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OXIDATION OF HETEROCYCLIC COMPOUNDS BY MANGANESE DIOXIDE (REVIEW)*

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Data on the transformations of heterocyclic compounds during oxidation with manganese dioxide are reviewed.

Keywords: heterocycles, manganese dioxide, oxidation.

The widespread use of active manganese dioxide (subsequently MnO_2) began more than a half century ago, but great interest in MnO_2 had already begun in 1948 after the successful selective oxidation of retinol (a form of vitamin A_1) to retinal [1]. Now MnO_2 has found use in the production of a series of medical products, such as heterocyclic vitamins E (tocopherol) and B_6 (pyridoxal) [2]. This mild and frequently selective reagent has found an important place among the oxidants used in organic chemistry (see the reviews [1, 3, 4] and also chapters in various books [5-8], where oxidation with manganese dioxide is discussed.) The main feature of the use of MnO_2 is the difficulty of achieving its standard activity [5]. One of the most active freshly prepared forms is produced by the action of $KMnO_4$ on $MnSO_4$ in an alkaline medium or on $MnCl_2$ in an acidic medium [4]. The thermal decomposition of $MnCO_3$ or the reduction of $KMnO_4$ with acetone give less active forms of MnO_2 [4]. Depending on the method of production, freshly prepared MnO_2 contains between 4 and 15% of non-bonded (adsorbed) water, 2-4% of bonded water (hydroxyl ligands), and 0–2% of bonded oxygen (oxygen ligands) [4, 5], and its oxidizing activity and selectivity can therefore depend on the structural characteristics of the sample. If it contains up to 25% of water even hydration and hydrolysis are possible [9]. Usually MnO_2 is used in an excess of many times (4-40 parts by weight to one part of the substrate), and this gives rise to the need for very intensive agitation and considerably complicates the isolation of the reaction products that are readily adsorbed on the solid oxidizing agent [6-8]. Selective oxidation is achieved at room temperature, but heat is also used [1]. The oxidizing ability of MnO_2 increases sharply above 70°C usually with loss of selectivity [7, 8]. Manganese dioxide has the highest oxidizing activity in an acidic medium, moderate activity in a neutral medium, and close to zero activity in an alkaline medium [4].

In this review the results from papers on the oxidation of heterocyclic compounds with MnO_2, published mainly in the last 10-15 years, are summarized. The topics discussed include: Oxidation of substituents in the

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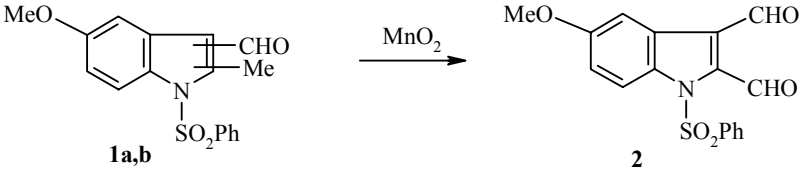
heterocycle (section 1); oxidation of fragments of the heterocycle (2); dehydrogenation of partly saturated heterocycles (3); oxidative coupling of C–C and C–N (4); intramolecular (5) and intermolecular cyclizations controlled by MnO_2 (6).

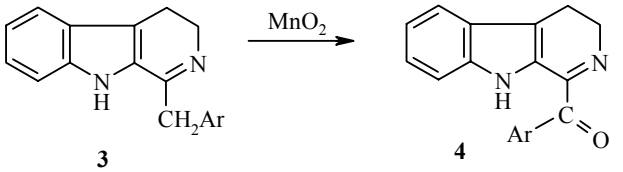
1. Oxidation of Substituents in Heterocycles

In the early papers, mentioned in the reviews [3, 4], it was established that only active methylene groups at the α- and γ-positions of the pyridine and quinoline rings can be oxidized with MnO_2 to a COOH group by boiling the reagents in benzene. The possibility of the oxidation of such substituents with increased CH acidity is probably due to their ability to be transformed *in situ* to *exo*-methylene groups, which are then oxidized by the hydrated form $O{=}Mn(OH)_2$. As a rule methyl groups in five-membered heterocycles are not oxidized by MnO_2 [10]. However, 3-formyl-2-methyl-substituted (**1a**) and 2-formyl-3-methyl-substituted (**1b**) indoles are oxidized to the dialdehyde **2** on account evidently of the activating effect of the CHO group [10].



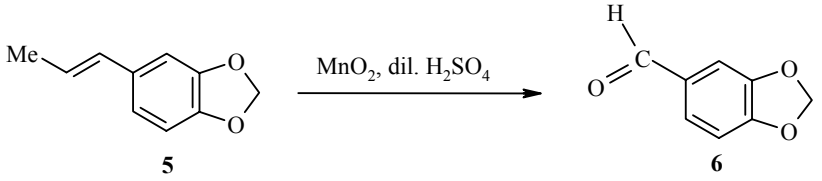
1a,b **2**

Oxidation of the $ArCH_2$ group in the dihydrocarboline **3** (yield of product **4** 99%) [11] and of the propenyl group in isosafrole **5** (yield of product **6** 54%) [12] was realized at room temperature. In the last case MnO_2 suspended in dilute H_2SO_4, produced during recirculation of a MnO_2–$MnSO_4$–H_2SO_4 mixture through an electrochemical cell, was used.



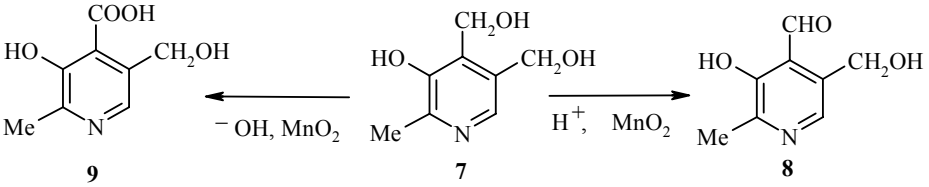
3 **4**

Ar = C_6H_4Br-*o*



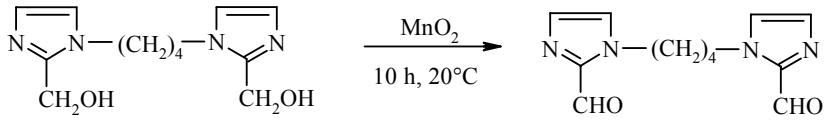
5 **6**

The largest numbers of papers have been devoted to oxidation of the substituent CH_2OH. It is easily converted into a CHO group during the action of MnO_2 on hydroxymethyl-substituted pyrroles [13], 1,2,3-thiadiazoles [14], and 1,2,3,6-tetrahydropyridines [15]. Manganese dioxide was used successfully in the synthesis of new derivatives of vitamin B_6 at the stage of oxidation of pyridoxine **7** to pyridoxal **8** (yields 60-80%) [16]. In an alkaline medium, however, the pyridoxine acid **9** is formed with a yield of 82% [17].



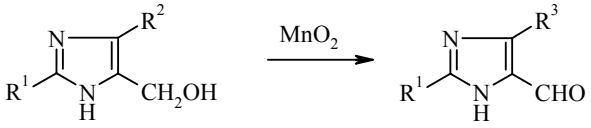
9 **7** **8**

Good results were obtained when MnO_2 was used for the production of ketones of the benzoxazole [18] and furan, thiophene, and imidazole dialdehyde series [19]. In the latter case compound **10** is readily oxidized to the dialdehyde **11** (yield 91%) [19].



10 **11**

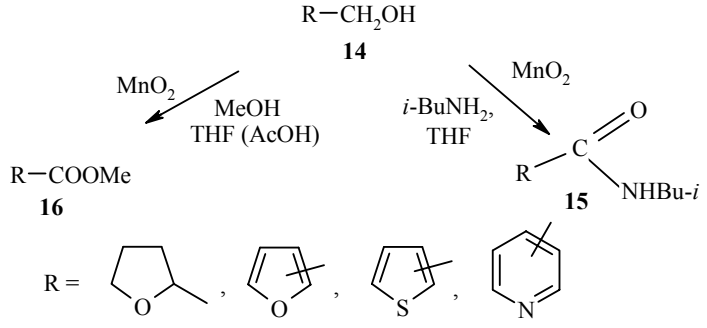
At the same time the oxidation of one or two CH_2OH groups of the imidazole **12** requires boiling in propanol for up to 7 h. The yields of the aldehydes are 85-92% [20, 21].



12 **13**

R^1 = Me, Et, Bn, Ph; R^2 = Cl, CH_2OH; R^3 = Cl, CHO

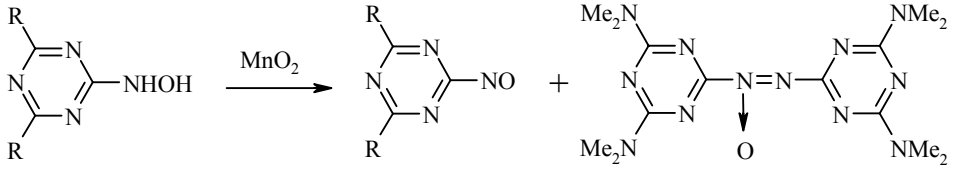
The amides **15** or methyl esters **16** were obtained by the oxidation of alcohols of type **14** in the presence of alkylamine or methanol respectively [22].



The addition of 0.2-5.0 equiv. of NaCN to the reaction mixture increased the yields of the required products to 41-77%. Methods were developed for the analogous oxidative transformation of alcohols $HetCH_2OH$ into the corresponding imines (in the presence of primary amines) [23], oximes [24], and nitriles (in the presence of NH_3) [25, 26] and also alkenes (in the presence of $Ph_3P^+CHBr_2Br^-$) [27-29].

The PhCHOH group is easily oxidized to PhC=O with MnO_2 (20°C, 2 h, yield 87% [30]) during the synthesis of the cyclopentano[*b*]indole fragment present in alkaloids – mycotoxins (causing tremor) and alkaloids recently isolated from the roots of *Murraya paniculata* (with high anti-implantation activity).

There are few examples of the oxidation of other substituents attached to a heterocycle. 3-Pyridinecarbaldehydes and 3-indolecarbaldehydes were converted into the corresponding nitriles (yields 76-84%) by the action of MnO_2 (15 equiv.) in the presence of NH_3 and $MgSO_4$ in solution in 2-propanol and THF (20°C, 16 h) [31]. From 5-hydroxyaminoalkyl-substituted isoxazoles and pyrazoles the corresponding nitroso derivatives were obtained (a sixfold excess of MnO_2, $CHCl_3$, 20°C, 1 h, yields 75-80%) [32]. Under the same conditions the *sym*-triazines **17a**,**b** are easily oxidized to the nitroso compounds **18a**,**b**, and in the case of the dimethylamino-substituted **17b** the product **19** is also formed [33].

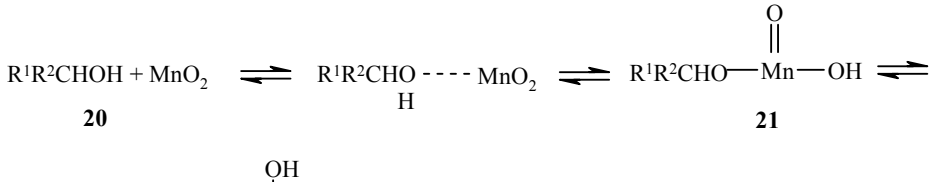


17a,b **18a,b** **19**

17, 18 **a** R = piperidino, **b** R = NMe_2

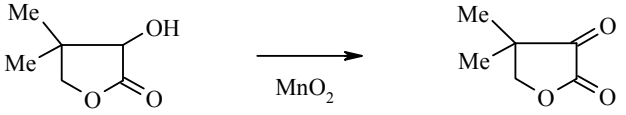
2. Oxidation of Fragments of the Heterocycles

The preferred mechanism for the oxidation of fragments of heterocycles with MnO_2 is considered to be the free-radical mechanism, presented below for the case of the alcohols **20** with the intermediate formation of a coordination complex after adsorption of the substrate on the surface of the MnO_2. The coordination complex is then transformed by reversible proton transfer into the manganese ester **21** and then (after transfer of a hydrogen atom) into a free radical with the valence of the manganese reduced to three [4-6]. This radical dissociates irreversibly with the formation of the final oxo compound **22**.



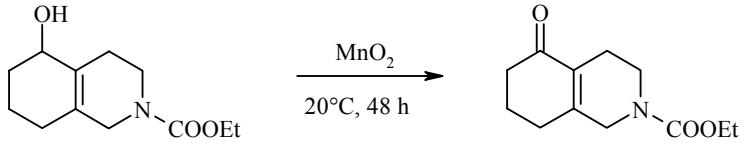
20 **21** **22**

The OH group, directly attached to the ring, is easily oxidized to an oxo group. Thus, the oxidation of pantolactone **23** gave the ketopantolactone **24** with a yield of 97% [34].



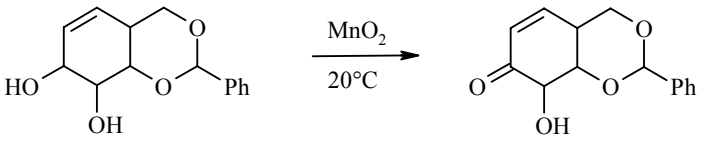
23 **24**

The selectivity of the oxidation of the carbamate **25** only to the ketone **26** (yield 43%) with a 25-fold excess of MnO_2 [35] makes it possible to use it in the synthesis of important analgesics having a reduced narcotic component.



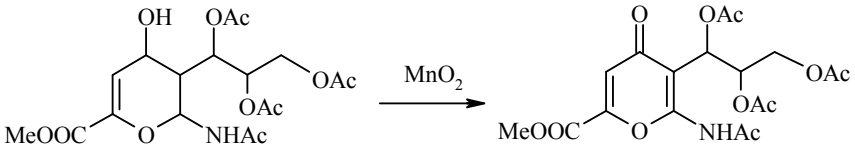
25 **26**

It was shown that of the two adjacent hydroxyl groups in tetrahydro-4H-1,3-benzodioxine **27** only the one in the allyl fragment (7-OH) is oxidized [36]. The yield of the ketone **28** was 81%.



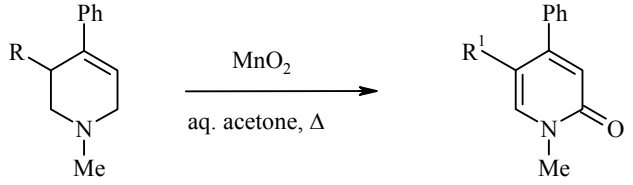
27 **28**

During the oxidation of the derivative of neuraminic acid **29** the transformation of the OH group into a ketone group is accompanied by dehydrogenation with the formation of the γ-pyrone **30** [37].



29 **30**

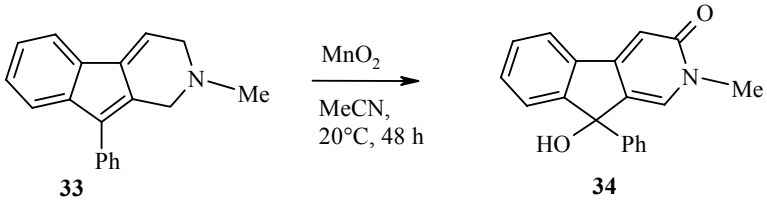
Dehydrogenation also takes place during the oxidation of the CH_2 group of the ring to a C=O fragment. Thus, boiling of the substituted tetrahydropyridines **31** with MnO_2 in aqueous acetone leads to the formation of the α-pyridones **32** (yields 21-57%) [38].



31 **32**

R = CH_2OH, –COPh; R^1 = CHO, –COPh

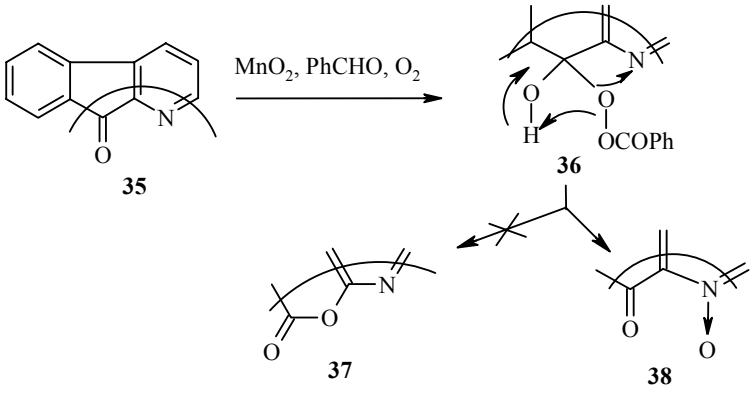
During the action of MnO_2 on 2,3-dihydro-1H-2-azafluorene **33** its heterocyclic fragment is oxidized to a lactam fragment, which is stabilized as a result of migration of the double bond with the formation of the azafluorene derivative **34** (yield 20%) [39, 40].



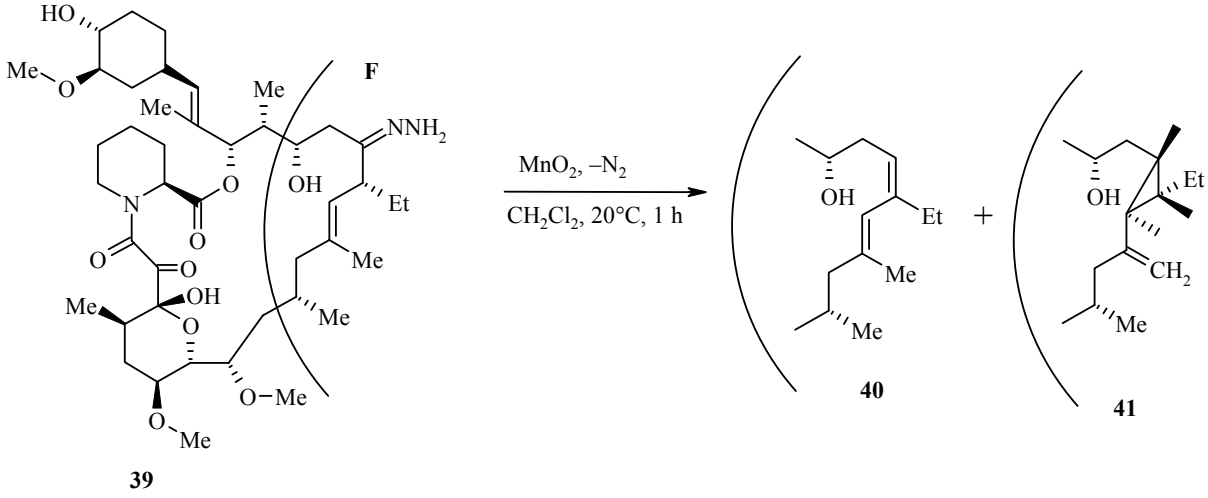
33 **34**

The quaternary salts of di- and tricyclic heteroaromatic compounds containing a pyridinium ring are oxidized by MnO_2 to the corresponding N-substituted derivatives of annulated α- or γ-pyridones. Thus, 1,10-phenanthrolinium methiodide is oxidized with a quantitative yield to N-methylphenanthrolone [41].

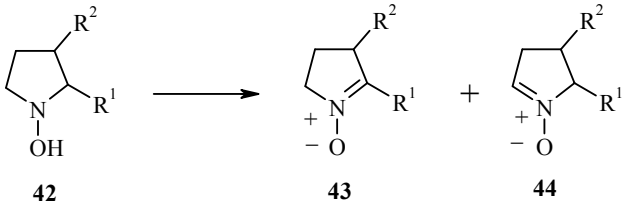
If a modified system is used for the oxidative Baeyer–Villiger rearrangement (O_2, PhCHO, MnO_2) in the azafluorene series oxidation only occurs in compounds of type **35** (having a 9-CO group) through the intermediate adduct **36**. N-Oxides of type **38** are formed (yields 70-75%) instead of the expected lactones. The impossibility of the rearrangement **36** → **37** is probably due to the fact that the nitrogen atom in the adduct **36** plays the role of an effective trap for the active oxygen atom [42].



Oxidation of the 22-hydrazone of the macrolactam antibiotic ascomycin **39** takes place at the **F** fragment with the formation of a mixture of five products, of which the main products are compounds **40** and **41**. In methanol the cyclopropane derivative **41** is formed exclusively [43].

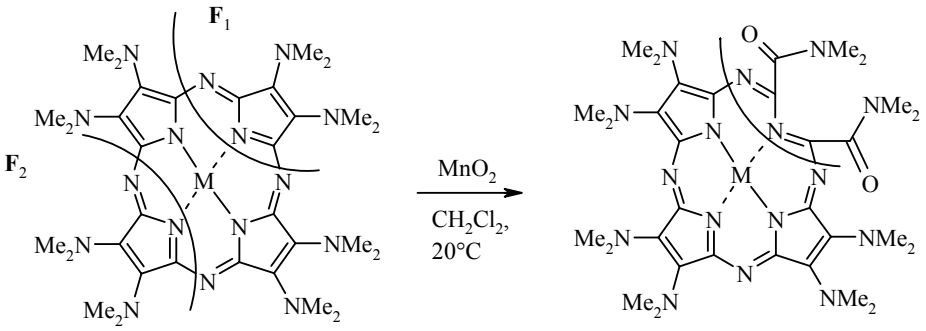


The N-hydroxypyrrolidines **42** were oxidized to the corresponding nitrones **43** and **44** with overall yields of 85-92% [44]. (The **43**:**44** ratio varied between 5 and 7.)



42–**44** R^1 = Me, R^2 = H; R^1 = H, R^2 = OBu-*t*

During the action of an equimolar amount of MnO_2 on the base **45a** or the salt **45b** the heterocycle of fragment $\mathbf{F}_1$ is easily opened and oxidized with the formation of the products **46a**,**b** (yields 77-97%). Treatment of the salt **45b** with twice the amount of MnO_2 leads to an analogous transformation in fragment $\mathbf{F}_2$ with the formation of a product containing four $CONH_2$ groups (yield 41%) [45].



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

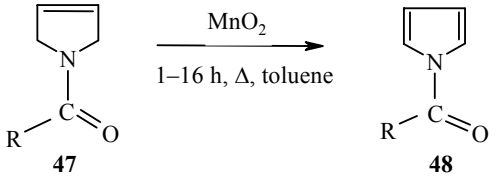
45, **46 a** M = 2H, **b** M = Zn

During a study of the oxidation of cyclic thioethers to sulfoxides by MnO_2 in the absence of solvents it was found that additions of silica gel treated with H_2SO_4 significantly increase the yield of the required products [46].

3. Dehydrogenation of Partly Saturated Heterocycles

A large, constantly increasing, number of examples of the use of MnO_2 for the partial dehydrogenation or aromatization of heterocyclic compounds are known. The main advantages in comparison with metallic catalysts are the availability, low price, and the acceptable (with rare exceptions) degree and selectivity of the transformations even at room temperature.

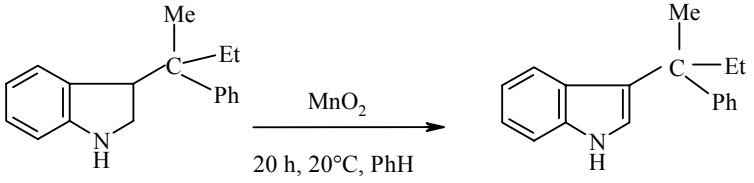
Manganese dioxide is recognized as the most suitable dehydrogenizing agent for the synthesis of 2,4-diacylfurans [47] and also N-benzyl- and N-acylpyrroles [48, 49]. Thus, N-acylpyrroles **48** were obtained from N-acylpyrrolines **47** with yields of 78-91%.



47 **48**

R = CH_2CH_2Ph, $CH_2CH_2CH(OH)Me$, $CH_2CH(Me)COOCH_2Br$

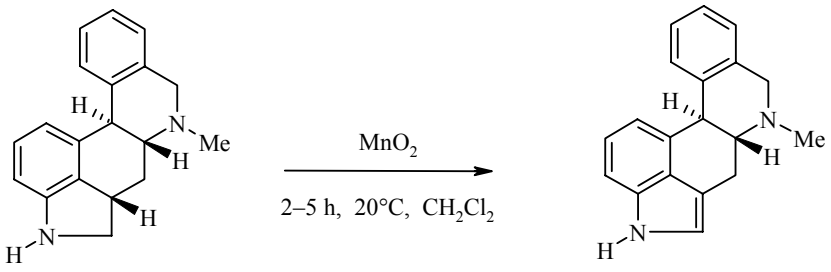
Substituted indolines are also easily converted into the corresponding indoles [50-53]. For example, each of the two individual diastereomers of the indoline **49** was converted by the action of a fivefold excess of MnO_2 into one and the same optically active indole **50** (yield 76%) [51].



49 **50**

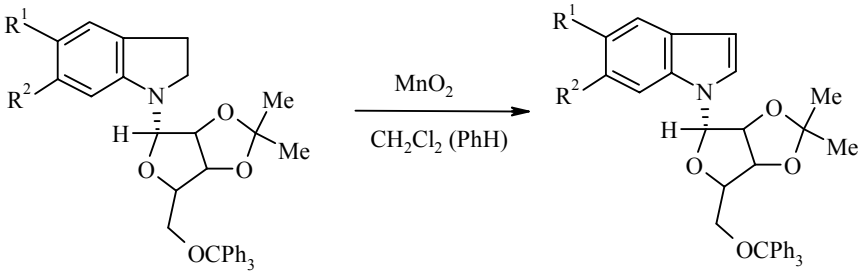
It should, however, be noted that cleavage of the pyrrole ring at the 2–3 bond, leading to the formation of high yields of N-formylanthranilic acid and (N-acetylamino)benzophenone respectively, was observed during the formation of unsubstituted indole and 2,3-dimethylindole [4].

Dehydrogenation of only pyrroline ring was observed during the synthesis of representatives of a new class of powerful and selective agonists of dopamine receptors; "benzergoline" **52** was obtained from a solution of octahydrophenanthridine **51** with a yield of 61% [54].



51 **52**

Recently [55], by the action of MnO_2 in the presence of 4 Å molecular sieves it was possible to realize the effective dehydrogenation of substituted α-D-ribofuranosylindolines **53** to the corresponding α-indole nucleosides **54**, which can serve as synthons for the production of vitamin B_{12}.

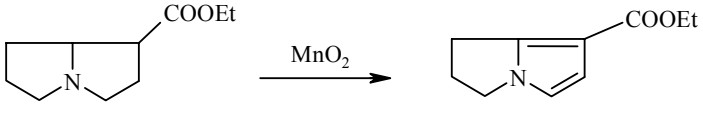


53a–c **54a–c**

a $R^1 = R^2 = H$; **b** $R^1 = R^2 = Me$; **c** $R^1 = Br$, $R^2 = H$

Substituted pyrrolidines can also be transformed into the corresponding pyrroles by boiling with a fivefold excess of MnO_2 in THF [56]. In a number of cases *cis*-3,4-substituted pyrrolidines give higher yields of pyrroles than the analogous *trans* isomers. The yields of the indoles are increased significantly by the use of microwave radiation [57].

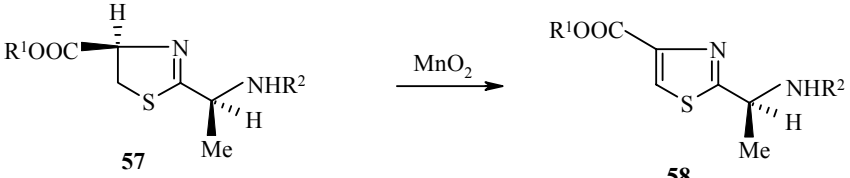
In pyrrolizidine **55** only the substituted ring is dehydrogenated, and the ester group is retained in the product **56** [58].



55 **56**

Dehydrogenation with MnO_2 was also realized successfully in five-membered heterocycles with two heteroatoms: The dihydro derivatives of pyrazoles [59, 60], imidazoles [61], isoxazoles [62], and thiazoles [63, 64] and also tetrahydrothiazoles [63-66].

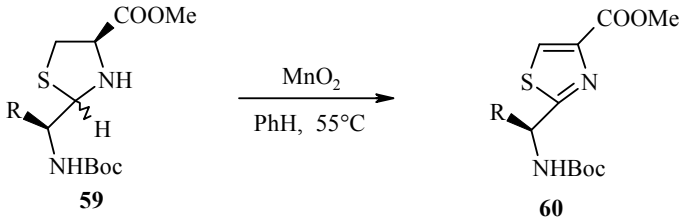
During the synthesis of fragments of cyclic peptides isolated from marine organisms it was found that the dehydrogenation of thiazolines **57** having a substituent with the L-configuration takes place without racemization. The yields of the thiazoles **58** amount to 51-81% [63, 64].



57 **58**

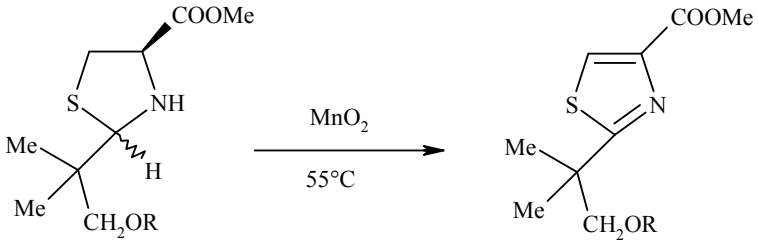
R^1 = Me, $PhCH_2$; R^2 = BnCOO

Manganese dioxide has also been used for the production of esters of type **60**, which are the base synthons in the synthesis of lyngbyabellins (powerful natural cytotoxic lipopeptides isolated from marine cyanobacteria) [65], and esters of type **62** – intermediate compounds in the synthesis of mycothiazole (an anticancer natural compound isolated from a marine sponge). The yields of the products **62** amount to 15-62% (with the use of a 25-100-fold excess of MnO_2) [66].



59 **60**

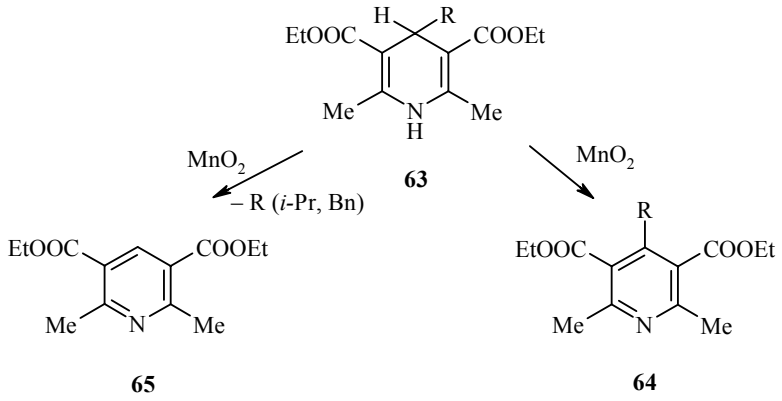
R = –$CHMe_2$, CH(Me)Et



61 **62**

In [67, 68] it was established that boiling of 4-aryl-1-methyl-1,2,3,6-tetrahydropyridines with MnO_2 (a tenfold excess) in toluene leads to 4-arylpyridines with yields of up to 45%.

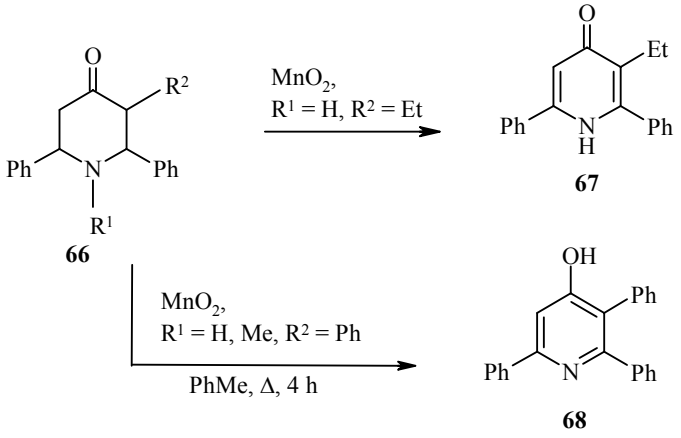
The aromatization of Hantsch 1,4-dihydro-1H-pyridines (with 4-Ar or 4-Het substituents) [69-72] and N-substituted 1,2-dihydropyridines [73-75] was realized with MnO_2 under mild conditions. It was shown that the duration of the reaction is greatly reduced with the use of microwave radiation (MnO_2/bentonite, no solvent, 5-20 min) or with ultrasonic irradiation [76, 77]. For example, the pyridines **64** were obtained with yields of 81-95% from dihydropyridines **63** (a 5-10-fold excess of MnO_2, CH_2Cl_2, 20°C) after exposure for 5 min (20 kHz).



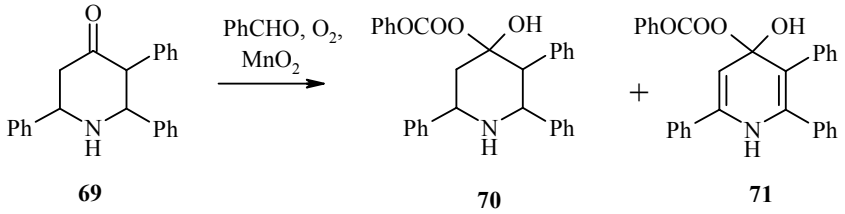
R = Et, Pr-*i*, Ph, Bn, $C_6H_4R^1$, R^1 = 4-Cl, 4-OH, 2(4)-OMe, 3(4)-NO_2, 2-thienyl, 2-furyl

Here it was noticed that the substituent R can be removed with the formation of compounds **65** as side products [76, 78].

The piperidones **66** are dehydrogenated by MnO_2 to the dihydropyridine **67** (yield 48%) or hydroxypyridine **68** (yields 62-74%) depending on the substitution [79]. In the latter case demethylation and prototropic shift evidently occur.

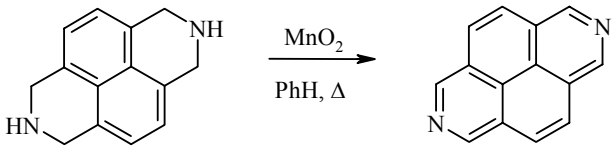


During an attempt at the transformation of the piperidone **69** to a seven-membered lactone under the conditions of the modified Baeyer–Villiger method (the system with PhCHO, O_2, MnO_2) only the intermediate peroxide **70** (yield 7.5%) and its dehydro derivative **71** (11%) were isolated from the complex mixture of products [80].



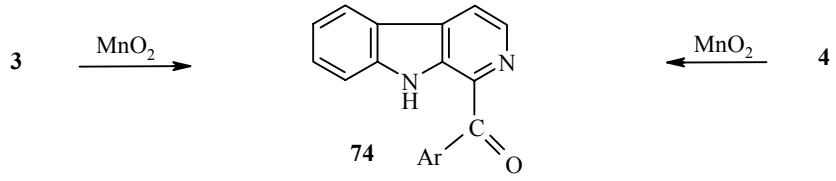
Boiling of benzene solutions of substituted 1,2-dihydroquinolines with MnO_2 leads to their almost quantitative aromatization [81].

Under the same conditions and just as easily hexahydro-2,7-diazapyrene **72** is converted into diazapyrene **73** (yield 71%) [82].



72 **73**

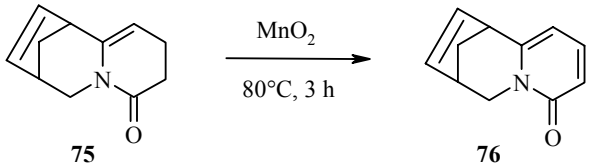
A simple reliable method was developed for the synthesis of fascaplysin (a red pigment of a marine sponge, having antimicrobial and cytotoxic activity), where one of the key stages was the oxidation of bromobenzyldihydrocarboline **3** to the aroylcarboline **74** [11]. It was shown that the $ArCH_2$ group is oxidized at room temperature (see section 1), while with boiling in chloroform aromatization of the dihydropyridine fragment occurs, and the product **74** is obtained with a yield of 86%; the latter is also formed with a yield of 91% during dehydrogenation of the dihydrocarboline **4** under analogous conditions.



74

Ar = C_6H_4Br-2

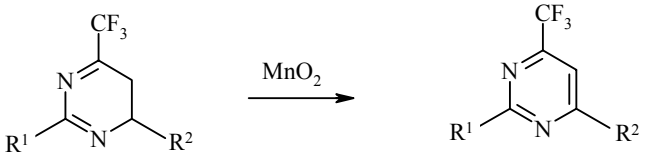
In the synthesis of cytisine – an alkaloid of the lupin series – MnO_2 (a 10-20-fold excess) was the most effective oxidizing agent for the conversion of the intermediate lactam **75** into the pyridone **76** [83, 84].



75 **76**

The dihydro and tetrahydro derivatives of diazines are also aromatized successfully by MnO_2. Thus, 4-aryl-1,4-dihydropyridazines [69], 4-aryl-1,4-dihydropyrimidines [85], 2,4-diaryl-1,2,3,4-tetrahydropyrimidines [86], and dihydropurines [87] are transformed by heating with MnO_2 into the corresponding pyridazines and pyrimidines, which were tested for antitumor, antioxidant, and coronary-protecting activity.

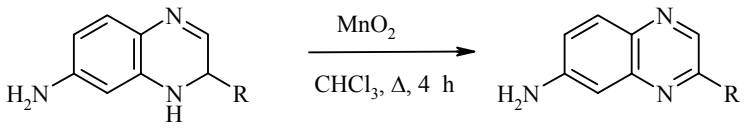
During the oxidation of dihydropyrimidines **77** to pyrimidines **78** it was shown that the yields of the latter (9-86%) depend on the nature of the substituents and on their arrangement in the diazine ring [88].



77 **78**

R^1, R^2 = Alk, Ar

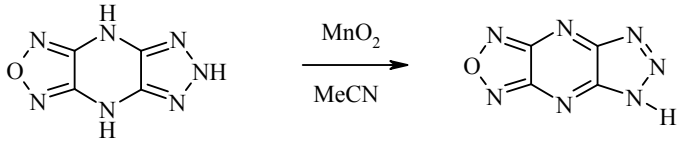
By boiling 7-amino-1,2-dihydroquinoxalines **79** with MnO_2 it is possible to obtain quinoxalines **80** with yields from 8 (R = Me) to 75% [89].



79 **80**

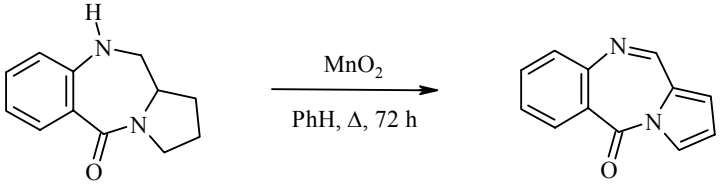
R = Me, Bu, Bu-*t*, *cyclo*-C_6H_{11}, Ph

The dehydrogenation of triazolofurazanopiperazine **81** to the pyrazine derivative **82** with migration of the multiple bond by the action of MnO_2 in acetonitrile was described [90].



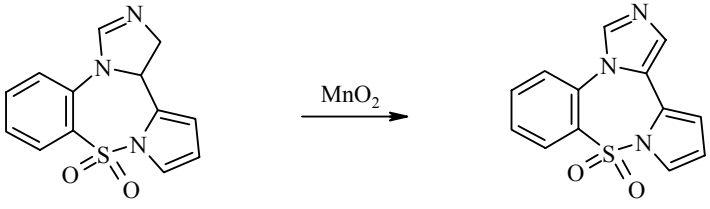
81 **82**

Two examples of the dehydrogenation of compounds containing a seven-membered heterocycle are also known. Thus, when hexahydropyrrolo[1,4]benzodiazepinone **83** is boiled with MnO_2 in benzene the seven- and five-membered heterocycles are dehydrogenated with the formation of the product **84** [91].



83 **84**

The annelated 1,2,5-benzothiadiazepinedione **85** is converted very easily into compound **86** by the action of MnO_2 [92].

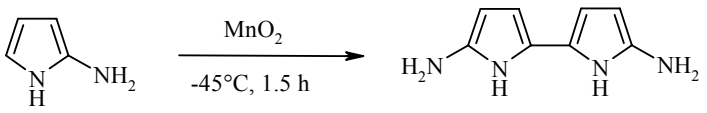


85 **86**

4. Oxidative Coupling Reactions

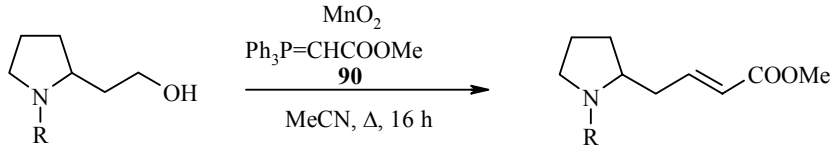
Papers in which the possibility of oxidative N–N coupling of aromatic amines, under the influence of MnO_2, leading to azobenzenes was established were mentioned in the review [3]. However, it was shown

recently that at low temperature (-45°C) the C–C coupling product **88** was formed from aminopyrrole **87** with yields of up to 49% instead of the expected azo compound [93].



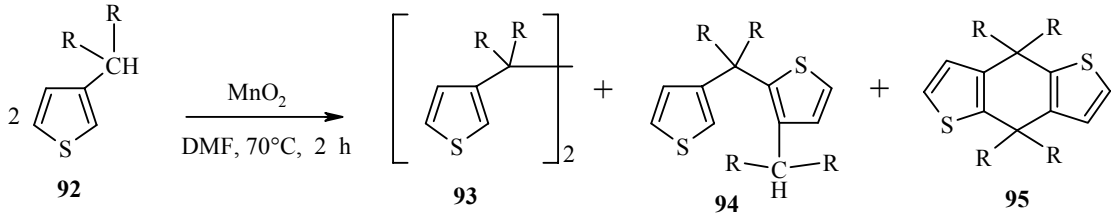
87 **88**

Oxidation of a mixture of the alcohol **89** with the phosphorane **90** (with a 25-fold excess of MnO_2) led to the corresponding aldehyde, which entered *in situ* into a Wittig reaction, forming the alkene derivative **91** (a cross-coupling product) with a high yield [94]. Certain other hetaryl-substituted alkenes were obtained in a similar way [27-29].



89 R = COOEt, COOBn **91**

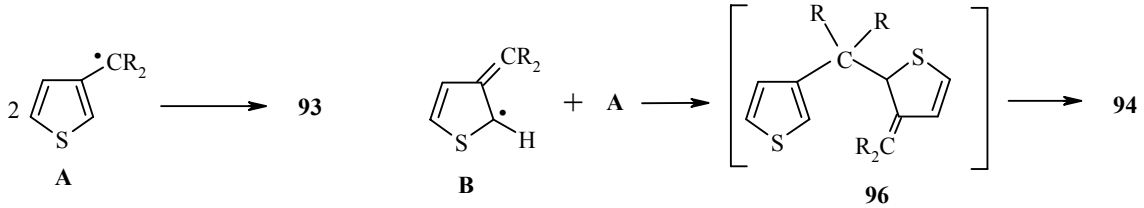
The dimers **93** (yield 39%) and **94** (56%) [95] and also the product from intramolecular cyclization **95** (yield 8%) were obtained by heating diethyl 3-thienylmalonate **92** and MnO_2 in DMF.



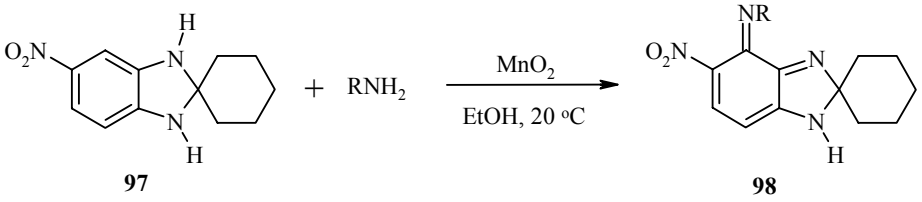
92 **93** **94** **95**

R = COOEt

The product **93** was formed from the radical **A** during dimerization, while the product **94** was formed by the cross coupling of radicals **A** and **B**. It was assumed that the intermediate unstable dimer **96** (which could not be isolated) had high acidity and was converted into the dimer **94** by a prototopic shift.



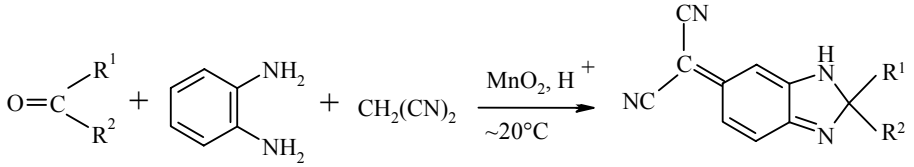
Under the influence of MnO_2 (**97**–MnO_2, 1.3:37) 5-nitro-2,2-pentamethylene-1,2-dihydrobenzimidazole **97** enters into oxidative C–N coupling with cyclohexylamine and 4-amino-2,2,6,6-tetramethylpiperidine, leading to the *ortho*-quinone diamines **98** (yields 77-78%) [96].



97 **98**

R = *cyclo*-C_6H_{11}, 4-(2,2,6,6-tetramethylpiperidyl)

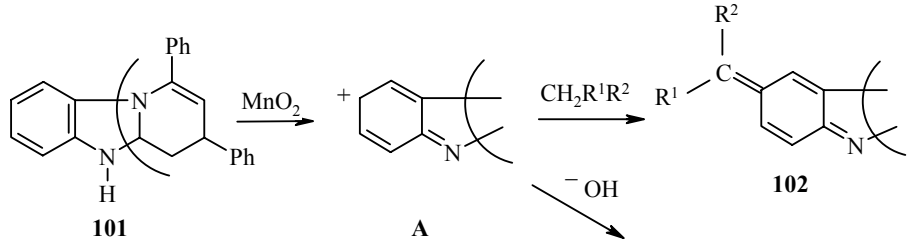
With MnO_2 and acidic catalysts (HCl, AcOH, BF_3, etc.) it was possible to realize the condensation of ketones **99** with *ortho*-phenylenediamine and malononitrile in one stage [97]. The yield of the products **100** was 14-47%. The role of the MnO_2 in this cascade transformation is initiation of the final stage of C–C cross coupling.



99a–f **100a–f**

99, **100 a** $R^1 = R^2 =$ Me; **b** R^1 = Me, R^2 = Et; **c** R^1 = Me, R^2 = Bn; **d–f** $R^1+R^2 = (CH_2)_n$, n = 4–6

The analogous oxidative coupling of tetrahydro[1,2-*a*]benzimidazoles **101** and their annelated derivatives was realized successfully with a series of CH acids [98-102]. Condensation takes place regioselectively in the benzene ring, the oxidative dehydrogenation of which leads to the cation **A**. Reaction of the latter with the CH acid leads to the formation of the product **102**, but the formation of the ketone **103** is also possible. The yields of the products **102** and **103** depend largely on their stability and on the structure of the initial substrates. Products of the **103** type were obtained from compounds of the **101** type and aromatic or aliphatic amines, ammonia, and thiourea [103, 104].

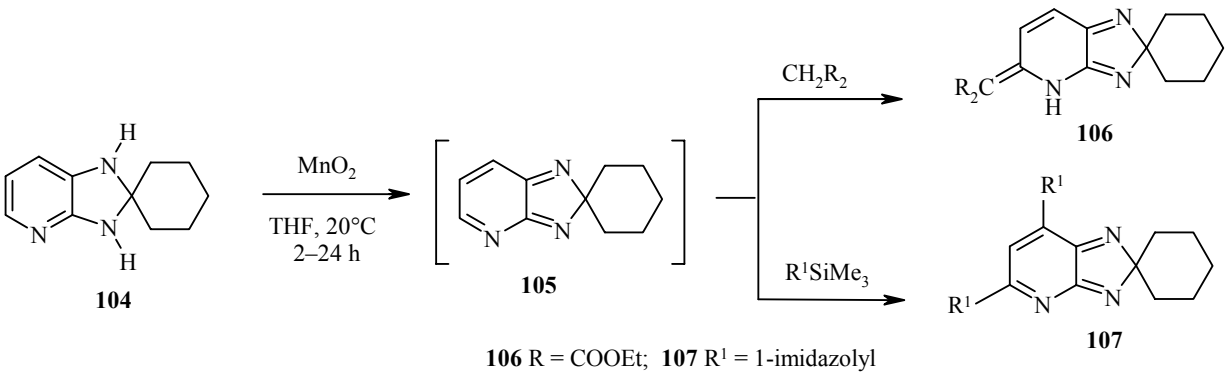


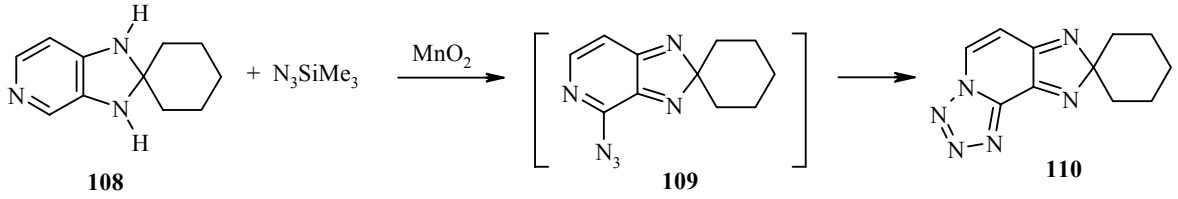
101 **A** **102** **103**

102 R^1 = H, R^2 = H, NO_2, CN, Ph, C_6H_4COOH-4, $C_6H_4SO_3H$-4, $C_6H_3(NO_2)_2$-2.4 , $C_6H_4(N{=}NPh)$-4; R^1 = CN, $R^2 = CONH_2$; $R^1 = R^2$ = CN, COOEt

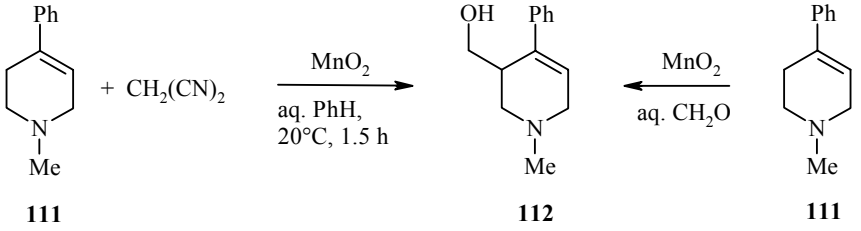
In the case of 2,3-dihydro-1H-imidazo[4,5-*b*]pyridine **104** oxidation also takes place initially (with a fivefold excess of MnO_2), leading to the imidazopyridine **105** (which could not be isolated). Reaction of the latter with ethyl malonate or trimethylsilylimidazole leads to the products **106** (yield 55%) or **107** (yield 12%) [105]. If there is a bromine atom at position 6 of the initial imidazopyridine **104** the diethyl malonate only

attacks position 7. With trimethylsilyl azide the product from oxidation of 2,3-dihydro-1H-imidazo-[4,5-*c*]pyridine **108** forms the 4-azido derivative **109**, which is quickly transformed into the tetrazole **110** (yield 46%) [105].



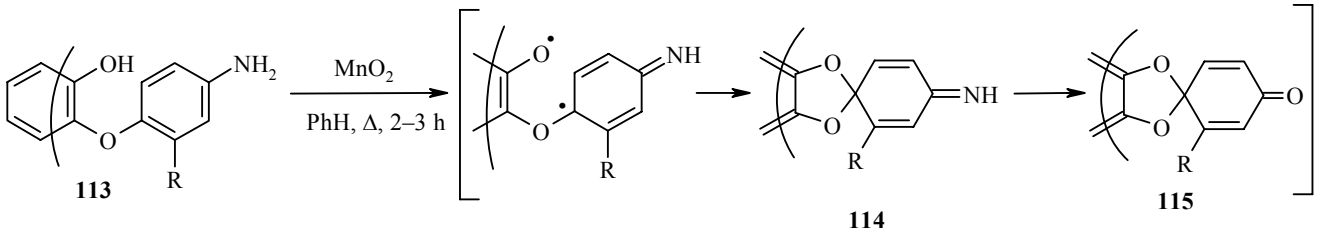


When a mixture of tetrahydropyridine **111** with MnO_2 (a fivefold excess) and malononitrile was kept without heat the hydroxymethylation product **112** was obtained (yield 36.5%) [106, 107]. It is assumed that formaldehyde or its imine can be formed from the dinitrile under the reaction conditions and then adds at the multiple bond of the heterocycle. In fact, holding a mixture of compound **111** with aqueous formaldehyde and MnO_2 led to compound **112** with a yield of 22%. (Without MnO_2 the reaction does not occur.)

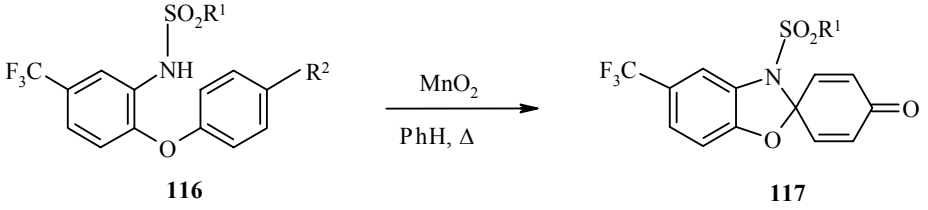


5. Intramolecular Cyclizations

The previously discovered effectiveness of MnO_2 in the cyclization of substituted phenols with the formation of heterocyclic spiro compounds [108] was recently [9] confirmed for the case of the analogous transformation of 4-(2-hydroxyphenoxy)anilines **113** into the spiro compounds **115**. It is considered that the reaction takes place through a biradical, which cyclizes to the ketal of quinone imine **114**, where the NH group is readily hydrolyzed to a ketone. (The MnO_2 samples contained up to 25% of adsorbed and ligand water). The low yields of the products **115** (31-40%) are probably due to polymerization of the intermediate radicals and the formation of azobenzene derivatives from them. According to the same paper [9], in compounds **116** the substituted NH group takes part in cyclization, leading to 50-60% yields of the products **117** containing an oxazolidine ring.

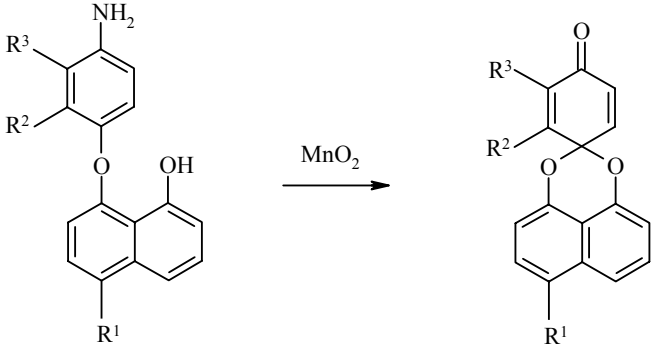


R = H, F, CF_3



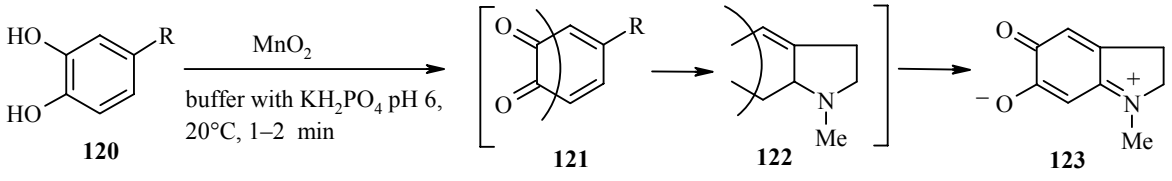
R^1 = Me, *p*-Tol; R^2 = OH, NH_2

The synthesis of the spiro compounds **119** (close structural analogs of palmarumycin, which is the parent of a series of metabolites of the fungus *Coniothyrium sp.* and exhibits antimicrobial and fungicidal activity) from derivatives of 1,8-dihydroxynaphthalene **118** was based on a similar oxidative cyclization. The products **119** (yields 25-86%) also have significant antimicrobial activity.



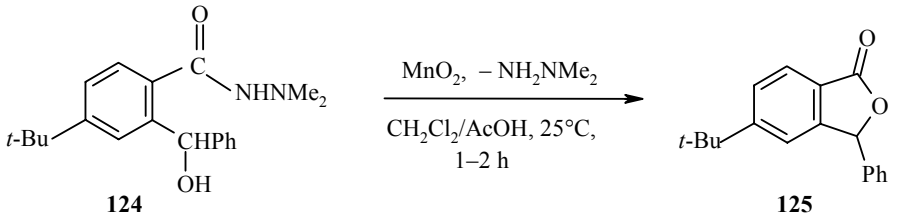
a $R^1 = R^2 = H$, R^3 = OMe; **b** $R^1 = R^3$ = OMe, R^2 = H; **c** R^1 = OMe, $R^2 = CF_3$, R^3 = H

The epinine **120** is quickly transformed by the action of MnO_2 into the *ortho*-quinone **121**, which undergoes cyclization by a Michael type of reaction to the indoline **122**. The latter is dehydrogenated with a high yield to the relatively stable epinochrome **123** [110], which is used in the production of 5,6-dihydroxyindole and the antioxidants, dyes, and polymers produced from it. In this respect MnO_2 has great advantages over such oxidants as H_2O_2, $H_2O_2/FeSO_4$, NaOCl, $NaClO_3/V_2O_5$, Ag_2O, and $K_3Fe(CN)_6$.



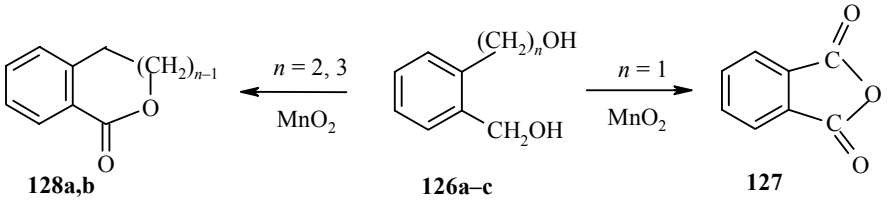
R = CH_2CH_2NHMe

Treatment of the dimethylhydrazide **124** with a 10-fold excess of MnO_2 leads to the oxidative elimination of dimethylhydrazine and intramolecular esterification with the quantitative formation of the phthalide **125** [111].



124 **125**

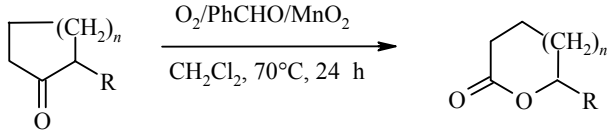
The use of MnO_2 proved very effective in the oxidative intramolecular cyclization of compounds **126a**,**c** to the phthalide **127** and dihydroisocoumarin **128a** respectively, which were obtained with high yields [112]. When n = 3 the yield of the lactone **128b** was very low, and it was possible mainly to isolate only *ortho*-(γ-hydroxypropyl)benzaldehyde. In this connection it was considered that substituted benzaldehydes are also formed initially from compounds **126a**,**c**, and their semiacetals are oxidized to the respective products **127** and **128a**.



128a,b **126a–c** **127**

126 a n = 1, **b** n = 2, **c** n = 3; **128 a** n = 2, **b** n = 3

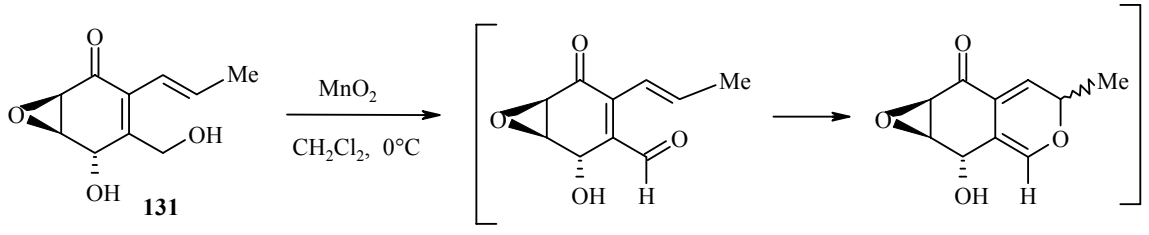
When oxygen is bubbled through a mixture of the ketone **129** with a 2-3-fold excess of benzaldehyde in the presence of catalytic amounts of MnO_2 the lactone **130** is formed (yields 71-95%) [113]. The addition of lithium perchlorate or molecular sieves reduces the time of the Baeyer–Villiger type of reaction from 24 to 6 h.



129a–d **130a–d**

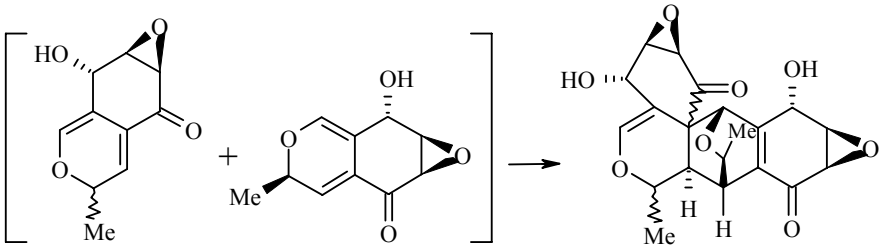
129, **130 a** R = H, **b**, **c** R = Ph, **d** R = C_6H_4Cl-3; **a**, **b** n = 1, **c**, **d** n = 2

During oxidation of the CH_2OH group in the epoxide **131** with MnO_2 the formed aldehyde **132** (not isolated) undergoes 6π-electrocyclization to the stereoisomeric derivatives of 2H-pyran **133a**,**b**.



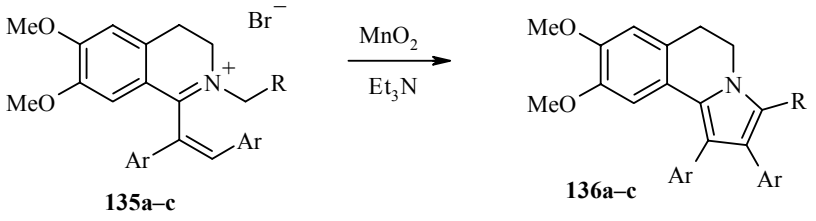
131 **132** **133a,b**

The diastereomers **133a**,**b** enter into a Diels–Alder reaction, in which the dienophile may be compound **133a** or **133b** while the diene is compound **133a** in both cases. As a result the α,α-diastereomer **134a** (epoxyquinolol **A**) and the β,β-diastereomer **134b** (epoxyquinolol **B**), which are inhibitors of angiotensin, are formed [114].



133a/133b **133a** **134a,b**

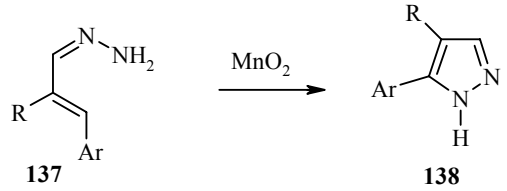
During the action of a base and MnO_2 the quaternary salts of substituted 3,4-dihydroisoquinoliniums **135** generate N-ylides, which undergo 1,5-electrocyclization and oxidation, leading to pyrrolo[2,1-*a*]isoquinolines **136** [115].



135a–c **136a–c**

135, 136 a R = Ar = Ph; **b** R= COPh, Ar = C_6H_4Me-4; **c** R = COOMe, Ar = $C_6H_4NO_2$-4

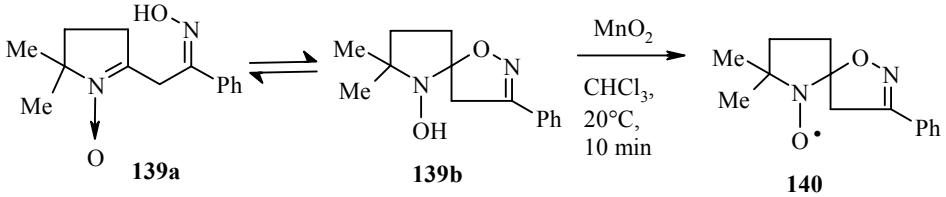
Oxidative heterocyclization of the hydrazones **137** leads to the formation of the pyrazoles **138** [116].



137 **138**

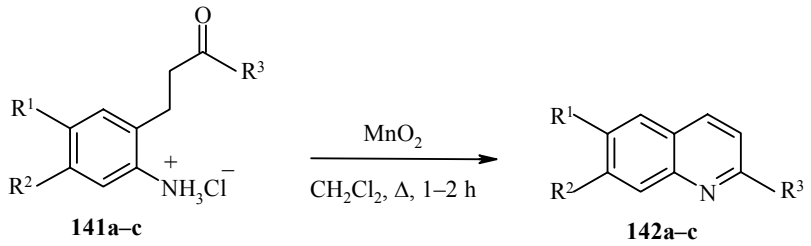
Ar = Ph, $C_6H_4NO_2$-4; R = H, Me

The oxidation of the nitrone oxime **139a** is preceded by the formation of the spirocyclic tautomer **139b**, containing a hydroxyamino group, and this is easily oxidized by MnO_2 to the stable free radical **140** (yield 85%) [32].



139a **139b** **140**

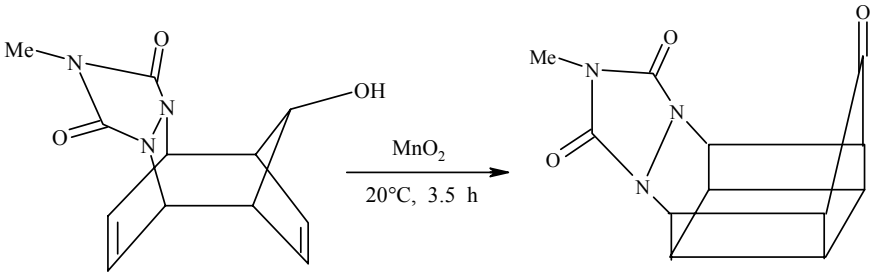
When the arylammonium salts **141** are boiled with MnO_2 in CH_2Cl_2 successive cyclization and dehydrogenation lead to the formation of the quinolines **142** (yields 41-67%) [117].



141a–c **142a–c**

141, **142 a** R^1 = OMe, R^2 = H, R^3 = CH_2CH_2Ph; **b** R^1+R^2 = OCH_2O, R^3 = $CH{=}CMe_2$;
c R^1 = H, R^2 = OMe, R^3 = 3-furyl

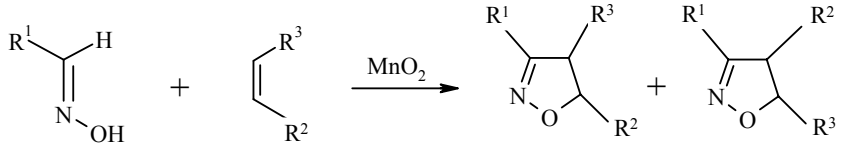
During the action of MnO_2 (a fourfold excess) on the alcohol **143**, in addition to oxidation of the OH group to ketone, intramolecular [2+2] cycloaddition ($2\pi \rightarrow 2\sigma$ isomerization) occurred readily, leading to the formation of the homocubane structure **144** (yield 85%) [118].



143 **144**

6. Intermolecular Cyclizations

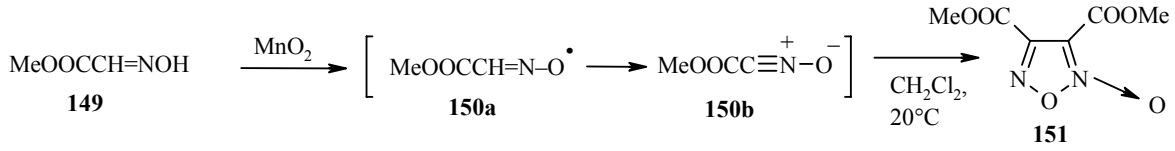
In the presence of MnO_2 (an 18-fold excess) the aldoximes **145** enter into 1,3-dipolar cycloaddition with dipolarophiles (a threefold excess). Only the products **147a**,**b** are formed from compounds **145a**,**b** and **146a**,**b** with yields of 42-48%, but a mixture of regioisomers **147c** and **148** is formed from **145c** and **146c** [119].



145a–c **146a–c** **147a–c** **148**

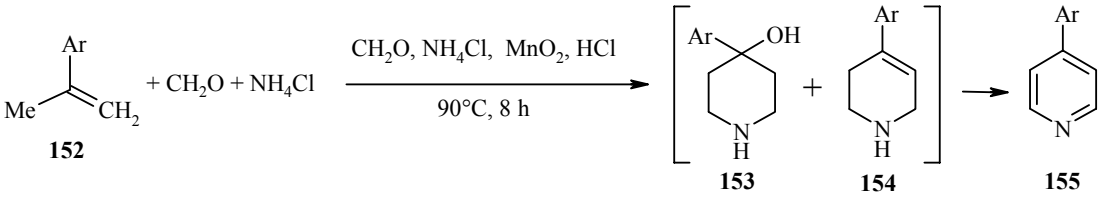
145–147 a R^1 = R^2 = COOMe, R^3 = H; **b** R^1 = Ph, R^2 = OAc, R^3 = H;
145–147 c, 148 R^1 = CCl_3, R^2 = Ph, R^3 = COPh

Methyl acetohydroximate **149** evidently dimerizes through the intermediate radical **150a** and nitrile oxide **150b** resulting in the formation of the furoxane **151** (yield 87%) [119].



149 **150a** **150b** **151**

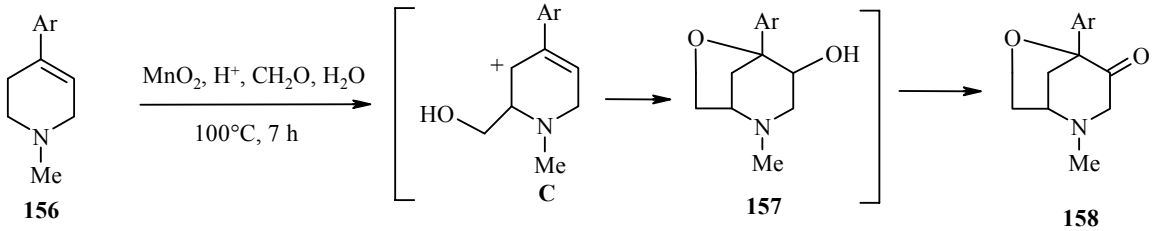
4-Arylpyridines **155** (yields 27-32%) were obtained during the condensation of 2-arylpropenes **152** with formaldehyde and ammonium chloride (probably through the intermediate piperidols **153** and tetrahydropyridines **154**) [120].



152 **153** **154** **155**

Ar = Ph, C_6H_4Me-4

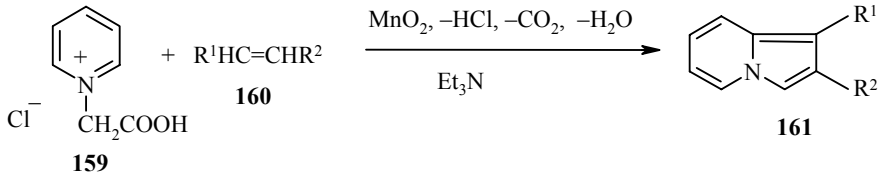
The reaction of formaldehyde and MnO_2 with tetrahydropyridines **156** apparently takes place through dehydrogenation at the C(5)–C(6) bond followed by addition of the hydrated formaldehyde to form the carbocation **C**. Cyclization and hydration of the latter lead to the alcohol **157**, and subsequent oxidation leads to the ketone **158** – a nonclassical product of the Prins reaction.



156 **C** **157** **158**

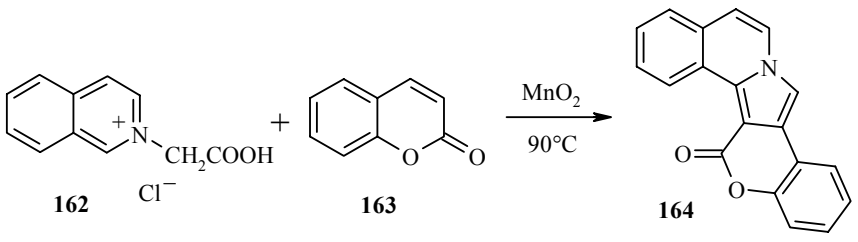
Ar = Ph, C_6H_4Me-4

Pyridinium salts of the **159** type, which do not even react with electron-deficient ethylenes **160**, react with the latter in the presence of MnO_2 with the formation of unstable intermediate 1,2-dihydroindolizines, which are dehydrogenated to the indolizines **161** (yields 63-92%) [121]. Here decarboxylation is observed at the ylide generation stage. The product **164** (58%) was obtained similarly from the isoquinolinium salt **162** and 1,2-benzopyrone **163** [121].



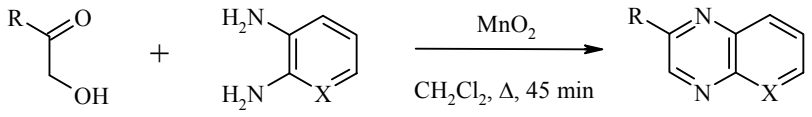
159 **160** **161**

160, **161** **a** R^1 = H, R^2 = COMe; **b** R^1 = Ph, R^2 = COOMe; **c** R^1 = COOEt, R^2 = COMe; **d** R^1 = Ph, R^2 = CN



162 **163** **164**

During the oxidation of a mixture of α-hydroxy ketones **165** and diamines **166** with MnO_2 in the presence of molecular sieves quinoxalines or 5-azaquinoxalines **167** are formed in high yields [122].

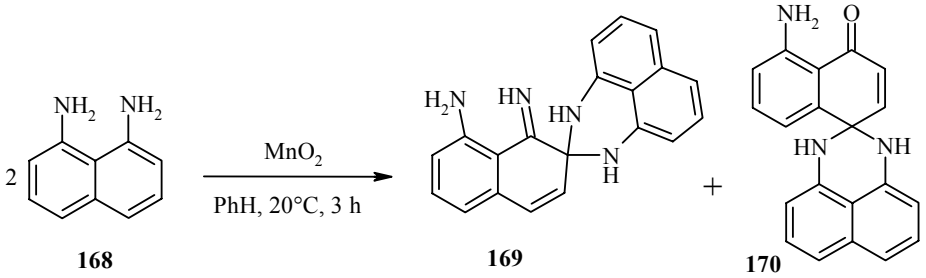


165 **166** **167**

R = Me, *cyclo*-C_6H_{11}, Ph, 2-thienyl; X = CH, N

Analogous oxidative heterocyclization involving 1,2-diaminoethane and its homologs leads to piperazines and pyrazines [122].

The action of MnO_2 on 1,8-diaminonaphthalene **168** gave the spiro products **169** and **170**, which exhibit thermally reversible photochromism [123].



168 **169** **170**

Analysis of the data examined above shows that over the last 10-15 years the oxidizing properties of MnO_2 have continued to be used widely and successfully in the chemistry of heterocycles. The oxidation of hydroxyl groups both in the side chains and directly attached to the heterocycle to C=O groups became a completely standard procedure in research work and has even found application in industry. The use of MnO_2 for the dehydrogenation of five-membered heterocycles and 1,4-dihydropyridines has also become generally accepted. Reliable methods have been developed for oxidative intra- and intermolecular cyclization, leading to complex difficultly obtainable compounds. At the same time the possibility of realizing similar types of cyclocondensation along various pathways has been revealed, and it is obvious from this that the potential of MnO_2 as an initiator of the oxidative transformations of heterocyclic compounds has not yet been fully realized.

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