ing off the ether the residue was reconverted into the hydrochloride. Constants are given in Table 1.

Methiodides of α-Phenyl-β-hexamethylenimino 4-Substituted Propiophenones. A mixture of an ether solution of α-phenyl-β-hexamethylenimino 4-substituted propiophenone (0.01 mole) and methyl iodide (0.01 mole) was kept at room temperature for 24 h. The solid which separated was filtered off and washed with absolute ether (see Table 1).

LITERATURE CITED

1. A. N. Kudrin and V. G. Vorob'ev, Aminoketones [in Russian], Moscow (1970).
2. O. L. Mndzhoyan and G. I. Pogosyan, Izv. Akad. Nauk Arm. SSR, Khim. Nauki, 13, 361 (1960).

IMIDAZOLES.

XII. SYNTHESIS OF SUBSTITUTED BENZYLTHIOALKYLIMIDAZOLINES

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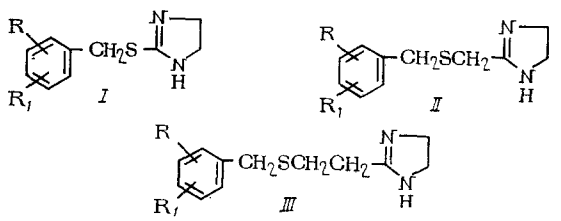
L. A. Ktsoyan, and A. A. Aroyan*

UDC 615.225.2:547.785.5/.012.1

In order to test them for hypotensive properties, we have previously obtained 2-benzylimidazolines substituted with halogen, alkoxy, and nitrogroups in the benzyl radical [1, 2].

This paper describes the preparation and examination of imidazolines (I-III) in which the aryl substituent and the heterocycle are separated by carbon and sulfur atoms, which according to the literature [3-7] often results in modification of the active compounds.



*Deceased.

TABLE 1. Substituted Benzylthioalkylimidazolines

Compound	R	R_1	Yield, %	Melting point, deg	Found, %		Molecular formula	Calculated %		Hydrochloride, mp, deg
					N	S		N	S	
Ia*	4-C_3H_7O	H	89,0	99—100	11,21	12,50	$C_{13}H_{18}N_2OS$	11,19	12,81	115—6
Ib*	4-CH_3O	3-CH_3O	88,2	106—7	10,87	12,43	$C_{12}H_{16}N_2O_2S$	11,10	12,71	192—3
Ic	4-CH_3O	3-Cl	86,6	108—9	10,78	12,20	$C_{11}H_{13}ClN_2OS$	10,91	12,49	226—8
Id*	4-C_3H_7O	3-Cl	87,2	70—1	10,01	10,98	$C_{13}H_{17}ClN_2OS$	9,84	11,26	152—3
Ie*	4-CH_3O	3-Br	89,7	124—5	9,44	10,39	$C_{11}H_{13}BrN_2OS$	9,30	10,64	231—2
If*	4-C_3H_7O	3-Br	86,8	83—4	8,82	9,85	$C_{13}H_{17}BrN_2OS$	8,51	9,74	165—6
Ig	2-CH_3O	5-Br	90,0	133—4	9,32	10,51	$C_{11}H_{13}BrN_2OS$	9,30	10,64	235—6
Ih	2-C_2H_5O	5-Br	85,1	108—10	8,81	9,85	$C_{12}H_{15}BrN_2OS$	8,89	10,17	220—1
Ii	2-C_3H_7O	5-Br	87,8	103—4	8,23	9,50	$C_{13}H_{17}BrN_2OS$	8,51	9,74	174—5

*Biological activity examined.

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TABLE 2. Substituted 2-Benzylthioalkyl-2-imidazolines

Compound	R	R_1	Yield, %	Boiling point, deg*	Found, %	
					N	S
IIa	4-C_3H_7O	H	63,4	63—5	10,87	11,85
IIb *	4-CH_3O	3-CH_3O	81,8	—	8,92	10,22
IIc *	4-CH_3O	3-Cl	58,8	100—101	10,10	11,66
IId	4-C_3H_7O	3-Cl	56,7	—	8,13	9,31
IIe	4-CH_3O	3-Br	83,5	104—5	8,58	10,45
IIf	2-CH_3O	5-Br	76,2	99—100	9,22	10,00
IIg	2-C_3H_7O	5-Br	80,4	86—8	7,95	9,57
IIIa	4-C_3H_7O	H	59,2	107—8	10,02	11,14
IIIb	2-CH_3O	5-Br	75,5	122—4	8,46	9,58
IIIc*	2-C_2H_5O	5-Br	68,4	96—7	7,84	9,20

Compound	Molecular formula	Calculated, %		Hydrochloride, mp, deg
		N	S	
IIa	$C_{14}H_{20}N_2OS$	10,60	12,13	180—1
IIb*	$C_{13}H_{18}N_2O_2S \cdot HCl$	9,25	10,59	188—9
IIc*	$C_{12}H_{15}ClN_2OS$	10,35	11,84	215—6
IId	$C_{14}H_{19}ClN_2OS \cdot HCl$	8,36	9,56	152—3
IIe	$C_{12}H_{15}BrN_2OS$	8,89	10,17	179—80
IIf	$C_{12}H_{15}BrN_2OS$	8,89	10,17	107—8
IIg	$C_{14}H_{19}BrN_2OS$	8,16	9,34	112—3
IIIa	$C_{15}H_{22}N_2OS$	10,06	11,52	—
IIIb*	$C_{13}H_{17}BrN_2OS$	8,51	9,74	175—6
IIIc*	$C_{14}H_{19}BrN_2OS$	8,16	9,34	170—1

*Biological activity examined.

TABLE 3. Substituted Benzyl Mercaptans

Compound	R	R_1	Yield, %	Boiling point, deg*	d_4^{20}	n_D^{20}	Found, %	Molecular formula	Calculated, %
Va	4-C_3H_7O	H	67,8	111—3	1,0391	1,5482	17,81	$C_{10}H_{14}OS$	17,59
Vb	4-CH_3O	3-CH_3O	77,8	136—8	1,1370	1,5738	17,35	$C_9H_{12}O_2S$	17,40
Vc	4-CH_3O	3-Cl	66,2	125—7	1,2477	1,5919	17,11	C_8H_9ClOS	16,99
Vd	4-C_3H_7O	3-Cl	68,5	133—5	1,2205	1,6131	15,03	$C_{10}H_{13}ClOS$	14,79
Ve	4-CH_3O	3-Br	64,8	127—9	1,4892	1,5235	13,62	C_8H_9BrOS	13,75
Vf	2-CH_3O	5-Br	69,9	114—6	1,6112	1,5000	14,01	C_8H_9BrOS	13,75
Vg	2-C_3H_7O	5-Br	72,7	132—4	1,3933	1,5739	12,55	$C_{10}H_{13}BrOS$	12,28

*At 1 mm pressure.

The compounds I were obtained by alklation of ethylenethiourea with benzyl chlorides, and II and III were obtained as follows:

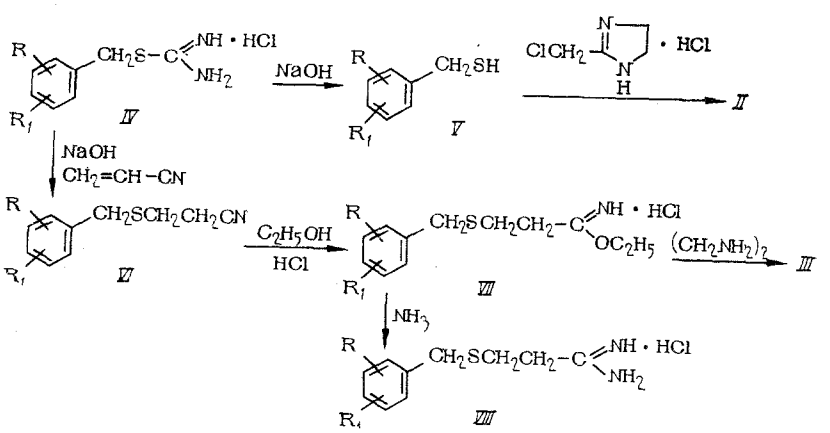


TABLE 4. Benzylthiopropionitriles

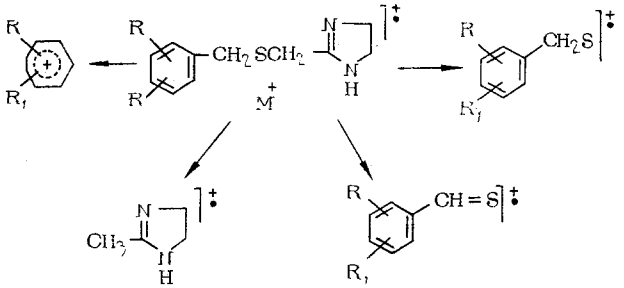
Compound	R	R_1	Yield, %	Boiling point, deg*	Melting point, deg	d_4^{20}
VIa	4-CH_3O	3-CH_3O	81,3	169—171	—	1,1591
VIb	4-C_3H_7O	3-Cl	80,2	170—2	—	1,2289
VIc	2-CH_3O	5-Br	85,0	178—80	58—9	—
VId	2-C_2H_5O	5-Br	83,5	186—8	40—1	—

Compound	n_D^{20}	Found, *		Molecular formula	Calculated, *	
		N	S		N	S
VIa	1,5662	5,68	13,28	$C_{12}H_{15}NO_2S$	5,90	13,51
VIb	1,5772	5,35	11,61	$C_{13}H_{16}ClNOS$	5,19	11,89
VIc	—	4,84	10,89	$C_{11}H_{12}BrNOS$	4,89	11,20
VId	—	4,38	10,66	$C_2H_{14}BrNOS$	4,67	10,68

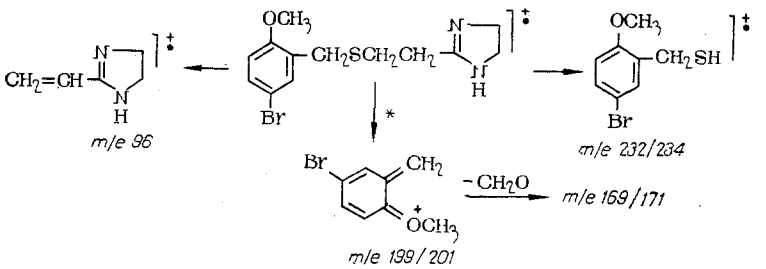
*At 1 mm pressure.

The structures of the compounds contained (Tables 1-5) were confirmed by mass spectrometry. The spectrum of I displayed strong peaks due to the molecular ion, and peaks for ions of masses 241/143 $(M-15)^+$, 223/225 $(M-SH)^+$, and 155/157 $(M-C_3H_5N_2S)^+$. Elimination of the SH group is known to be observed frequently in the mass spectra of aryl sulfides [8].

The structure of II was confirmed by the characteristic routes of breakdown of the molecular ion:



Molecular ion peaks were absent from the mass spectra of the benzylthioethylimidazolines. However, breakdown of the molecular ion leads to the formation of a number of characteristic fragments which establish the structure. A probable scheme for the fragmentation of IIIb is as follows:



The hypotensive activity of the compounds was examined. The experiments were carried out with rats of both sexes, of weight 200-300 g. The animals were narcotized with nembutal (intraperitoneal, 50 mg/kg). Testing of ten compounds (see Tables 1 and 2) showed them to be without effect on the arterial pressure in the rat. The use of control of clonidium [2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride] in a dose of 0.1 mg/kg caused a pronounced and prolonged reduction in arterial pressure.

EXPERIMENTAL

Mass spectra were recorded on an MX-1303 instrument with direct introduction of the sample into the ion source at a temperature 20-30° below the melting point of the compound.

TABLE 5. Benzylthiopropionimidates and -amidines

Compound	R	R_1	Yield, %	Melting point, deg*	Found, %		Molecular formula	Calculated, %	
					N	S		N	S
VIIa	4-C_3H_7O	H	74,5	105—7	4,26	10,35	$C_{15}H_{23}NO_2S \cdot HCl$	4,41	10,09
VIIb	4-CH_3O	3-CH_3O	68,3	105—6	4,14	9,75	$C_{14}H_{21}NO_3S \cdot HCl$	4,38	10,02
VIIc	4-C_3H_7O	3-Cl	70,1	99—100	3,81	9,38	$C_{15}H_{22}ClNO_2S \cdot HCl$	3,98	9,10
VIId	2-CH_3O	5-Br	80,5	116—7	4,03	8,50	$C_{13}H_{18}BrNO_2S \cdot HCl$	3,80	8,70
VIIe	2-C_2H_5O	5-Br	69,2	107—8	3,87	8,40	$C_{14}H_{20}BrNO_2S \cdot HCl$	3,66	8,38
VIIIa	4-C_3H_7O	H	91,3	122—3	9,70	10,85	$C_{13}H_{20}N_2OS \cdot HCl$	9,70	11,10
VIIIb	4-C_3H_7O	3-CH_3O	95,8	116—7	9,41	10,71	$C_{12}H_{18}N_2O_2S \cdot HCl$	9,63	11,03
VIIIc	4-C_3H_7O	3-Cl	84,7	102—3	8,38	9,65	$C_{13}H_{19}ClN_2OS \cdot HCl$	8,67	9,92
VIIId	2-CH_3O	5-Br	86,2	90—2	8,53	9,21	$C_{11}H_{15}BrN_2OS \cdot HCl$	8,25	9,44
VIIIe	2-C_2H_5O	5-Br	89,8	114—5	7,78	8,98	$C_{12}H_{17}BrN_2OS \cdot HCl$	7,92	9,07

*Compounds VIIa-VIIe melted with decomposition.

Substituted Benzylthioimidazolines (I). A mixture of 0.01 moles of the substituted benzyl chloride [9, 10], 0.01 moles of ethylenethiourea, and 30 ml of absolute ethanol was heated for 6-7 h. Part of the ethanol was distilled off, and the precipitate which separated was filtered off (see Table 1). Mass spectrum of Ia*: 250 (60), 217 (19), 207 (36), 175 (9), 149 (39), 114 (18), 107 (100), 102 (14).

Mass spectrum of Id: 258 (47), 256 (100), 243 (27), 241 (57), 225 (10), 223 (33), 198 (10), 196 (19), 157 (46), 155 (96), 105 (19), 102 (14).

S-3,4-Dimethoxybenzylisothiuronium Chloride (IV). A mixture of 9.3 g of 3,4-dimethoxybenzyl chloride, 3.8 g of thiourea, and 50 ml of absolute ethanol was heated for 5-6 h. The solid which separated was filtered off. Yield 11.2 g (85.0%), mp 162-163°. Found, %: N 10.31; S 11.83. $C_{10}H_{14}N_2O_2S \cdot HCl$. Calculated, %: N 10.66; S 12.20.

The remaining compounds IV were obtained as in references [10, 11].

Substituted Benzyl Mercaptans (V). A mixture of 0.01 moles of IV and 50 ml of a 10% solution of sodium hydroxide was heated for 2 h, then acidified with acetic acid and extracted with ether. The ether extracts were dried over sodium sulfate, the ether was removed, and the residue was distilled in vacuo (see Table 3).

Substituted Benzylthiomethylimidazolines (II). A mixture of 0.01 moles of V, 1.5 g (0.01 moles) of 2-chloromethyl-2-imidazoline hydrochloride, and 50 ml of absolute ethanol was heated for 6-8 h. The solvent was distilled off, and the residue was dissolved in water and added to a 15-20% solution of sodium hydroxide. The precipitated II was filtered off and recrystallized from a mixture of ethanol and water (see Table 2).

Mass spectrum of IIb: 261 (9), 183 (10), 182 (5), 151 (57), 137 (6), 84 (100).

Mass spectrum of IIf: 316 (40), 314 (40), 285 (10), 283 (11), 235 (20), 233 (20), 232 (4), 231 (10), 230 (4), 201 (95), 199 (100), 171 (73), 169 (75), 84 (75).

Benzylthiopropionitriles (VI). A mixture of 0.01 moles of IV and 5 ml of ethanol was heated on the water bath, and a solution of 2 g (0.05 moles) of sodium hydroxide in 20 ml of 50% ethanol was added slowly. The mixture was then cooled to room temperature, 0.8 g (0.015 moles) of acrylonitrile added, stirred for a further 3 h, extracted with ether, and the ether extracts dried over calcined sodium sulfate. After removal of the solvent, the residue was distilled *in vacuo* (see Table 4). Compound VI (R = 4—C_3H_7O, R_1 = H) was obtained as in [12].

Ethyl Benzylthiopropionimidate Hydrochlorides (VII). Dry hydrogen chloride was passed into a mixture of 0.1 mole of VI, 4.6 g (0.1 mole) of absolute ethanol, and 60 ml of absolute ether until it was saturated. The mixture was kept overnight, then part of the solvent was removed, and the solid which separated was washed with absolute ether (see Table 5).

*Here and below the masses of the ions are given, with the peak intensities as a percentage of that of the most intense peak given in parentheses.

Benzylthiopropionamidine Hydrochlorides (VIII). A mixture of 0.01 mole of VII in 20 ml of absolute ethanol was saturated with ammonia (approximately 30 min), followed by removal of the ethanol and addition of absolute ether. The solid which separated was filtered off (see Table 5).

Substituted Benzylthioethylimidazolines (III). A mixture of 0.05 mole of VII, 3.3 g (0.055 mole) of anhydrous ethylenediamine, and 50 ml of absolute ethanol was heated for 6-8 h, the solvent distilled off, and the residue dissolved in water and added to a 15-20% solution of sodium hydroxide. The solid which separated was filtered off and recrystallized from aqueous ethanol (see Table 2).

Mass spectrum of IIIb: 234 (71), 232 (68), 201 (99), 199 (100), 171 (40), 169 (39), 152 (6), 151 (14), 120 (8), 96 (11), 95 (5).

Mass spectrum of IIIc: 248 (74), 246 (72), 215 (98), 213 (100), 187 (52), 185 (56), 171 (13), 169 (14), 157 (9), 155 (10), 134 (79), 106 (30), 96 (44), 95 (28), 85 (22), 84 (32).

LITERATURE CITED

1. M. A. Iradyan, R. A. Aroyan, and A. A. Aroyan, Arm. Khim. Zh., No. 10, 851 (1973).
2. A. A. Aroyan, M. A. Iradyan, and R. A. Aroyan, Arm. Khim. Zh., No. 2, 136 (1973).
3. US Patent No. 3775478 (1973); Chem. Abstr., 80, 36,880 (1974).
4. US Patent No. 3714179 (1973); Chem. Abstr., 78, 111,325 (1973).
5. West German Patent No. 2104158 (1971); Chem. Abstr., 75, 151,791 (1971).
6. US Patent No. 3715367 (1973); Chem. Abstr., 78, 136295 (1973).
7. Canadian Patent No. 736484 (1966); Chem. Abstr., 65, 12211 (1966).
8. R. T. Aplin, M. Fisher, and D. Becner, J. Am. Chem. Soc., 21, 4888 (1965).
9. A. A. Aroyan, T. R. Ovsepyan, R. G. Melik-Ogandzhanyan, et al., Arm. Khim. Zh., No. 5, 406 (1969).
10. A. S. Azaryan, Sh. A. Avetyan, and A. A. Aroyan, Arm. Khim. Zh., No. 2, 151 (1972).
11. P. R. Ovsepyan and A. A. Aroyan, Arm. Khim. Zh., No. 1, 42 (1972).
12. A. A. Aroyan, T. R. Ovsepyan, and P. R. Akopyan, Arm. Khim. Zh., No. 7, 629 (1970).

SYNTHESIS AND GERMISTATIC ACTIVITY OF syn AND anti ISOMERS OF ARYLFURFURAL OXIME ACETATES

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We have described previously [1] the synthesis and established the structure of the anti isomers of arylfurfural oxime acetates. The present investigation was concerned with the development of a method for the synthesis of the syn isomers of arylfurfural oxime acetates. As a result of this work, conditions were found which afforded a mixture of the oxime acetate isomers in which the syn form predominated.

An examination of the biological activity of the mixed arylfurfural oxime acetate isomers carried out in the chemotherapy section of the All-Union Scientific-Research Institute of Pharmaceutical Chemistry (VNIKhFI) showed that these compounds possessed high germistatic activity, this activity differing for the syn and anti isomers.

An examination of the condition for the acetylation of arylfurfural oximes showed that

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