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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-NITROFURFURAL HETERYL HYDRAZONES

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Derivatives of 5-nitrofurfurol (furazolidone, furadonine, furazoline) are being used extensively as antimicrobial and diuretic preparations [5]. These compounds have been primarily obtained from substituted 2-oxazolidines and aminohydantoins.

For the purpose of finding new antimicrobial substances we synthesized heretofore undescribed heteryl hydrazones of 5-nitrofurfurol with quinazoline and oxazolidine rings as well as substituted aminohydrazides of imidazol-4,5-dicarboxylic acid.

We know from [3, 4] that the diamides of diimidazopyrazine-5,10-dione-1,6-dicarboxylic acid are easily broken down upon reacting with bases to the corresponding amino acids, amido esters, and diamides. In a similar manner we split compounds (I-VIII) with hydrazine hydrate to the amido hydrazides (IX-XVI) which formed hydrazones (XVII-XXIV) upon condensation with 5-nitrofurfurol.

When diethyl imidazol-4,5-dicarboxylate was reacted with 5-nitrofurfurol we obtained 4,5-bis(5-nitro-2-furfurylidene hydrazinecarbonyl)imidazole (XXV).

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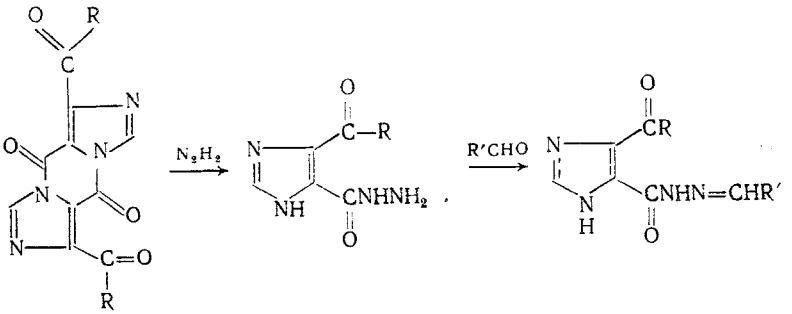
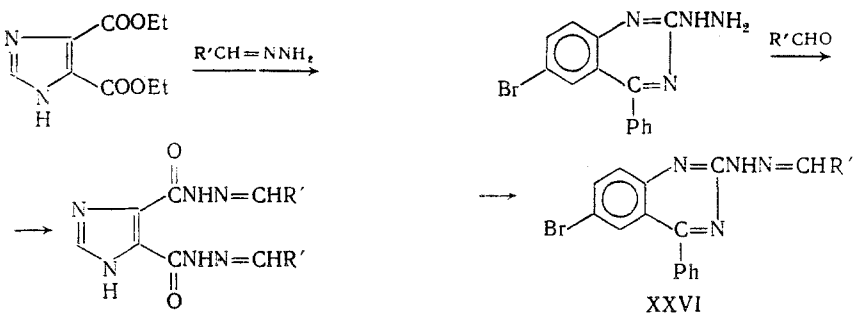


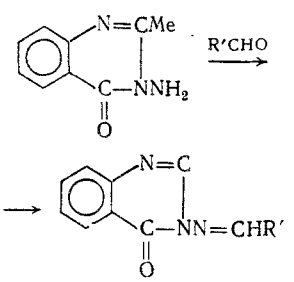
I—VIII IX—XVI XVII—XXIV

R = HNPh (I, IX, XVII), imidazolyl-1 (II, X, XVII), benzimidazolyl-1 (III, XI, XIX), 2-methylbenzimidazolyl-1(IV,XII,XX) morpholino (V, XIII, XXI) piperidino (VI, XIV, XXII), 4-methylpiperazine-1-yl (VII, XV, XXIII); 2-(o-chlorobenzoyl)-4-bromophenylamine (VIII, XVI, XXIV); henceforth R' = 5-nitrofuryl-2



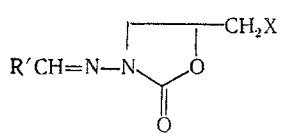
XXV XXVI

The initial reactant quinazolines with 5-nitrofurfurol were 6-bromo-4-phenyl-2-hydrazinoquinazoline [2] and 2-methyl-3-aminoquinazolone-4 [9].



XXVII

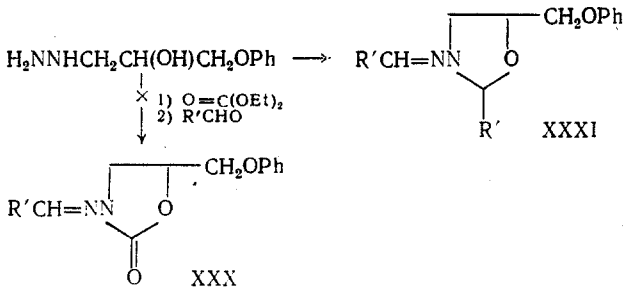
The derivatives of 2-oxazolidines (XXVIII) and (XXIX) were obtained by the previously described method and their constants correspond to [6].



XXVIII, XXIX

X=OMe (XXVIII), SBu (XXIX)

Our attempt to obtain 5-phenoxymethyl-3-(5-nitro-2-furfurylideneamino)-2-oxazolidone (XXX) under the same conditions was not successful. The primary separated product was 5-phenoxymethyl-3-(5-nitro-2-furfurylideneamino)-2-(5-nitro-2-2-furyl)oxazolidine (XXXI).



The physicochemical characteristics of the compounds are given in Table 1. The substances' composition and structure were confirmed by IR spectra, polarography, and element analysis.

The IR spectra of diamides I-VIII have intensive absorption band stretching vibrations of the carbonyl groups in the pyrazine ring at 1740-1770 cm^{-1} [10] as well as stretching vibration bands of the exocyclic groups of the amide fragment at 1650-1680 cm^{-1}. The molecular weights of substances I-VII were confirmed by mass spectrometry.

The symmetrical cleavage of a molecular ion and the subsequent elimination of COR fragments is a special feature of the mass spectra of compounds I-VII. The IR spectra of the amidohydrazides in IX-XVI have stretching vibration bands of the carbonyl groups of the amide and hydrazine fragments in the 1650-1700 cm^{-1} region, and hydrazine group stretching vibrations in the 3150-3190 and 3410-3450 cm^{-1} region. The IR spectra of the heteryl hydrazones XVII-XXVII have absorption bands corresponding to the vibrations of the NH, CO, C=N, C=C, and NO_2 groups in the 3100-3400, 1650-1700, 1590-1615, and 1340-1350 cm^{-1} regions. The following sets of absorption bands are present for the indicated compounds dependent upon the nature of the heterocyclic compound: for compounds XXVI and XXVII – absorption bands for the azomethine bond and the quinazoline ring at 1650-1660, 1550-1600, and 1450-1500 cm^{-1}; for compounds XVII-XXVII – furane ring vibrations at 1000-1015, 965-975, and 800-820 cm^{-1}. The polarographs of the heteryl hydrazones XVII-XXVII under investigation indicate the presence of two functional groups, namely a nitro group ($E_{1/2}$ = 450-650 mV) and an exocyclic azomethine bond ($E_{1/2}$ = 1150-1300 mV) [7].

EXPERIMENTAL CHEMICAL

TLC on Silufol UV-245 plates in an acetone–hexane (1:2) system with development in UV-light and a $KMnO_4$ solution was used to control the chemical process and the purity of the synthesized compounds. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer (GDR) in KBr pellets. Polarography was performed in a cell at 25°C in aqueous dimethylformamide solutions (acetone buffer = 1:1) on a mercury-drop electrode with forced drop release (clapper) (m = 1.24 mg/sec, T = 1.2 sec) in a three-electrode system where the anode has a mercury bottom and the reference electrode is a saturated calomel electrode. The polarographs were recorded on a PPT-1 (USSR) ac instrument (trapezoid shape). Mass spectra of the compounds were obtained on a MKh-1303 instrument (USSR) at an ionization energy of 70 eV and source temperature of 150-250°C. The found element analysis values corresponded to the calculated ones.

4H,9H-Diimidazo[1,5-a; 1'5'-d]piperazine-5,10-dione-1,6-dicarboxylic Diamides (I-VII). A 6.0 ml (0.02 mole) portion of diimidazo[1,5-a; 1'5'-d]pyrazine-5,10-dione-1,6-dicarboxylic dichloroanhydride [3] and 2 ml of dry Et_3N was gradually added upon stirring to a solution of 2 ml (0.02 mole) of morpholine in 150 ml of absolute $CHCl_3$. The reaction mixture was stirred at room temperature for 1 h. The precipitate was filtered off and washed with water, acetone, and ether. Yield of compound V was 3.7 g. Substances I-IV and VI were obtained in a similar manner. Compound VII is described in [4].

Mixed Amido Hydrazides of Imidazole-4,5-dicarboxylic Acid (IX-XVI). A 0.6 ml (0.02 mole) portion of absolute hydrazine hydrate was added to a solution of 2.0 g (0.005 mole) of diamide V in 30 ml of absolute DMFA and stirred for 1 h at room temperature. The solvent was removed with a rotary evaporator to dryness after which 100 ml was added to the residue. The precipitate was filtered off, washed with ethanol and ether, and dried. Substance XVI is described in [4].

TABLE 1. Compounds I-XXXI

Compound	Yield, %	mp, °C	Empirical formula
I	83	193—5	$C_{22}H_{14}N_6O_4$
II	85	245—8	$C_{16}H_8N_6O_4$
III	90	246—8	$C_{24}H_{12}N_6O_4$
IV	85	270—3	$C_{28}H_{16}N_6O_4$
V	70	>360	$C_{18}H_{16}N_6O_6$
VI	80	343—5	$C_{20}H_{22}N_6O_4$
VIII	78	275—6	$C_{20}H_{24}N_6O_4$
IX	80	305—7	$C_{11}H_{11}N_5O_2$
X	90	330 carbnzd.)	$C_9H_8N_6O_2$
XI	92	320(carbnzd.)	$C_{12}H_{10}N_6O_2$
XII	85	335(decomp.)	$C_{15}H_{12}N_6O_2$
XIII	80	360—1	$C_9H_{12}N_6O_3$
XIV	60	238—41	$C_{10}H_{15}N_5O_2$
XV	70	360—1	$C_{10}H_{14}N_6O_2$
XVII	68	343—5	$C_{16}H_{12}N_6O_6$
XVIII	65	302—5	$C_{13}H_9N_7O_6$
XIX	70	248—50	$C_{17}H_{11}N_7O_5$
XX	75	234—5	$C_{18}H_{13}N_7O_5$
XXI	65	210—2	$C_{14}H_{14}N_6O_6$
XXIII	70	251—3	$C_{15}H_{17}N_7O_5$
XXIV	63	278—80	$C_{22}H_{14}ClBrN_6O_6$
XXV	65	350—1	$C_{15}H_{10}N_6O_8$
XXVI	80	241—3	$C_{19}H_{12}BrN_5O_3$
XXVII	65	226—8	$C_{14}H_{10}N_4O_4$
XXXI	35	250—1	$C_{19}H_{11}N_4O_6$

Hydrazones of 5-Nitrofurfurol and Amidohydrazides of Imidazole-4,5-dicarboxylic Acid (XVII-XXIV). A 1.4 g (0.01 mole) portion of 5-nitrofurfurol was added to a solution of 2.35 g (0.01 mole) of compound XIII in 300 ml of DMFA and boiled for 1.5 h. The solvent was distilled off with a rotary evaporator after which 80 ml of ethanol was added to the residue. The precipitate was filtered off and washed with ethanol. Yield of compound XXI was 2.3 g. Substances XVII-XX and XXII-XXIV were obtained in the same manner.

4,5-Bis(5-nitro-2-furfurylidene hydrazinocarbonyl)imidazole (XXV). A 1.05 g (0.005 mole) portion of diethyl imidazole-4,5-dicarboxylate was added to a solution of 1.6 g (0.01 mole) of 5-nitrofurfurol hydrazine in 120 ml of absolute ethanol. The reaction mixture was then boiled for 1 h, cooled, and the precipitate was filtered off, dried, and recrystallized from DMFA. Yield was 1.3 g.

6-Bromo-4-phenyl-2-(5-nitro-2-furfurylidene hydrazino)quinazoline (XXVI). A 3.49 g (0.01 mole) portion of 6-bromo-4-phenyl-2-hydrazinoquinazoline was dissolved with boiling in 300 ml of ethyl alcohol to which 1.41 g (0.01 mole) of 5-nitrofurfurol was added, and the mixture was boiled for 1.5 h. After cooling the precipitated crystals were filtered off and washed with ethanol and ether. The yield was 4.0 g. Substance XXVII was obtained in a similar manner.

5-Phenoxymethyl-3-(5-nitro-2-furfurylideneamino)-5-nitro-2-furyl)oxazolidine (XXXI). A solution of NaOMe obtained from 0.12 g of Na and 4 ml of absolute MeOH and 18.3 g (0.1 mole) of 1-phenoxy-3-hydrazinopropanol-2 [8], was added to 12 ml (0.1 mole) of diethylcarbonate. The excess MeOH and ethanol was distilled off after which 14.1 g (0.1 mole) of 5-nitrofurfurol in 50 ml of absolute ethanol was added. The mixture was stirred at room temperature for 1 h. The precipitate was filtered off, resulting in 15 g of compound XXXI. IR spectra: ν_{max}, cm^{-1} 1635 (C=N), 1350 (NO_2), 1190, 1160, 1030 (oxazolidine ring); polarography: $E_{1/2}$ = 500 mV (NO_2), $E_{1/2}$ = 600 mV (NO_2), $E_{1/2}$ = 1250 mV (C=N).

EXPERIMENTAL BIOLOGICAL

The antimicrobial activity of compounds XVII-XXVII was evaluated by the minimum concentrations required to suppress the growth of the employed cultures of microorganisms. The minimal suppressive concentrations (MSC) were assayed on simple periodic cultures (liquids) of microorganisms by the double series dilution method. The screening results for the most active compounds are given in Table 2.

As a reference base the sensitivity of the test cultures were tested against the widely used antimicrobial agent furacilin. As can be seen from Table 2, the tested compounds exhibit antimicrobial activity in the concentration range of 3-350 μg/ml. The greatest activity against most of the employed cultures of microorganisms was exhibited by compounds XXVII and XXVIII which belong to the oxazolidine and quinazoline derivatives of 5-nitrofurfurol. Compounds XXI and XXII (imidazole-containing derivatives of 5-nitrofurfurol)

TABLE 2. Bacteriostatic Activity of Synthesized Compounds

Compound	Minimal suppressive concentrations for employed test-cultures, μg/ml				
	Micrococcus lysodeiticus	Staphylococcus aureus P-209	Streptococcus faecalis	Bacillus subtilis BKMB-428	Escherichia coli K-12
XXIX	80	92	140	350	140
XXVIII	5	3	112	320	12,5
XXXI	60	47	93	220	185
XXI	23	25	40	320	200
XXII	26	18	92	290	250
XVIII	250	350	350	350	350
XXIV	350	350	350	350	350
XXV	350	350	350	350	350
XXVI	21	18	41	200	140
XXVII	3	4	23	250	340
Furacilin	7	12	21	26	17

actively suppress the growth of Gram-positive coccal cultures. The introduction of two molecules of 5-nitrofurfurol or two volume substituents into the imidazole fragment markedly reduced their antimicrobial activity (compounds XVIII, XXIV, XXV).

A similar situation was observed in the case of the oxazolidines, i.e., substances XXIX and XXXI (see Table 2) are less active than XXVIII.

The spectrum of antimicrobial activity among the quinazoline derivatives is particularly interesting. The nature of bacteriostatic activity was also shown to be dependent upon the position of the 5-nitrofurfurol substituent in the quinazoline molecule. Thus, compound XXVII very effectively suppressed the growth of Gram-positive microbes whereas compound XXVI exhibited pronounced Gram-negative action (MSC for E. coli was reduced by 2.5 times).

The Gram-positive bacteria Bacillus subtilis were the most resistant to the action of the investigated compounds. All of the examined compounds exhibited a characteristic strong bacteriostatic activity against Gram-positive cocci and less so against the representatives of the E. coli Gram-positive microflora.

Substances XVII-XXVII were non-toxic at doses from 300 to 500 mg/kg. Acute toxicity was measured within a 24-h period at a constant temperature by method [1] on white non-pedigree mice weighing 18-20 g.

The results of our experiments have demonstrated that the new heteryl hydrazones of 5-nitrofurfurol exhibit pronounced antimicrobial activity, and some of them (compounds XXVII and XXVIII) exhibit a bacteriostatic spectrum which is close to that of the preparation furacilin.

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