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SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE-5-CARBOXAMIDES

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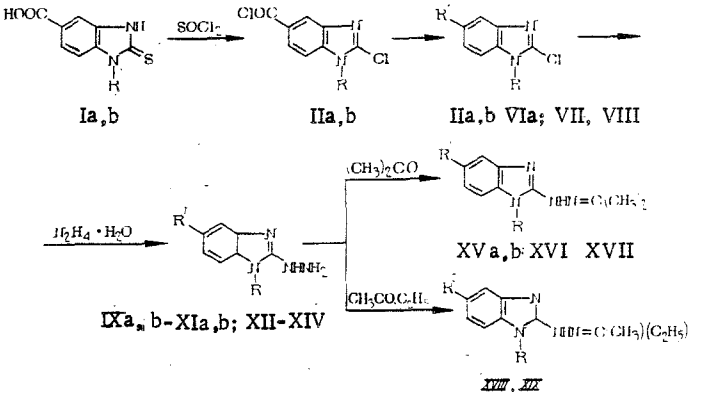
We have previously reported [4] that in 2-hydrazinobenzimidazoles, the greatest antiviral activity is shown by compounds bearing a carboxy or ethoxycarbonyl group in the 5-position. Continuing work on the synthesis and examination of the antiviral activity of benzimidazoles, we have synthesized some benzimidazole-5-carboxamides substituted in the 2-position with chloro-, hydrazine-, and isopropylidene (and isobutylidene)hydrazino-groups (III-XIX).



R = Me (Ia—VIa, IXa—XIa, XVa), CH_2Ph (Ib—VIb, VII, VIII, IXb—XIb, XII—XIV, XVb, XVI—XIX); R^1 = $CONMe_2$ (VII, XIII), $CONEt_2$ (III, IX, XV, XVIII), $CONHCMe_3$ (VI, XII, XVII), $CONHCH_2Ph$ (IV, X, XVI, XIX), $CONHC_{18}H_{37}$ (V, XI), $CON(CH_2CHMe_2)_2$ (VIII, XIV); R^2 = Cl(III—VIII)

These compounds have become accessible as a result of our observation of the replacement of the mercapto-group by chlorine on treatment of the thiones (Ia, b) with thionyl chloride [3], high yields of 1-methyl(and benzyl)-2-chlorobenzimidazole-5-carbonyl chlorides (IIa, b) being obtained. Treatment of the acid chlorides with amines (diethylamine, benzylamine, octadecylamine, tert-butylamine, and diisobutylamine) gave the 1-methyl (and benzyl)-2-chlorobenzmidazole-5-carboxamides (IIIa, b-VIa, b, VII, and VIII). Hydrazinolysis of the 5-amido-2-chlorobenzimidazoles proceeded under milder conditions than in the case of the 5-unsubstituted 2-chlorobenzimidazole, namely on boiling (III-VIII) with an excess of hydrazine hydrate for 15-30 min. It should be noted that some of the hydrazino-compounds are unstable, darkening rapidly on keeping, and for this reason only (IXa,b-XIa, b, XII, and XIV) could be synthesized and submitted for testing for antiviral and antimicrobial activity. On brief boiling in acetone or ethyl methyl ketone, the corresponding hydrazones (XVa, b, XVI-XIX) were obtained. The structures of the hydrazino-compounds were confirmed by their PMR spectra, and their conversion into the hydrazones. The PMR spectra of the products showed a complex multiplet in the aromatic proton region (6.8-7.7 ppm), and a broadened signal for the NH proton at 3.5-4.5 ppm. The signals for the substituents in the amide group were in full agreement with the multiplicity and chemical shifts of the structures assigned to them.

The 2-chloro- and 2-hydrazino-derivatives and the hydrazones were examined for antiviral (against A and B influenza viruses) and antimicrobal activity. The testing results for those

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TABLE 1. Properties of 1,2,5-Substituted Benzimidazoles

Compound	Yield, %	mp, °C (solvent)	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIIa	54	203—5 (acetonitrile)	60,5	6,3	15,3	$C_{14}H_{18}N_3ClO$	60,1	6,5	15,0
IIIb	70	108—9 (30% ethanol)	66,6	6,2	12,4	$C_{19}H_{20}N_3ClO$	66,8	5,9	12,3
IVa	75	158—60 (50% ethanol)	64,4	4,8	13,9	$C_{16}H_{14}N_3ClO$	64,1	4,7	14,0
IVb	68	168—9 (isopropanol)	69,9	4,9	11,2	$C_{22}H_{18}N_3ClO$	70,3	4,8	11,2
Va	70	122—5 (ethyl acetate)	69,9	9,8	9,1	$C_{27}H_{44}N_3ClO$	70,2	9,6	9,1
Vb	65	125—7 (ethyl acetate)	73,6	9,0	7,8	$C_{33}H_{48}N_3ClO$	73,4	8,8	7,4
VIa	75	160—1 (ethanol)	58,8	6,1	16,1	$C_{13}H_{16}N_3ClO$	58,8	6,1	15,8
VIb	68	166—7 (DMF)	66,6	5,9	12,5	$C_{19}H_{20}N_3ClO$	66,6	5,9	12,3
VII	64	118—20 (benzene)	65,1	5,2	13,4	$C_{17}H_{16}N_3ClO$	65,1	5,1	13,4
VIII	60	103—5 (ethyl acetone)	69,0	7,1	10,2	$C_{23}H_{26}N_3ClO$	69,4	7,0	10,7
IXa	80	160—1 (benzene)	59,7	7,3	27,0	$C_{13}H_{19}N_5O$	59,8	7,2	27,5
IXb	75	166—7 (benzene)	67,3	6,6	21,0	$C_{19}H_{23}N_5O$	67,6	6,9	20,8
Xa	68	235—8 (40% DMF)	65,1	5,8	23,8	$C_{16}H_{17}N_5O$	65,0	5,8	23,7
Xb	75	110—1 (50% ethanol)	70,7	5,6	18,5	$C_{22}H_{21}N_5O$	71,1	5,7	18,9
XIa	65	120—1 (ethyl acetate)	70,7	10,0	15,3	$C_{27}H_{47}N_5O$	70,8	10,3	15,3
XIb	60	118—9 (ethyl acetate)	69,8	9,7	12,1	$C_{33}H_{52}N_5O$	69,5	9,2	12,3
XII	72	252—4 (ethanol)	67,9	6,9	20,5	$C_{19}H_{23}N_5O$	67,6	6,9	20,8
XIII	58	198—9 (ethanol)	65,6	6,6	22,4	$C_{17}H_{20}N_5O$	65,8	6,6	22,6
XIV	65	130—2 (ethyl acetate)	69,9	8,2	17,4	$C_{13}H_{31}N_5O$	70,2	7,9	17,8
XVa	70	172—3 (acetone)	64,1	7,9	23,1	$C_{16}H_{23}N_5O$	63,7	7,7	23,3
XVb	75	167—8 (acetone)	69,9	7,3	18,6	$C_{22}H_{28}N_5O$	69,8	7,4	18,5
XVI	70	220—1 (acetone)	72,7	6,3	17,3	$C_{25}H_{25}N_5O$	72,9	6,1	17,0
XVII	70	178—9 (ethanol)	70,4	7,2	18,7	$C_{22}H_{27}N_5O$	70,0	7,2	18,6
XVIII	72	168—9 (30% ethanol)	70,5	7,5	17,9	$C_{23}H_{29}N_5O$	70,5	7,5	17,2
XIX	68	194—5 (ethanol	73,4	6,8	16,2	$C_{26}H_{28}N_5O$	73,2	6,6	16,4

TABLE 2. Antiviral Activity of Benzimidazoles*

Compound	Influenza virus A		Influenza virus B	
	in ovo	in vivo	in ovo	in vivo
IXb	—	—	—	++
XIa	±	++	—	...
XIV	±	++	+++	—
XVa	±	—	—	...
XVI	—	++	+++	—
XVII	—	...	±	±
XIX	±	++	++	±

*Index of effectiveness: —) less than 30%, +) 30-39%, ++) 40-59%, +++) 60-79%.

compounds which showed activity are given in Tables 2 and 3. As will be seen from Table 2, the hydrazinobenzimidazoles (IXb), (XIa), and (XIV), and the hydrazones (XV-XVII) and (XIX) were active against both A and B influenza viruses. In tests on developing chick embryos, the index of effectiveness of these drugs was 33-71%. In animal experiments, the index was no greater than 54%, for the most part against influenze virus A. It is interesting that in some instances the activity in mice was greater than in chick embryos (compounds (XIV), (XVI), and (XIX)). 2-Chlorobenzimidazoles failed to show any activity.

Antibacterial and antifungal activity was determined in Gram-positive and Gram-negative representative pathogenic microorganisms, yeasts, and phytopathogenic fungi. The test results are shown in Table 3. 1-Methyl(and benzyl)-2-chlorobenzimidazoles carrying a tert-butylaminocarbonyl substituent in the 5-position showed high antifungal activity, inhibiting the growth of Verticillium dahliae at concentrations of 20-50 μg/ml. No antibacterial activity was shown by these compounds. The hydrazino-compounds (IXa, b) and (XII), and the hydrazone (XVb) inhibited the growth of both Gram-positive and Gram-negative microorganisms. The bacteriostatic dose was 50-400 μg/ml.

These results of tests for antiviral, antibacterial, and antifungal activity therefore suggest that a further search for new antifungal and antimicrobial compounds in these benzimidazoles holds promise.

TABLE 3. Antimicrobial Activity of Benzimidazoles

Compound	Bacteriostatic and Fungistatic doses, μg/ml									
	Staphylococcus aureus	Staphylococcus albus	Bacillus cereus	Corynebacterium deverticatum	Mycobacterium B_5	E. coli	Proteus vulgaris	Pseudomonas aeruginosa	Candida albicans	Verticillium dahliae
VIa	—	—	—	—	—	—	—	—	100	20
VIb	—	—	—	—	—	—	—	—	—	50
IXa	100	200	200	100	100	200	100	100	400	400
IXb	50	50	100	50	50	100	100	100	400	400
XII	400	400	400	400	200	200	200	200	200	400
XVb	100	100	100	100	100	200	200	200	400	400

Note. None of the test compounds showed antimicrobial activity.

EXPERIMENTAL CHEMICAL

1-Methyl(and benzyl)-2-chloro-5-aminocarbonylbenzimidazoles (III-VIII). The acid chloride (IIa, b) (0.01 mole) was dissolved in benzene, and a benzene solution of the appropriate amine added. The mixture was kept at 20-30°C for 3 h, evaporated to dryness, and the residue crystallized from a suitable solvent. The properties of the compounds are given in Table 1.

1-Methyl(and benzyl)-5-aminocarbonyl-2-hydrazinobenzimidazoles were obtained by boiling 0.01 mole of the 2-chlorobenzimidazole in 10-15 ml of hydrazine hydrate for 30 min. The solid which separated on cooling was filtered off and crystallized. If no solid separated on cooling the reaction mixture, it was precipitated with water.

Isopropylidene(and isobutylidene)hydrazones (XVa, b) and (XVI-XIX) were obtained by boiling the hydrazino-compounds in acetone or ethyl methyl ketone for 30 min, followed by evaporation to dryness. The properties of the compounds are given in Table 1.

EXPERIMENTAL BIOLOGICAL

Antimicrobial activity was examined by serial dilution of the drug in liquid nutrient media which were optimum for the growth of the test cultures used, against Gram-positive and Gram-negative representative pathogenic microorganisms, dermatophytes, yeasts, and phytopathogenic fungi [1]. The strains of Staphylococcus aureus, S. Albus, Bacillus cereus, Mycobacterium B_5, Escherichia coli, Proteus vulgaris, Pseudomonas aeruglinisa were grown on meat-peptone agar and broth for 18-24 h at 37°C, the strain of Corynebacterium devericatum under the same conditions at 28°C, the strain of yeast Candida albicans at 37°C for 18-24 h on agarized must, and the pathogenic fungi strain Verticillium dahliae on the same medium for 72-168 h at 28°C. The microbial loading was 200,000 microbial bodies per ml of medium. The antimicrobial activity of the compound was expressed as the minimum bacteriostatic dose giving total inhibition of the growth of the test culture.

Examination for antiviral activity was carried out in developing chick embryos and in white mice infected with influenza viruses A and B. In each test for activity in developing chick embryos and white mice three groups were used: embryos (mice) treated with the test compound, embryos (mice) treated with a compound active against the test virus (remantadine in the case of the A group virus and adapromine in testing for activity with type B virus), and embryos (mice) treated with a placebo (the solvent, usually physiological saline or distilled water). In tests on mice, five doses of the compound were given, at 24 h and 1 h before infection, and 24, 48, and 72 h after infection. This mode of testing comprises simultaneously tests for prophylactic and therapeutic activity. The examinations and assessment of the activity of the compounds was carried out as described in the methodological instructions approved by the Ministry of Health of the USSR [2].

Examinations for antimicrobial activity were carried out in the D. K. Zabolotnii Institute of Microbiology and Virology of the Academy of Sciences of the Ukrainian SSR (Kiev), and for antiviral activity at the All-Union Research Institute for Influenza, Ministry of Health of the USSR (Leningrad).

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

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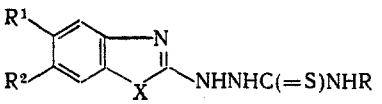
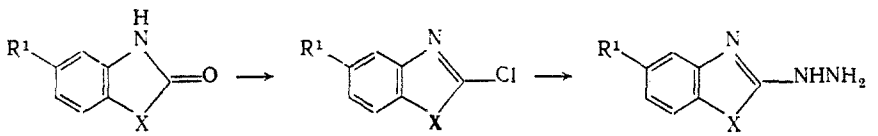
The search for drugs with antiviral activity is currently being carried out amongst various types of compounds. Many compounds with antiviral activity have been found in heterocycles, in particular benzimidazole and benzothiazole [1, 5, 6]. A number of ureido, thioureido, and hydrazinocarbothiamides (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:

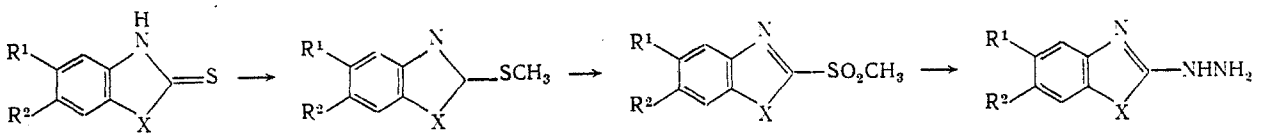


I—XXVII X = NH (I, II), NCH_3 (III—VI, XI, XII, XVII, XVIII, XXII, XXIII), $NCH_2C_6H_5$ (VII—X, XV, XVI), NC_4H_9 (XIII, XIV), NC_6H_5 (XIX), NCH_2CH_2OH (XX, XXI), S (XXIV, XXV), O (XXVI, XXVII); R = CH_3 (III, VII), C_6H_5 (V, IX, XIII, XV, XVII, XIX, XX, XXII, XXVI), p-ClC_6H_4 (II, VI, X, XII, XIV, 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]);

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