DMJ) (95TL1767), well known for their biological effects, particularly with respect to the chemotherapy of AIDS, cancer, and diabetes. The tetraacetate of the aminoaltrose **82h** has a chair conformation (Fig. 1).



(8) **(81)** **(82)**

(a) R' = H, R = OMe
(h) R' = Me, R = OBn
(i) R' = H, R = OBn



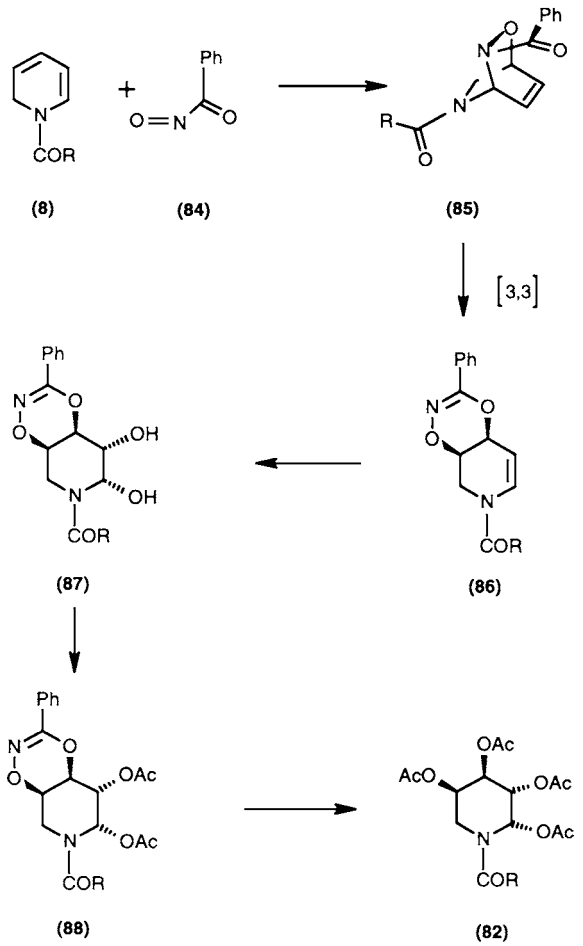
(83)
R = H, Ac

(82h) R = OBn

FIG. 1.

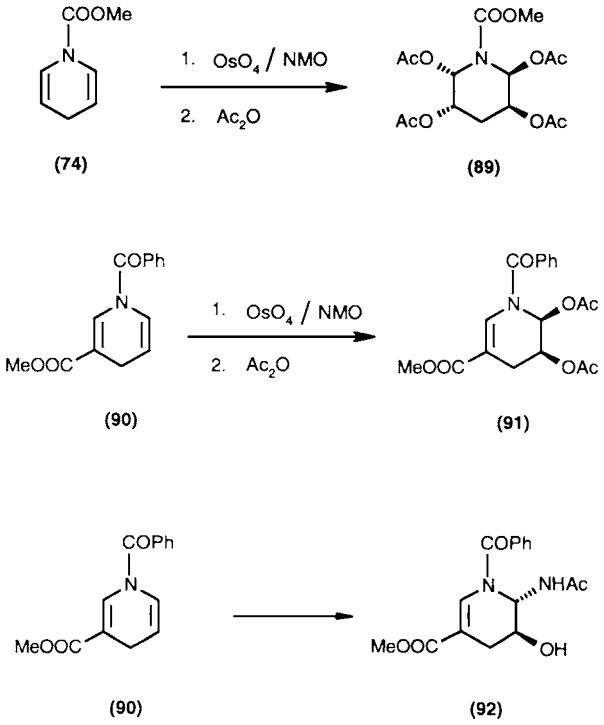
Attempted double hydroxylation of 1,2-dihydropyridines with $KMnO_4$ did not result in any defined products (76CPB2651).

Alternatively, aminoarabinose derivatives **81a** and **81i** (90TL2139) were prepared from 1,2-dihydropyridines **8a** and **8i** by Diels–Alder cycloaddition with benzoylnitroso dienophile (**84**). The resulting cycloadducts **85a** and **85i,** on hetero-Cope rearrangement in the presence of silicic acid, gave stereospecifically the corresponding dioxazines **86a** and **86i,** respectively. *cis*-Glycolization of the latter products that occurred *anti* with respect to the dioxazine ring gave **87a** and **87i,**



SCHEME 4

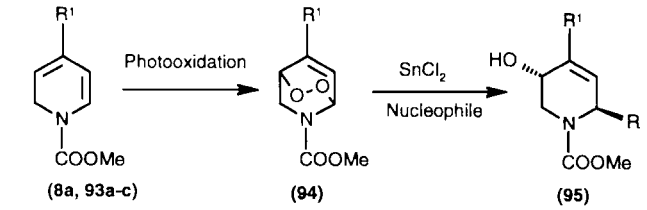
which, on acetylation followed by reductive destruction of the diacetates **88a** and **88i** with Raney nickel, gave **82a** and **82i,** respectively (Scheme 4). The yield of **82** is very poor on the last step; thus, the better methodology for preparing piperidinoses is the double osmylation of 1,2-dihydropyridines.



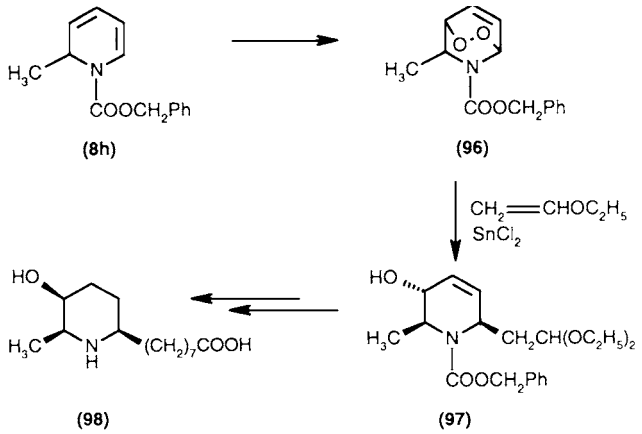
Similarly, osmylation of 1-methoxycarbonyl-1,4-dihydropyridine (**74**) with OsO_4 (catalytic amount) in the presence of NMO (stoichiometric amount) followed by acetylation gave the corresponding piperidine derivatives **89** as a single stereoisomer in 77% yield (98JOC10001). The second oxidation takes place on the less substituted face of the tetrahydropyridine intermediate. Analogously, *N*-benzoyl-3-substituted-1,4-dihydropyridine **90** gave only diacetoxy tetrahydropyridine **91** and not tetraacetoxy piperidine. Aminohydroxylation (96AGE451, 96AGE2813, 97AGE1483) of 1-benzoyl-1,4-dihydropyridines afforded a very poor yield of the corresponding 2-acetamido-3-hydroxytetrahydropyridines **92** (98JOC10001). No useful products were isolated by the aminohydroxylation of other dihydropyridines.

G. PHOTOOXYGENATION REACTIONS

N-Methoxycarbonyl-1,2-dihydropyridine (**8a**) or *N*-methoxycarbonyl 4-substituted 1,2-dihydropyridines **93a–c** derived from pyridine or a 4-substituted pyridine, respectively, readily react with singlet oxygen. Reductive ring opening of the resulting *endo*-peroxides **94** with tin chloride in the presence of various kinds of carbon nucleophiles, such as trimethylsilylated enol ethers, vinyl ethers, enamines, indole, *N*-methylpyrrole, and furan, produced the corresponding *N*-methoxycarbonyl-1,2,3,6-tetrahydropyridine derivatives (**95**) (79TL3473). This route establishes a novel type of carbon–carbon bond formation on a piperidine ring in a noncarbanion manner. The ^{1}H NMR spectra of **95** confirmed that the incoming group, R, at C2 and the original oxygen function at C5 were oriented in an axial fashion with a *trans* relationship.

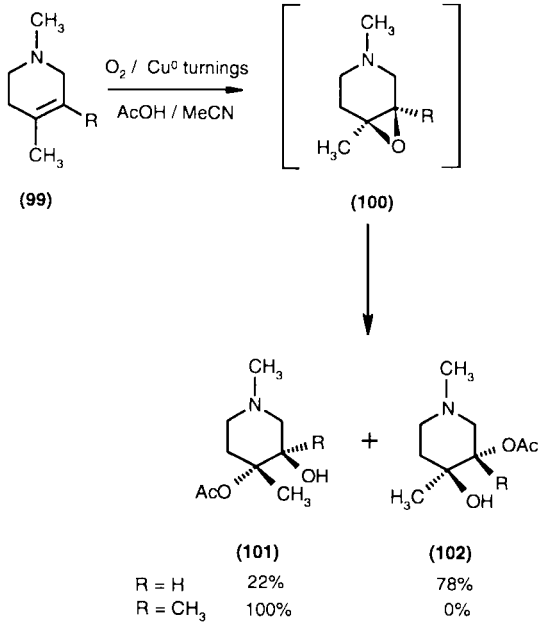


(8a) R^1 = H
(93a) R^1 = CN
(93b) R^1 = COOMe
(93c) R^1 = $COOCH_2Ph$



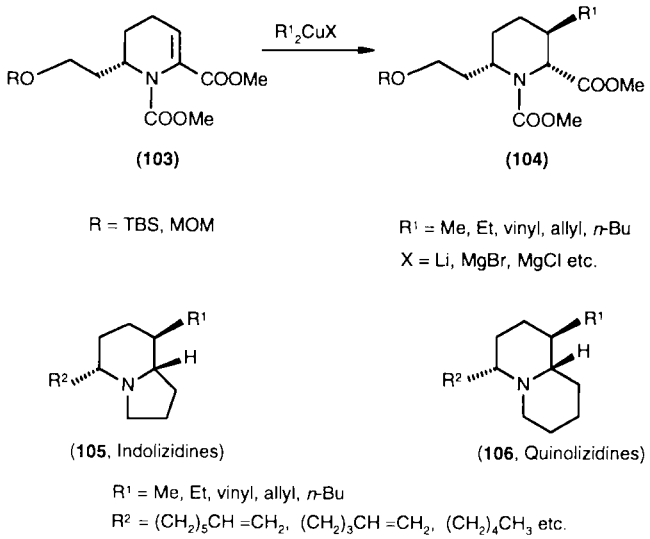
In the synthesis of carpamic acid (**98**), Mitsutaka and Ogawa have used 1,2-dihydropyridine as a starting material [80H(14)169]. Photooxygenation of dihydropyridine **8h** afforded *endo*-peroxide **96.** Subsequent stereoselective nucleophilic reaction of **96** with ethyl vinyl ether in the presence of tin chloride gave tetrahydropyridinol **97,** which was then converted into carpamic acid (**98**) in six more steps.

Tetrahydropyridines **99** are oxidized in an O_2/Cu^{I}OAc system to **100** (which were not isolated), which then ring-opened into a mixture of acetoxyhydroxypiperidines **101** and **102** (96TL8497). The regioselectivity observed in oxirane ring opening in **100** is attributed to intramolecular hydrogen bonding between O and N atoms, known to exist in 3-hydroxy-*N*-methyl piperidine (having a chair conformation). Such bonding is not present in 4-hydroxy-*N*-methylpiperidines.



H. MICHAEL REACTIONS

Tetrahydropyridines **103** undergo a Michael reaction to afford *trans*-(2,3)-*cis*-(2,6)-trisubstituted piperidines **104** (97T9553). The reaction is stereoselective (a single stereoisomer was obtained) and provides a convenient route to the 5,8-disubstituted indolizidine **105** and 1,4-disubstituted quinolizidine system **106** (found in Dendrobates alkaloids) by introduction of various alkyl, alkenyl, or



alkynyl groups in the 3-position of the core piperidine ring. The α-axial attack of the alkyl or alkenyl anion is preferred, and this leads to a chairlike intermediate where the C6 side chain occupies a quasi-axial orientation. The utility of these piperidines as chiral building blocks was demonstrated by the synthesis of indolizidines and quinolizidines.

The addition reactions of phenols and thiophenols with several dihydropyridines and tetrahydropyridines were investigated and the stereochemistry of the products was determined. For example, reaction of 1-methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile (**107a**) with *p*-chlorothiophenol (**108**) afforded the expected Michael addition product **109** in 40% yield (84JHC981). The preferred orientation of an *N*-methyl piperidine ring (chair conformer) has an equatorial methyl group. The added proton at C4 and thiophenoxy group at C3 are equatorial and *trans* to each other (Fig. 2). However, reaction of 1-methyl-1,2,5,6-tetrahydropyridine-4-carbonitrile (**107a**) (49OR79) with 2-naphthol (**110**) under basic conditions afforded product **111** and not the expected Michael addition product (82TL4485). It was presumed that under the basic conditions of the reaction, **107a** is converted into isomer **107b,** which reacts with 2-naphthol to give **111.**

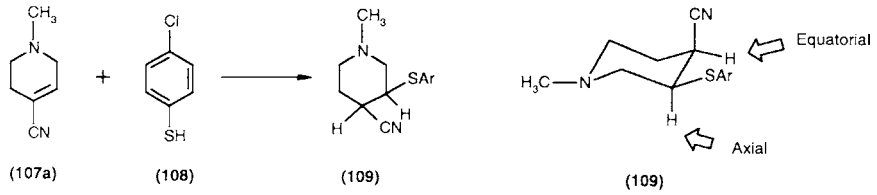
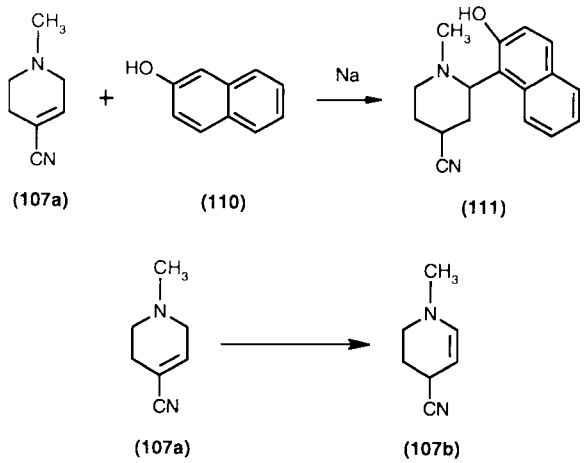


FIG. 2.



In a similar manner, overnight refluxing of 1-methyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (**112**) with *p*-chlorothiophenol (**108**) at 100°C gave a Michael addition product as a 1:1 mixture of two isomers **113a** and **113b** in 70% total yield (Fig. 3). However, if the reaction was carried out at low temperature for 4 hours, kinetic isomer **113a** was detected in 50% yield (84JHC981).

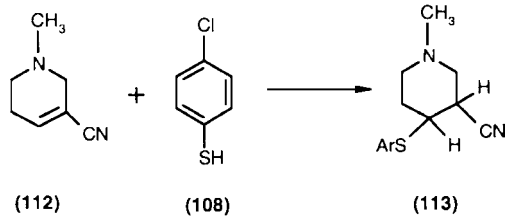
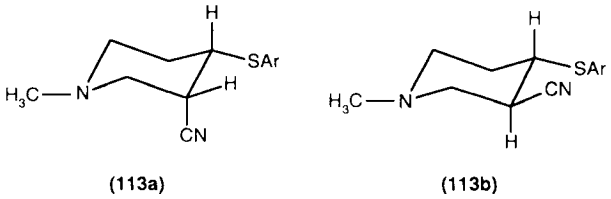
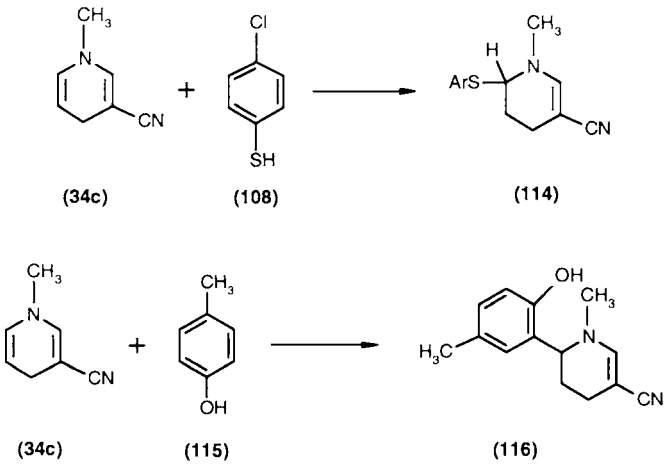


FIG. 3.



1,4-Dihydro-1-methylpyridine-3-carbonitrile (**34c**) also reacts with *p*-chlorothiophenol (**108**) and *p*-cresol (**115**) to yield single products **114** and **116** in 46% and 26% yield, respectively. In both products, H6 is axial and the ring is not a rigid because there is considerable flexibility around C4,5 as in the case of an analogous saturated ring (84JHC981).

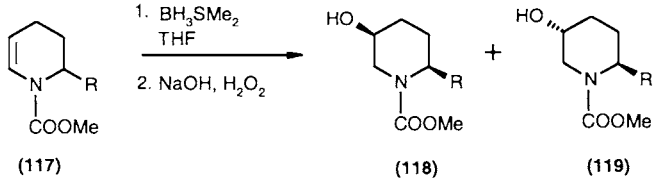


(34c) (108) (114)

(34c) (115) (116)

I. HYDROBORATION–OXIDATION

When racemic **117a** and **117b** and optically pure **117c** (2*S*,8*S*) were subjected to a hydroboration–oxidation sequence (82JA6697), the corresponding alcohols were obtained as mixtures of two diastereomers **118a–c** and **119a–c** (93TL7569). The total yields and relative ratios of alcohols **118a–c** and **119a–c** are given in Table I.

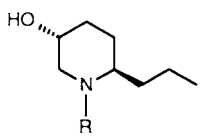


(117) (118) (119)

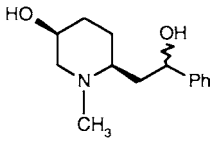
(a) R = CH_3
(b) R = $CH_2CH_2CH_3$
(c) R = $CH_2CH(OAc)Ph$

TABLE I

Tetrahydro pyridine	Temp.	Total yield (**118** + **119**)	Ratio (**118**:**119**)
117a	20°C	79%	1:2
117b	−78°C	71%	1:6
117c	20°C	75%	1:2



(**120**, R = H)
(**121**, R = CH_3)



(**122**)

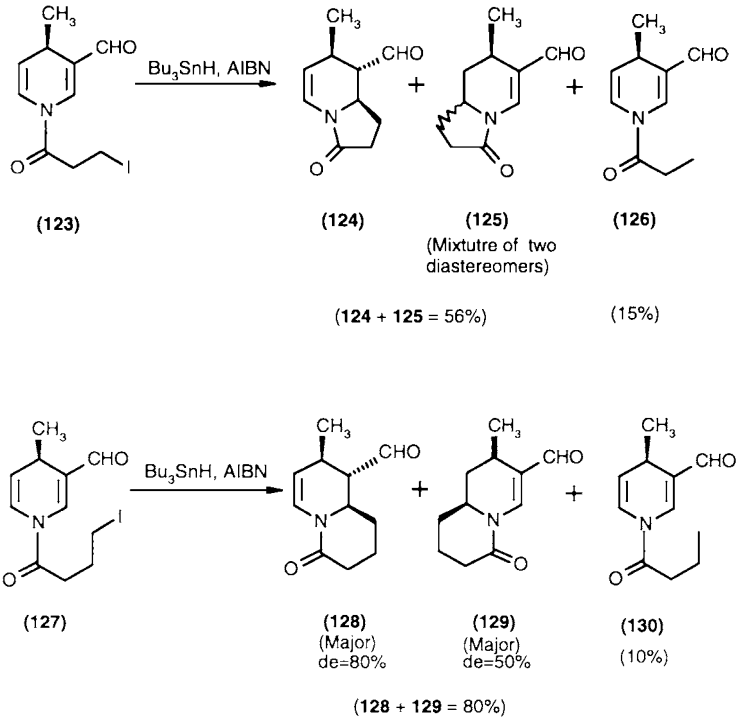
Hydroboration preferentially gives the 2,5-*trans* isomer resulting from the attack of a borane from the less hindered side of a molecule, and hydroboration does not proceed to the trialkyl borane stage. Further elaboration of these alcohols afforded β-hydroxypiperidine alkaloids such as racemic pseudoconhydrine **120,** racemic *N*-methyl pseudoconhydrine **121,** and (−)-5-hydroxysedamine **122.**

III. Cyclizations

A. Radical Cyclizations

1,4-Dihydropyridines bearing an exocyclic functionalized nitrogen substituent are excellent precursors of quinolizidine and indolizidine alkaloids by the way of radical cyclization onto the C2−C3 double bond (94JOC1877). Alkaloids containing indolizidine and quinolizidine rings are widespread naturally and are found in a number of compounds of considerable biological importance. For instance, indolizidine castanospermine showed significant anticancer and anti-HIV activities *in vitro* (85BJ759, 86MI1, 87NAT74). The radical cyclization of a 4-substituted-1,4-dihydropyridine (91CRV1237) having an electron-withdrawing group (–COOR, –CHO or –CN) on the C3 position and bearing a suitable exocyclic nitrogen substituent in the presence of Bu_3SnH and AIBN afforded the corresponding cyclized products and the reduced dihydropyridine (96TL1599, 98T10349). Thus, radical cyclization of dihydropyridine aldehyde **123** with Bu_3SnH and AIBN in benzene under reflux gave bicyclics **124** and **125** in a 2:1 ratio (**124** + **125** = 56%), along with reduced dihydropyridine (**126,** 15%). The cyclized product **124** was obtained as a single diastereomer (de > 95%), resulting from the cyclization onto the C2−C3 double bond and showed a *cis* relationship between C2 and the C4 substituents. Compound **125** was obtained as a mixture of two diastereomers (*cis* and *trans*, de = 50%), resulting from the cyclization onto the C5−C6 double bond. Under similar conditions, 1,4-dihydropyridine **127** afforded the cyclized products **128** and **129** in a 2:1 ratio (80% total yield), resulting from the cyclization on to the C2−C3 or C5−C6 double bonds, respectively. The reduced dihydropyridine **130** was also obtained in 10% yield. The bicyclic **128** was obtained as a mixture of two diastereomers (de = 80%); isomerization at C3 occurs under the basic reaction conditions. It was confirmed by NMR analysis (NOE studies) that cyclization

occurred mainly *cis* to the C4 substituent. The bicyclic **129** was also obtained as a mixture of two diastereomers (*cis* and *trans*, de = 50%). The NMR analysis of **129** showed that the major isomer is again *cis* and therefore the cyclization onto the C2–C3 and C5–C6 double bonds occurred mainly *cis* to the C4 substituent (Fig. 4). 3-Cyano-4-methyl-1,4-dihydropyridine, under the same conditions used for the cyclization of **123,** gave similar results. There is a *cis* relationship between the C2 and C4 substituents and the regioselectivity of the reaction favors the C2 cyclization. However, under the conditions described by Luche and coworkers, the regioselectivity is complete as there was no C-6 cyclization product detected (91SC643). For instance, when **131** was irradiated in the presence of Zn and CuI in 2-propanol, the (1R,2R,9aR)-2-triphenylsilyl-6-oxo-2,6,7,8,9,9a-hexahydro-1*H*-quinolizine-1-carbaldehyde (**132**) was obtained in 57% yield as the *cis* diastereomer, which was further converted into quinolizine alkaloids, (−)-lupinine (**133,** ee = 85%) and (+)-epilupinine (**134a,** ee = 85%) (96TL1599, 98T10349).



1-(2-Bromobenzyl)-1,4-dihydro-3-methoxycarbonylpyridine (**135a**) upon treatment with Bu_3SnH undergoes intramolecular radical cyclization to give both

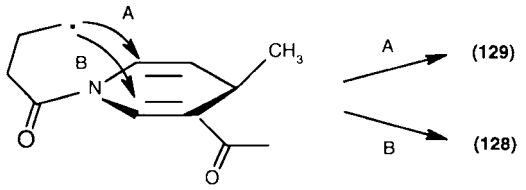
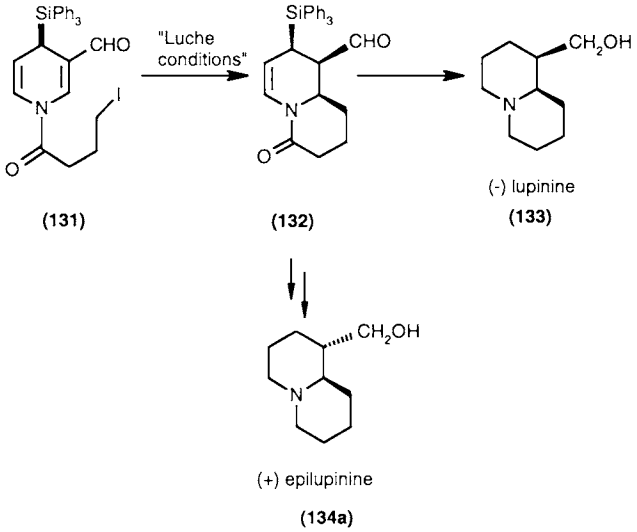
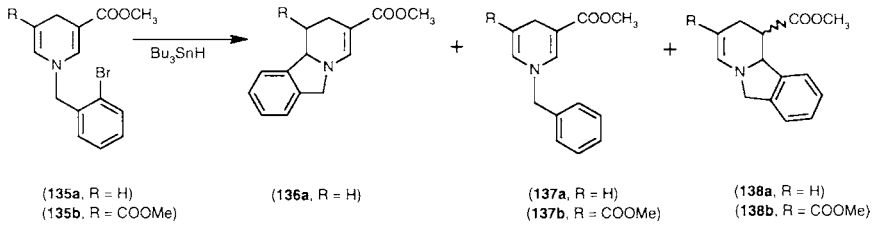


FIG. 4.



vinylogous urethane **136a** resulting from the cyclization onto the unsubstituted double bond and the direct reduction product **137a** in 34% and 22% yields, respectively (89T5269). The tricylic compound **138a** resulting from the cyclization onto the C2–C3 double bond was not isolated because it decomposed. When excess (5 equiv) Bu_3SnH was used, the product **139a** in 12% yield was obtained in addition to the usual products (**136a,** 33%, and **137a,** 22%). This indicates that the reaction proceeds through formation of **138a,** which further reacted with Bu_3SnH to give **139a** or to decompose. However, symmetrical 1,4-dihydropyridine **135b** gave, in addition to the direct reduction product (1-benzyl-1,4-dihydro-3,5-dimethoxycarbonylpyridine, **137b,** 13%), only a mixture of the two possible isomers of **138** (52% yield), the *cis* isomer having axial carbomethoxy group on the six membered ring, that is, *syn* to the fused five-membered ring. The required dihydropyridines **135a** and **135b** were prepared from methyl nicotinate and dimethyl dinicotinate, respectively, by alkylation with *ortho*-bromobenzylbromide and sodium dithionite reduction of the resulting pyridinium salts.

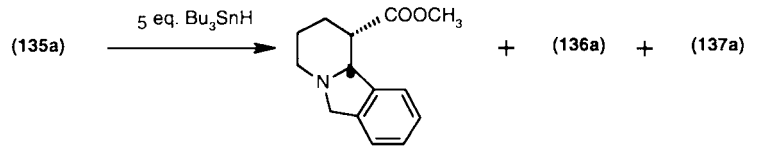


(**135a**, R = H)
(**135b**, R = COOMe)

(**136a**, R = H)

(**137a**, R = H)
(**137b**, R = COOMe)

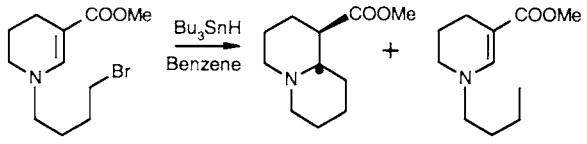
(**138a**, R = H)
(**138b**, R = COOMe)



(**139a**)

The intramolecular cyclization of 1-(4-bromobutyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (**140**) and 1-(3-bromopropyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (**143**) (89T5269) resulted in the synthesis of quinolizidine ring system **141** and indolizidine ring system **144** in 43% and 72% yields along with the reduced tetrahydropyridines **142** and **145** in 21% and 8% yields, respectively. All the cyclized products appeared to be *trans*-fused indolizidines or quinolizidines. The *trans*-fused simple indolizidines are known to be some 2.4 kcal mol^{-1} more stable than the *cis*-fused isomers (68TL6191). In the *anti*-isomer the methoxycarbonyl substituent occupies an equatorial position.

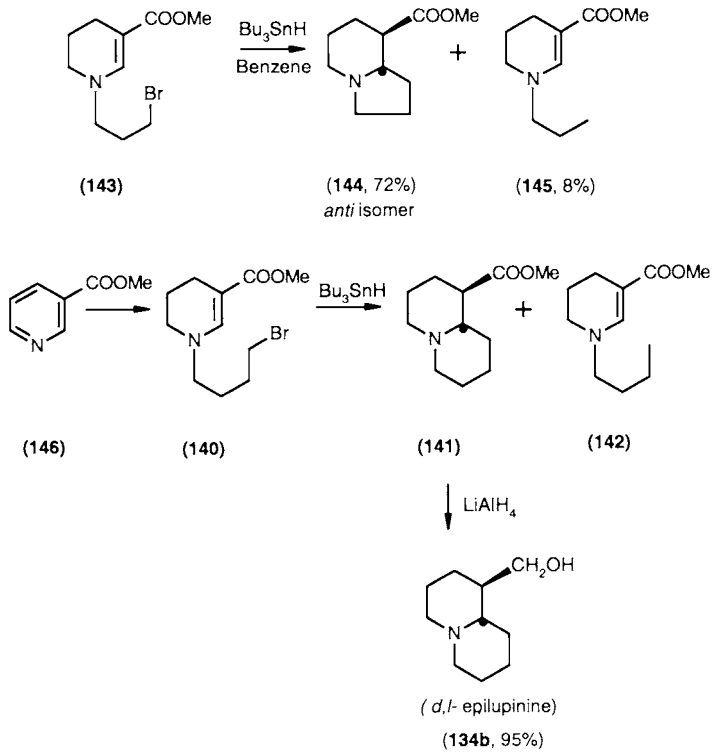
The synthetic utility of radical cyclization was used as the key step in a four-step synthesis of the natural product (*d,l*)-epilupinine (**134b,** a quinolizidine alkaloid) (75CB1043) from methyl nicotinate (**146**). Thus, 1-(4-bromobutyl)-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine (**140**), obtained from methyl nicotinate (**146**), was cyclized to **141** (43%), which on reduction with $LiAlH_4$ in THF provided **134b** in 95% yield (89T5269).



(**140**)

(**141**, 43%)
anti isomer

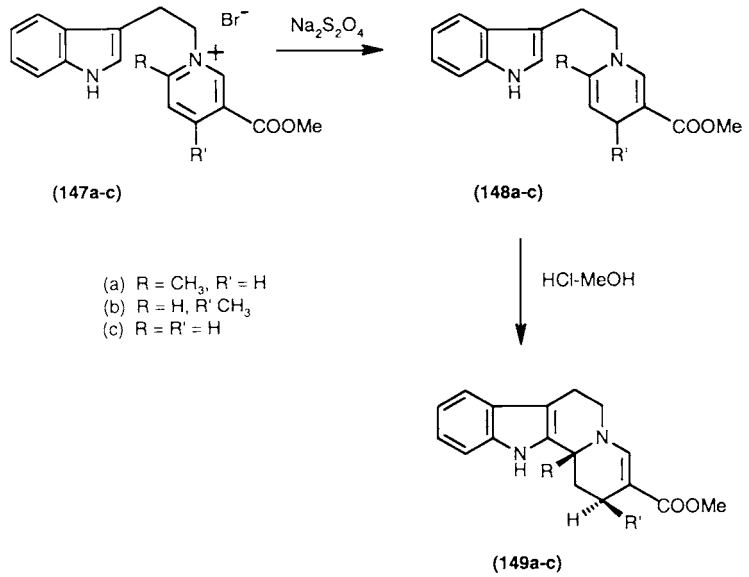
(**142**, 21%)



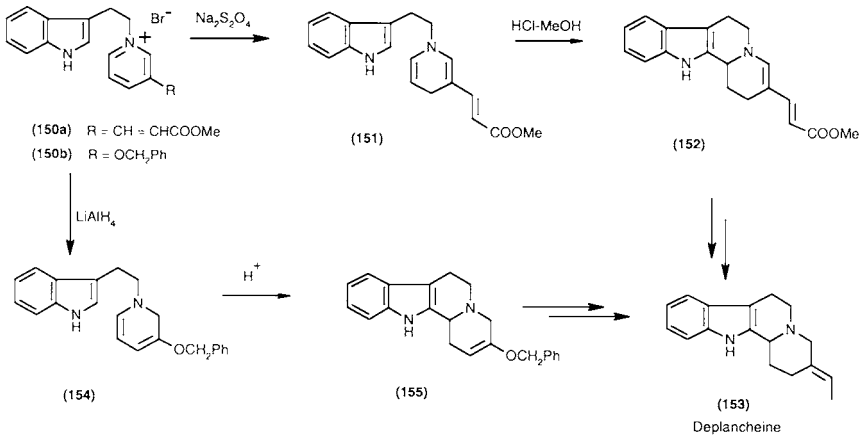
B. Lewis or Protic Acid Promoted Cyclizations

1. *Synthesis of Indoloquinolizines*

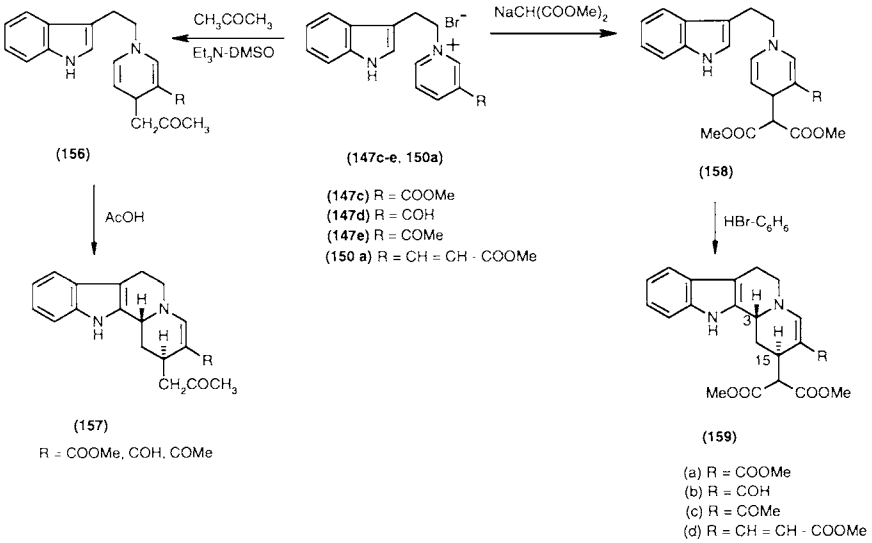
The two-step reaction sequence involving reduction of pyridinium salts to dihydropyridines followed by acidic cyclization has been exploited for the synthesis of the indoloquinolizine framework characteristic for many indole alkaloids (78T2995; 82TL1489). For example, pyridinium salts **147a–c,** prepared by *N*-alkylation of methyl 6-methyl nicotinate (67NKZ553), methyl 4-methyl nicotinate (73JOC4305), and methyl nicotinate, respectively, with tryptopyl bromide, on sodium dithionite reduction gave dihydropyridines **148a–c.** Acid-catalyzed cyclization of dihydropyridine derivatives **148a, 148b,** and **148c** afforded 1,2,6,7-tetrahydroindolo[2,3-*a*]quinolizines **149a** (50%), **149b** (35%), and **149c** (60%), respectively (63TL1645). This two-step reaction sequence has excellent potential for the synthesis of indole alkaloids. Thus, reduction of pyridinium salt **150a** with sodium dithionite yielded 1,4-dihydropyridine **151** (70%), which was directly cyclized under acidic conditions (HCl and MeOH) to indoloquinolizidine **152**



(60%). Further elaboration of **152** resulted in the synthesis of (*d,l*)-deplancheine alkaloid (**153**) (80TL63). Deplancheine alkaloid was also produced from 1,2-dihydropyridine **154,** derived from the reduction of pyridinium salt **150b** with excess of $LiAlH_4$ in THF. Acid-catalyzed cyclization of **154** led to indoloquinolizidine **155** (25% yield from **150b**), a precursor of deplancheine (80TL2341) (Scheme 5).



SCHEME 5



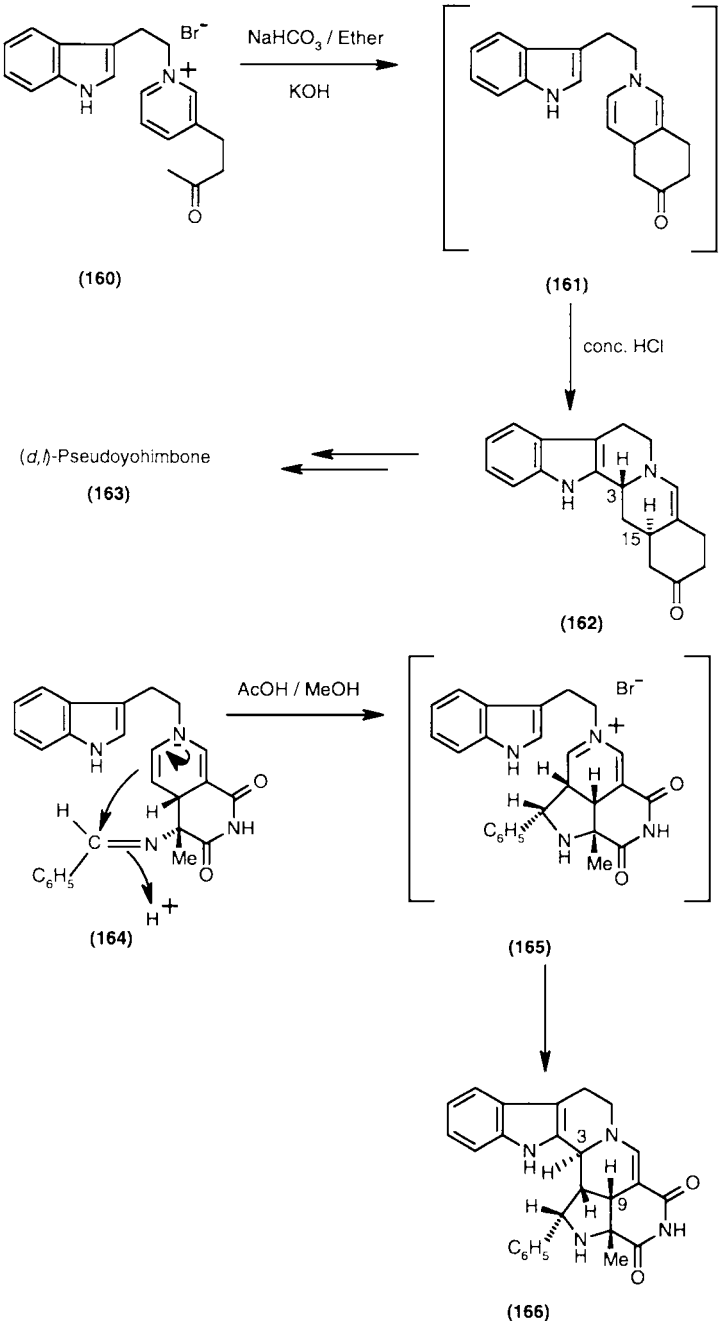
SCHEME 6

Wenkert and co-workers have produced 1,4-dihydropyridine intermediates **156** and **158** by addition of a stabilized carbon nucleophile such as acetone in the presence of base and diethyl sodium malonate, respectively, to pyridinium salts **147c–e** and **150a** (76JA3645, 79JA5370). Cyclization of **156** with acetic acid and of **158** with benzene saturated with hydrogen bromide gave the corresponding tetracyclic systems **157** and **159,** respectively (Scheme 6). The *trans* relationship between 3H and 15H was confirmed by NMR analysis. The formation of the *trans* isomer on acid-catalyzed cyclization is a consequence of the axial attack of the indole ring on the iminium double bond.

Further elaboration of tetracycle **159c** resulted in the syntheses of the racemate of indole alkaloids of the ajmalicine (61JA2594), tetrahydroalstunine (56JOC1315, 71JA5907), and akuammigine type (ajmalicinoid alkaloids). Similarly, **159d** can be converted into yohimboid alkaloids (79JA5370).

The intramolecular cyclization of enolate of 1-tryptophyl-3-(β-ketobutyl) pyridinium bromide (**160**) afforded enamine **161,** which undergoes stereoselective acid cyclization with conc. HCl to give the pentacyclic ketone **162** (*d,l*-20,21-didehydropseudoyohimbone) (96MI1). Catalytic hydrogenation of **162** led to (*d,l*)-pseudoyohimbone (**163**) (76JA3645). Again, H3–H15 were found to have the *trans* configuration in **162.**

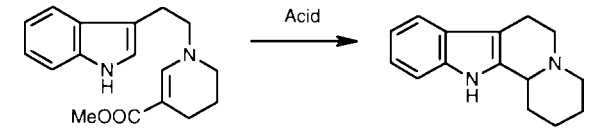
The iminium salt **165,** derived from acid treatment of 1,4-dihydropyridine **164,** on intramolecular cyclization on the indole nucleus gave pentacyclic compound **166** (83T3673). The *trans* stereochemistry of H3 and H9 in **166** (biogenetic



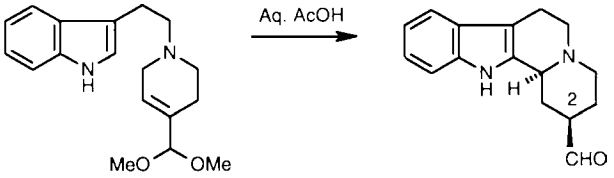
(160) (161) (162) (163) (164) (165) (166)

numbering) has been established by NMR analysis (differential nuclear Overhauser spectroscopy).

The methodology based on the addition of nucleophiles at the α- and γ-positions of *N*-alkylpyridinium salts to give substituted 1,2- and 1,4-dihydropyridines (often not isolated) as intermediates, respectively, which can be further elaborated into complex polycyclic alkaloids, was reviewed by Joan Bosch and M.-Lluiesa Bennasar in 1995 (95SL587).



(167) **(168)**



(169a) **(170)**

Acid-catalyzed cyclization and decarbomethoxylation of tetrahydropyridine **167** has been exploited to construct indoloquinolizidine system **168** (65JA5461). Tetrahydropyridine derivatives, such as **169,** under the same conditions undergo isomerization–cyclization to the indoloquinolizines. Bonjoch and co-workers (95CC2317) in the synthesis of desethylibophyllidine alkaloid treated the 1,2,3,6-tetrahydropyridine **169a** (90BSF648) with aq. acetic acid, which brought about deprotection of the acetal group, isomerization of the double bond, and cyclization of the resulting enamine via an iminium ion to give 2-formylindolo[2,3-*a*]quinolizine system **170** (biogenetic numbering) as a 7:2 mixture of epimers (not separated) (95CC2317). They have also described the synthesis of 4-ethyl-octahydroindolo-[2,3-*a*]quinolizine-2-carbaldehydes **172a** by using the same procedure (97T9407). Thus, 2-ethyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine-4-carbaldehyde (**171**), derived by hydrolysis of 2-ethyl-4-(dimethoxy)methyl-1-[2-(3-indolyl)-ethyl]-1,2,3,6-tetrahydropyridine (**169b**) with 5% aqueous oxalic acid, gave **172a** upon treatment with glacial acetic acid in 89% yield. The yield of the major isomer (2*RS*,4*SR*,12b*SR*)-4-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-2-carbaldehyde (**172a**) is 80%. ^{13}C NMR and ^{1}H NMR of its acetal (**172b**) showed that the two substituents at C2 and C4 have equatorial positions and that the relationship between hydrogens attached to C12b and C2 is *cis* (Fig. 5), whereas the preferred conformation of all the isomers has a *trans* relationship between the C

and D rings. The minor isomers are epimers at C2 and C4. The reaction occurs by means of isomerization of the double bond to the enamine, its protonation, and finally, cyclization (path a) of the generated iminium salt (A) as described by Joule and co-workers [71JCS(C)736]. Cyclization of **169b** with aqueous AcOH generated **171** *in situ* and promoted isomerization–cyclization to give an unexpected indolizidinoindole **173** together with the expected indoloquinolizine **172a** in a 1:3 ratio. The formation of **173** can be explained by hydrolysis (path b) of the intermediate iminium salt (A) to dialdehyde (B), which on cyclization in two steps gave **173** (Scheme 7).

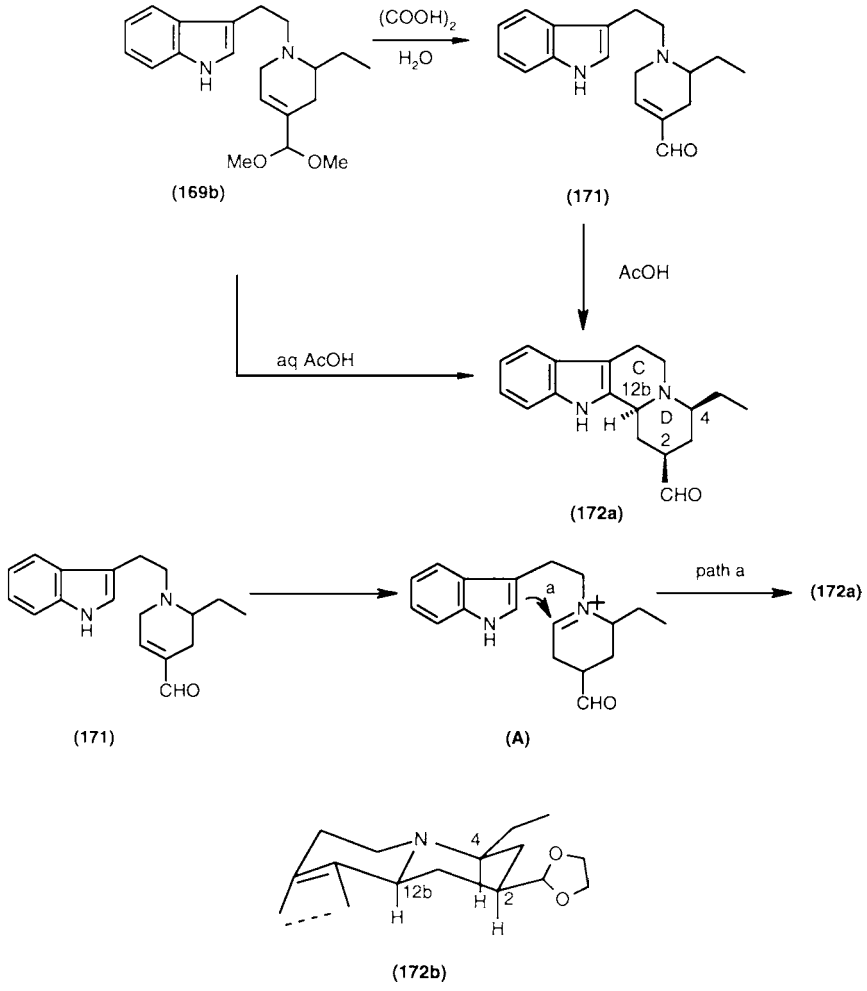
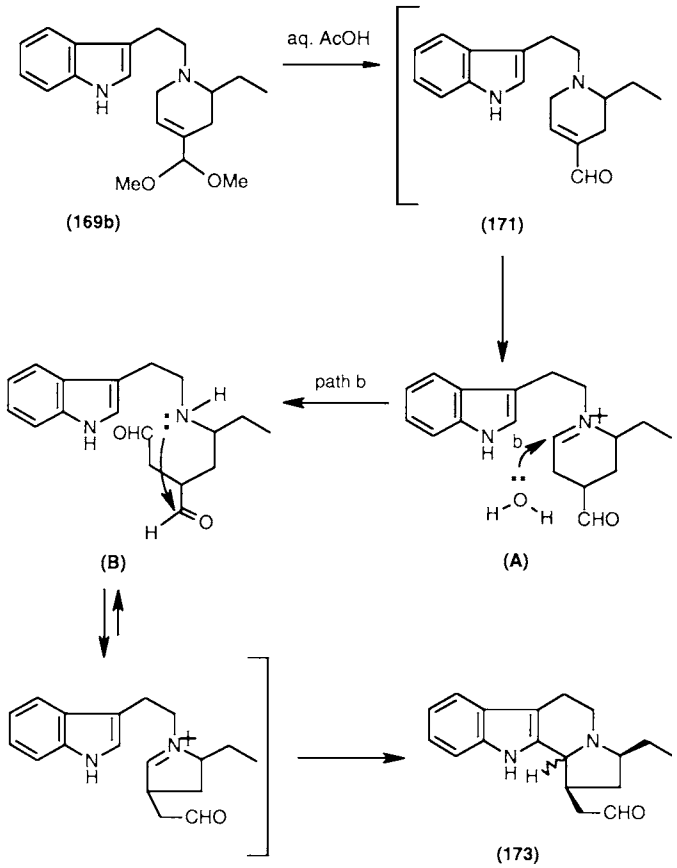


FIG. 5.

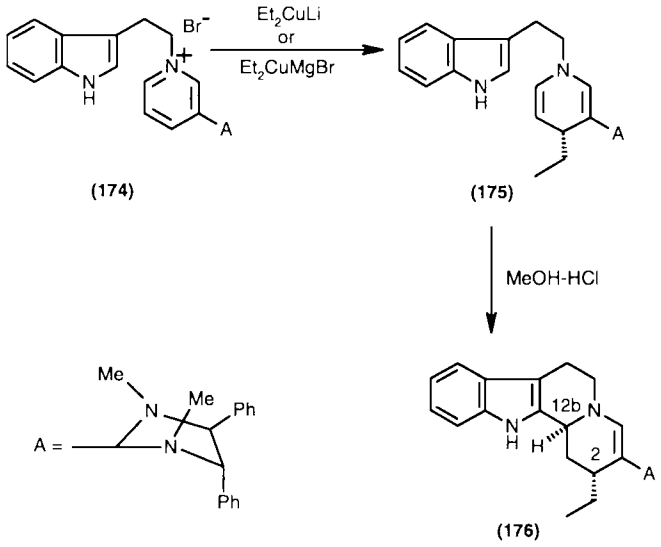


SCHEME 7

The dihydropyridine **175,** obtained by attack of organometallic reagent (organocopper) on indolylpyridinium salt **174** gave on cyclization only one diastereomer, indoloquinolizine **176,** in 70% overall yield (94JOC1877). The *R* configuration was assigned to the C2 and the *S* configuration to the C12b, and the NMR spectra of **176** confirmed the *trans* relationship (88MI1) between C12b−H and C2−H, which is the consequence of intramolecular cyclization of the indolyl group to the iminium base from the less hindered β-side (86CPB3135).

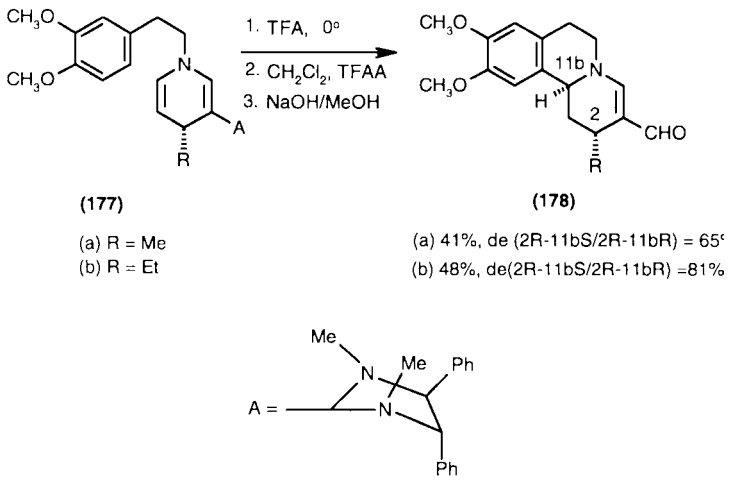
2. *Synthesis of Benzoquinolizines*

The same strategy as described previously was applied to the synthesis of the benzoquinolizine framework [92JCS(P1)517]. Mangeney cyclized 1,4-dihydropyridines **177a** and **177b** to the corresponding benzoquinolizine derivatives **178a**



(174) (175) (176)

and **178b** in 41% and 48% yields, respectively. Both the cyclized products **178a** and **178b** were obtained as mixtures of two diastereomers (**178a,** de = 65%, and **178b,** de = 81%). The *S* configuration was assigned to the C11b atom of the major diastereomer (94JOC1877).



(177)

(a) R = Me
(b) R = Et

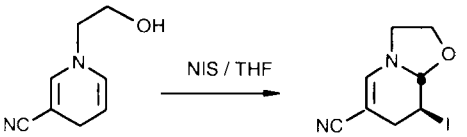
(178)

(a) 41%, de (2R-11bS/2R-11bR) = 65%
(b) 48%, de(2R-11bS/2R-11bR) =81%

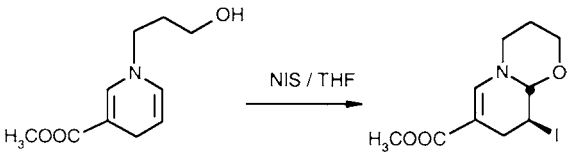
C. IODOCYCLIZATIONS

1,4-Dihydropyridines can also generate an iminium ion in a regioselective manner through the attack of iodide ion at the β-position of an unsubstituted enamine function. The *anti* intramolecular nucleophilic attack (confirmed by NMR spectra, COSY, NOE, ROESY, HMQC) on 3-iodotetrahydropyridinium ion leads to iodobi(poly)heterocyclic ring systems regio- and stereoselectively in good yields. This methodology can be used for the synthesis of β-iodotetrahydropyridines (98TL5089), which can be further elaborated into the complex polycyclic alkaloid systems (vincamine and tacamine types).

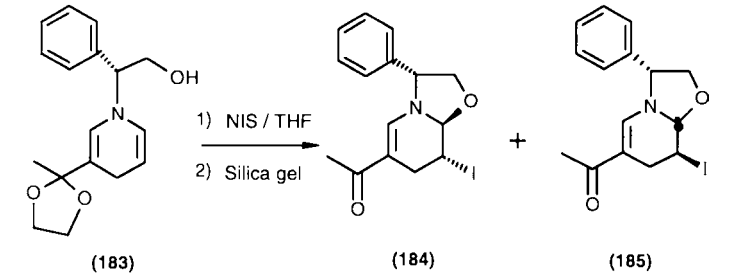
Thus, 1,4-dihydropyridines **179** and **181** reacted with NIS or iodine in THF to give stereoselectively *trans* oxazolidine **180** and *trans* iodinated oxazine **182** in 30% and 67% yields, respectively. Under similar conditions chiral nonracemic dihydropyridine **183** afforded a diastereomeric mixture of iodotetrahydropyridines, which were separated after ketal hydrolysis to afford **184** and **185** in a 3:1 ratio in 38% total yield (97JOC729, 97JOC2106). Trapping the iminium ions generated from *N*-tryptophyl derivative **148c** through stereocontrolled intramolecular electrophilic addition (*anti*) to the indole ring led to indoloquinolizidine **186** (85%). However, the iminium ion generated from homoallyl dihydropyridine **187** was trapped through electrophilic addition (*anti*) to the olefin moiety to give quinolizidine diiodide **188** as an epimeric mixture at the tetrasubstituted sp^3 carbon atom.



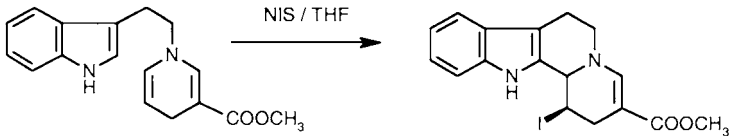
(179) (180)



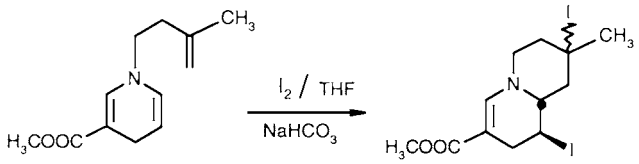
(181) (182)



(183) (184) (185)



(148c) (186)



(187) (188)

IV. Conclusion

Dihydropyridines and tetrahydropyridines represent key intermediates for the enantioselective synthesis of indoloquinolizidine, benzoquinolizidine, indolizidine, and quinolizidine frameworks, which, in turn, might be transformed into various natural products. An electron-withdrawing group either on a nitrogen atom or on a ring stabilizes a dihydropyridine ring toward oxidation and polymerization. An electron-withdrawing substituent at a β-position enhances the electronegativity of the pyridine ring for nucleophilic addition and stabilizes one of the double bonds of the dienamine (dihydropyridine) toward acid or radical cyclization, that is, an unsubstituted enamine function cyclizes in a regiospecific manner onto the C2 position of the indole nucleus. Moreover, the presence of an electron-withdrawing group at the β-position of a dihydropyridine or tetrahydropyridine is often a requirement for their synthetic exploitation. The two-step sequence involving

(a) the preparation of a dihydropyridine derivative from a pyridinum salt either by reduction, as exemplified by the transformation of **147a** to **148a,** or by carbanion addition, as exemplified by the transformation of **147c** to **158,** followed by (b) cyclization in a regioselective and stereoselective manner affords the indoloquinolizidine derivatives, which serve as excellent intermediates in the synthesis of indole alkaloids. Similarly, interaction of dihydropyridines with a halogen acting as an electrophile rather than with a proton, followed by intermolecular or intramolecular attack of various nucleophiles, constitutes a new method for the regio- and stereoselective transformation of dihydropyridines into polysubstituted tetrahydropyridines and halo bi(poly)heterocyclic systems, respectively. Intermolecular and intramolecular cycloaddition reactions of dihydro- and tetrahydropyridines have been shown to play an important role in the synthesis of alkaloids and substituted piperidines of pharmaceutical importance. This review highlights the applications of the methodology based on the "nonbiomimetic" oxidation of dihydropyridines for the diastereoselective synthesis of functionalized heterocyclic systems as potential precursors for bioactive or natural products. With the aim of developing alternative procedures for the synthesis of natural products, the preceding results significantly expand the scope and the potential of the use of dihydropyridines and tetrahydropyridines as starting materials or intermediates. More interesting examples and applications will appear in the future.

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Preface

Volume 78 of *Advances in Heterocyclic Chemistry* contains four contributions. A. P. Sadimenko of Fort Hare University of South Africa has covered organometallic compounds of furan, thiophene, and their benzannulated derivatives. This constitutes the first installment of a projected series on the organometallic chemistry of heteroaromatic ligands, a subject of great fundamental and technical importance that has exploded in the 1990s.

A. B. Sheremetev and N. N. Makhova (N. D. Zelinsky Institute of Organic Chemistry, Moscow, Russia) and W. Friedrichsen (University of Kiel, Germany) have reviewed the monocyclic furazans and furoxans. While much of the early work in this area was published in the German and Italian literature, more recently, a large amount has appeared in Russian journals, much of it being released for publication only during the last ten years. This survey should be of great utility to Western readers.

V. Milata of the Slovak Technical University, Bratislava, has covered tricyclic azoloquinolines. Although these compounds were only cited 57 times in Chemical Abstracts through 1976, there were 3000 citations in the twenty year period 1977 to 1996.

The final chapter in this volume by R. Kumar and R. Chandra (University of Delhi, India) deals with stereocontrolled additions to di- and tetrahydropyridines and particularly their application to natural product synthesis.

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