IMIDAZOLE DERIVATIVES.

XVIII. SYNTHESIS AND ANTITUMOR ACTIVITY OF SOME BIS[2-CHLOROETHYL]AMINO IMIDAZOLE DERIVATIVES

M. A. Iradyan, N. S. Iradyan, A. A. Ovagimyan,
G. M. Stepanyan, F. G. Arsenyan,
and B. T. Garibdzhanyan

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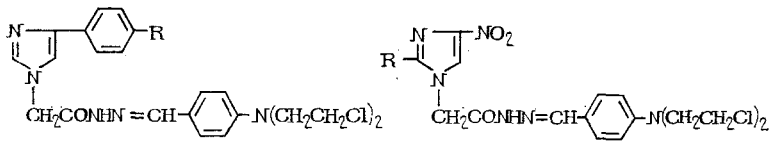
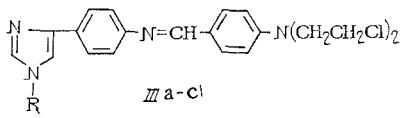
In order to study antitumor properties, the hydrazones (Ia-*l*, IIa and b) were synthesized from the hydrazides of substituted 4-phenylimidazole-1-acetic acids [1] and 4-nitroimidazole-1-acetic acids, and 4-[bis(2-chloroethyl)amino]benzaldehyde



Ia-l *II a,b*

Ia: R = R¹ = H; Ib: R = F, R¹ = H; Ic: R = Cl, R¹ = H; d: R = Br, R¹ = H; Ie: R = NO_2, R¹ = H; If: R = CH_3CONH, R¹ = H; Ig: R = CH_3O, R¹ = H; Ih: R = C_3H_7O, R¹ = H; Ii: R = NO_2, R¹ = NO_2; Ij: R = CH_3O, R¹ = NO_2; Ik: R = = C_2H_5O, R¹ = NO_2; *Il*: R = C_3H_7O, R¹ = NO_2; IIa: R = H; IIb: R = CH_3.

The benzylidenaminophenylimidazoles (IIIa-c), which contain a bis(2-chloroethyl)amino group, and which are based on 4(5)-(4-aminophenyl)imidazole and its 1-benzyl derivatives, were also prepared.



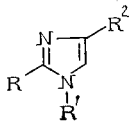
III a-c

IIIa: R = H; IIIb: R = $CH_2C_6H_5$; IIIc: R = $CH_2C_6H_3$ (3-NO_2)(4-CH_3O).

A benzyl group was introduced into compounds IIIa-c because this group is known to lower the toxicity of bis(2-chloroethyl)amino derivaties [4].

To synthesize the hydrazidohydrazones If, IIa and b [1], the hydrazides of 2-methyl-4-nitroimidazole (IVd and e) and 4-(4-acetylaminophenyl)imidazole-1-acetic acids (IVf) were obtained from the corresponding esters(IVa-c).

The 1-benzyl substituted imidazoles (IV g and h) were obtained by the alkylation of the sodium salt of 4(5)-(4-acetylaminophenyl)imidazole with benzyl chloride with subsequent deacetylation of the 1-benzyl-4(4-acetylaminophenyl) imidazoles.



IV a-h

IVa: R = H, R¹ = $CH_2COOC_2H_5$, R² = NO_2; IVb: R = CH_3, R¹ = $CH_2COOC_2H_5$, R² = NO_2; IVc: R = H, R¹ = $CH_2COOC_2H_5$, R² = 4-$CH_3CONHC_6H_4$; IVd: R = H, R¹ = $CH_2CONHNH_2$, R² = NO_2; IVe: R = CH_3, R¹ = $CH_2CONHNH_2$, R² = NO_2; IVf: R = H, R¹ = $CH_2CONHNH_2$, R² = 4-$CH_3CONHC_6H_4$; IVg: R = H, R¹ = = $CH_2C_6H_5$, R² = 4-$H_2NC_6H_4$; IVh: R = H, R¹ = $CH_2C_6H_3$ (3-NO_2)(4-CH_3O), R² = =4-$H_2NC_6H_4$.

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TABLE 1. Physicochemical Constants of the Synthesized Compounds

Compound	Yield, %	mp, °C	R_f	Found, %				Empirical formula	Calculated, %			
				C	H	N	Cl		C	H	N	Cl
Ia	72	165—6	0,47	59,16	4,92	15,81	15,69	$C_{22}H_{23}Cl_2N_5O$	59,46	5,22	15,76	15,96
Ib	78	156—7	0,49	57,45	4,60	15,40	15,35	$C_{22}H_{22}FCl_2N_5O$	57,15	4,80	15,15	15,33
Ic	74	188—9	0,54	54,94	4,80	14,46	22,00	$C_{22}H_{22}Cl_3N_5O$	55,17	4,63	14,63	22,21
Id	80	187—8	0,70	50,85	4,42	13,23	...	$C_{22}H_{22}BrCl_2N_5O$	50,49	4,24	13,38	...
Ie	82	213—5	0,57	54,15	4,54	16,94	14,70	$C_{22}H_{22}Cl_2N_6O_3$	54,00	4,53	17,17	14,49
If	70	145—7	0,56	57,63	5,40	16,51	13,92	$C_{24}H_{26}Cl_2N_6O_2$	57,49	5,23	16,76	14,14
Ig	68	175—6	0,70	58,10	5,30	14,62	14,72	$C_{23}H_{25}Cl_2N_5O_2$	58,23	5,31	14,76	14,95
Ih	65	104—6	0,67	59,64	6,10	14,19	14,20	$C_{25}H_{29}Cl_2N_5O_2$	59,76	5,82	13,94	14,11
Ii	76	222—4	0,81	49,25	4,16	18,11	13,06	$C_{22}H_{21}Cl_2N_7O_5$	49,45	3,96	18,35	13,27
Ij	73	174—6	0,65	52,90	4,41	16,48	13,60	$C_{23}H_{24}Cl_2N_6O_4$	53,19	4,66	10,18	13,65
Ik	70	147—9	0,66	53,80	5,20	16,02	13,50	$C_{24}H_{26}Cl_2N_6O_4$	54,04	4,91	15,76	12,29
Il	66	150—2	0,64	54,70	5,31	15,29	12,70	$C_{25}H_{28}Cl_2N_6O_4$	54,85	5,16	15,35	12,95
IIa	81	213—5	0,73	46,35	4,10	20,61	16,90	$C_{16}H_{18}Cl_2N_6O_3$	46,50	4,39	20,34	17,16
IIb	80	213—4	0,64	47,55	4,93	19,40	16,80	$C_{17}H_{20}Cl_2N_6O_3$	47,78	4,72	19,67	16,59
IIIa	55	165—7	0,41	61,87	5,04	14,66	18,53	$C_{20}H_{20}Cl_2N_4$	62,02	5,21	14,47	18,31
IIIb	73	184—6	0,32	58,80	5,23	10,00	25,50	$C_{27}H_{26}Cl_2N_4 \cdot 2HCl$	58,92	5,13	10,18	25,77
IIIc	54	128—130	0,35	60,64	4,73	12,65	12,75	$C_{28}H_{27}Cl_2N_5O_3$	60,87	4,95	12,68	12,83
IVa	75	112—3	0,71	42,47	4,70	21,23		$C_7H_9N_3O_4$	42,21	4,55	21,10	
IVb	70	102—3	0,70	45,35	5,48	20,00		$C_8H_{11}N_3O_4$	45,07	5,20	19,71	
IVc	65	154—6	0,55	62,55	5,70	14,44		$C_{15}H_{17}N_3O_3$	62,70	5,96	14,63	
IVd	77	114—6	...	32,18	3,90	37,60		$C_5H_7N_5O_3$	32,44	3,81	37,83	
IVe	80	214—5	...	35,90	4,60	34,95		$C_6H_9N_5O_3$	36,18	4,55	35,16	
IVf	73	256—7	0,33	57,40	5,60	25,80		$C_{13}H_{15}N_5O_2$	57,13	5,53	25,63	
IVg	68	180—2	0,46	76,98	6,30	16,55		$C_{16}H_{15}N_3$	77,08	6,06	16,85	
IVh	66	153—4	0,70	62,93	5,10	17,10		$C_{17}H_{16}N_4O_3$	62,95	4,97	17,27	

Physicochemical properties are given in Table 1.

EXPERIMENTAL CHEMISTRY

Infrared spectra of the compounds in mineral oil were taken on a Specord IR spectrophotometer, NMR spectra on a Varian T-60 spectrometer (internal standard, TMS), mass spectra on an MX-1303 with direct introduction of the sample into the ion source at a temperature 30-40°C lower than the melting point of the compound.

Compounds I and II were chromatographed on Silufol UV-254 plates in ethyl acetate–ether (3:1), III and IV in n-butanol–acetic acid–water (4:1:5); chromatograms were visualized in UV light.

Hydrazidohydrazones I and II. A mixture of 10 mmoles of the hydrazide, 2.4 g (10 mmoles) of 4-[bis-(2-chloroethyl)amino]benzaldehyde [3] and 80 ml of absolute ethanol (for Ie and j, DMF) was heated on the water bath for 6-8 h, and the precipitated material filtered off. If no precipitate formed, the solution was evaporated and the residue heated with boiling absolute ether (see Table 1). Infrared spectrum of Ij, ν, cm^{-1} 1340, 1540 (NO_2), 1610 (C=C), 1625 (N=CH), 1700 (C=O), 3120, 3210 (NH). IR spectrum of IIb, ν, cm^{-1}: 1345, 1535 (NO_2), 1610 (C=C), 1625 (N=CH), 1695 (C=O), 3140, 3225 (NH). NMR spectrum of IIb (d_5-pyridine), δ, ppm 2.46 singlet (CH_3), 3.76 singlet $(CH_2CH_2)_2$, 3.53 singlet (CH_2), 6.96 and 7.76 multiplet (Ph), 8.23 singlet (5H), 8.36 singlet (CH=N).

The 4[bis-(2-chloroethyl)amino]benzylidenaminophenylimidazoles IIIa-c were prepared in the same way.

Sodium Salt of 4-(4-Acetylaminophenyl)imidazole. To sodium ethoxide, prepared from 0.23 g (0.01 moles) of metallic sodium and 40 ml of absolute ethanol, was added 2 g (10 mmoles) of 4-(4-acetylaminophenyl)imidazole [2]. The solvent was removed and absolute ether added. The residue was filtered off to give a quantitative yield.

Ethyl-4-(4-acetylaminophenyl)imidazole-1-acetate (IVc). A mixture of 2.2 g (10 mmoles) of sodium 4-(4-acetylaminophenyl)imidazole, 35 ml of DMF and 1.8 g (15 mmoles) of ethyl monochloroacetate was refluxed for 8-10 h. The precipitate material was filtered off, the solvent evaporated under vacuum (aspirator), and ether added. The oil which separated crystallized on standing (see Table 1).

Ethyl Esters of 4-Nitroimidazole- and 2-Methyl-4-nitroimidazole-1-acetic Acids (IVa and b). To sodium ethoxide, prepared from 0.46 g (0.02 moles) of sodium and 40 ml of absolute ethanol, was added 20 mmoles of nitroimidazole, and 3 g (24 mmoles) of ethyl monochloroacetate. The mixture was refluxed for 6 h and worked up in the same way as IVc. Compounds IVa and b were recrystallized from absolute ethanol (see Table 1).

Hydrazide of 4-(4-Acetylaminophenyl)imidazole-1-acetic Acid (IVf). A mixture of 2.9 g (10 mmoles) of IVc, 1.6 g (50 mmoles) of hydrazine, and 30 ml of absolute ethanol was refluxed for 6-7 h. The precipitated material was filtered off and recrystallized from water (see Table 1).

The hydrazides IVd were prepared in the same way, and recrystallized from propyl alcohol (see Table 1).

The molecular weights of the hydrazides IVa-c were determined by mass spectrometry.

1-Benzyl-4-(4-aminophenyl)imidazole (IVg). To a solution of 2.2 g (10 mmoles) of sodium 4-(4-acetylaminophenyl)imidazole in 60 ml of liquid ammonia was added 1.3 g (10 mmoles) of benzyl chloride dissolved in 6 ml of DMF. The mixture was cooled (dry ice in acetone), stirred for 2 h and left to stand overnight. Hydrochloric acid (80 ml; 15%) was then added and the mixture refluxed for a further 7-8 h. After cooling, the solution was filtered and recrystallized from a mixture of ethanol and water (1:1). Mass spectrum of IVg, m/z, %: 249 (80) M^+, 158 (100), 131 (15), 104 (20), 91 (90).

1-(4-Methoxy-3-nitrobenzyl)-4-(4-aminophenyl)imidazole (IVh). This was obtained by the same method (see Table 1). Mass spectrum of IVh, m/z, %: 324 (80) M^+, 294 (12), 173 (40), 166 (100), 158 (62), 132 (15), 131 (25), 119 (30), 105 (14), 104 (16).

TABLE 2. Toxicity and Antitumor Activity of Bis(2-chloroethyl)amino Imidazole Derivatives

Compound	Toxicity for mice, mg/kg LD_{100}	MED	Dose, mg/kg	Decrease in antitumor growth, %	
				sarcoma 45	KSU-256
Ia	2500	2000	120	38	Ineffective
Ib	2500	2000	120	29	»
Ic	2000	1500	100	0	»
Id	>2500		120	41	»
Ie	>2500		120	28	»
If	2000	1500	100	46	»
Ig	>2500		120	39	»
Ih	>2500		120	46	»
Ii	>2500		120	53	32
Ij	>2500		120	41	0
Ik	>2500		120	32	48
Il	>2500		150	35	37
IIa	>2500		150	38	52
IIb	400	300	40	54	40
IIIa	1000	750	80	52	91
IIIb	750	500	50	0	29

Note. $T \leq 0.05$, except for Ib, e, and IIIb.

EXPERIMENTAL BIOLOGY

The toxicity and antitumor activity of the compounds were determined by standard methods [5]. The toxicity was determined from a single intraperitoneal injection of the compound into nonpedigree white mice; the absolute lethal dose (LD_{100}) and the maximum endurable dose (MED) were also determined for each compound. The antiblastic properties of the compounds were studied on rats and mice with transplanted tumors — using doses from 1/10-1/20 of the LD_{100}.

The hydrazidohydrazones Ia-h were found to be only slightly toxic. The LD_{100} for compounds Ia-c is 2000-2500 mg/kg (Table 2). Replacement of the halogen or acetylamino groups by a nitro or alkoxy group gave compounds with very low toxicity (Ie-h; LD_{100} 2500 mg/kg). The introduction of a nitro group at position 5 of the imidazole ring did not affect the toxicity of the compounds (compare Ii-l with Ie-h); toxicity was also unaffected by the replacement of the phenyl group at position 4 by a nitro group (IIa and b). The introduction of a methyl group to the imidazole ring (IIb) or transfer of the cytotoxic group (IIIa-c) brought about a marked increase in the toxicity of the compounds (LD_{100} 400-1000 mg/kg).

Chemotherapeutic experiments showed that the majority of the hydrazidohydrazones Ia-h had a low antitumor action on sarcoma 45; tumor growth was decreased by 30-46% (see Table 2). They had no effect on Walker's carcinoma. The introduction of a nitro group at position 4 or 5 of the imidazole ring (Ii-l, IIa and b) led to an increase in the antiblastic action of the compounds on Walker's carcinoma.

Of the compounds studied, IIIa was the most active; in therapeutic doses, it suppressed the growth of sarcoma 45 and Walker's carcinoma by 52 and 91%, respectively.

All the 2-chloroethylamino imidazole derivatives examined were ineffective against Ehrlich's carcinoma.

Thus, the imidazole derivatives studied are shown to have low toxicity and weak antitumor activity which is not characteristic for compounds containing the bis-(2-chloroethyl)-amino group.

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