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Influence of Structure on Antimicrobial Activity of Some Heterocycles IV. 1-(3-Alkylamino-2-hydroxypropyl)-2-methyl-5-nitroimidazoles

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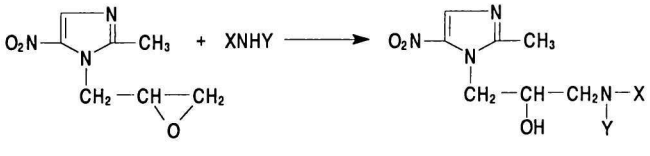
Several 1-(3-alkylamino-2-hydroxypropyl)-2-methyl-5-nitroimidazoles were prepared by the ring-opening displacement reaction of 1-(2,3-epoxypropyl)-2-methyl-5nitroimidazole with some amines. The structure of the prepared compounds was confirmed on the basis of IR, mass, NMR spectral data and elemental analysis. Antimicrobial activity of these compounds against selected bacteria and fungi was also determined. No significant effects were found in this respect.

1-Alkyl-2-methyl-5-nitroimidazoles represent a very important group of chemotherapeutics known as antiprotozoal and antibacterial agents [1—4]. Among them, 1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole (secnidazole) and its derivatives are reported as compounds exhibiting good antiamebic and trichomonacidal activity [5—7]. Antiparasitic activity of these derivatives was also described [8].

Recently, we have found [9, 10] that some nitrogen heterocycles substituted with a longer alkyl chain exhibit remarkable antibacterial activity, especially against gram-positive bacteria. Therefore, in our previous paper [11] we have studied in this respect some 1-(3-alkylthio-2-hydroxypropyl)-2-methyl-5-nitroimidazoles. This paper deals with corresponding 1-(3-alkylamino) analogues.

Starting from 1-(2,3-epoxypropyl)-2-methyl-5-nitroimidazole (*I*), prepared from 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (ornidazole) by alkaline dehydrohalogenation [12], we have synthesized several 1-(3-alkylamino-2-hydroxypropyl)-2-methyl-5-nitroimidazoles *II—XXXII* (Scheme 1). The yields of ring-opening displacement reaction of *I* with amine nucleophiles depend on the basicity of corresponding amine. Generally, very basic starting amines afforded lower yields of desired products. When primary amines were used as reactants, the main products represented monoalkylated amines with minority of corresponding dialkylated amines. Secondary starting amines afforded exclusively monoalkylated products. Reaction of *I* with piperazine (in the mole ratio 1 : 1) gave a mixture (x_r = 1 : 1) of mono- and dialkylated products (*XXXI*, *XXXII*). This mixture was separated by preparative TLC and both compounds were isolated and characterized. When



I *II—XXXII*

Scheme 1

the mole ratio of *I* and piperazine was 2 : 1, only *XXXII* was isolated. The survey and characterization of the prepared compounds is summarized in Table 1. Their structure was confirmed on the basis of

Table 1. Characterization of the Prepared Compounds

Compound	X	Y	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
					C	H	N	%	°C
II	Isopropyl	H	$C_{10}H_{18}N_4O_3$	242.32	49.56 49.51	7.50 7.54	23.13 23.18	71	68—69
III	Isobutyl	H	$C_{11}H_{20}N_4O_3$	256.35	51.54 51.57	7.88 7.91	21.86 21.82	77	73—74
IV	2,2-Diethoxyethyl	H	$C_{13}H_{24}N_4O_5$	316.41	49.34 49.30	7.66 7.72	17.71 17.75	89	109—110
V	2-Methoxyethyl	H	$C_{10}H_{18}N_4O_4$	258.32	46.49 46.47	7.04 7.07	21.69 21.73	84	86—87
VI	2-Dimethylaminoethyl	H	$C_{11}H_{21}N_5O_3$	271.37	48.68 48.73	7.82 7.84	25.81 25.85	79	95—96
VII	3,3-Dimethoxypropyl	H	$C_{12}H_{22}N_4O_5$	302.38	47.66 47.60	7.35 7.37	18.53 18.49	82	113—114
VIII	3-Dimethylaminopropyl	H	$C_{12}H_{23}N_5O_3$	285.40	50.50 50.56	8.14 8.18	24.54 24.50	78	98—99
IX	Benzyl	H	$C_{14}H_{18}N_4O_3$	290.36	57.91 57.87	6.26 6.30	19.30 19.32	80	101—102
X	Furfuryl	H	$C_{12}H_{16}N_4O_4$	280.32	51.41 51.43	5.76 5.78	19.99 19.95	81	104—105
XI	Hexyl	H	$C_{13}H_{24}N_4O_3$	284.41	54.90 54.93	8.52 8.56	19.70 19.66	78	90—91
XII	Heptyl	H	$C_{14}H_{26}N_4O_3$	298.44	56.34 56.32	8.80 8.83	18.78 18.77	79	92—93
XIII	Octyl	H	$C_{15}H_{28}N_4O_3$	312.47	57.65 57.66	9.05 9.09	17.93 17.95	78	86—87
XIV	Nonyl	H	$C_{16}H_{30}N_4O_3$	326.50	58.85 58.81	9.28 9.30	17.16 17.12	78	89—91
XV	Decyl	H	$C_{17}H_{32}N_4O_3$	340.53	59.96 59.99	9.49 9.55	16.46 16.48	79	92—94
XVI	Dodecyl	H	$C_{19}H_{36}N_4O_3$	368.59	61.91 61.88	9.86 9.90	15.20 15.17	77	95—97
XVII	Piperidino[a]		$C_{12}H_{20}N_4O_3$	268.36	53.70 53.74	7.53 7.55	20.88 20.84	72	123—124
XVIII	2-Ethylpiperidino[a]		$C_{14}H_{24}N_4O_3$	296.42	56.72 56.77	8.18 8.23	18.91 18.86	70	117—118
XIX	Morpholino[a]		$C_{11}H_{18}N_4O_4$	270.33	48.87 48.90	6.73 6.74	20.73 20.79	74	137—138
XX	Ethyl	Ethyl	$C_{11}H_{20}N_4O_3$	256.35	51.54 51.58	7.88 7.91	21.86 21.82	70	75—76
XXI	2-Hydroxyethyl	Methyl	$C_{10}H_{18}N_4O_4$	258.32	46.49 46.46	7.04 7.09	21.69 21.67	73	97—98
XXII	2-Cyanoethyl	Methyl	$C_{11}H_{17}N_5O_3$	267.33	49.42 49.36	6.42 6.44	26.20 26.23	75	91—92
XXIII	Butyl	Methyl	$C_{12}H_{22}N_4O_3$	270.38	53.30 53.35	8.22 8.25	20.73 20.69	71	86—87
XXIV	2-Hydroxyethyl	2-Hydroxyethyl	$C_{11}H_{20}N_4O_5$	288.35	45.82 45.79	7.01 7.05	19.43 19.45	74	103—104
XXV	Propyl	Propyl	$C_{13}H_{24}N_4O_3$	284.41	54.90 54.94	8.52 8.53	19.70 19.73	71	78—79
XXVI	Allyl	Allyl	$C_{13}H_{20}N_4O_3$	280.37	55.69 55.75	7.20 7.19	19.99 19.95	73	73—74
XXVII	Benzyl	Methyl	$C_{15}H_{20}N_4O_3$	304.39	50.18 50.15	6.64 6.65	18.41 18.45	75	91—92
XXVIII	Hexyl	Hexyl	$C_{19}H_{36}N_4O_3$	368.59	61.91 61.97	9.86 9.89	15.20 15.19	75	139—141
XXIX	2-Hydroxypropyl	Octyl	$C_{18}H_{34}N_4O_4$	370.56	58.34 58.38	9.27 9.30	15.12 15.16	76	71—73
XXX	2-Hydroxypropyl	Dodecyl	$C_{22}H_{42}N_4O_4$	426.68	61.92 61.98	9.94 9.97	13.13 13.11	75	78—80
XXXI	1-Piperazinyl[a]		$C_{11}H_{19}N_5O_3$	269.35	49.05 49.01	7.12 7.11	26.01 26.07	34[b]	111—112
XXXII	4-[3-(5-nitro-2-methyl-1-imidazolyl)-2-hydroxypropyl]-1-piperazinyl[a]		$C_{18}H_{28}N_8O_6$	452.54	47.77 47.80	6.25 6.29	24.77 24.75	36[b] 71[c]	132—133

a) Substituent represents NXY part of the molecule; *b*) when the mole ratio of reactants is 1 : 1; *c*) when the mole ratio of *I* and piperazine is 2 : 1.

elemental analysis and IR, mass, ^1H and ^{13}C NMR spectral data.

In the IR spectra of the prepared compounds strong absorption bands in the region of $\tilde{\nu}$ = 1324 cm^{-1}, 1434 cm^{-1}, and 1465 cm^{-1} (stretching vibrations of the imidazole ring), $\tilde{\nu}$ = 1265 cm^{-1} (deformation vibrations of C—H bond of imidazole ring), and $\tilde{\nu}$ = 1368 cm^{-1} and 1525 cm^{-1} (stretching vibrations of the nitro group) were observed. In the case of secondary amines *II*—*XVI* the bands in the region of $\tilde{\nu}$ = 3328—3360 cm^{-1} corresponding to the stretching vibrations of N—H bonds were registered.

Mass spectra of the prepared compounds *II*—*XXXII* did not exhibit the peaks of molecular ions $[M]^+$. The base peaks (I_r = 100 %) corresponded to the ions $XYN^+{=}CH_2$ formed by α-cleavage. Further significant peaks (I_r = 63—96 %) were registered for $[M - NO_2]^+$ fragments. Surprisingly, like in the case of analogical alkylthio derivatives [11], no rearrangement with elimination of an aldehyde or ketone, characteristic of 1-alkyl-5-nitroimidazoles [13], was observed.

Characteristic NMR data of selected compounds are given in Experimental.

Similarly, like for corresponding alkylthio analogues [11], the results of antimicrobial activity testing revealed only low efficiency against selected microorganisms. Mostly, the values of minimum inhibitory concentration (MIC) were about 1000 ppm excepting compounds *XI*—*XV* exhibiting MIC about 10 ppm against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis* (Table 2). This fact is in accordance with our previous observations [9, 10], where hexyl, heptyl, and octyl derivatives exhibited the best activity against some gram-positive bacteria.

EXPERIMENTAL

Starting 1-(2,3-epoxypropyl)-2-methyl-5-nitroimidazole (*I*) was prepared according to the known method [12]. Ornidazole as well as the other used chemicals were commercially available products (Lachema, Brno; Fluka, Buchs; Merck, Darmstadt).

Melting points were determined on a Kofler hot-stage. IR spectra (in KBr pellets) were obtained on a Perkin—Elmer G-983 instrument. Mass spectra (70 eV) were measured on a Jeol JMS-100D spectrometer at an emission current of 300 μA, applying direct sample-introduction technique. ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-

Table 2. Antimicrobial Activity (MIC/(μg cm^{-3})) of the Prepared Compounds

Compound	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Bacillus subtilis*	*Streptococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella typhimurium*
II	1000	1000	1000	1000	1000	1000	1000
III	1000	1000	<1000	1000	1000	1000	1000
IV	1000	1000	1000	1000	1000	1000	1000
V	1000	1000	1000	1000	1000	1000	1000
VI	<1000	<1000	100	1000	1000	1000	1000
VII	<1000	<1000	100	1000	1000	1000	1000
VIII	100	100	100	1000	1000	1000	<1000
IX	1000	1000	1000	1000	1000	1000	1000
X	1000	1000	1000	1000	1000	1000	1000
XI	<10	<10	10	1000	1000	1000	<1000
XII	<10	<10	<10	1000	1000	1000	100
XIII	10	10	10	1000	1000	1000	100
XIV	10	10	<100	1000	1000	1000	1000
XV	<100	<100	100	1000	1000	1000	1000
XVI	<1000	<1000	<1000	1000	1000	1000	<1000
XVII	1000	1000	1000	1000	1000	1000	1000
XVIII	1000	1000	1000	1000	1000	1000	1000
XIX	1000	1000	1000	1000	1000	1000	1000
XX	1000	1000	1000	1000	1000	1000	1000
XXI	<1000	<1000	1000	1000	1000	1000	1000
XXII	<1000	<1000	1000	1000	1000	1000	1000
XXIII	100	<1000	<1000	1000	1000	1000	1000
XXIV	1000	1000	1000	1000	1000	1000	1000
XXV	<1000	<1000	<1000	1000	1000	1000	<1000
XXVI	<1000	<1000	100	1000	1000	1000	<1000
XXVII	1000	1000	1000	1000	1000	1000	1000
XXVIII	100	100	<1000	1000	1000	1000	100
XXIX	100	100	100	1000	1000	1000	<1000
XXX	<1000	<1000	<1000	1000	1000	1000	1000
XXXI	1000	1000	1000	1000	1000	1000	1000
XXXII	1000	1000	1000	1000	1000	1000	1000

300 spectrometer operating at 300.13 MHz or 75.46 MHz working frequencies in $CDCl_3$ or DMSO-d_6 solutions with TMS as an internal standard. For the assignment of signals in ^{13}C NMR spectra DEPT and semiselective INEPT techniques were used. (*Note*: Comma index refers to the positions of 2-hydroxypropyl grouping; positions of the furan ring are two-comma indexed). Elemental analyses were performed on a Perkin—Elmer 240 analyzer.

MIC was determined by using the suspension method on solid cultivation media [9]. [1-(Ethoxycarbonyl)pentadecyl]trimethylammonium bromide (Septonex), an antiseptic agent usually applied in practice, was used as a standard [14].

1-(3-Heptylamino-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*XII*)

A mixture of epoxide *I* (1.83 g; 0.01 mol) and heptylamine (1.15 g; 0.01 mol) in dry methanol (30 cm^3) was heated under reflux for 3 h. Then the solvent was evaporated under diminished pressure and cold dry ether (20 cm^3) was added to the residue. Separated solid was filtered off and after decolourizing using charcoal it was recrystallized from ether (in freezer) giving 2.71 g (91 % of theory) of product, m.p. = 92—93 °C.

The above given procedure is general for the preparation of compounds *II*—*XXXII*. Reaction time was 3—8 h (monitored by TLC on Silufol plates with chloroform—methanol (φ_r = 4 : 1) as an eluent). For the separation of compounds *XXXI* and *XXXII*, silica gel TLC preparative plates (thickness 200 μm, 20 cm × 20 cm) and the same eluent were used.

Compound *XII*: ^1H NMR spectrum ($CDCl_3$), δ: 7.94 (s, 1H, H-4 in imidazole), 4.55 (dd, 1H, H_a-1′, J = 14.0 Hz and 2.6 Hz), 4.09 (dd, 1H, H_b-1′, J = 8.5 Hz and 14.0 Hz), 3.93 (m, 1H, H-2′), 2.88 (dd, 1H, H_a-3′, J = 12.1 Hz and 3.5 Hz), 2.59 (dd, 1H, H_b-3′, J = 8.4 Hz and 12.1 Hz), 2.58 (m, 2H, the first CH_2 in heptyl), 2.56 (s, 3H, CH_3 in imidazole), 1.45 (m, 2H, the second CH_2 in heptyl), 1.29 (br, 8H, the other CH_2 in heptyl), 0.90 (t, 3H, CH_3 in heptyl). ^{13}C NMR spectrum ($CDCl_3$), δ: 151.9 (C-2), 138.0 (C-5), 133.1 (C-4), 68.9 (C-2′), 52.2 (C-3′), 50.2 (C-1′), 49.7 (the first CH_2 in heptyl), 31.8, 30.1, 29.1, 27.1, 22.6 (the other CH_2 in heptyl), 14.7 (CH_3 in imidazole), 14.1 (CH_3 in heptyl).

Compound *X*: ^1H NMR spectrum ($CDCl_3$), δ: 7.93 (s, 1H, H-4 in imidazole), 7.38 (d, 1H, H-5″, J = 1.9 Hz), 6.34 (dd, 1H, H-4″, J = 3.2 Hz and 1.9 Hz), 6.20 (d, 1H, H-3″, J = 3.2 Hz), 4.54 (dd, 1H, H_a-1′, J = 14.0 Hz and 2.6 Hz), 4.09 (dd, 1H, H_b-1′, J = 8.7 Hz and 14.0 Hz), 3.94 (m, 1H, H-2′), 3.80 (s, 2H, CH_2—furyl), 2.90 (dd, 1H, H_a-3′, J = 12.2 Hz and 3.5 Hz), 2.58 (dd, 1H, H_b-3′, J = 8.4 Hz and 12.2 Hz), 2.54 (s, 3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 153.0 (C-2″), 151.8 (C-2), 142.1 (C-5″), 138.3 (C-5), 133.1 (C-4), 110.2 (C-4″), 107.4 (C-3″), 69.2 (C-2′), 51.3 (C-3′), 50.1 (C-1′), 45.7 (CH_2—furyl), 14.7 (CH_3).

Compound *XX*: ^1H NMR spectrum ($CDCl_3$), δ: 7.95 (s, 1H, H-4 in imidazole), 4.56 (dd, 1H, H_a-1′, J = 13.8 Hz and 1.8 Hz), 4.01 (dd, 1H, H_b-1′, J = 8.4 Hz and 13.8 Hz), 3.91 (m, 1H, H-2′), 2.64 (dd, 1H, H_a-3′, J = 12.6 Hz and 8.2 Hz), 2.48—2.69 (m, 4H, CH_2 in ethyls), 2.57 (s, 3H, CH_3 in imidazole), 2.35 (dd, 1H, H_b-3′, J = 10.0 Hz and 12.6 Hz), 1.02 (t, 6H, CH_3 in ethyls). ^{13}C NMR spectrum ($CDCl_3$), δ: 152.0 (C-2), 138.3 (C-5), 133.1 (C-4), 67.2 (C-2′), 56.3 (C-3′), 50.4 (C-1′), 47.1 (CH_2 in ethyls), 14.8 (CH_3 in imidazole), 11.9 (CH_3 in ethyls).

Compound *XXIII*: ^1H NMR spectrum ($CDCl_3$), δ: 7.96 (s, 1H, H-4 in imidazole), 4.56 (dd, 1H, H_a-1′, J = 13.5 Hz and 1.4 Hz), 4.03 (dd, 1H, H_b-1′, J = 8.4 Hz and 13.5 Hz), 3.95 (m, 1H, H-2′), 2.57 (s, 3H, CH_3 in imidazole), 2.32—2.54 (m, 4H, CH_2—N—CH_2), 2.26 (s, 3H, N—CH_3), 1.43 (m, 2H, the second CH_2 in butyl), 1.32 (m, 2H, the third CH_2 in butyl), 0.92 (t, 3H, CH_3 in butyl). ^{13}C NMR spectrum ($CDCl_3$), δ: 152.0 (C-2), 138.2 (C-5), 133.1 (C-4), 67.2 (C-2′), 60.5 (the first CH_2 in butyl), 57.6 (C-3′), 50.4 (C-1′), 42.0 (N—CH_3), 29.3 and 20.3 (the second and the third CH_2 in butyl), 14.8 (CH_3 in imidazole), 14.0 (CH_3 in butyl).

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