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NITRODIHYDROPYRIMIDINES (REVIEW)

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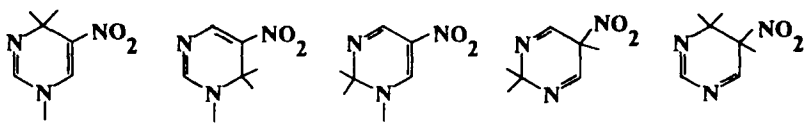
Published data on the production and chemical transformations of nitrodihydropyrimidines are reviewed. Examples of substances having high biological activity are given.

The pyrimidine fragment is present in the molecules of a series of biologically active compounds, many of which have found use in medical practice (soporific, antiinflammatory, antitumor, and other products) [1, 2]. In this connection, great attention has recently been paid to derivatives of pyrimidine, including their hydrogenation products. The first investigations into the synthesis of such compounds appeared more than a hundred years ago (e.g., the Biginelli reaction [3]), and for a long time they remained unused. Only in the last decade have methods been developed specifically for the production of hydrogenated pyrimidine systems and their physicochemical properties been studied. This is explained by the high reactivity and by the wide range of biological activity in these derivatives. Thus, for example, 2-substituted 5-alkoxycarbonyl-4-aryl-1,4-dihydropyrimidines, which are structural analogs of Hantsch esters, are modulators of the transport of calcium through membranes [4-7]. Recently, non-nucleosidic inhibitors of reverse transcriptase, which have high activity against HIV-1, have been found among hydrogenated quinazolines [8-10]. Many hydrogenated pyrimidines exhibit antimicrobial [11], hypoglemic [12], herbicidal [13], and pesticidal [14] activity. Publications devoted to these problems have been summarized in a number of reviews [15-18].

Of great interest among the investigated compounds are the nitro-substituted dihydropyrimidines. They readily undergo various chemical transformations, among which the unique ability to undergo recyclization to heterocyclic and carbocyclic compounds should be noted in particular.

The interest in the nitrodihydropyrimidines is also due to the fact that these compounds represent the active principle or act as metabolites responsible for the physiological action of nitropyrimidines. Recently, products having antimicrobial [19] and antiviral [20-22] activity and also products suitable for the treatment of cardiovascular diseases [23-26] have been found among them. The present review is therefore devoted to the production, chemical transformations, and biological characteristics of dihydropyrimidines containing a nitro group at position 5 of the heterocycle. In addition, derivatives of furoxano[3,4-*d*]pyrimidine with a nitro group inserted into the five-membered ring (which can be regarded as analogs of 5-nitrodihydropyrimidines) are also included in the review.

5-Nitrodihydropyrimidines can be described by five structures, having one (1,4-, 1,6-, and 1,2-) or two (2,5- and 4,5-dihydropyrimidine systems) geminal centers, the carbon atoms of which are characterized by sp^3 hybridization.



1,4- 1,6- 1,2- 2,5- 4,5-

The 5-nitro-1,2-, 5-nitro-1,4-, and 5-nitro-1,6-dihydropyrimidines are cyclic enamines, in which the electron pair of the sp^3-hybridized nitrogen atom is in conjugation with the four π electrons of the C=C and C=N double bonds. On account of the mobility of the hydrogen atom of the NH group, the 5-nitro-1,4- and 5-nitro-1,6-dihydropyrimidines can be in tautomeric

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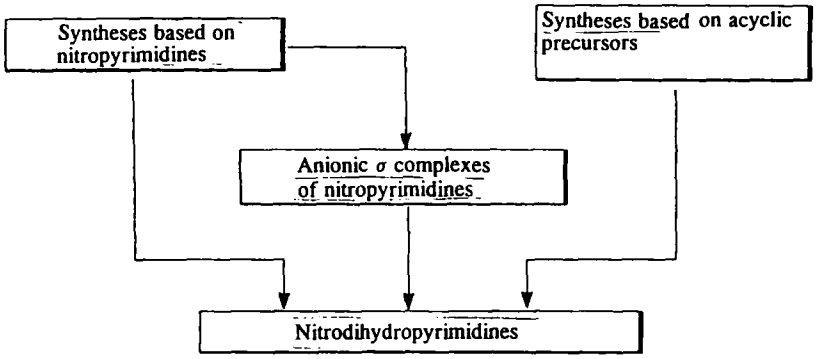
equilibrium. At the same time the 5-nitro-2,5- and 5-nitro-4,5-dihydropyrimidines are cyclic imines, in which there is no conjugation.

1. METHODS FOR THE PREPARATION OF NITRODIHYDROPYRIMIDINES

The methods for the production of dihydropyrimidines described in the literature can be divided into two main groups: synthesis from acyclic compounds; transformations based on pyrimidine derivatives. Analysis of the published data makes it possible to conclude that the first methods have advantages. However, the second methods are used more widely if an electron-withdrawing group, and particularly a nitro group, is introduced into the pyrimidine molecule (Scheme 1). (One of the acyclic compounds contains a nitro group.)

Scheme 1

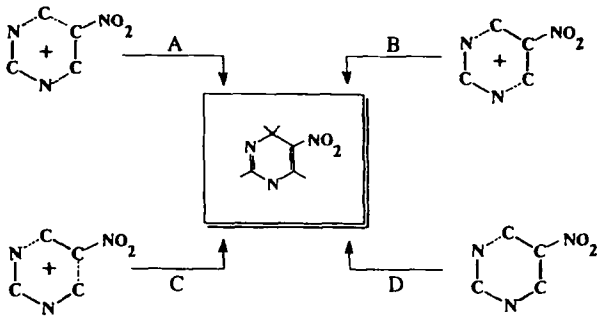


Paths for the synthesis of nitrodihydropyrimidines

1.1. Synthesis from Acyclic Compounds

Only derivatives of 5-nitro-1,4-dihydropyrimidine have been obtained from acyclic compounds. Three-component (A) and two-component (B, C) versions of cyclocondensation, based on the Biginelli reaction [18, 27-29], and also intramolecular cyclization of the already prepared six-membered chain (version D) (Scheme 2) have been used for this. Nitro ketones (versions A, C) and 1-arylidene-1-nitropropan-2-ones (version B) are used as nitro components in these reactions and derivatives of urea, aminopyrazole, and amidines are used as N–C–N fragments.

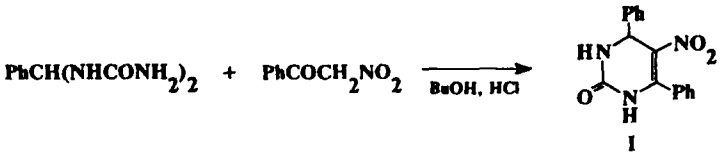
Scheme 2



Methods for the synthesis of 5-nitro-1,4-dihydropyrimidines from acyclic compounds

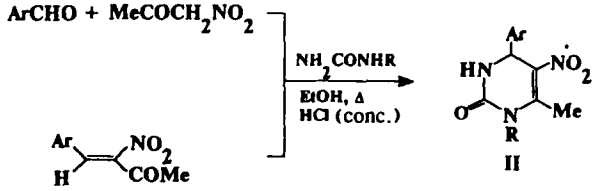
The proposed methods of cyclocondensation are interrelated. As a rule, realization of the reactions by one of the methods leads not to the final product but to an intermediate compound, which is in turn the starting compound for another method of cyclization.

The formation of 5-nitro-4,6-diphenyl-1,4-dihydropyrimidin-2(1H)-one (I) from benzylidenebisurea and ω-nitroacetophenone (method C) was first described in [30]. According to the mechanism of the Biginelli reaction [28], at the first stage the urea fragment is clearly substituted by the nitroketone residue, and this is followed by cyclization of the six-membered intermediate in the acidic medium.



I

In the reaction of aromatic aldehydes with nitroacetone and a twofold excess of urea or N-methylurea in boiling ethanol in the presence of HCl (method A) 4-aryl-6-methyl- or 4-aryl-1,6-dimethyl-5-nitro-1,4-dihydropyrimidin-2(1H)-ones (II) were obtained [25, 31]. The latter are also formed as a result of the two-component cyclization (method B) of the respective 1-arylidene-1-nitropropan-2-ones with urea or N-methylurea.

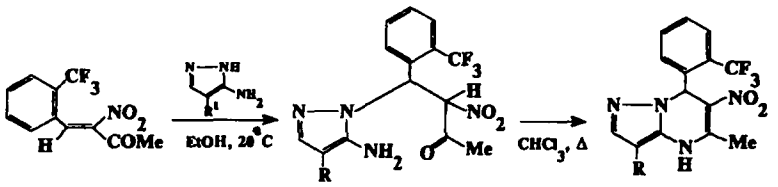


II

R = H, Me

By analysis of the spectral characteristics it is possible to assign compounds (II) the 1,2,3,4-tetrahydropyrimidine structure. It should be noted that almost any aromatic aldehydes enter into the described transformations. This is important during comparison of the pharmacological activity of compounds of this series with the corresponding derivatives of 4-aryl-1,4-dihydropyridines (see Section 3).

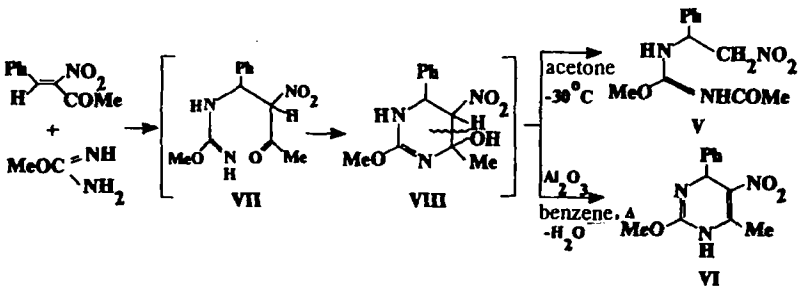
The nitrodihydropyrimidine ring is constructed in the same way when substituted 5-aminopyrazoles are used as N–C–N fragment [32-34]. Reaction in the cold leads to the noncyclic six-membered intermediates (III), which undergo cyclization to 5-nitropyrazolo[1,5-*a*]dihydropyrimidines (IV) when boiled in chloroform (method D).



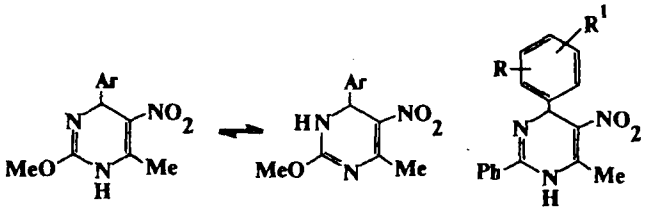
III IV

R = H, Cl, CN, CO_2H, CO_2Et, $CONH_2$, COPh, NH_2, NO_2, Me, Pr and others

Method B was also used for the synthesis of 2-substituted 4-aryl-5-nitro-6-methyl-1,4-dihydropyrimidines. By varying the conditions in the reaction of 1-benzylidene-1-nitropropan-2-one with free O-methylisourea it was possible to direct the reaction toward the formation of a derivative of O-methylisourea (V) or 5-nitro-1,4-dihydropyrimidine (VI) [35, 36]. The Michael addition product (VII) is clearly formed at the first stage of this reaction and then undergoes cyclization to the unstable 5-nitro-3,4,5,6-tetrahydropyrimidine (VIII). The latter can undergo changes in two directions, depending on the conditions, i.e., opening of the pyrimidine ring at the $C_{(5)}-C_{(6)}$ bond with the formation of the isourea derivative (V) or elimination of a water molecule, leading to the 1,4-dihydropyrimidine (VI).



The double set of signals in the PMR spectra of 4-aryl-2-methoxy-substituted 5-nitro-1,4-dihydropyrimidines (IXa) can be explained by the fact that they exist as a mixture of two tautomeric forms. The ratio of the 1,4 and 3,4 tautomers here does not depend on the nature or position of the substituents in the aryl fragment of the molecule and amounts to 1:3 for each compound. The phenyl derivatives (IXb) (the synthesis of these compounds was conducted under analogous conditions [36]) only exist in the 1,4-dihydropyrimidine form, which is clearly explained by the steric effect of the phenyl substituent.



IXa IXb

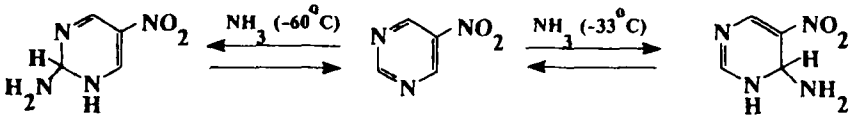
R = H, OMe-3; R^1 = H, OMe-4, Cl-4

Analogous relationships are observed in the series of 2-substituted 5-alkoxycarbonyl-4-aryl-6-methyldihydropyrimidines [37]. Thus, substitution of the nitro group at position 5 by an ester group has practically no effect on the tautomeric equilibrium.

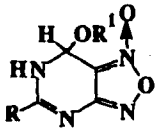
1.2. Synthesis Based on Nitropyrimidines

Owing to their reactivity, nitropyrimidines, which contain accepting nitro groups and "pyridine" nitrogen atoms, have found use as synthons for the production of various derivatives of pyrimidine and also various other types of organic compounds whose synthesis by other methods is difficult or practically impossible [38-40]. In reaction with charged nucleophiles, nitropyrimidines form anionic σ complexes, which are converted by the action of electrophilic reagents into derivatives of nitrodihydropyrimidine.

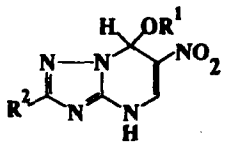
5-Nitropyrimidines do not form covalent σ adducts with uncharged O-nucleophiles. The amination of highly π-deficient six-membered nitroaza aromatic compounds was conducted successfully in the liquid ammonia – potassium permanganate system [41]. When dissolved in liquid ammonia, depending on the temperature, 5-nitropyrimidine forms σ adducts at positions 2 and 4 of the heterocycle, and they are detected spectrally [42].



Annellation of the pyrimidine and also of the nitropyrimidine rings by the azole fragment at the *d* and *a* bonds significantly increases the electrophilicity of the pyrimidine ring. In most cases the reaction of these compounds with nucleophiles takes place without additional activation of the reagent and substrate, which makes it possible to assign them to pyrimidine "superelectrophiles." Thus, when 5-substituted furoxano[3,4-*d*]pyrimidine and 6-nitroazolo[1,5-*a*]pyrimidine are dissolved in primary, secondary, and tertiary alcohols and water nucleophilic attack takes place at the most electron-deficient position of the pyrimidine ring with the formation of the σ adducts (X) and (XI) respectively [43-45].



X

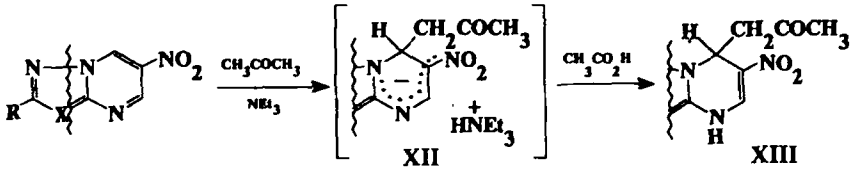


XI

R = NEt_2, OMe; R^1 = H, Me, Et, Bu, Pr-i, Bu-t; R^2 = H, Me

6-Nitroazolo[1,5-*a*]pyrimidines react with indoles [45], polyphenols, N,N-dialkylanilines [19], and cyclic β-diketones [48] in a similar way. Depending on the solvent, pyrrole and N-methylpyrrole form σ adducts at positions 5 and 7 of the pyrimidine ring [38]. 7-Methoxyfuroxano[3,4-*d*]pyrimidine, in which the substituent is at the most electron-deficient position, does not react with uncharged O-nucleophiles but forms a hemiacetal σ complex under the influence of sodium methoxide [44]. Thus, the position of the substituents in the pyrimidine ring also has a substantial effect on the possibility of the formation of dihydropyrimidines.

Acetone, which is a weak CH acid and does not react with 6-nitroazolo[1,5-*a*]pyrimidines without additional activation, forms an anionic Meisenheimer σ complex (XII) in the presence of triethylamine (or other bases). Under acidic conditions, (XII) changes into the stable hydrogenated form (XIII), which can be isolated from the reaction zone [47].

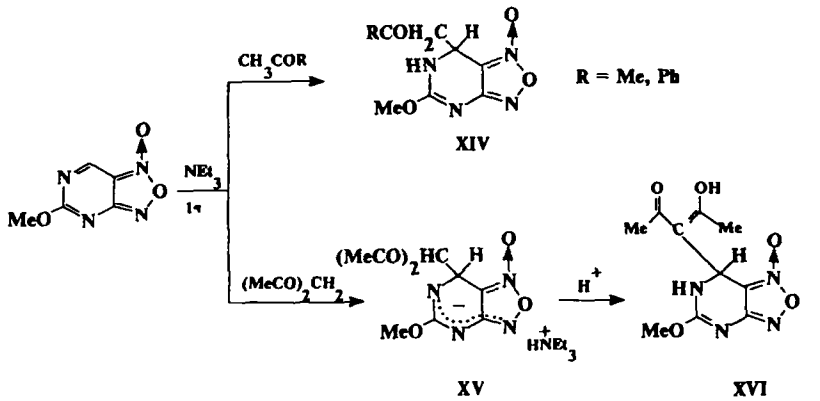


XII XIII

R = H, Me, Et, Ph, SMe, CO_2Et, CF_3, Cl, NH_2, NMe_2; X = N, CCO_2Et

The reactivity of azoloannellated nitropyrimidines depends on the degree of π deficiency in the system. 6-Nitropyrazolo[1,5-*a*]pyrimidines are capable of adding nucleophilic reagents in the presence of accepting substituents in the pyrazole fragment. The aza analogs of these compounds, which contain an additional nitrogen atom in the azole part of the molecule, are characterized by higher reactivity. Conversely, the introduction of donating substituents into the azole fragment leads to deactivation of the system. Quantum-chemical calculations [47] showed that the center of nucleophilic attack is determined by the total charge of the fragment of the valence-bonded atoms and is at the $C_{(7)}$ atom.

The reaction of 5-methoxyfuroxano[3,4-*d*]pyrimidine with acetone and acetophenone in the presence of triethylamine leads to the corresponding σ adducts (XIV) [48], whereas the stable anionic σ complex (XV) obtained when the acetylacetone carbanion is used in this reaction is changed into furoxano[3,4-*d*]-6,7-dihydropyrimidine (XVI) by the action of acid [48]. According to the PMR spectra, (XVI) is characterized by the presence of a mixture of the keto and enolic forms in the diacetylmethyl fragment. This agrees with the structure of the σ adduct of 4,6-dinitrobenzofuroxan with acetylacetone [49]. The reaction with the dimedone carbanion (a stronger CH acid) takes place in a similar way [48].

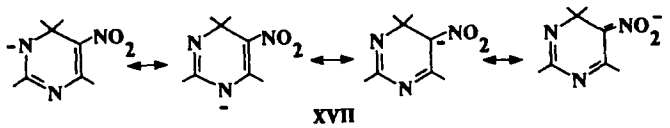


XIV XV XVI

Thus, the furoxan ring activates the double bond of the azadiene fragment $N_{(6)}=C_{(7)}$ to a significant degree, leading to nucleophilic attack by the carbanions at the $C_{(7)}$ position. The increased general π deficiency of the furoxano[3,4-*d*]pyrimidine ring compared with 5-nitropyrimidines makes it possible to extend the limits of the CH acids whose carbanions are able to attack the pyrimidine ring nucleophilically and to bring their lower limit closer to the pK_a values of the conjugate acids whose anions form σ complexes with *sym*-trinitrobenzene [50].

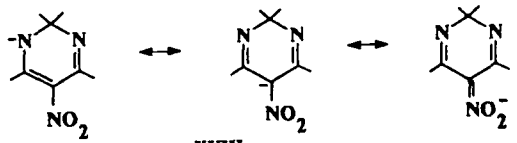
The interest in anionic σ complexes (the first σ-bonded intermediates of aromatic nucleophilic reactions) has not abated over recent decades [51-53]. In many cases, a knowledge of the structure and the conditions of formation and the possibility of isolating these complexes from the reaction zone in the individual state have made it possible to use them as starting materials for further transformations.

Anionic σ complexes are extremely reactive compounds with strong nucleophilic characteristics. On account of the considerable delocalization of the negative charge [see the limiting structures of types (XVII, XVIII)] it was possible to achieve reaction of the stable acetonyl anionic σ complexes of 5-nitropyrimidine, containing a geminal fragment at positions 4 [type (XVII)] and 2 [type (XVIII)] of the pyrimidine ring, with some nucleophilic agents [54, 55]. The different direction of nucleophilic attack in each specific case leads to various types of hydrogenated pyrimidines.



XVII

A B C D



XVIII

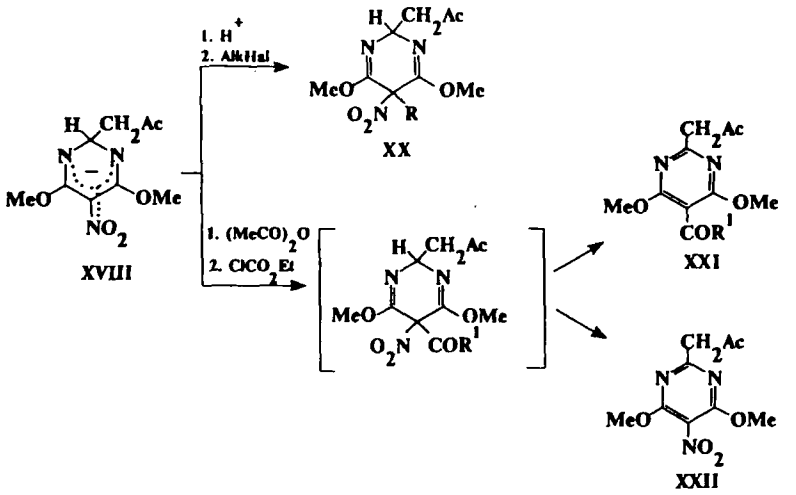
A B C

It is known that classical Meisenheimer σ complexes do not as a rule react with the usual alkylating agents (alkyl halides) [53]. With the use of triethyloxonium salts or during the alkylation of the silver salts of Meisenheimer spiro σ complexes (as a result of the electrophilic assistance of the silver ion in heterolysis of the carbon–halogen bond) it is possible to realize a reaction leading to the formation of a mixture of the corresponding *ortho*- and *para*-nitronic esters [53]. The optimum condition for anionic σ complexes of the 5-nitropyrimidine series in reactions with electrophilic reagents is the presence of a phase-transfer catalyst [56, 57].

During the protonation [58], alkylation [56], ethoxycarbonylation and acylation [57] of the anionic σ complex (XVII), 5-nitro-1,6-dihydropyrimidines (XIX) are formed as a result of the preferential formation of the resonance structure (XVIIA), in which the negative charge is localized at the $N_{(3)}$ nitrogen atom of the pyrimidine ring. Analogous transformations of the anionic σ complex (XVIII), in which the geminal unit is at the *para* position to the nitro group, are realized regioselectively at position 5 of the pyrimidine ring with the formation of the 5-substituted 5-nitro-2,5-dihydropyrimidines (XX) [56, 59], isolated in the form of a mixture of diastereomers. In this case, the resonance structure (XIX) is formed. For the 5-benzyl derivative the mixture of diastereomers was separated by chromatography, and the signals in the spectra of the other compounds of this series were assigned on the basis of the PMR spectra of each of them [56]. The 2,5-dihydropyrimidines formed during the acylation and ethoxycarbonylation of the anionic σ complex (XIX) are unstable and are aromatized during the reaction, being converted into compounds (XXI) and (XXII) [59].

XVII XIX

R = H, Me, Et, All, COMe, COPh, CO_2Et,

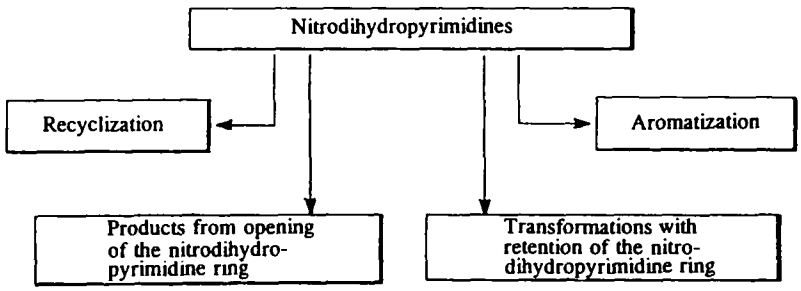


R = H, Me, Et, Pr, Bu, All, CH_2Ph, $CH_2C_6H_4NO_2$-4, $CH_2C_6H_4OMe$-4; R^1 = Me, OEt

2. CHEMICAL TRANSFORMATIONS OF NITRODIHYDROPYRIMIDINES

The derivatives of 5-nitrodihydropyrimidine are highly reactive compounds. The nature and the position of substituents in the ring have a substantial effect on their stability and reactivity. These compounds are easily aromatized by the action of dehydrogenating agents and enter into reactions characterized by opening and also by retention of the hydrogenated ring. Such a unique property as recyclization to heterocyclic and carbocyclic compounds has already been mentioned in the introduction to the review (see Scheme 3).

Scheme 3



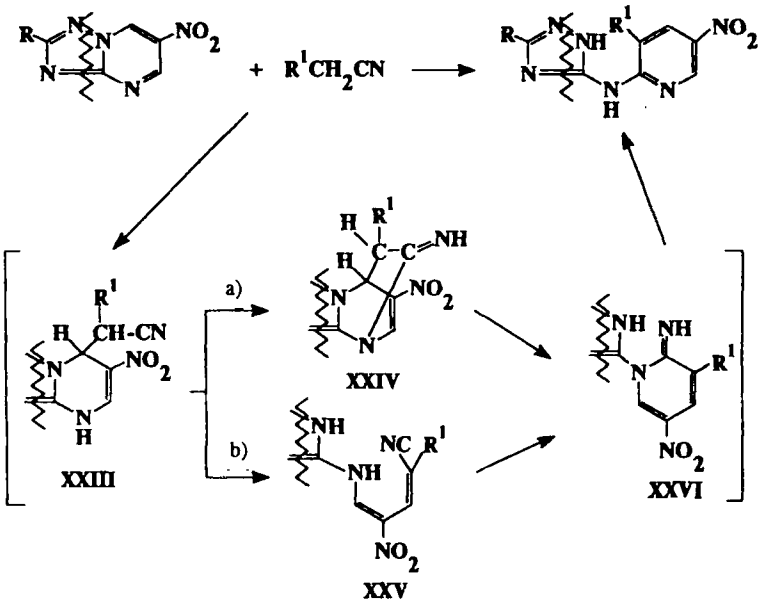
The paths of the chemical transformations of nitrodihydropyrimidines

This transformation is characteristic of the most unstable nitrodihydropyrimidines, which usually act here as intermediates. Such transformations were discussed in detail in the reviews [39, 60] and in the monograph [61]. In this section (see Section 2.1) we give some new examples of the opening of the dihydropyrimidine ring and its transformation into other heterocyclic and/or carbocyclic compounds. We then examine the chemical properties of more stable nitrodihydropyrimidines (see Section 2.2).

2.1. Transformations of Unstable Nitrodihydropyrimidines

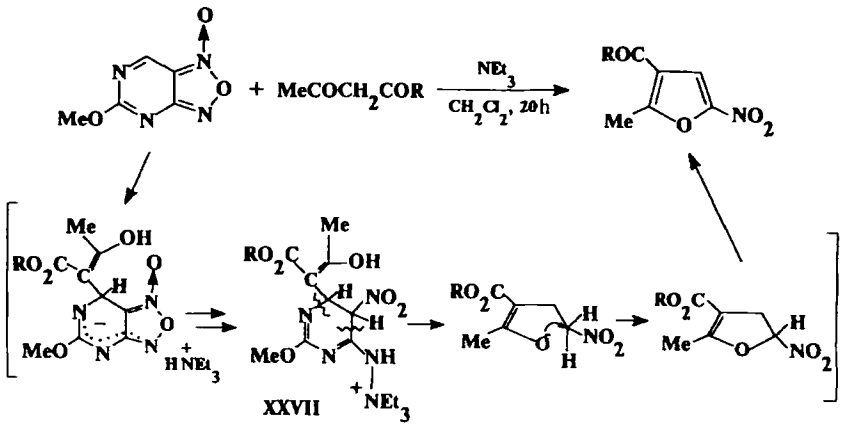
During investigation of the transformations of the nitropyrimidine ring under the influence of carbanions, leading to compounds of the nitropyridine and benzene series [39, 61], it was shown that they take place through the formation of anionic

σ complexes, which as a result of prototropy are in equilibrium with the corresponding unstable dihydropyrimidines [39]. In [62, 63] examples were given of the unusual transformations of 6-nitroazolo[1,5-*a*]pyrimidines into 2-azolylamino-5-nitropyrimidines under the influence of CH-active nitriles. On the basis of a combination of experimental and published data we proposed a scheme for this recyclization involving the formation at the first stage of a σ adduct (XXIII), which is then transformed through the cyclic σ adduct (XXIV) (path *a*) or through the intermediate (XXV) with an open chain (path *b*) to the N-azolyl-2-imino-5-nitropyridine (XXVI). The latter undergoes a Dimroth rearrangement with the formation of 2-azolylamino-3-nitro-5-R-pyridine (XXIV). Detection of the σ adduct (XXIV) by spectral methods makes path *a* more likely in this transformation.



XXIII–XXVI R = H, NH_2, CF_3; R^1 = CO_2Et, CN, $CONH_2$, $CSNH_2$, CO_2Ph

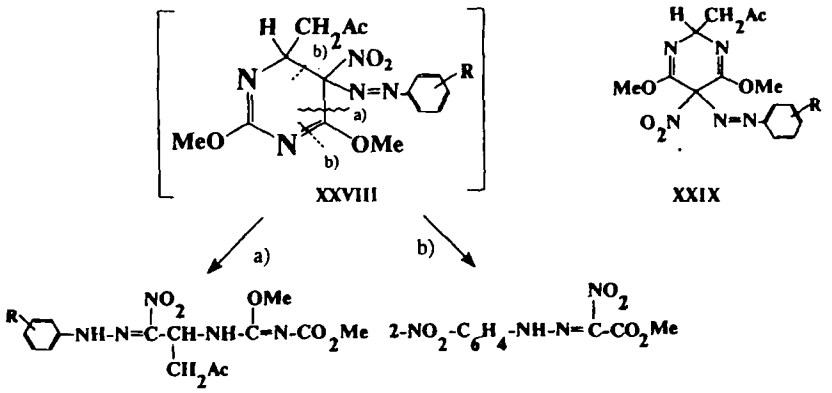
Under the influence of the carbanions of acetylacetone and methyl and ethyl acetoacetate, 5-methoxyfuroxano[3,4-*d*]pyrimidine undergoes recyclization to the corresponding derivatives of 2-methyl-5-nitrofuran [64]. In the literature there are data to the effect that the reaction of furoxano[3,4-*d*]pyrimidines with nucleophiles is accompanied by opening of both the pyrimidine and the furoxan (the Beirutskii reaction) rings [65-67]. On the basis of the structure of the obtained nitrofuran derivatives it is possible to propose the following scheme for their formation:



R = Me, OMe, OEt

At the first stage of the reaction the carbanion attacks the most electron-deficient position of the pyrimidine ring with the formation of anionic σ complexes. The latter are transformed as a result of opening of the furoxan ring under the influence of an excess of triethylamine into the unstable 5-nitro-4,5-dihydropyrimidines (XXVI). Cleavage of the $N_{(3)}-C_{(4)}$ and $C_{(5)}-C_{(6)}$ bonds and cyclization of the nitroenols that form by the Feist–Benary method [68, 69] lead to 5-nitrofurans. The possibility of such a scheme of transformations is demonstrated by the fact that the stable anionic σ complex (XV) likewise undergoes recyclization to 3-acetyl-2-methyl-5-nitrofuran when boiled in ethanol [64]. Moreover, the substituent at the geminal center or its fragment must be in the enolic form, which is clearly essential for successful cyclization to the nitrofuran ring.

We cite yet another example of opening of the 5-nitrodihydropyrimidine ring. Irrespective of the position of the geminal unit, the reaction of the acetonyl anionic σ complexes (XVII) and (XVIII) with arenediazonium salts leads to the formation of the limiting structures (XVIIC) and (XVIIB) respectively, in which the negative charge is localized at the carbon atom attached to the nitro group [70]. The 5-arylazo-5-nitro-4,5-dihydropyrimidines (XXVIII) formed at the first stage are unstable and are converted into acyclic compounds during the reaction; conversely, their 2,5-dihydropyrimidine analogs (XXIX) are stable substances.



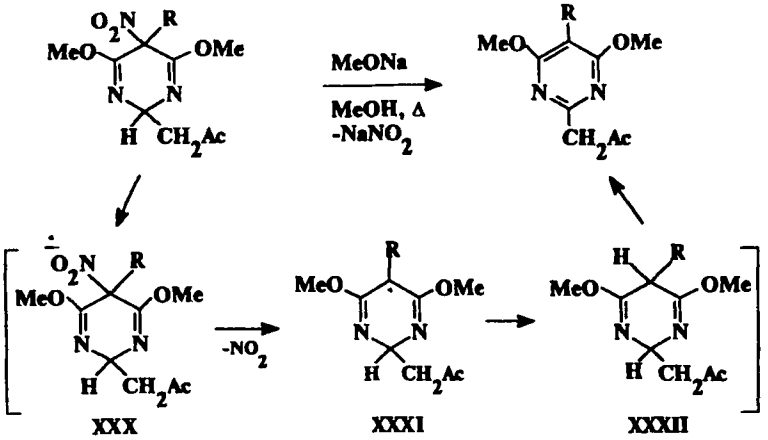
2.2. Transformations of Stable Nitrodihydropyrimidines

The reactions of nitrodihydropyrimidines not accompanied by decomposition of the heterocycle will be examined below. Here it is necessary to mention primarily the capacity of these compounds for dehydrogenation.

The σ adducts of 5-nitropyrimidine with an amide anion are oxidized by potassium permanganate [41]. 5-Nitro-4-phenyl-1,4-dihydropyrimidin-2(1H)-one (I) is dehydrogenated smoothly in acetic acid (the bromination–dehydrobromination method) [30]. 5-Nitro-2,5-, 5-nitro-1,4-, and 5-nitro-1,6-dihydropyrimidines are easily aromatized by the action of dichlorodicyanobenzoquinone [57, 58].

A few derivatives of 2,5-dihydropyrimidine not containing electron-accepting groups at position 5 of the pyrimidine ring are characterized by low stability [15, 71, 72]. At the same time, 5-nitro-2,5-dihydropyrimidines can be regarded as cyclic imines containing donating substituents at the α position and accepting substituents at the β position of the imine fragment. Such a combination of substituents differing in nature increases the stability of the synthesized compounds. The introduction of a second electron-accepting substituent at the β position of the imine fragment (position 5 of the 2,5-dihydropyrimidine ring) does not increase the stability of the molecule. It was shown in section 1.2 that the 5-acyl(ethoxycarbonyl)-5-nitro-substituted 2,5-dihydropyrimidines formed from the σ complex (XVIII) are unstable and are aromatized with the formation of the derivatives (XXI) and (XXII).

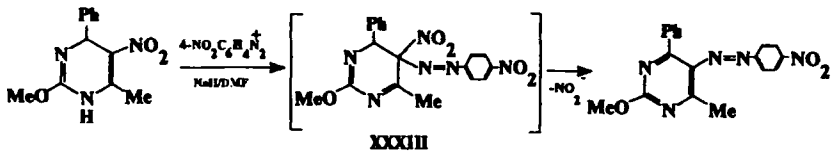
When 5-nitro-5-alkyl(arylaza)-2-acetonyl-2,5-dihydropyrimidines are boiled with sodium methoxide in methanol solution the dihydropyrimidine ring is aromatized with the formation of the corresponding 2-acetonylpyrimidines [73]. On the basis of the published data [74, 75] it is possible to present the following mechanism for this reaction. Since aromatic and aliphatic nitro compounds are capable of accepting an electron from strong reducing agents, being converted into radical-anions [75], the radical-anion salt (XXX) is formed as a result, clearly, of the transfer of an electron from the methoxide ion to the nitro group of 5-nitro-2,5-dihydropyrimidine. It then eliminates a nitrite ion and is converted into the dihydropyrimidinyl radical (XXX).



R = Me, Et, Pr, All, N=N-C_6H_4-R^1; R^1 = H, NO_2-2, NO_2-4, OMe-4

The latter removes a hydrogen atom from the solvent with the formation of 5-alkyl(arylaza)-5-H-2,5-dihydropyrimidines (XXXI), which as a result of their instability are aromatized during the isolation process. The synthetic value of this reaction rests on the fact that it makes it possible to produce difficultly obtainable 5-alkyl(arylaza)pyrimidines.

The 5-aza-5-nitro-4,5-dihydropyrimidine (XXXIII) formed as intermediate compound during the reaction of 5-nitro-1,4-dihydropyrimidine with a 4-nitrobenzenediazonium salt is aromatized in a similar way in an alkaline medium [36].



4,5-Dihydropyrimidines not containing electron-accepting groups are the most unstable compounds in the dihydropyrimidine series [15]. The introduction of a nitro group also does not affect their stability.

Transformations with retention of the nitrodihydropyrimidine ring have special significance, since they make it possible to modify the molecule without affecting its nitrodihydropyrimidine structure. The reaction of 2-substituted 4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidines, having several reaction centers, with electrophilic agents was investigated. A vicinal nitro group substantially increases the mobility of the hydrogen atoms in the methyl group at position 6 of the heterocycle. The reaction of these compounds with dimethylformamide diethyl acetal and 3-nitrobenzaldehyde gave enamines and styrenes respectively [31, 36]. Vilsmeier–Haack formylation and also the acetylation of 5-nitrodihydropyrimidin-2(1H)-ones take place selectively at the $N_{(3)}$ atom [31]. Nitration is conducted with potassium nitrate in sulfuric acid. The nitronium ion here attacks the *meta* position of the phenyl ring [31]. Depending on the conditions, the methylation of 5-nitro-4-phenyl-1,4-dihydropyrimidine takes place selectively at the $N_{(1)}$ and $N_{(3)}$ atoms with the formation of the corresponding hydrogenated derivatives [36].

Recently, an original method was proposed for the synthesis of C- and N-carbacyclonucleosides containing 5-nitro-2,5- and 5-nitro-1,6-dihydropyrimidines as heterocyclic base [21].

3. BIOLOGICAL ACTIVITY OF NITRODIHYDROPYRIMIDINES

Hydrogenated 6-nitroazolo[1,5-*a*]pyrimidines exhibit antimicrobial activity toward relatively pathogenic Gram-positive and Gram-negative microorganisms (*Bacillus sereus, Corynebacterium divercanum*) and the yeast-like fungus *Candida albicans* [19]. The antimicrobial activity depends little on the substituent in the azole fragment and is as a rule related to the nature of the substituent at position 7 of the pyrimidine part of the molecule. The introduction of resorcinol, indole, or alcohol residues increases the ability of these compounds to suppress the growth of Gram-positive microorganisms.

4-Aryl-3,5-dialkoxycarbonyl-1,4-dihydropyridines (nifedipine, phoridone, nimodipine, nicardipine hydrochloride, and others), which in their pharmacological activity belong to the group of calcium antagonists, are used successfully as effective cardiovascular and antihypertensive preparations [76-78]. Substitution of one of the ester groups by a nitro group leads to a

radical change in the physiological characteristics of these compounds [78, 79]. However, the highly effective calcium antagonist Bay K 8644 has not found use in medical practice on account of its high toxicity [79]. The interest in 4-aryl-5-nitro-1,4-dihydropyrimidines is due primarily to the fact that these compounds are the aza analogs of Bay K 8644. Investigation of the activity in the series of 6-nitroazolo[1,5-*a*]pyrimidines did not reveal compounds having a strong hypotensive effect [23]. Investigation of the effect of 4-aryl-6-methyl-5-nitro-1,4-dihydropyrimidin-2(1H)-ones on the contracting action of the myocardium and the principal hemodynamic indices [24-26] showed that, depending on the position of the substituent in the aryl fragment of the molecule, these compounds exhibit the characteristics of calcium antagonists and agonists. While not being inferior in activity to the reference products (strofantine, digoxin, Bay K 8644), calcium agonists with this structure are characterized by significantly lower toxicity. Thus, in the derivatives of 5-nitrodihydropyrimidine there are favorable prospects for the further discovery of compounds effective in the treatment of cardiovascular disease.

Analysis of the antiviral activity in the series of 7-substituted 6-nitro-4,7-dihydro[1,5-*a*]azolopyrimidines showed that the 7-indolyl-substituted compounds have the greatest effect [20]. The direction and the magnitude of the antiviral effect also depend of the nature of the substituent in the azole part of the molecule.

6-Acetonyl-1-(2,3-dihydroxypropyl)-5-nitro-2,4-dimethoxy-1,6-dihydropyrimidine [21] with low cytotoxicity exhibits activity against HIV-1 comparable with the effective antiviral agent azidothymidine [22]. Its analog 1-(2,3-dihydroxypropyl)-5-nitrouracil does not exhibit antiviral characteristics [80]. At the present time an intensive search is being made in the series of hydrogenated pyrimidines for non-nucleosidic inhibitors of reverse transcriptase [8-10]. Thus, it was found that derivatives of 3,4-dihydroquinazolin-2-one (in particular the product L-608,788) [8] have high activity against the HIV-1 virus. These data indicate the specific participation of the hydrogenated pyrimidine fragment in the inhibition of reverse transcriptase.

The data presented in the present review make it possible to conclude that the nitrodihydropyrimidines are extremely important as intermediates in the chemical transformations of π-deficient nitropyrimidine systems and also as synthons for the production of representatives of other types of organic compounds. The prospects for the further use of this direction of research are also favored by the high biological activity of the nitropyrimidines.

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