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SYNTHESIS AND ANTIVIRAL ACTIVITY OF SPINACEAMINES

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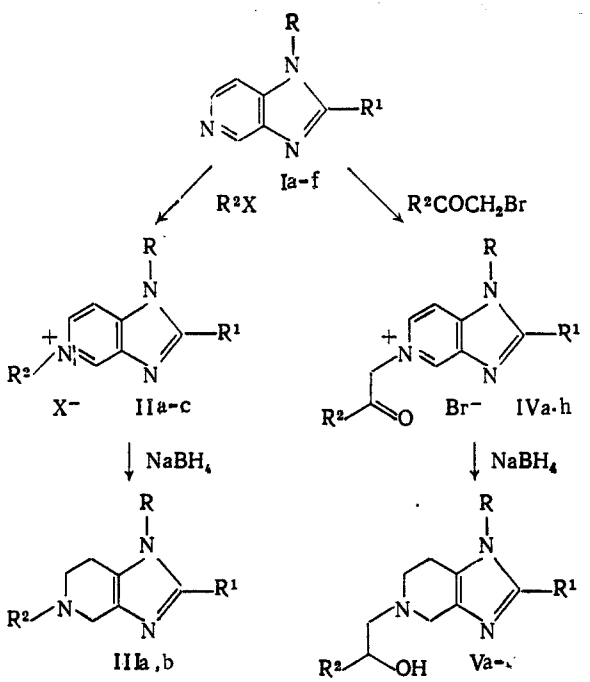
Spinaceamine (4,5,6,7-tetrahydroimidazo[4,5-c]pyridine) is present in the secretions of several species of amphibia, and since it has bacteriostatic properties, it protects the surface of the skin of these animals [10-12]. Substituted spinaceamines have recently been shown [13] to have high antiviral activity and can be used in medicine [13].

In order to extend studies in this area, we have examined the antiviral activity of some novel spinaceamines and their precursors (IIc), (IVd-h), (Va, b, d, e), together with compounds of this type previously reported by us (IIa, b), (IIIa, b), (IVa-c), and (Vc) [2-9].

Reaction of 1-substituted and 1,2-disubstituted imidazo[4,5-c]pyridines (Ia-f) with haloalkanes and α-bromoketones afforded the monoquaternary and acylmethyl salts of imidazo-[4,5-c]pyridines (IIa-c) and (IVa-h), which were then reduced with $NaBH_4$ in alcoholic solution to the spinaceamines (IIIa, b) and (Va-e).



R = Me (Ia, b, a-f; IIa-c; IIIa, b; IVa-c, e-h; Va,e), CH_2Ph (Ic; IVd); R^1 = H (Ia; IIa, b; IIIa, b; IVa-c; Vd), Me (Ic, e; IVd; Va), SMe (Ib; IIc; IVe, j, h; Vb,e), $SCH_2COC_6H_4Me$-4 (Id; IVe), $C_6H_3(OMe)_2$-3,4 (If; Vc); R^2 = Me (IIa, c; IIb), CH_2CH_2OH(IIb; IIIa), 2-napthyl (IVa), C_6H_4OMe-4 (IVb, f, g; Va, c, e), Ph (IVc-e; Vb), Ad-2 (IVh; Vd); X = I (IIa,), Cl (II).

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TABLE 1. Imidazo[4,5-c]pyridines

Compound	Yield, %	mp, °C (solvent for recrystallization)	Emprical formula
IVd	81	244—5 (MeOH)	$C_{22}H_{20}BrN_3O$
IVe	85	209—11 (alcohol)	$C_{16}H_{14}BrN_3OS$
IVf	74	155—7 (alcohol)	$C_{28}H_{24}BrN_3O_4S$
IVg	73	216—7 (alcohol)	$C_{17}H_{16}BrN_3O_2S$
IVh	81	213—4 (*i*-PrOH)	$C_{20}H_{26}BrN_3OS$
Va	97	205—7 (*i*-PrOH)	$C_{17}H_{23}Cl_2N_3O_2$
Vb	93	144—6 (*i*-PrOH)	$C_{16}H_{21}N_3OS$
Vd	73	184—5 (octane)	$C_{19}H_{23}N_3O$
Ve	66	124—6 (*i*-PrOH)	$C_{17}H_{23}N_3O_2S$

As expected, the UV spectra of these spinaceamines showed one short wavelength absorption band at 207-208 nm, characteristic of imidazole. However, the starting salts showed long-wavelength band at 250-260 nm in addition to that at short wavelength. The IR spectra of the acylmethyl salts (IVa-h), obtained in Vaseline oil, show carbonyl absorption at 1670-1710 cm^{-1}, which is absent from the spectra of the spinaceamines (Va-e).

The structures of the spinaceamines (Vb, e), like those of the starting phenacylium salts (IVe, g), were confirmed by PMR spectroscopy. For example, in the spectrum of the salt (IVg) (CF_3COOH, δ, ppm), three singlets for the methyl groups were seen at 3.09 (3-CH_3), 3.88 (NCH_3), and 4.01 (OCH_3) were seen, together with a singlet for the methylene group of the phenacyl substituent (6.51), two doublets for the benzene ring (7.07 and 8.04), signals for the two vicinal protons of the heterocyclic ring [H(5) and H(6)], and a singlet for the proton at C(4). In the spectrum of the spinaceamine (Vc) obtained from this salt, there were no signals for the protons of the heterocyclic system [at C(4,6,7)]. In their place, signals for the aliphatic protons appeared at high field [4.63 ppm, CH_2 (4); 2.76 ppm, CH_2 (6), and 2.5 ppm, CH_2 (7)].

EXPERIMENTAL (CHEMISTRY)

UV spectra were obtained on a Spectromom-204 spectrophotometer (Hungary) in water, IR spectra on a UR-20 spectrophotometer (East Germany) in vaseline oil, and PMR spectra on a Tesla spectrometer (60 MHz, Czech SSR) in CF_3COOH with TMS as internal standard. The elemental analyses were in agreement with the calculated values.

1-Methylthio-1,5-dimethyl-1H-imidazo[4,5-c]pyridinium Iodide (IIc). A mixture of 2 g (10 mmole) of 1-methyl-2-methylthioimidazo[4,5-c]pyridine (Ib) and 1.5 g (12 mmole) of MeI in 10 ml of alcohol was boiled under reflux for 2 h. Excess MeI and alcohol were removed at the water pump, and the resulting salt crystallized from alcohol. Yield of (IIc) 89%, mp 220-222°C.

Acylmethyl Salts (IVa-h). The 1-substituted or 1,2-disubstituted imidazo[4,5-c]pyridine (Ia-f) (10 mmole) was dissolved in 50 ml of acetone, and mixed with 12 mmole of the appropriate α-bromoketone dissolved in 20 ml of acetone. The mixture was kept at ambient temperature for 4-6 h, then the salt which separated was filtered off, washed with acetone and ether, and recrystallized from an alcohol (Table 1).

Spinaceamines (Va-e). To a solution of 10 mmole of the acylmethyl salt of the 1-substituted or 1,2-disubstituted imidazo[4,5-c]pyridine in 200 ml of water and 200 ml of methanol was added portionwise with stirring over 2 h 60 mmole of $NaBH_4$. The mixture was kept for 2 h at 60-70°C, then the solvent was removed at the water pump to a volume of 20-25 ml, and the oil which separated and subsequently solidified was filtered off, washed with water, and recrystallized from a suitable solvent (Table 1).

Compounds (IIa) and (IIb) were obtained by quaternizing the base (Ia) with methyl iodide or ethylene chlorohydrin [6, 8]. The salts (IIa, b) were reduced to (IIIa, b) with $NaBH_4$ in alcohol [3, 7]. The synthesis of (VIa-c) and (Vc) has been reported previously [4, 5, 9].

TABLE 2. Antiviral Activity of Imidazo[4,5-c]pyridines

Compound	Virus	Diameter (in mm) of zones in primary screening test		Platelet reduction test		
		toxicity	inhibition of platelet formation	concentration in test, μg/ml	viral titer, lg BOU/ml	CTI
IIc	VVV	0	21	100*	2,12	1
				50	3,36	
				25	3,61	
				12	3,90	
				0	3,85	
	ECHO-6	0	23	100	3,5	2
				50	4,5	
				25	6,5	
				12	6,5	
				0	6,5	
IVb	VVV	12	11	12	2,12	4
				6	2,12	
				3	2,12	
				1,5	3,75	
				0	3,85	
IVc	CAPV	0	20	100	4,0	4
				50	4,0	
				25	4,0	
				12	4,66	
				0	5,36	
	ECHO-6	0	26	100	3,0	4
				50	3,0	
				25	5,0	
				12	6,5	
				0	6,5	
IVd	VVV	11	16	50	2,12	2
				25	2,12	
				12	3,61	
				6	3,75	
				0	3,85	
IVe	CAPV	0	20	50	4,0	2
				25	4,32	
				12	4,6	
				0	5,36	
IVf	VVV	10	24	3,0	2,12	8
				1,5	2,12	
				0,7	2,12	
				0,3	2,12	
				0,15	3,7	
IVg	VVV	30	10	25	2,12	1
				12	3,38	
				6	3,85	
				3	3,81	
				0	3,85	
Va	VVV	18	12	25	3,0	1
				12	3,99	
				6	4,39	
				3	4,53	
				0	4,57	
	VVV	16	18	25	6,0	1
				12	7,04	
				6	7,32	
				3	7,47	
				0	7,56	
Vb	VVV	0	14	100	3,0	4
				50	3,0	
				25	3,0	
				12	4,46	
				0	4,57	
Ve	VVV	10	14	400	2,12	4
				200	2,12	
				100	2,12	
				50	3,35	
				0	3,85	
	CAPV	26	24	400	4,35	1
				200	5,11	
				100	5,27	
				50	5,02	
				0	5,36	

*Maximum tolerated concentration.

EXPERIMENTAL (BIOLOGY)

The antiviral activity of the compounds was determined in tissue culture against the following viruses: herpes simplex type I (HSV), variola vaccine (VVV), classical avian plague (CAPV), Newcastle disease (NCD), vesicular stomatitis (VSV), Venezuelan equine encephalomyelitis (VEEV), and ECHO-6 using screening tests, reduction in platelets beneath an agar coating, and by incorporating the compounds into the supporting medium [1]. With ECHO-6, studies were carried out in monolayer cultures of passivated dermomuscular cells of the human embryo, and with the other viruses, using primarily trypsinized chick embryo fibroblasts.

The test compounds were for the most part of low toxicity towards the tissue cultures, except for (IVf). Antiviral activity was found in nearly a quarter of the compounds, the most active compounds (IVb, f) and (Vb, e) being detected mainly in the variola vaccine test (Table 2). Of considerable interest is (IVc), which displays activity against the classical avian plague and ECHO-6 viruses.

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