LITERATURE CITED

1. N. S. Egorov, Scientific Fundamentals of Antibiotics [in Russian], 3rd edition, Moscow (1979), pp. 46-47.
2. V. I. Il'enko, Methods of Testing and Assessment of the Antiviral Activity of Chemical Compounds against Influenze Virus. Methodology [in Russian], Leningrad (1977).
3. G. A. Mokrushina, S. K. Kotovskaya, and G. A. Yurchenko, Conference on the Chemistry and Technology of Organic Sulfur Compounds and Sulfur-Containing Petroleum Oils. No. 16: Abstracts of Papers [in Russian], Riga, 1984, p. 187.
4. G. A. Mokrushina, S. K. Kotovskaya, G. N. Tyurenkova, et al., Khim.-farm. Zh., No. 2, 195 (1988).

SYNTHESIS AND ANTI-INFLUENZA ACTIVITY OF N-SUBSTITUTED-2-BENZAZOL-2-YLHYDRAZINOCARBOTHIOAMIDES

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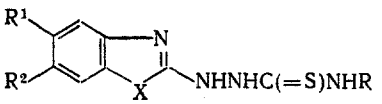
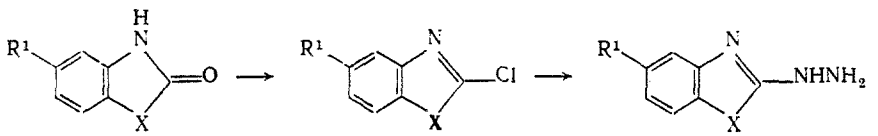
The search for drugs with antiviral activity is currently being carried out amongst various types of compounds. Many compounds with antiviral activity have been found in heterocycles, in particular benzimidazole and benzothiazole [1, 5, 6]. A number of ureido, thioureido, and hydrazinocarbothiamides (thiosemicarbazides) are known to display antirival activity [1, 2, 4]. In order to study anti-influenza activity, some compounds have been synthesized containing two potentially active groupings, benzazole and hydrazinocarbothioamide, namely N-substituted-2-(benzazol-2-yl)hydrazinocarbothioamides of general formula:

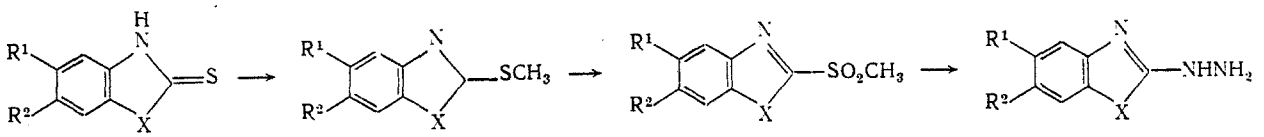


I—XXVII X = NH (I, II), NCH_3 (III—VI, XI, XII, XVII, XVIII, XXII, XXIII), $NCH_2C_6H_5$ (VII—X, XV, XVI), NC_4H_9 (XIII, XIV), NC_6H_5 (XIX), NCH_2CH_2OH (XX, XXI), S (XXIV, XXV), O (XXVI, XXVII); R = CH_3 (III, VII), C_6H_5 (V, IX, XIII, XV, XVII, XIX, XX, XXII, XXVI), p-ClC_6H_4 (II, VI, X, XII, XIV, XVI, XVIII, XXI, XXIII, XXV, XXVII), p-$C_2H_5OC_6H_4$ (I), allyl (IV, VIII, XI, XXIV); R^1 = H (I—X, XIX—XXI, XXIV—XXVII),), CH_3 (XI, XII), NO_2 (XIII—XIV), $COOC_2H_5$ (XVII, XVIII), $CO(NH)_2C(=S)NHC_6H_5$ (XXII), $CO(NH)_2C(=S)NHC_6H_4Cl$-p (XXIII); R^2 = H (I—X, XIII—XXVII), CH_3 (XI, XII).

Compounds (I-XXVII) were obtained from the appropriate 2-hydrazinobenzazoles and alkyl (or aryl) isothicyanates at ambient temperature or with gentle heating. The starting 2-hydrazinobenzazoles were obtained by hydrazinolysis of 2-chloro- or 2-methylsulfonyl-compounds, or of the benzazole-2-sulfonic acids:



(for (XVII), (XVIII), and (XX-XXII) as in [1]);



(for (XI-XVI) and (XIX) as in [2, 4]);

S. M. Kirov Urals Polytechnic Institute, Sverdlovsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 3, pp. 320-323, March, 1988. Original article submitted October 17, 1986.

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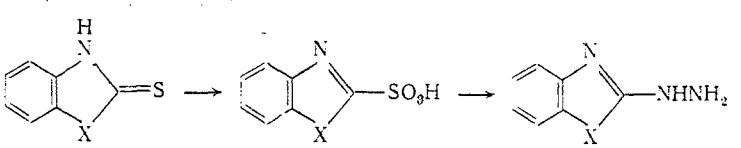
TABLE 1. Physicochemical Properties of (I-XXVII)

Compound	mp, °C (from ethanol)	Found, %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
I	179—80	58,8	5,2	21.6	$C_{16}H_{17}N_5OS$	58,7	5,2	21,4
II	154—5	53,1	3,7	22.2	$C_{14}H_{12}ClN_5S$	52.9	3,8	22,0
III	197—8	51.0	5,7	29.8	$C_{10}H_{12}N_5S$	51,1	5,5	29,8
IV	166—7	55,7	5,9	26.6	$C_{12}H_{15}N_5S$	55.2	5,7	26,8
V	158—9	60.6	5,0	23.6	$C_{15}H_{15}N_5S$	60,6	5,0	23,6
VI	161—2	54,3	4,7	20.7	$C_{15}H_{14}ClN_5S$	54,3	4,2	21,1
VII	177—8	61,3	5,5	22.4	$C_{16}H_{17}N_5S$	61.7	5,5	22,5
VIII	166—7	64,0	5,7	21.4	$C_{18}H_{19}N_5S$	64,1	5,6	20,8
IX	111—3	65,5	5,8	16.7	$C_{21}H_{19}N_5S \cdot C_2H_5OH$	65.8	5,9	16,7
X	153—4	60,9	4,9	15.7	$C_{21}H_{18}ClN_5S \cdot C_2H_5OH$	60,8	5,3	15,4
XI	201	58.2	6,9	24.3	$C_{14}H_{19}N_5S$	58,1	6,6	24,2
XII	239—40	56,7	5,4	19,7	$C_{17}H_{18}ClN_5S$	56,7	5,0	19,5
XIII	174—5	56,2	5,2	22.1	$C_{18}H_{20}N_6O_2S$	56,2	5,2	22,4
XIV	154—6	49,7	4,8	19.8	$C_{18}H_{19}ClN_6O_2S \cdot H_2O$	49,5	4,8	19,3
XV	189—90	56,4	5,0	19.0	$C_{21}H_{18}N_6O_2S \cdot 1{,}5\ H_2O$	56,6	4,7	18,9
XVI	142—5	55,5	3,8	18.7	$C_{21}H_{17}ClN_6O_2S$	55,7	3,7	18,7
XVII	166—7	58,5	5,2	19.3	$C_{18}H_{19}N_5O_2S$	58,5	5,1	18,9
XVIII	249—50	53,5	4,5	17,1	$C_{18}H_{18}ClN_5O_2S$	53,5	4,5	17,3
XIX	141—5	66,8	4,8	18,9	$C_{20}H_{17}N_5S$	66,8	4,7	19,5
XX	85—6* 144—6	57.9	6.1	18.9	$C_{16}H_{17}N_5OS \cdot C_2H_5OH$	57,9	6.4	18,8
XXI	154—5	52,7	5,1	18.9	$C_{16}H_{16}ClN_5OS$	53,1	4,5	19,3
XXII	184—6	56,3	4,4	23.0	$C_{23}H_{22}N_6OS$	56,3	4,5	22,9
XXIII	183—6	49,3	3,7	20.2	$C_{23}H_{20}Cl_2N_6OS$	49,4	3,6	20,0
XXIV	164—5	50,0	4,3	24.6**	$C_{11}H_{12}N_4S_2$	50,0	4,5	24,2**
XXV	171—4	50,4	3.2	16.9	$C_{14}H_{11}ClN_4S_2$	50,2	3.3	16,7
XXVI	253—4	59,2	4,3	19.7	$C_{14}H_{12}N_4OS$	59,2	4,2	19,7
XXVII	264—5	53,2	3.9	9.6**	$C_{14}H_{11}ClN_4OS$	52,9	3.5	10,0**

*Loss of a molecule of alcohol.
**Sulfur.

TABLE 2. Antiinfluenza Activity of Some of the Compounds Synthesized

Compound	Influenza A virus		Influenza B virus	
	in ovo	in vivo	in ovo	in vivo
I	++	—	—	—
II	++++	++	—	—
X	—	—	—	—
XI	+	++	—	
XII	+	—	—	
XIII	—		++++	—
XV	++		—	
XVIII	+	++		++
XX		+		—
XXI		++	—	
XXII		—		++
XXIII		—		++
XXV	+++	—	—	—

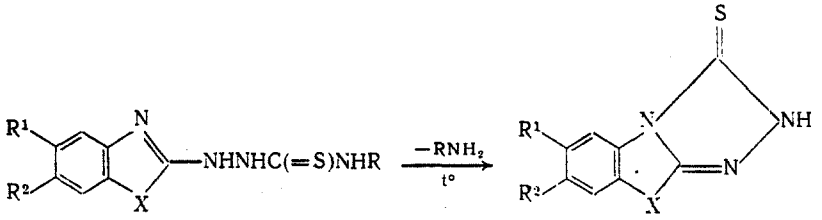


X = O, S.

(for (XXIV-XXVII) as in [8]).

The properties of the hydrazinocarbothioamides obtained are given in Table 1. They were colorless or pale yellow crystalline solids which were insoluble in water, but soluble in ethanol, dimethylformamide, and dimethyl-sulfoxide.

The N-alkyl (and aryl)-2-(1-R-benzimidazol-2-yl)- and N-aryl-2-(benzothiazol-2-yl)hydrazinocarbothioamides were sensitive to heat, being converted on heating the crystals at 170-200°C or boiling the ethanolic solutions with loss of amine into the S-triazolo[3,4-b]benzimidazole-3-thiones (XXVIII) and S-triazolo[3,4-b]benzothiazole-3-thiones (XXIX) respectively:



XXVIII, XXIX

The formation of (XXVIII) and (XXIX) was proved by direct synthesis from the appropriate 2-hydrazinobenzazoles and carbon disulfide in pyridine, and confirmed by elemental analysis and the identity of the IR and UV spectra The benzoxazole hydrazinocarbothioamides (XXVI) and (XXVII) were stable to heat.

The results of the testing of compounds with antiinfluenza activity are shown in Table 2. Of the 27 compounds tested, 14 showed antiinfluenza activity in developing chick embryos (activity coefficient 30-85%). In the animal experiments, activity was lower, being no greater than 56%. Of greatest interest as potential antiinfluenza compounds are the benzimidazole derivatives. These compounds include substances which show activity against influenza viruses A and B. It is, however, difficult to draw any valid conclusions as to the relationship between their structure and antiinfluenza activity. From the data presented in Table 2, it may be concluded that N-alkylhydrazinocarbothioamides are as a rule either inactive, or less active than the corresponding N-aryl compounds, the greatest activity being shown by the p-chloro-compounds. The presence of substituents in the benzene ring of benzimidazole confers activity on the compounds, while the presence of a methyl, phenyl, or benzyl group in the 1-position of the benzimidazole ring (when there are no substituents in the benzene ring of the benzimidazole) eliminates this activity (VI, VII, XV). N-substituted 2(-benzoxazol-2-yl)hydrazinocarbothioamides were inactive against the influenza viruses.

These studies have thus confirmed the desirability of a search for antiinfluenza compounds in the benzimidazole series, in particular N-aryl-2-substituted benzimidazol-2-ylhydrazinocarbothioamides.

EXPERIMENTAL CHEMICAL

N-Alkyl (and aryl)-2-(benzimidazol-2-yl)hydrazinocarbothioamides (I-XXIII). The appropriate 2-hydrazinobenzimidazole (0.01 mole) was dissolves with heating in such a volume of ethanol that solution was complete at 40-50°C (usually 50-100 ml). To this solution was added an alcoholic solution of the alkyl (or aryl) isothiocyanate (0.01 mole), the mixture stirred thoroughly, placed in a closed flask, and kept at ambient temperature until a solid separated (usually after one day). In the preparation of (XI) and (XII), the reaction mixture was heated on a water bath for 10-15 min. The solid was filtered off, washed with small amounds of ethanol and dry ether, and crystallized from ethanol, prolonged heating of the ethanolic solution being avoided. The properties of the products are given in Table 1.

9-Methyl-S-triazolo[4,3-a]benzimidazole-3-thione. A. A mixture of 1 g (0.006 mole) of 1-methyl-2-hydrazinobenzimidazole, 15 ml of dry pyridine, and 1 ml of carbon disulfide was heated for 4 h on the water bath. It was then cooled, poured into water, acidified with acetic acid, and the solid filtered off to give colorless needles, mp 250°C (decomp., from aqueous ethanol). Yield 0.7 g (46.6%). Found, %: C 53.1; H 3.7; S 15.7. $C_9H_8N_4S$. Calculated, %: C 52.9; H 3.0; S 15.7. UV spectrum, λ_{max}, nm (lg ε): 227 (4.24), 268 (4.13), 319 (4.18).

B. N-Phenyl-2-(1-methylbenzimidazol-2-yl)hydrazinocarbothioamide (V) was heated at 200-210°C for a few minutes, whereupon the compound fused and resolidified, with evolution of aniline. The product was cooled and recrystallized from ethanol, mp 250-215°C. The IR and UV spectra of this material were identical with those of the compound obtained by method A.

EXPERIMENTAL BIOLOGICAL

Examination for antiinfluenza activity was carried out in developing chick embryos and white mice infected with influenza viruses A and B. In each test for activity of the compounds in developing chick embryos and white mice, three subjects were used, namely embryos (mice) treated with the test compound, embryos (mice) treated with a drug active against the virus in question (remantadine for virus A and adapromine in testing for activity against

virus B), and embryos (mice) treated with a placebo (normally physiological saline or distilled water). Examination for activity was carried out by the method given in the methodological procedures approved by the Ministry of Health of the USSR [3].

LITERATURE CITED

1. N. P. Bednyagina and I. Ya. Postovskii, Zh. Obshch. Khim., 30, 1431-1437 (1960).
2. N. N. Bershchagina, I. Ya. Postovskii, and N. P. Bednyagina, Khim. Geterotsikl. Soedin., Coll. 1., 162-165 (1967).
3. V. I. Il'enko, Methods of Testing and Calculation of Antiviral Activity of Chemical Compounds against Influenza Virus (Methodology) [in Russian], Leningrad (1977).
4. G. A. Mokrushina and N. P. Bendnyagina, Khim. Geterotsikl. Soedin., No. 10, 1397-1400 (1970).
5. British Pat. No. 1 272,920; Chem. Abstr., 77, 48-81 (1972).
6. West German Pat. No. 2,003,841; Chem. Abstr., 73, 879920 (1970).
7. G. N. Pershin, and N. S. Bogdanova, The Chemotherapy of Viral Infections [in Russian], Moscow (1973), p. 69.
8. L. S. Efros, B. A. Porai-Koshits, and S. G. Farbenshtein, Zh. Obshch. Khim., 23, 1691-1696 (1953).
9. B. Rada, E. Holbova, S. Inkulasek, et al., Acta Virol., 23, 203-209 (1979); Chem. Abstr., 91, 117174 (1979).
10. H. Willitzer, H. Breuniger, D. Engelman, et al., Pharmazie, 30, 30-34 (1978).