6. G. M. Paronikyan, L. G. Akopyan, T. R. Akopyan, and V. G. Paronikyan, Biol. Zh. Armenii, 32, No. 11, 1146 (1979).
7. L. M. Fonshtein, S. K. Abilev, A. M. Zekhnov, and A. A. Shapiro, Genetika, 12, No. 5, 119 (1976).

STRUCTURE AND BIOLOGICAL ACTIVITY OF PHENACYLTHIOIMIDAZOLINES AND 3-PHENYL-5,6-DIHYDROIMIDAZO[2,1-b]THIAZOLES

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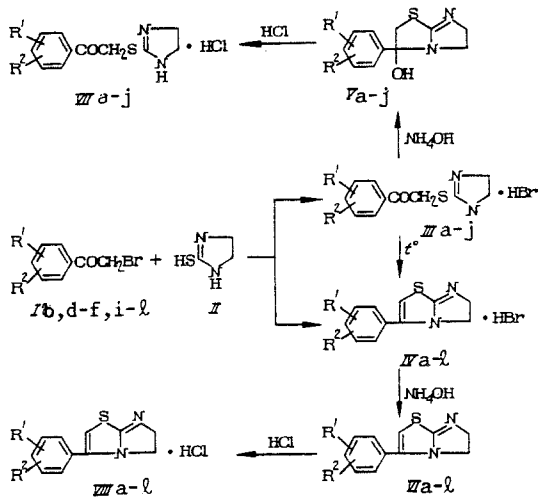
Phenacylthioimidazolines are known to possess antidepressant [10, 11, 19] and antiarrhythmic [9] activity. They are also readily-accessible intermediates for the synthesis of the bicyclic imidazo[2,1-b]thiazoles, derivatives of which display antiinflammatory [8], hypotensive [20], and analgesic [12] properties. Levamizole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole), used in medicine as an anthelmintic, also possesses antitumor activity [15, 17].

Methods have been developed for the synthesis of imidazothiazoles starting from β-formyl(oxo-, hydroxy-, or carboxy)alkylthioimidazoles [5, 6] and 1-phenacyl-2-thioimidazoles [7].

We here describe the synthesis of 3-hydroxy-3-phenyl-2,3,5,6-tetrahydroimidazo[2,1,-b]-thiazoles (V) and the corresponding 3-phenyl-5,6-dihydroimidazo[2,1-b]thiazoles (VI) with a variety of substituents in the benzene ring.



IIIa-j–VIIIaj; R^1=4-PrO (a,h), 4-AmO (b, i), 4-AcNH (c, d), 2-MeO (e), 2-PrO (f), 4-MeO (g), 4-NH_2 (j); R^2=H (a-c), 3-Br (d), 5-Br (e, f), 3-NO_2 (g, j); IVk, l, VIk, l, VIIIk, l: R^1=4-PrO (k), 4-BuO (l); R^2=Cl (k, l).

The phenacylthioimidazoline hydrobromides (IIa-j) were obtained by reacting the phenacyl bromides (I) with 2-thio-2-imidazoline (II) in acetone. On boiling in water or

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TABLE 1. Phenacyl Bromides

Compound	Yield, %	mp, °C	Empirical formula
Ib*	77	Oil	$C_{13}H_{17}BrO_2$
Id	75	118—120	$C_{10}H_9Br_2NO_2$
Ie	71	68—69	$C_9H_8Br_2O_2$
If	77	88—90	$C_{11}H_{12}Br_2O_2$
Ii	82	Oil	$C_{13}H_{16}BrNo_4$
Ij	68	167—169	$C_8H_7BrN_2O_3$
Ik**	71	36—38	$C_{11}H_{12}BrClO_2$
Iℓ***	69	Oil	$C_{12}H_{14}BrClO_2$

*bp 186-188°C (1 mm).
**bp 170-172°C (1 mm).
***bp 184-186°C (1 mm).

TABLE 2. Physicochemical Constants of 3-Hydroxy-3-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles, 3-Phenyl-5,6-dihydroimidazo[2,1-b]thiazoles, and Their Salts

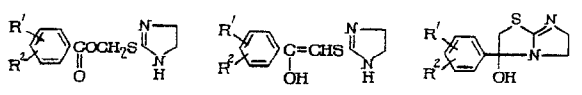
Compound	Yield, %	mp, °C	R_f	Empirical formula	mp, °C of hydrobromides (III), (IV)	mp of hydrochlorides (VII, VIII)
Va	86	132—3	0,56	$C_{14}H_{18}N_2O_2S$	164—165	162—163
Vb	75	132—3	0,80	$C_{16}H_{22}N_2O_2S$	181—182	158—159
Vc	83	182—3	0,65	$C_{13}H_{15}N_3O_2S$	286—287	
Vd	80	124—6	0,62	$C_{13}H_{14}BrN_3O_2S$	176—177	
Ve	78	149—150	0,76	$C_{12}H_{13}BrN_2O_2S$	165—166	199—200
Vf	81	143—5	0,79	$C_{14}H_{17}BrN_2O_2S$	152—153	168—169
Vg	76	148—9	0,60	$C_{12}H_{13}N_3O_4S$	187—188	206—207
Vh	71	135—6	0,65	$C_{14}H_{17}N_3O_4S$	179—180	201—222
Vi	75	151—2	0,68	$C_{16}H_{21}N_3O_4S$	192—193	175—176
Vj	78	170—171	0,63	$C_{11}H_{12}N_4O_3S$	200—202	162—163
VIa	68	53—5	0,67	$C_{14}H_{16}N_2OS$	223—224	192—194
VIb	64	68—70	0,83	$C_{16}H_{20}N_2OS$	197—198	175—176
VIc	84	250—251	0,71	$C_{13}H_{13}N_3OS$	302—303	285—286
VId	86	91—2	0,70	$C_{13}H_{12}BrN_3OS$	278—279	264—266
VIe	75	109—110	0,75	$C_{12}H_{11}BrN_2OS$	192—193	210—211
VIf	82	100—101	0,77	$C_{14}H_{15}BrN_2OS$	176—177	209—210
VIg	76	175—6	0,55	$C_{12}H_{11}N_3O_3S$	227—228	218—219*
VIh	74	131—2	0,58	$C_{14}H_{15}N_3O_3S$	208—209*	210—211*
VIi	72	92—3	0,75	$C_{16}H_{19}N_3O_3S$	202—204	163—164
VIj	68	228—230	0,67	$C_{11}H_{10}N_4O_2S$	276—277	238—239
VIk	74	93—4	0,68	$C_{14}H_{15}ClN_2OS$	184—185	197—198
VIℓ	75	90—91	0,71	$C_{15}H_{17}ClN_2OS$	183—184	170—172

*With decomposition.

ethanol, (IIIa-j) undergo cyclization to the imidazothiazole hydrobromides (IVa-ℓ). The imidazothiazoles (VIk, ℓ) were also obtained directly by boiling (I) and (II) in acetone.

The hydrobromides (III-IV) were converted into the free bases (V-VI), from which were obtained the phenacylthioimidazoline hydrochlorides (VIIa-j) and the 3-phenyl-5,6-dihydroimidazo[2,1-b]thiazole hydrochlorides (VIIIa-ℓ).

The structures of phenacylthioimidazolines have attracted the attention of investigators. These compounds could exist in the three tautomeric forms A, B, and C.



A B C

It has been shown by IR and PMR spectroscopy that phenacylthioimidazoline hydrobromides exist as mixtures of the ketonic (A) and hydroxybicyclic (C) forms [14, 18, 19].

The phenacylthioimidazoline bases have been assigned the hydroxybicyclic form (C) [18]. However, mass spectrometry of the bases shows them to be 2,3,5,6-tetrahydroimidazo-[2,1-b]thiazoles (form C), together with forms A and B [4]. We have now examined the

TABLE 3. Effects of Hydrochlorides (VII) and (VIII) on Transmission of Excitation along the Sympathetic Nerves and the Adrenoreceptors of Rat Vas Deferens

Compound	Decrease in contraction of the duct caused by transmural stimuli, as % of controls		Decrease in contraction of the duct caused by noradrenalin, as % of the controls	
	10 min	60 min	10 min	60 min
VIIa	59 (38,7—79,3)	32 (26,3—37,7)	50 (17,3—82,7)	41 (23,2—58,8)
VIIf	89 (86,8—91,2)	70 (56,4—83,6)	81 (73,2—88,8)	17 (—19,2—53,2)
VIIg	27 (24,8—29,2)	125 (—68,3—318,3)*	143 (—71,8—357,8)*	32 (3,2—60,8)
VIIi	35 (20—58)	38 (27,6—48,4)	28 (—25,1—81,1)	24 (—19,2—47,2)
VIIIa	53 (34—72)	54 (21,3—86,7)	15 (—4,3—34,3)	35 (—48,6—118,6)
VIIIf	66 (24,8—107,2)	16 (—28,7—60,7)	56 (—38,6—150,6)	18 (—23,7—59,7)
VIIIg	36 (5,5—66,5)	32 (12—52)	103 (—5—211)*	75 (—5—155)
VIIIi	43 (19,2—66,8)	82 (46,7—117,3)	75 (32,1—117,9)	74 (25,7—122,3)
VIIIk	98 (94,5—101,5)	97 (91—103)	88 (58,1—117,9)	49 (—9,2—107,2)
VIIIℓ	92 (85,1—98,9)	100	79 (56,8—101,2)	54 (4—104)

Note. An asterisk indicates an increase in contraction of the duct (as a % of the controls). The range of variation is given in brackets.

effects of substituents in the benzene ring on the proportion of the keto-form present in the phenacylthioimidazoline hydrobromides (III) by PMR spectroscopy.

No signal for the vinyl proton in form B was seen in the PMR spectra of (III). In addition, the spectra showed singlet signals for the $COCH_2$ methylene group at 5.2-5.3 ppm, for the protons of the imidazoline ring at 3.6-4.3 ppm, for the benzene ring at 7-8.5 ppm, and for the protons of the alkoxy groups.

The amounts of the keto-forms, calculated from the integral intensities of the signals for the CH_2CO group, were 75 and 55% for the alkoxy-compounds (IIIa, b), respectively, for the 4-acetylamino-compound (IIIc) 60%, the 4-acetylamino-3-bromo-compound (IIId) 20%, the 2-alkoxy-5-bromo-compounds (IIIe, f) 15 and 10%, the 4-alkoxy-3-nitro-compounds (IIIg, i) 33 and 30%, and the 4-amino-3-nitro-compound (IIIj) 75%.

The hydrobromides (III) and the hydrochlorides (VII) display two melting points. This is due to the thermal elimination of water to give the 3-phenyl-5,6-dihydroimidazo[2,1-b]-thiazole salts. Similar behavior has been seen in phenacylthioimidazoline salts [19].

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a UR-20 (East Germany) spectrophotometer in Vaseline grease, and PMR spectra on a Varian T-60 in deuterized dimethyl sulfoxide (internal standard, TMS). The purity of (V) and (VI) were checked by TLC on Silufol UV-254 in the solvent system butanol—acetic acid—water (4:2:5), visualized by UV. Melting points were measured on a Boetius micro-hot plate. The elemental analyses were in agreement with the calculated values.

2-Alkoxy-5-bromo- and 4-Alkoxy-3-chlorophenacyl Bromides (Ie, f, k, ℓ). To 0.04 mole of the appropriate acetophenone in 100 ml of dry ether was added dropwise with stirring 2.2 ml (0.04 mole) of bromine. Stirring was continued for one hour, then the solvent was distilled off, and water added. The oil which separated was extracted with ether, dried over sodium sulfate, the solvent removed, and (Ie, f) recrystallized from absolute ethanol; (Ik, ℓ) were vacuum distilled (Table 1).

4-Amino-3-nitrophenacyl bromide (Id) was prepared in dry chloroform as for (Ie, f) (Table 1). 4-Pentyloxy-3-nitrophenacyl bromide (Ii, Table 1) was obtained as described in [3]. 4-Acetylaminophenacyl bromide had mp 199-200°C (lit. mp [16], 190-193°C).

2-(2-Imidazolin-2-ylthio)acetophenone Hydrobromides (IIIa-j). A solution of 4.1 g (0.04 mole) of (II) in 300 ml of acetone was treated with stirring with 0.04 mole of (I) dissolved in 80 ml of acetone. The mixture was stirred at room temperature for 2 h, and the solid which separated was filtered off and washed on the filter with acetone (Table 2). Absorption of the CO group in the IR spectra of (III) (cm^{-1}): (IIIa, c) 1680, (IIIb, j) 1675, (IIId, f, h) 1690, (IIIa) 1665, (IIIg) 1685, (IIIi) 1670.

3-Phenyl-3-hydroxy-2,3,5,6-tetrahydroimidazo[2,1-b]thiazoles (Va-j). The appropriate (III) (0.04 mole) was dissolved in 500 ml of water without heating, and neutralized with

TABLE 4. Toxicity and Antitumor Activity of the Hydrochlorides (VIII) on Sarcoma-45

Compound	Toxicity in mice, mg/kg		Dose, mg/kg	Inhibition of tumor growth	
	LD_{100}	MID		I, %	confidence level (α)
VIIIa	150	50	10	33	0,95
VIIIf	50	25	2,5	52	>0,95
VIIIh	150	50	8	45	0,95
VIIIi	100	60	5	32	0,95
VIIIj	75	45	4	39	0,95
VIIIk	40	15	2	35	0,95
VIIIℓ	50	30	2,5	51	>0,95

aqueous ammonia. The solid which separated was filtered off and recrystallized from a mixture of ethanol and water (1:1) (Table 2).

2-(2-Imidazolin-2-ylthio)acetophenone Hydrochlorides (VIIa-j). To a suspension of 0.01 mole of the appropriate (V) in 30 ml of acetone was added dropwise 0.5 ml of hydrochloric acid. The solid which separated was filtered off (Table 2).

Absorption of the CO group in the IR spectra of (VII) (cm^{-1}): (VIIa) 1665; (VIIb, f, g) 1670; (VIIe) 1660; (VIIh, i) 1675; (VIIj) 1645.

3-Phenyl-5,6-dihydroimidazo[2,1-b]thiazoles (VIa-ℓ). Method A. A mixture of 0.02 mole of the hydrobromide (III) and 50 ml of absolute ethanol was boiled for 2 h. The solvent was then distilled off, and dry ether added. The solid hydrobromide (IV) which separated was isolated, dissolved in water, and basified with 15% sodium hydroxide solution. The solid which separated was filtered off and recrystallized from a mixture of ethanol and water (1:1) (Table 2).

3-(4-Alkoxy-3-chlorophenyl)-5,6-dihydroimidazo[2,1-b]thiazoles (VIk, ℓ). Method B. A mixture of 0.04 mole of (Ik, ℓ), 4.1 g (0.04 mole) of (II), and 50 ml of absolute ethanol was boiled for 5-6 h. The workup was carried out as in method A (Table 2).

3-Phenyl-5,6-dihydroimidazo[2,1-b]thiazole Hydrochlorides (VIIa-ℓ). Dry hydrogen chloride was passed into a solution of 0.01 mole of (VI) in 36 ml of absolute ethanol, until the solution became acid to Congo Red. Part of the solvent was distilled off, and dry ether added. The solid which separated was filtered off and recrystallized from ethyl methyl ketone (Table 2).

EXPERIMENTAL (PHARMACOLOGY)

The effects of the hydrochlorides (VII) and (VIII) on α-adrenoreceptors and the transmission of impulses through the postgangliar sympathetic nerve fibers were examined in isolated rat vas deferens. The activity of the compounds was assessed by the changes in contraction of the vas deferens induced by transmural electrical stimulation and administration of noradrenalin in a concentration of $1 \cdot 10^{-6}$ g/ml. The effects of each compound were examined in tests on five organs in a final concentration of 0.05 mM [1].

Most of the compounds were found to have marked sympathetic and adrenal blocking activity, exceptions being methoxy-substituted compounds (VIIe, g) and (VIIIe, g), which showed short-lived adrenal sensitizing properties.

The most active compounds are shown in Table 3, from which it will be seen that the phenacylthioimidazoline hydrochlorides (VII) and the imidothiazole hydrochlorides (VIII) show similar activity. Powerful and prolonged sympatholytic activity (97 and 100%) was shown by 3-[4-propoxy(and butoxy)-3-chlorophenyl-5,6-dihydroimidazo[2,1-b]thiazole hydrochlorides (VIIIk, ℓ). It is noteworthy that (VIIIk, ℓ) also show high mutagenic activity in a range of biochemical mutants. For example, (VIIIk) was more active on the lysine locus in actinomycetes than the control mutagens ethyleneimine and N-nitrosomethylurea by factors of 14 and 8.5, respectively [2].

With this in view, the antitumor activity of the imidazothiazole hydrochlorides (VIIIa, f, h, i-ℓ) was examined. Tests were carried out in mongrel white mice and rats weighing

18-20 and 90-110 g, respectively, using a standard method [13]. The compounds were tested intraperitoneally in solution in 0.9% sodium chloride solution.

The toxicities of the compounds were examined in mice of both sexes following a single dose, the absolute lethal dose (LD_{100}) and maximum tolerated dose (MTD) being found for each compound.

The antitumor activity of the compounds was examined in experimental tumors in rats and mice, namely sarcomas 45 and 180, Walker's carcinosarcoma (WCS), and Ehrlich's ascitic carcinoma (EAC). Treatment of the animals with solid tumors was begun at the 4th-5th day of growth of the tumor, and those with EAC, 24 h after transplantation. The compounds were administered daily for eight days to the rats, and six days to the mice, in doses of 1/10 and 1/20 of the LD_{100}. Antitumor activity was measured by the percentage inhibition of tumor growth (I, %), and in the case of the ascitic disease, by the increase in lifespan of the animals. The numerical data obtained were evaluated by the Student–Fisher method. In all, 280 mice and 115 rats were used. The compounds were found to be highly toxic, with LD_{100} values ranging from 40 to 150 mg/kg (Table 4), the chloro-compounds (VIIIk, ℓ) being somewhat more toxic (LD_{100} 40-50 mg/kg) than those containing a nitro-group (VIIIh, i, j; LD_{100} 75-150 mg/kg).

In therapeutic doses, all the compounds caused a slight reduction (30-50%) in the growth of sarcoma-45. Against WCS and sarcoma-180, only the 4-amino-3-nitrophenyl- (VIIIj) and 4-propoxy(and butoxy)-3-chlorophenyl- (VIIIk, ℓ) compounds showed antiblastic activity (I = 30-42%). In tests with EAC, none of the test compounds were active.

These chemotherapeutic studies have therefore shown that these 3-phenyl-5,6-dihydroimidazo[2,1-b]thiazoles have weak antitumor activity. However, the high sympatholytic activity of some of these compounds indicates the desirability of further investigations in this series.

LITERATURE CITED

1. O. M. Avakyan, Farmakol. Toksikol., No. 5, 104-110 (1984).
2. Author's Cert. (USSR) No. 910,637; Byull. Izobret. v SSSR i za rubezhom. (Bull. Inventions in the USSR and Abroad. Organic Chemistry) [in Russian], No. 12, 12 (1982).
3. M. A. Iradyan, A. G. Torosyan, R. G. Mirozyan, and A. A. Aroyan, Khim. Geterotsikl. Soedin., No. 10, 1384-1388 (1977).
4. M. A. Iradyan, V. S. Mirozyan, and R. A. Aroyan, Arkh. Khim. Zh., No. 6, 506-511 (1980).
5. P. M. Kochergin, A. M. Tsyganova, and L. M. Viktorova, Khim. Geterotsikl. Soedin., No. 1, 93-96 (1967).
6. I. A. Mazur and P. M. Kochergin, ibid., No. 4, 512-514 (1970).
7. I. A. Mazur, P. M. Kochergin, and G. S. Tkachenko, ibid., No. 6, 824-826.
8. US Pat. No. 2,969,369; Chem. Abstr., 55, No. 16, 15513e (1961).
9. US Pat. No. 4,153,706; Izobret. SSSR. Rubezhom (Inventions in the USSR and Abroad. Organic Chemistry), No. 24, 149 (1979).
10. West German Pat. No. 1,924,769 (1970); Chem. Abstr., 72, No. 7, 31832p (1970).
11. West German Pat. No. 1,938,674 (1970); ibid., No. 21, 111502w.
12. Japanese Patent No. 7,912,393 (1979); ibid., 91, No. 1, 5226s (1979).
13. V. A. Chernov, Methods in Experimental Chemotherapy [in Russian], Moscow (1971), pp. 357-403.
14. M. Fefer and L. C. King, J. Org. Chem., 26, No. 3, 828-835 (1961).
15. T. Hozumi, T. Iwaguchi, H. Kitagawa, and H. Ozawa, Gann, 69, No. 3, 339-343 (1978); Chem. Abstr., 89, No. 13, 100133b (1978).
16. W. A. Jacobs and M. Heidelberger, J. Biol. Chem., 21, No. 2, 459 (1915).
17. M. Negwer, Organisch-Chemische Arzneimittel und Ihre Synonyma, Vol. 1, p. 288, Berlin (1978), p. 288 (no. 1587).
18. R. S. Shadbolt, J. Chem. Soc., Sect. C, No. 9, 1667-1669 (1971).
19. C. J. Sharpe, R. S. Shadbolt, A. Ashford, and J. W. Ross, J. Med. Chem., 14, No. 10, 977-982 (1971).
20. P. B. Timmermans and P. A. Van Zwieten, Pharmacology, 16, No. 2, 106-114 (1978); Chem. Abstr., 88, No. 19, 130715q (1978).