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IMIDAZOLE DERIVATIVES. XXVII. SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF SUBSTITUTED PHENACYLTHIOIMIDAZOLINE AND 3-PHENYL-5,6-DIHYDROIMIDAZO[2,1-B]THIAZOLE HYDROCHLORIDES

M. A. Iradyan, R. A. Aroyan, A. P. Engoyan, G. Kh. Grigoryan, S. É. Nersesyan, and A. G. Panosyan

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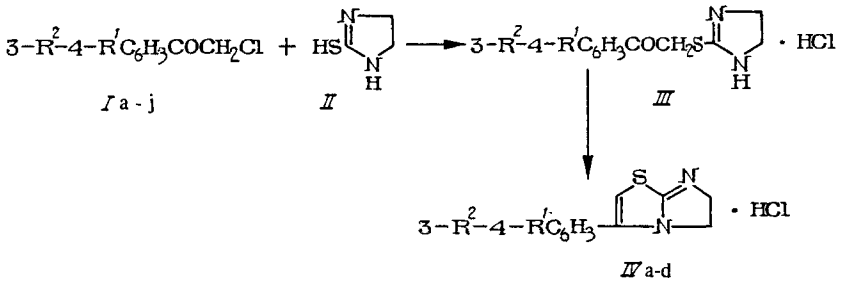
In a previous communication [2] we described the synthesis of phenacylthioimidazolines and their corresponding 3-phenyl-5,6-dihydroimidazo[2,1-b]thiazoles and investigated the biological properties of their hydrochlorides. It was found amongst other things that the 3-[4-propoxy(butoxy)-3-chlorophenyl]-5,6-dihydro-imidazo[2,1-b]thiazole hydrochlorides exhibited quite significant sympathicolytic and mutagenic activity [2, 3].

Due to the low solubility of substituted phenacylthioimidazoline hydrobromides in water and the fact that they can cyclize into imidazothiazoles it was difficult to convert the hydrobromides to the corresponding hydrochlorides. For this reason the phenacylthioimidazoline hydrochlorides (III) were synthesized in the present work by reacting the phenacyl chlorides (I) with 2-thio-2-imidazoline (II). Some of the hydrochlorides III cyclized into imidazothiazoles (IVa-d).



Compounds III are liable to keto-enol tautomerism and exist as a mixture of the ketone and hydroxybicyclic forms. The ketone form has the structure of phenacylthioimidazoline and the hydroxybicyclic form that of 3-phenyl-3-hydroxy-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole. As has been demonstrated in previous reports [2, 7], the ratio of these forms depends on the nature of the benzene ring substituents.

The ketone form content, calculated from the integral intensity of the CH_2CO group signal in the PMR spectra of III was 70% for the 4-methoxy and 4-propoxy derivatives IIIa and IIIb, 30 and 20% for the 4-methoxy-3-bromo and 2-hydroxy-5-bromo derivatives IIIc and IIId respectively, 55 and 50% for the 4-amyloxy-3-chloro and 4-hexyloxy-3-chloro derivatives IIIe and IIIf, 20% for the 4-methoxy-3-nitro derivative IIIg, 50 and 10-15% for the 4-acetylamino and 4-acetylamino-3-nitro derivatives IIIh and IIIi, and 80% for the 4-amino-3-nitro derivative IIIj.

It emerges from these results that the introduction of amino and alkoxy groups into the benzene ring of compounds III usually produces an increase in the ketone form content. A comparison of the findings obtained for hydrochlorides and hydrobromides [2] indicates that compounds with identical substituents in the benzene ring have almost the same ketone form content.

A. L. Mndzhoyan Institute of Precision Organic Chemistry, Armenian Academy of Sciences. Medical Radiology Research Institute, Armenian Ministry of Health, Yerevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 28, No. 7, pp. 13-15, July, 1994. Original article submitted June 8, 1993.

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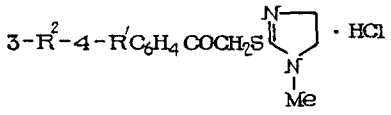
TABLE 1. Physicochemical Constants for Compounds I, III-V

Compound	R^1	R^2	Yield, %	mp, °C	R_f	Empirical formula	IR spectrum, CO absorbtion, cm^{-1}
Ib	PrO	H	66	57–9		$C_{11}H_{13}ClO_2$	
Ic	MeO	Br	60	106–7		$C_9H_8ClO_2$	
Id	2-OH	5-Br	66	73–4		$C_8H_6BrClO_2$	
Ie	AmO	Cl	53	53–4 (195–7)		$C_{13}H_{16}Cl_2O_2$	
If	HexO	Cl	46	Oil (202–4)		$C_{14}H_{18}Cl_2O_2$	
Ig	MeO	NO_2	55	127–8		$C_9H_8ClNO_4$	
Ii	AeNH	NO_2	75	126–8		$C_{10}H_9ClN_2O_4$	
Ij	NH_2	NO_2	68	98–100		$C_8H_7ClN_2O_3$	
Ik	MeO	Cl	76	87–8 (190–2)		$C_9H_8Cl_2O_2$	
Il	PrO	Cl	65	48–50 (175–7)		$C_{11}H_{12}Cl_2O_2$	
Im	BuO	Cl	57	41–3 (182–4)		$C_{12}H_{14}Cl_2O_2$	
IIIa	MeO	H	78	166–7	0,36	$C_{12}H_{15}ClN_2O_2S$	1670
IIIb	PrO	H	80	162–3	0,43	$C_{14}H_{19}ClN_2O_2S$	1680
IIIc	MeO	Br	73	181–2	0,41	$C_{12}H_{14}BrClN_2O_2S$	1660
IIId	2-OH	5-Br	67	134–6	0,80	$C_{11}H_{12}BrClN_2O_2S$	1670
IIIe	AmO	Cl	63	168–9	0,61	$C_{16}H_{22}Cl_2N_2O_2S$	1665
IIIf	HexO	Cl	58	165–7	0,76	$C_{17}H_{24}Cl_2N_2O_2S$	1650
IIIg	MeO	NO_2	65	170–1	0,37	$C_{12}H_{14}ClN_3O_4S$	1650
IIIh	AcNH	Cl	74	197–200	0,71	$C_{13}H_{16}ClN_3O_2S$	1650
IIIi	AcNH	NO_2	62	180–2	0,75	$C_{13}H_{15}ClN_4O_4S$	1665
IIIj	NH_2	NO_2	58	195–7	0,48	$C_{11}H_{13}ClH_3O_4S$	1660
IVa	AmO	Cl	63	143–5	0,56	$C_{16}H_{20}Cl_2N_2OS$	
IVb	HexO	Cl	76	157–9	0,76	$C_{17}H_{22}Cl_2N_2OS$	
IVc	2-OH	5-Br	85	234–6	0,43	$C_{11}H_{10}ClBrN_2OS$	
IVd	AcNH	NO_2	87	235–6	0,35	$C_{13}H_{13}ClN_4O_3S$	
Va	MeO	Cl	75	201–2	0,52	$C_{13}H_{16}Cl_2N_2O_2S$	1660
Vb	PrO	Cl	72	170–2	0,59	$C_{15}H_{20}Cl_2N_2O_2S$	1650
Vc	BuO	Cl	70	173–4	0,59	$C_{16}H_{22}Cl_2N_2O_2S$	1640
Vd	AmO	Cl	65	174–6	0,60	$C_{17}H_{24}Cl_2N_2O_2S$	1645

Note. For compounds Ie, f, k-m the figures in brackets indicate bp in °C/1 mm Hg. Elemental analysis was carried out for CH (I) and CHNS (III, IV, V).

Methylated derivates of compounds III (Va-d) were obtained by reacting I with 1-methyl-2-thio-2-imidazoline.

On examining the radioprotective properties of compounds III-V it was discovered that phenacylthioimidazolines IIId, h and i and imidazothioazoles IVa-d increased the survival rate and mean lifespan (ML) of irradiated animals by 20-35% compared to the control.



IVa-d

EXPERIMENTAL (CHEMICAL)

PMR spectra were recorded on a Varian T-60 spectrometer in deuterated DMSO (internal standard TMS) and IR spectra on an IR-20 instrument (Germany) in Vaseline oil. Compounds III-IV were chromatographed on Silufol UV-256 plates

TABLE 2. Comparative Assessment of Radioprotective Activity and Toxicity for Compounds III-V

Compound	Dosage, mg/kg	Radiation dosage, LD/30	Change in survival rate, % of control	Change in ML, % of control	Median lethal dose, LD_{50}, mg/kg
IIIa	30*	80	+5	+10,5	275(229–330)
	60	80	0	+9	
IIIb	30	80	+7	+15	302(242–377)
	60*	80	+17	+13	
IIIc	30	90	+10	−8	320(267–384)
	60*	90	+15	0	
IIId	20	90	0	−5	250(208–300)
	40*	90	+20	+19	
IIIe	30	100	0	0	305(254–366)
	60	100	−5	0	
IIIf	15	80	+8	−10	245(204–294)
	30	80	+5	0	
IIIg	20	80	0	0	280(233–336)
	40	80	−5	0	
IIIh	30	100	+10	−5	325(271–390)
IIIi	60*	100	+15	+17	334(278–401)
	30	100	0	+10	
	60*	100	+21	+28	
IIIj	20	80	0	−13	220(183–264)
	50	80	−10	−20	
IVa	30	90	+20	+28	325(271–390)
	60*	90	+25	+32	
IVb	30	80	+12	0	290(242–348)
	60*	80	+20	+18	
IVc	30	80	+18	+23	345(287–414)
	60*	80	+27	+18	
IVd	30	90	+30	+35	370(308–444)
	60*	90	+28	+20	
Va	30	90	0	+5	270(225–324)
	60	90	0	0	
Vb	30	80	+10	+17	320(267–384)
	60*	80	+21	+13	
Vc	30	80	0	+11	307(256–368)
	60	80	+10	+5	
Vd	30	90	+10	0	318(265–382)
	60	90	+10	+18	

Note. LD) Lethal dose (mortality as a % of control); *) optimum radioprotective dose (OPD); +) increase with respect to the radiation control; −) decrease with respect to control.

in a 4:1:5 butanol–acetic acid–water solvent system with UV light development. Melting points of the compounds were determined using a Boetius micro hotplate. Elemental analysis data were in line with calculated values.

4-Propoxy-(Ib), 4-Methoxy-3-bromo-(Ic), 2-Hydroxy-5-bromo-(Id), and 4-Alkoxy-3-chlorophenacyl Chlorides (Ie, f, k-m). A 20-g sample of anhydrous aluminum chloride was added with stirring and ice cooling to 0.15 moles of the corresponding alkoxy(hydroxy)benzene. With the mixture temperature kept at 4°C or less, 17 g (0.15 moles) of acetyl chloride was added dropwise over 1 h. The mixture was stirred at room temperature for 1 h and at 40°C for 3 h, then left to stand overnight. It was then decomposed with water while being cooled, and the resultant precipitate Ib-d was filtered off and recrystallized from ethanol. In the case of Ie, f, k-m the compound was extracted with ether, the ethereal extracts were dried over sodium sulfate, and after the solvent had been evaporated off, the residue was redistilled in vacuum (see Table 1).

4-Acetylamino-3-nitrophenacyl Chloride (Ii). With stirring and cooling (−3-5°C) 6.3 g (0.03 moles) of Ih (R^2 = AcNH, R^2 = H) was sprinkled onto 40 ml of concentrated nitro acid (d 1.50) over 30 min. The mixture was left to stand for 15 min, then poured into a water–ice mixture. The resultant precipitate was filtered off and recrystallized from a 2:1 ethanol–water mixture.

4-Amino-3-nitrophenacyl Chloride (Ij). A mixture of 2.6 g (0.01 moles) of Ii and 5 ml hydrochloric acid was boiled for 5-7 min. The resultant oil crystallized on cooling, and was recrystallized from ethanol.

4-Methoxy-3-nitrophenacyl Chloride (Ig) was obtained by nitrating Ia in a similar way to Ii.

4-Methoxyphenacyl chloride (Ia) and 4-acetylaminophenacyl (Ih) are described in previous works [5, 8].

Substituted 2-(2-Imidazolin-2-ylthio)acetophenone Hydrochlorides (IIIa-j). A 0.04 mole sample of compound Ia-j was dissolved in 50 ml acetone and added to a solution of 4.1 g (0.04 moles) of II in 250 ml acetone. After the mixture had been stirred for 8-10 h at room temperature, the resultant precipitate was filtered off and washed with acetone on the filter.

Substituted 3-Phenyl-5,6-dihydroimidazo[2,1-b]thiazole Hydrochlorides (IVa-d). A mixture of 0.04 moles of IIId-f and 50 ml abs. ethanol was boiled for 5-6 h. When part of the solvent had been distilled off, abs. ether was added and the resultant precipitate was filtered off.

Substituted 2-[2-(1-Methylimidazolin-2-ylthio)]acetophenone Hydrochlorides (Va-d). A mixture of 0.04 moles of Ie, k-m, 4.6 g (0.04 moles) of 1-methyl-2-thio-2-imidazoline [6] and 100 ml acetone was boiled with stirring for 4-5 h and left to stand overnight. The resultant precipitate was filtered off.

EXPERIMENTAL (PHARMACOLOGICAL)

Toxicity of the test compounds was studied using randomly bred white mice weighing 17-23 g. The compounds were administered by intraperitoneal injection in a variety of doses, each dose being tested on 6 mice. Behavior of the animals was observed for 2-3 h after administration of the test compounds and a count was made of surviving mice after 24 h. The results of the tests were statistically processed using the Litchfield–Wilkinson method [1]. Median lethal dose figures (LD_{50}) are shown in Table 2.

The radioprotective activity of the compounds was tested on randomly bred white rats weighing 150-170 g, with 15-20 animals being used in each group (biological control, radiation control and irradiated test group).

Test compounds were administered by intraperitoneal injection in the form of aqueous or water-alcohol solutions. Control group animals were injected with the same volume of the corresponding solvent.

Twenty or thirty minutes after the substance had been administered, the animals were exposed to a single overall dose of x-ray radiation using an RUM-17 apparatus. Radiation dose 0.37 g-r (g-r/min), voltage 200 kV, current 15 mA, filters 0.5 Cu + 1 Al, focal length 60 cm, radiation dose of 700 R, or 6.5 g-r, causing death in 80-100% of animals for radiation control ($LD_{80\text{-}100/30}$).

Radioprotective activity of the test compounds was assessed in terms of the survival rate of the animals and the mean lifespan of those animals not surviving after radiation exposure. Survival rate was observed over a period of 30 days (using the methodological recommendations outlined [4]). Investigation findings are shown in Table 2.

As is clear from Table 2, several phenacylthioimidazolines (IIId and h, Vb) and the whole imidazothiazole series (IVa-d) displayed radioprotective activity. An increase in survival rate of 20-30% compared to the $LD_{80\text{-}100/30}$ radiation control was observed when they were administered. The mean lifespan of the animals also increased by 17-35%. Phenacylthioimidazolines IIIe, IIIg and Va did not exhibit radioprotective effects, while compound IIIj reduced the survival rate and mean lifespan of the rats. The other phenacylthioimidazolines had little effect on the survival rate or mean lifespan of the animals.

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