NITROPYRAZOLES (REVIEW)

M. I. Kanishchev, N. V. Korneeva,
S. A. Shevelev, and A. A. Fainzil'berg

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Data on preparation, properties, transformations, and application of pyrazoles containing a nitro group in the pyrazole ring are correlated.

In the last 15-20 years the chemistry of nitropyrazoles has undergone substantial development due to the use of these compounds as valuable intermediates for the synthesis of biologically active substances, including some antibiotics and their analogs, and dyes. At the same time, the published data on nitropyrazoles virtually has not been previously correlated, i.e., there is only a short review by Fusco [1] in which publications up to 1965 were covered.

In the present review we correlated the literature data on the preparation, physicochemical properties, transformations, and application of pyrazoles containing nitro groups in the pyrazole ring (attached to both carbon and nitrogen atoms).

I. METHODS FOR OBTAINING NITROPYRAZOLES

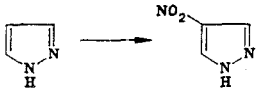
The methods for obtaining nitropyrazoles are quite diverse and depend on the character of the substituents in the pyrazole ring, the electron-density distribution in it, the nitration conditions, the nitrating mixtures used, the temperature, etc.

In many cases it is impossible to introduce a nitro group into the necessary position of the pyrazole ring by nitration, and indirect methods of introducing nitro groups are then used: thermal and other rearrangements involving the migration of nitro groups, recyclization of other nitroheterocycles, cyclization of nitro-containing synthones, and the conversion of some groupings in the pyrazole ring to nitro groups.

1. Nitration of Pyrazoles

The 4 position of the pyrazole ring is the most accessible for electrophilic attack, and 4-nitropyrazoles are usually formed by the action of various nitrating agents on pyrazoles with a free 4 position.

Thus 4-nitropyrazole is formed in 80% yield in the nitration of pyrazole (110°C, 48 h) with a nitrating mixture [a mixture of nitric (d = 1.5) and sulfuric acids] [2].



The introduction of alkyl substituents into the pyrazole ring facilitates nitration of pyrazole in the 4 position [3-5]. The presence of various substituents in the 3(5) position does not prevent nitration of the pyrazole ring. Thus the introduction of bulky substituents such as the tert-butyl group into the 3 or 5 position of the pyrazole ring does not give rise to significant hindrance to nitration in the 4 position [6]. The corresponding 3(5)-(3-pyridyl)-4-nitro-5(3)-R-pyrazoles (R = H, Cl, NO_2) can be obtained in high yields in the nitration of 3(5)-(3-pyridyl)-5(3)-R-pyrazoles [7-9]. The corresponding 4-nitropyrazoles are formed in the nitration of aryl- and thienylpyrazoles; the aryl and thienyl rings are also nitrated in this case [2, 10]. 3(5),4-Dinitropyrazole is formed in the nitration of 3(5)-nitropyrazole [7, 11]. The corresponding 4-nitropyrazole-3-carboxylic acids are obtained in the case of pyrazole-3-carboxylic acids [12, 13]. 4-Nitropyrazoles were also ob-

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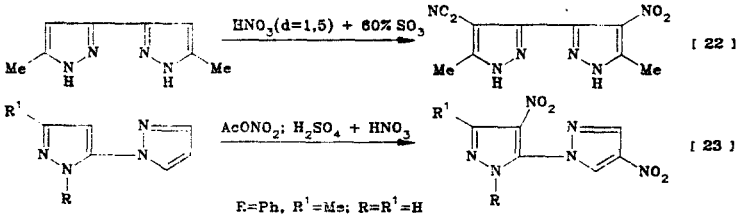
tained in high yields in the case of 3(5)-halo-5(3)-methylpyrazoles [14-17]. The nitration of 3-trimethylsilylpyrazole gave 4-nitro-3-trimethylsilylpyrazole, from which 4-nitropyrazole was then obtained in high yield [18].

The presence of an electron-acceptor substituent in the 1 position (for example, a picryl, 2,4-dinitrophenyl, or nitroguanidyl group) does not prevent nitration of the pyrazole ring in the 4 position [19-21].

4,4'-Dintiropyrazoles can also be obtained via acidic nitration:



N-Substituted 3- and 5-hydroxypyrazoles (3- and 5-pyrazolones) and the corresponding 5-alkoxy derivatives are nitrated by a nitrating mixture in the 4 position extremely readily (at ∿20°C) [24, 25]. In some cases 3- or 5-hydroxypyrazoles are nitrated under the influence of alkyl nitrites [25].

Interesting principles were observed in the nitration of 1-phenylpyrazoles with a vacant 4 position. Three types of compounds are formed, depending on the character of the substituents in the pyrazole ring, as well as on the nitrating agents used. A) 1-(4-Nitrophenyl)-4-nitropyrazoles are usually formed when a nitrating mixture is used for 1-phenylpyrazoles containing substituents such as phenyl, methyl, chloro, and thienyl in the 3 and 5 positions of the pyrazole ring [10, 26-29]. B) Exclusively 4-nitropyrazoles are formed in the case of nitration with acetyl nitrate [29-32] and nitronium tetrafluoroborate in sulfolane [33] (the aromatic ring is not involved under these conditions). C) p-Nitrophenylpyrazoles are initially formed in the case of nitration with nitric acid or nitrating mixtures under mild conditions [29-36]; the reaction goes further with the formation of 1-(4-nitrophenyl)-4-nitropyrazoles with an increase in the HNO_3 concentration in the mixture or when the mixture is heated [33, 36, 37].

The authors explain such different reaction pathways in the following way: in the case of nitration with a nitrating mixture or nitric acid the initial step is protonation of the pyrazole ring, which acts as a para orientor in nitration of the aromatic ring, and the products are 1-(4-nitrophenyl)pyrazoles, which are then nitrated to give 4-nitropyrazoles. This sort of protonation does not occur in the case of nitration with acetyl nitrate, as confirmed by data on nitration with $NO_2^+BF_4^-$ in sulfolane [33], and exclusively 1-phenyl-4-nitropyrazoles are formed.

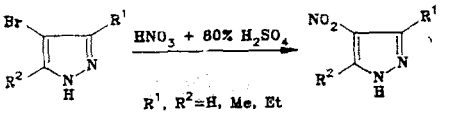
In fact, a detailed study of the kinetics of nitration with nitrating mixtures in the pyrazole series showed that pyrazole itself (pK_{BH^+} 2.52 [38]) and its C- and N-alkyl- and phenyl-substituted derivatives are nitrated in the protonated form, i.e., in the form of pyrazolium cations [31, 39, 40]. This also explains, for example, the need to use relatively severe conditions for the nitration of pyrazole (see above) and the fact that, with respect to its reactivity in nitration, it approaches nitrobenzene [31]. At the same time, according to the kinetic data, 1-(4-nitrophenyl)pyrazole is nitrated in the free-base form and therefore at a higher rate than pyrazole itself [30, 31].

Depending on the acidity of the medium, 3- and 5-hydroxypyrazoles are nitrated either in the free-base form in the 4 position (up to 90% H_2SO_4) or in the conjugate-acid form (92-98% H_2SO_4) [24, 25].

In the case of N-phenylpyrazoles it was shown by a kinetic method that the free bases are nitrated in the 4 position when acetyl nitrate is used [39].

For this reason the nitration of N-substituted pyrazoles with acetyl nitrate in the 4 position occurs under very mild conditions (∿20°C). The reaction of N-unsubstituted pyrazoles with acetyl nitrate is discussed below.

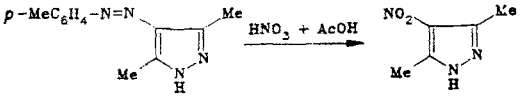
Some groupings in the 4 position of the pyrazole ring can be replaced by a nitro group by the action of acidic nitrating agents. Thus 4-nitropyrazoles are formed in the action of nitrating mixtures on N-unsubstituted 4-bromopyrazoles [12, 41-45]:



In the case of N-alkylpyrazoles two reaction pathways are realized under the influence of nitrating mixtures: nitrodebromination and successive nitration in the 3 and 5 positions with retention of the bromine atom (see below) [41, 42]. However, 1-methyl- and 1-phenyl-4-bromonitropyrazoles undergo only nitrodebromination under the influence of acetyl nitrate [41]. 4-Bromopyrazolecarboxylic acids are not capable of undergoing replacement of the bromine atom by a nitro group [41, 46].

It should be noted that nitrodebromination proceeds considerably more slowly than replacement in the same position (4) of a proton by a nitro group [41].

It has been shown that not only a bromine atom but also an aza group in the 4 position is capable of being replaced by a nitro group in the case of acidic nitration in the pyrazole series [47].

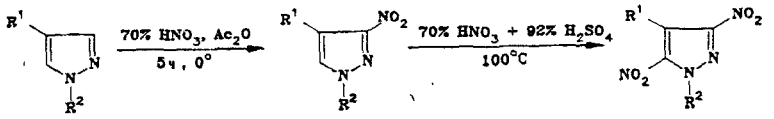


Substitutive nitration of a carboxyl group is also observed. Thus the corresponding 4-nitropyrazole is formed in the nitrodecarboxylation (HNO_3, 20% oleum) of 1,5-dimethylpyrazole-4-carboxylic acid [47].

Despite the fact that the 4 position is considerably more active than the 3 position in the electrophilic-substitution reactions, examples in which 3-nitropyrazoles are also formed along with 4-nitropyrazoles are known. Thus 1-phenyl-4-nitro-5-methylpyrazole and 1-phenyl-3-nitro-5-methylpyrazole were obtained when 1-phenyl-5-methylpyrazole was treated with a mixture of nitric acid with acetic anhydride [39]; the action of a mixture of fuming nitric acid and 80% sulfuric acid on 1-methylpyrazole gives, in addition to 1-methyl-4-nitropyrazole, 1-methyl-3-nitropyrazole, which is converted to 1-methyl-3,4-dinitropyrazole under these conditions [48].

If the 4 position is occupied by any substituent, nitration may occur in the 3 position and then the 5 position with the formation of 3,5-dinitro derivatives [11, 19, 20, 41, 49-53] (in some cases nitration proceeds simultaneously in the 3 and 5 positions but at different rates — the 3 position is more active [51]).

The presence of electron-donor substituents facilitates this process, while the presence of electron-acceptor substituents hinders it. Thus 4-nitropyrazole, 1-methyl-4-nitropyrazole, 1,3-dimethyl-4-nitropyrazole, and 1-methyl-4-nitropyrazole-5-carboxylic acid are not nitrated to the corresponding 3,4- or 4,5-dinitropyrazoles [11, 53]. However, 1,5-dimethyl-4-nitropyrazole is converted to 1,5-dimethyl-3,4-dinitropyrazole by heating in a mixture of nitric acid and 20% oleum (one can also obtain it starting from 1,5-dimethylpyrazole) [53], while 1-methyl-4-chloro-3-nitropyrazole gives the corresponding 3,5-dinitropyrazole under these conditions [53]. 1-Methyl-4-picrylpyrazole and 1-methyl-4-(2,4-dinitrophenyl)-pyrazole are converted to the corresponding 3-nitro derivatives and then to the 3,5-dinitro derivatives when they are heated with nitric acid or a mixture of nitric acid with sulfuric acid [49, 51]. 4-Alkylpyrazoles give 3-nitro derivatives under rather mild conditions, further nitration to the corresponding 3,5-dinitro derivatives occurs only with heating [53]:



R^1=Me, Et; R^2=Me, Et, Ph, 4-NO_2-C_6H_4, 2,4-$(NO_2)_2C_6H_3$

5-Nitropyrazoles gradually decompose under nitration conditions [20, 41]; an increase in the acidity of the medium slows down this process [20].

In the case of 1,4-dimethyl-, 1,4-dimethyl-3-nitro-, and 4-methyl-1-(4-nitrophenyl)-pyrazole it was shown by a kinetic method that the free bases are the active particles in

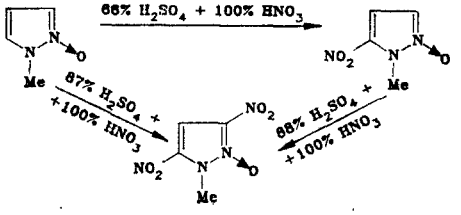
nitration with nitrating mixtures in the 3 and 5 positions, although their equilibrium concentrations are low under these conditions [20].

Proceeding from the higher reactivity of 1,4-dimethylpyrazole (nitration in the 3 position) as compared with toluene (nitration in the ortho position), it was concluded that activation of the pyrazole ring by the pyrrole nitrogen atom prevails over its deactivation by the pyridine nitrogen atom [20].

As noted above, in the case of 1-alkyl-4-bromopyrazoles successive nitration in the 3 and 5 positions with retention of the bromine atom occurs along with nitrodebromination [41, 42].

The formation of 3(5)-nitro- and 3,5-dinitropyrazole is also observed in the substitutive nitration of the carboxy group. Thus the corresponding 1-methyl-4-halo-3,5-dinitropyrazoles were obtained as a result of nitrodecarboxylation (HNO_3—20% oleum) of 1-methyl-4-halopyrazole-5-carboxylic and -3,5-dicarboxylic acids [47, 52]. N-Unsubstituted 4-halo-3(5)-carboxylic acids are not capable of nitrodecarboxylation — only nitration in the 5 position occurs [52].

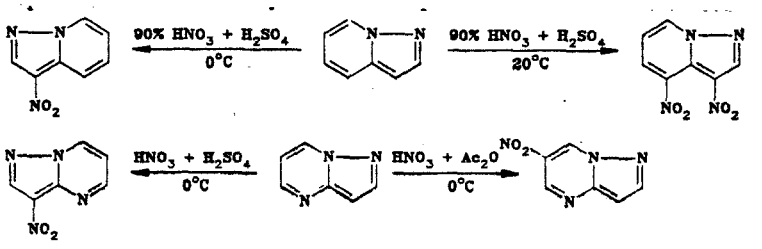
As in the pyridine series, in the case of pyrazole N-oxides the orientation in nitration changes: the 3 and 5 positions become the most reactive [54, 55].



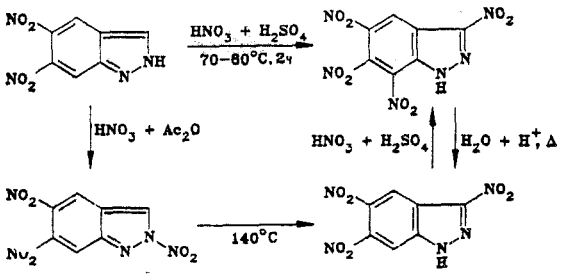
The N-oxides obtained are converted to the corresponding 5-nitro- 3,5-dinitro-1-methylpyrazole under the influence of PCl_3 [55].

It should be noted that nitration at the nitrogen atom with the formation of N-nitropyrazoles occurs in the case of N-unsubstituted pyrazoles under the influence of acetyl nitrate [$HNO_3 + Ac_2O$; $Cu(NO_3)_2 + Ac_2O$] [11, 56-61] or trifluoroacetyl nitrate [61] (the 4 position is not involved in this case); the NO_2 group virtually always goes to the nitrogen atom that is remote from the substituent, and the formation of a 2-nitro isomer as well is observed only in the case of 3-methylpyrazole [11]. It is interesting to note that 1-nitro-4-bromopyrazoles are formed by the action of the $AgNO_3 \cdot P(OMe_3)_3$ complex of 4,4-dibromopyrazolines [62].

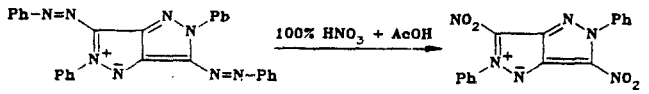
In concluding this section let us briefly examine the nitration of some condensed pyrazoles. Thus in the nitration of pyrazolopyridines [63] and pyrazolopyrimidines [64] the character of the final reaction products depends on the reaction conditions.



In the nitration of indazoles, depending on the conditions, the nitro group may enter the 2 (at nitrogen) or 3 (at carbon) position of the pyrazole ring, as well as the benzene ring [65, 66], for example:

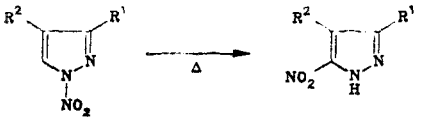


In mesoionic pyrazole[4, 3-c]pyrazole azo groups are capable of being replaced by a nitro group in the case of acidic nitration [67]:



2. Indirect Methods for the Introduction of a Nitro Group at a Carbon Atom of the Pyrazole Ring

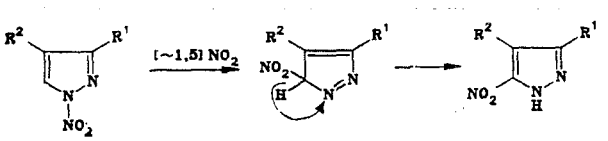
2.1. Thermal Rearrangement of N-Nitropyrazoles. N-Nitropyrazoles with a vacant 5 position undergo intramolecular rearrangement with the formation of 3(5)-nitropyrazoles at 120-190°C in high-boiling organic solvents, i.e., migration of a nitro group from a nitrogen atom to an adjacent carbon atom occurs [11, 57, 68] (also see [60]):



R^1=H, Me, Bu, Ph, *p*-MeC_6H_4-, NO_2; R″=H, Me, Et, Ph

A similar process also occurs in the case of N-nitroindazoles [67] with migration of the nitro group to the adjacent carbon atom of the pyrazole ring.

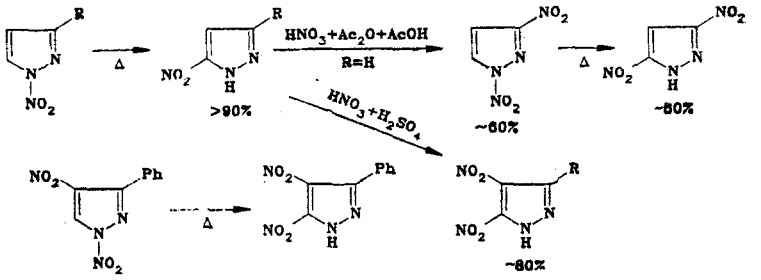
It is assumed that the first step in this thermal rearrangement is a synchronous [1, 5]-sigmatropic shift of the nitro group; this is followed by rapid rearomatization of the intermediate 3H-pyrazole [68]:



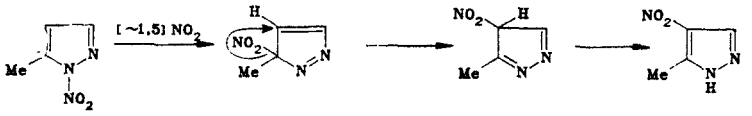
This rearrangement is irreversible and exothermic. The driving force of the reaction is the greater stability of C-nitropyrazoles as compared with N-nitropyrazoles. Its energy of activation is 30-36 kcal/mole, depending on the substance under consideration [69].

The side process in the rearrangement — denitration of the N-nitropyrazole — occurs, it is assumed, in the step involving the formation of the 3H-pyrazole [69]. Thermal rearrangement can serve as a convenient method for the synthesis of 3(5)-nitropyrazoles that are difficult to obtain by other methods [11, 57]. In the case of 4-unsubstituted N-nitropyrazoles the yields of 3(5)-nitropyrazoles exceed 80%; the yields of 3(5)-nitropyrazoles decrease when substituents (particularly electron-acceptor groups) are present in the 4 position [11].

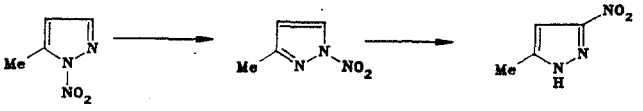
3(5),4- and 3(5),5(3)-Dinitropyrazoles can be readily obtained by means of thermal rearrangement of N-nitropyrazoles [11]:



The corresponding 4-nitropyrazole is formed in the thermolysis of a 5-substituted 1-nitropyrazole via the scheme [11, 69]



Slow migration of the nitro group from $N_{(1)}$ to $N_{(2)}$ with subsequent rearrangement occurs simultaneously [11, 69]:



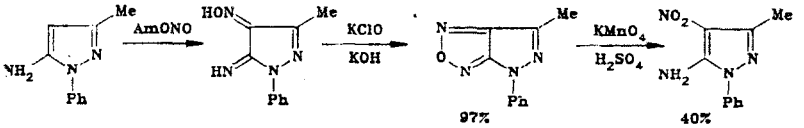
The ratio of 4-nitro- and 3-nitropyrazole in this process is 93:7. In contrast to thermal rearrangement, in sulfuric acid in the cold N-nitropyrazoles readily undergo rearrangement to 4-nitropyrazoles [56].

2.2. Conversion of Other Groupings to a Nitro Group. From among other methods for obtaining nitropyrazoles one should note methods of synthesis that involve the conversion of some groupings to a nitro group. The oxidation of nitrosopyrazoles and aminopyrazoles and the replacement of the diazonium groupings by a nitro group during diazotization are included among such methods.

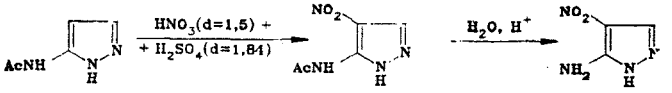
4-Nitropyrazoles are formed in high yields in the oxidation of 4-nitrosopyrazoles (usually with concentrated nitric acid) [2, 69-71].

According to [72], 3(5)-nitropyrazoles can be obtained by oxidation of some aminopyrazoles with trifluoroperacetic acid in methylene chloride.

Another interesting method for the synthesis of 4-nitropyrazoles is based on the formation of pyrazolofurazans, which are subsequently readily converted to aminonitropyrazoles [73]:



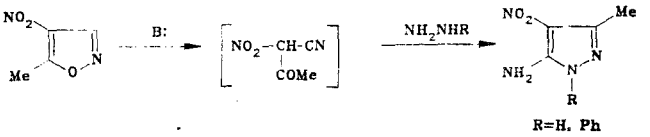
In some cases amino-4-nitropyrazoles can be obtained by nitration of amino- or acetamidopyrazoles [74, 75]:



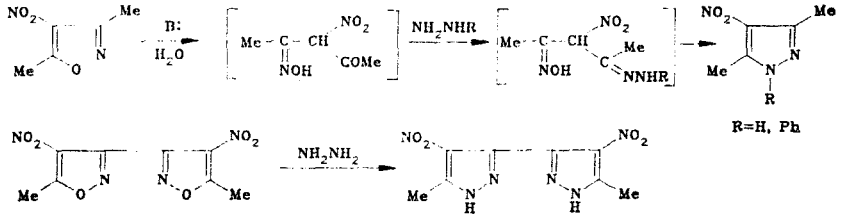
3(5)-Nitro- and 3(5)-4-dinitropyrazoles are also formed in the diazotization of the corresponding amino- or aminonitropyrazoles; the reaction proceeds through the formation of the diazonium salt with subsequent replacement of the diazonium grouping by the nitrite ion [76-79].

Attempts to introduce one or two nitro groups in the diazotization of 3(5),5(3)-diamino-4-nitropyrazole were unsuccessful: only replacement of the nitro group in the pyrazole ring by an OH group occurs [79].

2.3. Methods for Obtaining Nitropyrazoles by Recyclization of Other Nitro-Substituted Heterocycles and by Cyclization of Nitro-Containing Synthones. 4-Nitropyrazoles are formed as a result of recyclization of 4-nitroisoxazoles under the influence of hydrazines [22, 80-83]. The reaction of 3-unsubstituted 4-nitro-5-R-isoxazoles with hydrazines proceeds with the formation of intermediate α-nitro-α-cyano ketones and gives 3-R-4-nitro-5-aminopyrazoles [80-82].

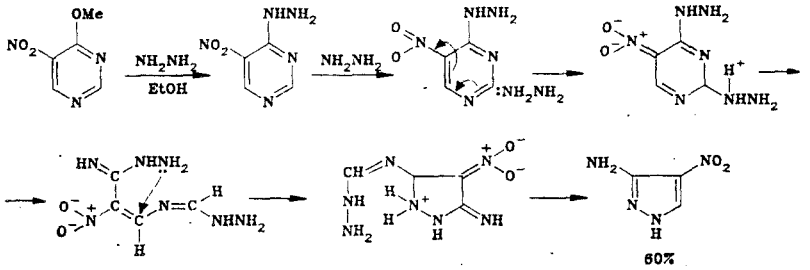


The reaction of 3,5-disubstituted 4-nitroisoxazoles with hydrazines proceeds via a different pathway — through the intermediate monoxime of an α-nitro-β-dicarbonyl compounds — and the final products are 3,5-disubstituted 4-nitropyrazoles [22, 80, 81].



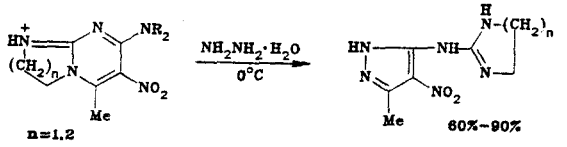
4-Nitroixoxazole reacts with phenylhydrazine to give 4-nitro-1-phenylpyrazole [83].

Another method for the synthesis of nitropyrazoles that contain, in addition to the nitro group, an amino group in the ring is the reaction of 5-nitro-4-methoxypyrimidines with 2 moles of hydrazine [84, 85].



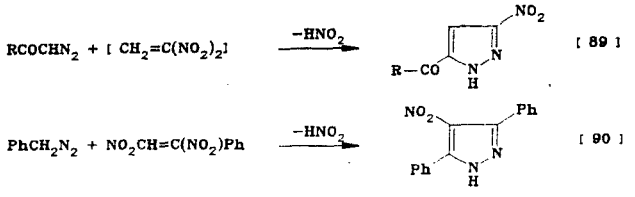
At the same time, 4-nitropyrazole is formed when hydrazine is heated with 5-nitropyrimidine in an acidic medium (86).

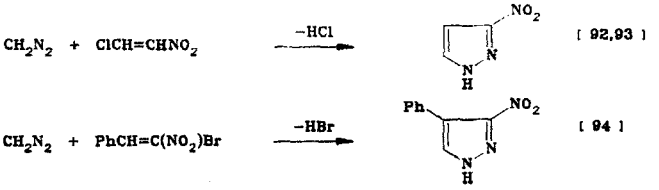
Some nitropyrazoles that are bonded to other heterocycles through an NH fragment were synthesized by means of a similar recyclization reaction [87]:



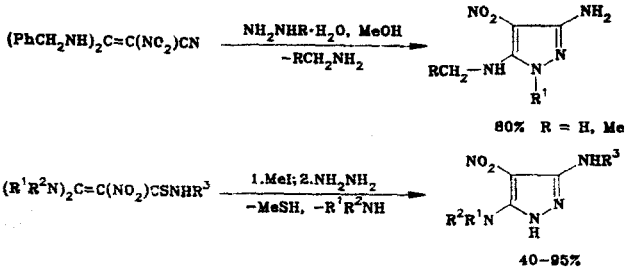
The recyclization of some nitropyrazines under the influence of aqueous bases leads to 5-nitropyrazolecarboxylic acids [88].

Nitropyrazoles can also be obtained by the addition of diazoalkanes to dinitro- or helonitro-substituted olefins. Both 3- and 4-nitropyrazoles can be synthesized on the basis of this reaction [89-94].



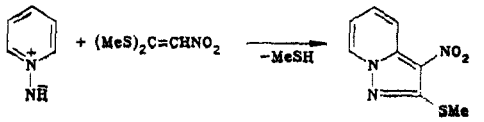


A convenient method for the synthesis of 4-nitropyrazoles that contain, in addition to nitro groups, amino groups in the ring is the cyclization of some nitro-substituted ketene aminals with hydrazone [95, 96]:

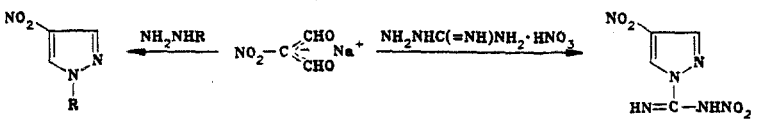


These methods for obtaining 4-nitro-3,5-diaminopyrazoles are convenient in that they make it possible to selectively introduce different substituents at one or two amino groups (see also [97]).

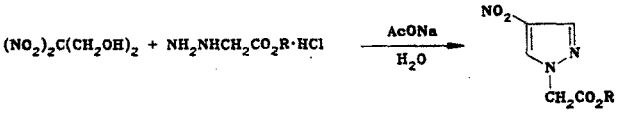
Nitropyrazolo[1,5-a]pyridines with methylthio grouping in the pyrazole ring are formed in the reaction of a nitro-substituted ketene thioacetal with pyridinia-N-imines [98].



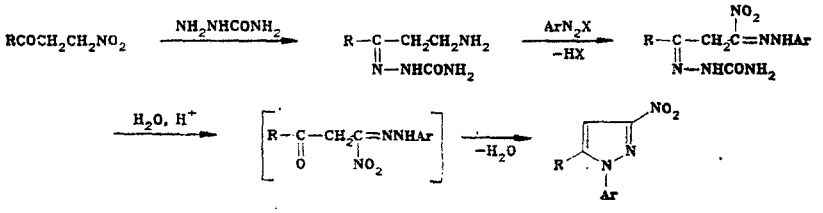
Another convenient method for the synthesis of 4-nitropyrazoles is cyclization of nitromalondialdehyde with hydrazines or aminoguanidine [21, 99-101].



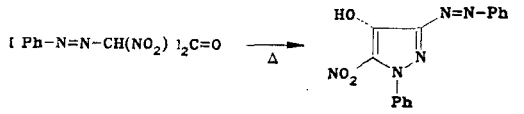
At the same time, nitromalondialdehyde dioxime diacetate, under the influence of alkali, is converted to 4-nitro-3-pyrazolone, which on treatment with $POCl_3$ gives 3(5)-chloro-4-nitropyrazone [102]. 4-Nitro-1-pyrazolylacetic acid esters are formed in high yields in the reaction of 2,2-dinitropropanediol with hydrazinoacetic acid esters [103]:



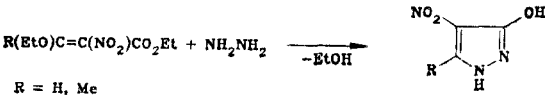
N-Aryl-3-nitro-5-R-pyrazoles can be obtained from semicarbazones of β-nitro carbonyl compounds by condensation with diazonium salts and subsequent hydrolysis [104]:



The product of diazo coupling of α,α'-dinitroacetone with benzenediazonium chloride undergoes cyclization to a substituted 4-hydroxy-5-nitropyrazole when it is heated [105]:



3-Hydroxy-4-nitropyrazoles can be obtained by the following cyclization [106]:



II. PHYSICOCHEMICAL PROPERTIES AND STRUCTURES OF NITROPYRAZOLES

According to the results of x-ray diffraction analysis of N-nitropyrazole [107], the N—NO_2 bond has an anomalously great length, while the nitro group lies in the plane of the ring.

It is interesting to note that, judging from calculations (by the INDO method), the energies of protonation of both 3- and 4-nitropyrazole at the ring nitrogen atom and the nitro group are close to one another [108]. On the basis of the dipole moments of some nitropyrazoles it was concluded that the pyrazole ring is strongly polarized under the influence of a nitro group (large differences in the experimentally found and calculated dipole moments) [109].

It was demonstrated by polarography and EPR spectroscopy that anion radicals are formed in the electrochemical reduction of C- and N-nitropyrazoles in the first one-electron step; in the case of N-unsubstituted nitropyrazoles these anion radicals decompose with the ejection of atomic hydrogen and the formation of nitropyrazolate anions, while in the case of N-nitropyrazoles they decompose with the formation of nitropyrazolyl radicals and NO_2^- ions. The anion radicals of N-alkylnitropyrazoles do not decompose but undergo further reduction [110-113]. Polarography (in an alkaline medium) has been used successfully for the analysis of mixtures of N-unsubstituted and N-nitro- and N-alkylnitropyrazoles [110-113].

An intense peak of a molecular ion and, as a rule, peaks of $[M - NO_2]^+$ and $[M - NO]^+$ ions are observed in the electron-impact mass spectra of C- and N-nitropyrazoles [114-116].

In the IR spectra the vibrations of the C—NO_2 group lie in the region that is characteristic for vibrations of aromatic nitro groups at 1500-1570 and 1320 and 1380 cm^{-1} [11, 68]; vibrations of the N—NO_2 group usually show up at 1270-1290 and 1625-1650 cm^{-1} [11, 69]. A weak-field shift of ∿0.5 ppm of the signal of the proton attached to the adjacent carbon atom occurs in the PMR spectra when a nitro group is introduced at a carbon atom of the pyrazole ring; this weak-field shift is ∿1 ppm when two nitro groups are introduced [11, 41, 69, 86]. A strong weak-field shift of more than 0.5 ppm of the signal of the adjacent 5-H proton occurs when a nitro group is introduced at a ring nitrogen atom, whereas the position of the signal of the 3-H proton remains virtually unchanged or else one even observes a small strong-field shift [11, 69]. This is a special case of the general rule for nitropyrazoles: when electron-acceptor substituents are attached to a ring nitrogen atom, the signals of the 3-H proton are found at stronger field than those of the 5-H proton; on the other hand, when donor substituents are attached to the nitrogen atom, the signals of the 3-H proton are found at weaker field than those of the 5-H proton [35, 48, 72].

The literature data on the ^{13}C NMR spectroscopy of nitropyrazoles are extremely limited [117-120]. From these studies one can conclude that, regardless of the character of the substituents attached to the nitrogen atom of the pyrazole ring, the signals of the $C_{(5)}$ atoms are found at stronger field than those of the $C_{(3)}$ atoms. The ^{15}N NMR spectra have been presented for some of the simplest nitropyrazoles; signals of only the ring nitrogen atoms were observed [117-121].

In the UV spectra of nitropyrazoles [38, 122] the absorption maxima generally are found at 260-290 nm (log ε ≈ 3.7-4). The absorption maximum of the corresponding N anion for N-unsubstituted nitropyrazoles is usually shifted 30-40 nm to the longer-wave region (log ε changes only slightly in this case). The position of the absorption maximum depends on the character and orientation of the substituents in the pyrazole ring [38, 122].

The NH acidities [122] and basicities [38] of a number of nitropyrazoles (in water) have been determined by spectrophotometry. Thus in series of nitropyrazoles that do not contain substituents other than nitro groups in the ring the NH acidities depend on both the number and position of the nitro groups in the ring and increase in the order 3(5)-nitropyrazole (pK_a 9.81), 4-nitropyrazole (pK_a 9.67), 3(5),4-dinitropyrazole (pK_a 5.48), 3(5),-5(3)-dinitropyrazole (pK_a 3.14) (the pK_a of pyrazole is 14.2 [114]). The basicities of 4- and 3(5)-nitrpyrazole and their N-alkyl derivatives, as well as N-nitropyrazole (pK_{BH^+} ≈ −2-4.8), where determined in [38]. For example, the pK_{BH^+} value of unsubstituted pyrazole is 2.52 and that of N-methylpyrazole is 2.09, whereas the values for 4-nitropyrazole, 3(5)-nitropyrazole, and N-nitropyrazole are, respectively, −1.96, −4.66, and −4.21.

III. TRANSFORMATIONS OF NITROPYRAZOLES

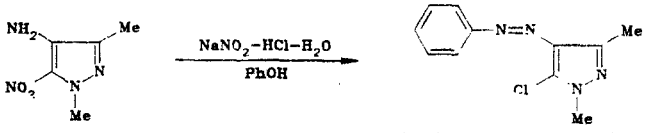
1. Transformations Involving the Nitro Group

Nitropyrazoles can be smoothly reduced by aminopyrazoles under various conditions — with molecular hydrogen in the presence of catalysts (palladium on carbon [19, 50, 59, 123, 124], Raney nickel [78], PtO_2 [94]), with hydrazine hydrate (in the presence of Raney nickel [44, 125] or Pd/C [126]), with sodium dithionite [7, 61], with tin in hydrochloric acic [3], with aluminum amalgam [4], and with hydrogen sulfide in an alkaline medium [7, 8]. 4-Aminopyrazoles [3, 4], 3-aminopyrazoles [8, 94, 124], and 3,4-diaminopyraoles [7, 84] can be obtained in this way.

In some cases reduction can be stopped at the step involving the formation of nitroso- [3] or hydroxylaminopyrazoles [7].

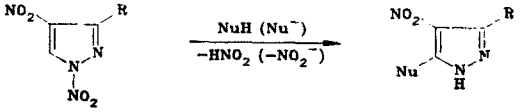
Let us note that a nitro group in the 4 position is reduced with substantially greater difficulty than one in the 3(5) position or in an aryl substituent. Consequently, one can selectively reduce the 3(5)-NO_2 group in the pyrazole ring or a nitro group in an aryl substitutent to an amino group without involving the 4-NO_2 group by the action of H_2S in an allakine medium [7, 11, 28] or to an NHOH group by the action of $SnCl_2$ [7].

The nitro group can be removed from nitropyrazoles by reduction to the corresponding aminopyrazoles with subsequent diazotization of the amino group and reductive replacement of the diazonium grouping by hydrogen via standard methods [7, 8, 28, 76, 126]. It is interesting to note that replacement of the nitro group by chlorine occurs along with diazo coupling in the diazotization of 1,3-dimethyl-4-amino-5-nitropyrazole in hydrochloric acid in the presence of phenol [127].



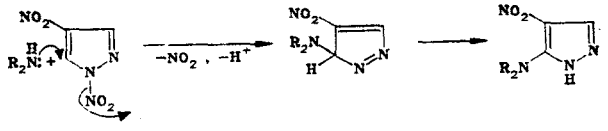
In the action of nucleophiles ($PhNH_2$, NH_3, NH_2NH_2, NaOH) on 3,4- or 4,5-dinitropyrazoles one of the nitro groups [the nitro group in the 3(5) position] is replaced by a nucleophile residue on heating [44, 45].

N-Nitropyrazoles differ substantially from C-nitropyrazoles with respect to chemical behavior. Here 1,4-dinitropyrazoles have particularly interesting properties: cine substitution of the N-nitro group with the formation of the corresponding 3(5)-substituted 4-nitropyrazoles occurs in the action of various types of nucleophiles on them [59-61, 63, 126, 128]:



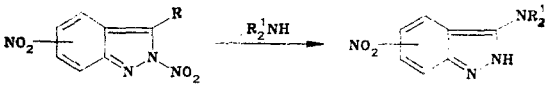
NuH(Nu⁻) = NH_3, Alk_2NH, pyrazoles, CN^-, O^-, S^-, $MeCO\bar{C}HCO_2Et$, $\bar{C}H(CO_2Et)_2$

The following mechanism of cine substitution was proposed in [128]:



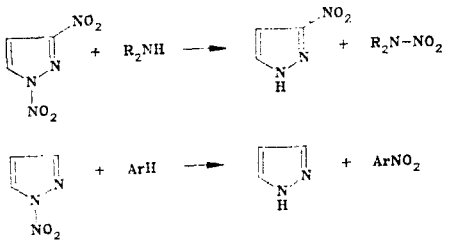
Nitro-containing 3(5),1'-bipyrazoles, as well as tripyrazoles joined by a C–N bond, have been obtained by means of transformations of this sort — using pyrazoles as nucleophiles [63, 126].

N-Nitroindazoles are also capable of undergoing cine substitution [65, 66, 129-131]:



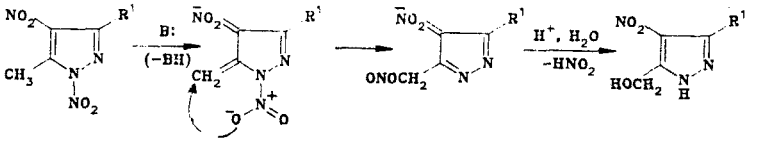
R=H, Cl

In the case of N-nitropyrazoles other than 1,4-dinitropyrazoles denitration with the formation of NH-pyrazoles occurs under the influence of nucleophiles [128]; 1-nitropyrazole is capable (in the presence of acids) of acting as a nitrating agent with respect to aromatic hydrocarbons [132].



Denitration occurs in the electrochemical reduction of N-nitropyrazole, and the corresponding NH-pyrazole is formed [133].

It is interesting to note that replacement of a hydrogen atom of the methyl group by an OH group also occurs along with removal of the N-nitro group in the case of 1,4-dinitro-5-methylpyrazoles on reaction with amines [58, 134]. It is assumed [58] that the reaction proceeds via the scheme

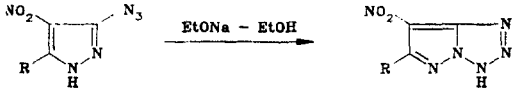


2. Transformations of Nitropyrazoles without Involving the Nitro Groups

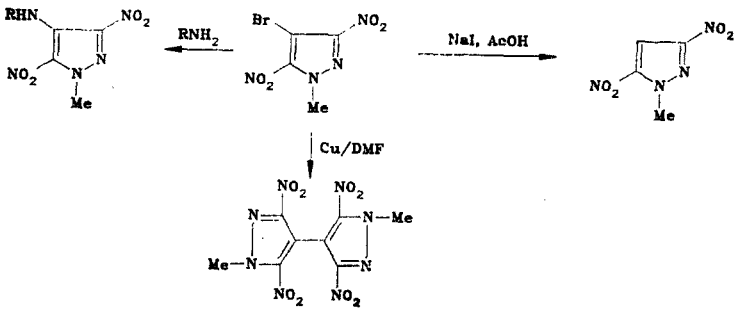
The oxidation of alkyl-4-nitropyrazoles with potassium permanganate [2, 13], with potassium dichromate in an acidic medium [123], or with ozone in sulfuric acid [135] can be used to obtain 4-nitropyrazolecarboxylic acids, which are readily decarboxylated to give 4-nitropyrazoles [136] and can also serve as intermediates for the synthesis of pyrazolopyrimidines [136, 137].

3-Nitropyrazoles are readily halogenated to give 3-nitro-4-halopyrazoles [8]. 1-Methyl-3-nitro-4-cyanopyrazoles are formed in the UV irradiation of 1-methyl-3-nitropyrazoles in the presence of potassium cyanide [138].

Under the influence of sodium ethoxide in ethanol 3(5)-azido-4-nitropyrazoles give nitropyrazolotetrazoles [139].



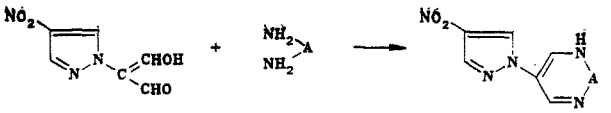
A halogen atom attached to a carbon atom adjacent to the nitro group, particularly in the 3 or 5 position, is capable of being readily replaced under the influence of nucleophiles. Thus 5-cyano-4-nitropyrazoles are formed in the reaction of 5-halo-4-nitropyrazoles with potassium cyanide [16], while 5-hydrazino-4-nitropyrazoles are formed with hydrazine [14, 17], and 5-amino-4-nitropyrazoles are formed with ammonia [43, 44]. 1-Methyl-3,5-dinitro-4-bromopyrazole undergoes interesting transformations [50]:



Two-ring N—C-bonded compounds are formed in the reaction of 1-phenyl-3-methyl-4-nitro-5-chloropyrazole with pyrazole, 4-nitroimidazole, and 2-methylimidazole [140]. The corresponding nitropyrazolyltetrazole is formed in the reaction of 1-phenyl-3-methyl-4-nitro-5-cyanppyrazole with sodium azide [140]. Nitro-containing 1,5-bipyrazoles are formed in the condensation of 1-phenyl-3-methyl-4-nitro-5-hydrazinopyrazole with β-dicarbonyl compounds [17]. 3(5)-Halo-4-nitropyrazoles are formed in the diazotization of 3(5)-amino-4-nitropyrazoles in hydrohalic acids [18, 127]. The diazotization of 3(5)-amino-4-nitropyrazoles can also be directed to favor the formation of triazines [141].

3(5)-Azido-4-nitropyrazole is obtained by diazotization of 3(5)-amino-4-nitropyrazole and subsequent reaction of the resulting diazonium salt with sodium azide [79].

4-Nitro-1-pyrazolylacetic acid is capable of being formulated by the Vilsmeier reagent at the methylene fragment with the formation of 1-diformylmethyl-4-nitropyrazole; condensation of the latter or its derivatives with bifunctional nucleophiles (urea, thiourean, guanidine, hydrazine, diamines) leads to the corresponding N-heteryl-4-nitropyrazoles [142].

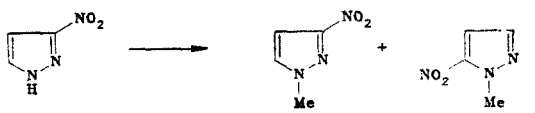


A = C=O; C=S; C=NH; $(CH_2)_n$ (n=0,2); o-C_6H_4

1-Bromo-4-nitropyrazole is formed in the halogenation of 4-nitropyrazole with sodium hypobromite in aqueous acetic acid [143], 1-chloro-4-nitropyrazole is formed in the halogenation of 4-nitropyrazole with sodium hypochlorite [144], and 1-acetyl-4-nitropyrazole is formed in the acylation of 4-nitropyrazole with acetyl chloride in benzene [145].

N-Unsubstituted 4-nitropyrazoles readily condense with formaldehyde in water to give N-hydroxymethyl derivatives in high yields; they also undergo the Mannich reaction with formaldehyde and secondary amines to give N-(dialkylamino)methylpyrazoles [146].

N-Unsubstituted nitropyrazoles can be alkylated or arylated at the nitrogen atom by halogen derivatives, alkyl sulfonates, or diazoalkanes; for example, 4-nitropyrazole in the presence of alcoholic or aqueous alcoholic alkali is alkylated by bromoacetic acid ester [142] and arylated by 2,4-dinitrochlorobenzene [99]. Mixtures of isomers [at the $N_{(1)}$ and $N_{(2)}$ atoms] can be formed in the case of alkylation (arylation) of unsymmetrical nitropyrazoles. The isomer ratio depends on the structure of the reagents and the reaction conditions; it is important that the nitropyrazole or its anion is alkylated. Thus 1-methyl-3-nitropyrazole and 1-methyl-5-nitropyrazole are formed in a ratio of 1.25:1 in the alkylation of 3(5)-nitropyrazole with dimethyl sulfate in methanol [147]; however, the ratio changes markedly and becomes 1:4 in the case of alkylation with dimethyl sulfate in the presence of sodium methoxide (the reactive particle is the nitropyrazole anion) [19, 147]. In the case of alkylation with CH_3I in the presence of KOH or CH_3ONa in methanol the ratio is 3:1 [8, 114], in the presence of sodium amide in liquid ammonia it is 4:1 [147], and, finally, in the action of diazomethane in acetonitrile the ratio of these isomers is 0.56:1 [147].



Exclusively the 1,3 isomer is formed in the Ullmann arylation of 3(5)-nitropyrazole [147]. Almost exclusively one isomer — 1-methyl-3-phenyl-5-nitropyrazole — is formed in the methylation of 3(5)-nitro-5(3)-phenylpyrazole, regardless of the conditions and the methylating agent [147]. Methylation of the silver salt of 3(5)-nitro-5(3)-(3-pyridyl)-pyrazole with CH_3I leads to a 5:1 ratio of isomers; however, the positions of the substituents were not established [148].

1-Methyl-3-nitro-4-bromopyrazole and 1-methyl-4-bromo-5-nitropyrazole are formed in a ratio of 6:1 in the action of dimethyl sulfate on 3-nitro-4-bromopyrazole in aqueous NaOH solution [149]. Only one isomer — 1,5-dimethyl-4-nitropyrazole — is formed in the alkylation of 3-methyl-4-nitropyrazole with methyl iodide in aqueous NaOH solution [150]. The alkylation of 3(5)-cyano-4-nitro-5(3)-methylpyrazole (with benzyl bromide and dimethyl sulfate) leads to 1-R-3-cyano-4-nitro-5-methylpyrazoles [151, 152], while methylation of 3(5)-nitro-4-cyanopyrazole gives 1-methyl-3-nitro-4-cyanopyrazole [153].

It follows from the data presented above that it is still difficult to draw sufficiently substantiated conclusions regarding the decisive effect of any given factors (electronic, steric, etc.) on the direction of alkylation of nitropyrazoles.

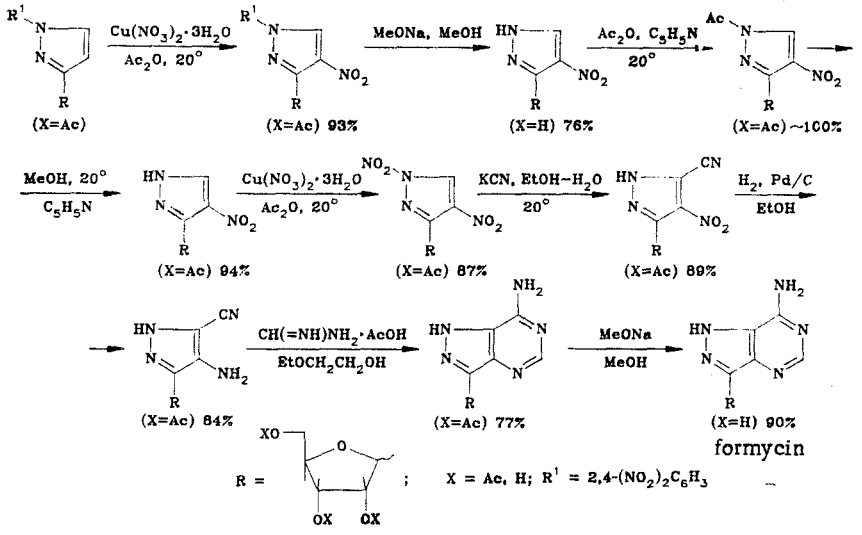
Despite their decreased basicities, N-substituted nitropyrazoles are capable of undergoing quaternization: 1,3-dimethyl-4-nitropyrazole under the influence of CH_3I at 100°C [150], and 1-phenyl-4-nitropyrazole on reaction with methyl tosylate at 130°C [30].

IV. APPLICATION OF NITROPYRAZOLES

In a large number of publications, a significant part of which consists of patents, 3(5)- and 4-nitropyrazoles, including condensed systems and compounds containing diverse substituents, are proposed as biologically active substances for various purposes, including medicinal preparations [153-174].

Nitropyrazoles have assumed great importance in recent years as intermediates for the synthesis of natural antibiotics and their analogs containing pyrazole rings.

Thus methods in the chemistry of nitropyrazoles such as C- and N-nitration of the pyrazole ring, cine substitution of the N-nitro group, and reduction of a C-nitro group to an amino group have been used for the synthesis of the natural C-nucleoside antibiotic formycin, which has antiviral and antitumorigenic activity [59, 60, 175]:



An analog of formycin, viz., araformycin [61], which differs from formycin in that the β-D-ribofuranosyl residue is replaced by a β-D-arabinofuranosyl residue, was obtained via a similar scheme but with the use of trifluoroacetyl nitrate for C and N nitration.

An intermediate in the synthesis of formycin — 3(5)-cyano-4-nitro-5(3)-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)pyrazole — was used to obtain another natural C-nucleoside antibiotic with antiviral and antitumorigenic activity — pyrazofurin (pyrazomycin), which contains a pyrazole ring [151] — as well as its synthetic analogs [152].

The hydroxylation of the 5-methyl group of 1,4-dinitro-3-R-5-methylpyrazoles under the influence of amines (see above) was used in the synthesis of an acyclic analog of formycin (acycloformycin) [58].

Preobrazhenskaya and co-workers have developed methods for the N-glycosylation of various 4-nitropyrazoles [176-181]. The products of this reaction can be used to obtain N-glycoside analogs of the antibiotics pyrazomycin and formycin and for the synthesis of the antitumorigenic antibiotics sagivamycin and toyacamycin [176-181].

The use of nitropyrazoles as intermediates for obtaining some other medicinal preparations was described in [182-185]. Their use as valuable intermediates for the creation of dyes and biologically active substances containing a pyrazole ring is no less important. Thus aminopyrazoles — products of the reduction of nitropyrazoles — and aminonitropyrazoles have served as the basis for the creation of azo dyes [53, 79, 186] and luminescent dyes [187] of the pyrazole series.

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2-DIAZOMETHYL-4-FURANONES. SYNTHESIS AND PROPERTIES

L. A. Tolochko, A. M. Sipyagin,
V. G. Kartsev, Z. G. Aliev,
L. O. Atovmyan, and A. T. Lebedev

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1,5-Bisdiazo-3-alkylpentane-2,4-diones were synthesized by the reaction of alkylmalonic acid chlorides with diazomethane; the products readily undergo intramolecular cyclization at the oxygen atom and one of the diazoacetyl groups under the influence of acidic agents with the formation of 2-diazomethyl-3-alkyl-4-furanones. It is shown that diazomethyl-4-furanones, which are vinylogs of α-diazo ketones, undergo reactions that are characteristic for aliphatic diazo compounds. The structure of the product of 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to a diazomethyl-4-furanone was investigated by means of x-ray diffraction analysis.

α-Diazo ketones are widely used in the synthesis of various classes of organic compounds [1]. Acid-catalyzed intramolecular cyclizations leading to the formation of carbocyclic and heterocyclic compounds are among the pathways for the realization of their synthetic possibilities [2]. From this point of view bisdiazo ketones, among which important biologically active compounds have been detected [3-5], are little-studied and extremely interesting compounds.

It is known that bisdiazo ketones are formed in the reaction of dicarboxylic acid chlorides with diazomethane. Their transformations at both diazocarbonyl groups under the influence of acids, which proceed with the liberation of a molecule of nitrogen and the formation of derivatives of α-methyl ketones, have been described [6]. Reactions with retention of diazo groups are virtually unknown in the literature.

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