chloroform (30 cm^3), the unreacted starting compound was extracted with 1 M-NaOH (2 × 10 cm^3), the organic layer was washed with water (2 × 10 cm^3), dried with Na_2SO_4 and purified through a short silica-gel packed column (100—160 μm, 6 g, eluent chloroform). The product obtained after removal of chloroform *in vacuo* was crystallized from tetrahydrofuran—*tert*-butyl methyl ether.

7-(5-Oxohexyl)-8-propyltheophylline (*IIIc*)

Method A was applied for preparation of the title compound; the starting compound *X* (20 mmol) was treated with 22 mmol of potassium carbonate (3.04 g), chloroacetone was replaced for 6-chloro-2-hexanone [7] (2.96 g, 2.86 cm^3, 21 mmol) and the temperature 120 °C was kept for 6 h.

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Influence of Structure on Antimicrobial Activity of Some Heterocycles
III. 1-Substituted 2-Methyl-5-nitroimidazoles

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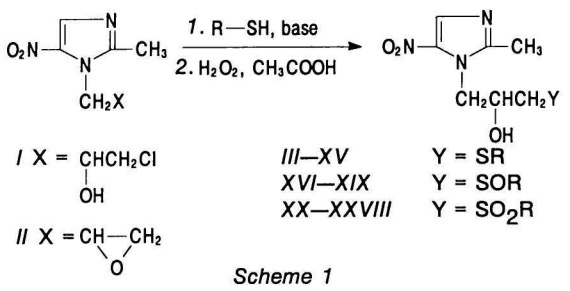
Several 1-(3-alkyl- resp. 3-arylthio-2-hydroxypropyl)-2-methyl-5-nitroimidazoles were prepared starting from ornidazole. Some sulfones as well as sulfoxides were obtained by oxidation of corresponding sulfides by hydrogen peroxide. The structure of the prepared compounds was confirmed on the basis of IR, mass, NMR spectral data and elemental analysis. Antimicrobial activity of these compounds was also determined. No significant results were found in this respect.

5-Nitroimidazoles are chemotherapeutically important as antiprotozoal and antibacterial agents [1—4]. Many of them are good amebicides [5] and trichomonacides [6—8]. Some other compounds of this group are very effective against a variety of protozoan infections [1, 8—11] or exhibit antibiotic properties [12].

In our previous papers [13, 14] we have found that some nitrogen heterocycles substituted with a longer alkyl chain exhibit remarkable antimicrobial activity especially against gram-positive bacteria. This finding promoted us to study in this respect also some 5-nitroimidazoles having various alkyl chain at N-1 atom. For comparison, aryl substitution was also studied. As a starting material we chose ornidazole — 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*I*) and 1-(2,3-epoxypropyl)-2-methyl-5-nitroimidazole (*II*) prepared from *I* by alkaline dehydrohalogenation [15].

Displacement of chlorine atom in *I* as well as the ring-opening displacement reaction of *II* with sulfur nucleophiles proceeded smoothly under formation of corresponding sulfides (*III—XV*) in good yields (Scheme 1). When the above sulfides were treated with hydrogen peroxide in acetic acid, corresponding sulfones were produced. In the case of com-



Scheme 1

pounds *V*—*VIII* (R = alkyl), careful control of the reaction temperature allowed us to stop the reaction in the first oxidation step and corresponding sulfoxides were isolated. In the case of the other starting sulfides, only sulfones were obtained regardless of reaction temperature. The survey of the prepared compounds and their characterization is summarized in Table 1. Their structure was confirmed on the basis of elemental analysis and IR, mass, ^{1}H and ^{13}C NMR spectral data.

Table 1. Characterization of the Prepared Compounds

Compound	R	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield	M.p.
				C	H	N	S	%	°C
III	Carboxymethyl	$C_9H_{13}N_3O_5S$	275.31	39.26	4.77	15.27	11.65	71	132—133
				39.08	4.84	15.33	11.57		
IV	2-Hydroxyethyl	$C_9H_{15}N_3O_4S$	261.31	41.36	5.80	16.08	12.27	78	71—72
				41.31	5.84	16.20	12.23		
V	Hexyl	$C_{13}H_{23}N_3O_3S$	301.45	51.79	7.71	13.94	10.64	92	66—67
				51.69	7.80	13.89	10.55		
VI	Heptyl	$C_{14}H_{25}N_3O_3S$	315.48	53.30	8.00	13.32	10.16	90	61—62
				53.37	8.08	13.24	10.18		
VII	Octyl	$C_{15}H_{27}N_3O_3S$	329.51	54.67	8.28	12.76	9.73	94	53—54
				54.69	8.33	12.78	9.70		
VIII	Dodecyl	$C_{19}H_{35}N_3O_3S$	385.63	59.17	9.17	10.90	8.31	91	59—60
				59.10	9.23	10.94	8.33		
IX	Phenyl	$C_{13}H_{15}N_3O_3S$	293.37	53.22	5.16	14.33	10.93	88	78—79
				53.28	5.21	14.29	10.91		
X	2-Pyrimidinyl	$C_{11}H_{13}N_5O_3S$	295.35	44.73	4.45	23.72	10.85	85	161—162
				44.79	4.48	23.80	10.81		
XI	2-Hydroxy-4-pyrimidinyl	$C_{11}H_{13}N_5O_4S$	311.35	42.43	4.22	22.50	10.30	82	157—158
				42.50	4.26	22.43	10.34		
XII	4-Hydroxy-6-methyl-2-pyrimidinyl	$C_{12}H_{15}N_5O_4S$	325.38	44.29	4.66	21.53	9.85	83	144—145
				44.21	4.74	21.59	9.89		
XIII	4,6-Dimethyl-2-pyrimidinyl	$C_{13}H_{17}N_5O_3S$	323.41	48.28	5.31	21.66	9.91	85	146—147
				48.33	5.34	21.58	9.87		
XIV	4,6-Diamino-2-pyrimidinyl	$C_{11}H_{15}N_7O_3S$	325.39	40.60	4.66	30.14	9.85	79	239—240
				40.53	4.71	30.08	9.83		
XV	2-Benzimidazolyl	$C_{14}H_{15}N_5O_3S$	333.40	50.43	4.54	21.01	9.62	83	189—190
				50.41	4.57	21.07	9.56		
XVI	Hexyl	$C_{13}H_{23}N_3O_4S$	317.45	49.18	7.32	13.24	10.10	62	28—29
				49.20	7.36	13.21	10.13		
XVII	Heptyl	$C_{14}H_{25}N_3O_4S$	331.48	50.72	7.62	12.68	9.67	58	Oil
				50.77	7.68	12.73	9.63		
XVIII	Octyl	$C_{15}H_{27}N_3O_4S$	345.51	52.14	7.89	12.16	9.28	63	Oil
				52.10	7.90	12.19	9.29		
XIX	Dodecyl	$C_{19}H_{35}N_3O_4S$	401.63	56.82	8.80	10.46	7.98	66	Oil
				56.89	8.86	10.42	7.97		
XX	Carboxymethyl	$C_9H_{13}N_3O_7S$	307.31	35.17	4.27	13.68	10.43	74	178—179
				35.21	4.33	13.66	10.45		
XXI	2-Hydroxyethyl	$C_9H_{15}N_3O_6S$	293.33	36.85	5.16	14.33	10.93	70	179—180
				36.81	5.18	14.30	10.89		
XXII	Hexyl	$C_{13}H_{23}N_3O_5S$	333.45	46.82	6.97	12.60	9.61	88	116—117
				46.85	6.95	12.63	9.60		
XXIII	Heptyl	$C_{14}H_{25}N_3O_5S$	347.48	48.39	7.27	12.10	9.23	83	107—108
				48.35	7.29	12.06	9.20		
XXIV	Octyl	$C_{15}H_{27}N_3O_5S$	361.51	49.83	7.54	11.63	8.87	86	121—122
				49.91	7.57	11.59	8.83		
XXV	Dodecyl	$C_{19}H_{35}N_3O_5S$	417.63	54.64	8.46	10.06	7.68	87	114—115
				54.61	8.45	10.01	7.66		
XXVI	Phenyl	$C_{13}H_{15}N_3O_5S$	325.37	47.99	4.66	12.92	9.85	83	172—173
				47.93	4.69	12.90	9.90		
XXVII	2-Pyrimidinyl	$C_{11}H_{13}N_5O_5S$	327.35	40.36	4.01	21.40	9.79	71	179—180
				40.32	4.05	21.33	9.76		
XXVIII	2-Benzimidazolyl	$C_{14}H_{15}N_5O_5S$	365.40	46.02	4.15	19.17	8.77	79	246—247
				46.08	4.18	19.09	8.79		

In the IR spectra of the prepared compounds strong absorption bands in the region of $\tilde{\nu}$ = 1368 cm^{-1} and 1525 cm^{-1} corresponding to the stretching vibrations (ν_s and ν_{as}) of the nitro group were observed. Stretching vibrations of the imidazole ring showed strong absorption bands in the region of $\tilde{\nu}$ = 1324 cm^{-1}, 1434 cm^{-1}, and 1465 cm^{-1}. Further strong absorption band at $\tilde{\nu}$ = 1265 cm^{-1} corresponded to the deformation vibration of C—H bond of imidazole ring. Absorption bands in the region of $\tilde{\nu}$ = 1040 cm^{-1} (S=O stretching deformation) or at $\tilde{\nu}$ = 1150 cm^{-1} and 1325 cm^{-1} (S=O stretching deformation) were characteristic of sulfoxides and sulfones, respectively.

Mass spectra of the prepared compounds *III*—*XXVIII* exhibited peaks of molecular ions M^+ (I_r = 5—13 %) only when R represented aromatic substituent. On the other hand, the peak at *m/z* = 171 (loss of an R radical from the $[M - NO_2]^+$ ion and rearrangement of hydrogen) was observed only for compounds where R = alkyl. In all cases, the base peak (I_r = 100 %) corresponded to the ion formed by the loss of NO_2 from molecular ion. Surprisingly, no rearrangement with elimination of an aldehyde, characteristic of 1-alkyl-5-nitroimidazoles [16], was observed.

Characteristic NMR data of selected compounds are given in Experimental.

The results of antimicrobial activity testing revealed relatively low effects against selected microorganisms. Mostly, the values of minimum inhibitory concentration (MIC) were about 1000 ppm (Table 2). In accordance with our previous observation [13, 14] the best activity against gram-positive bacteria was exhibited by the derivatives with R = hexyl, heptyl, and octyl.

EXPERIMENTAL

Starting 5-nitroimidazoles *I* and *II* were prepared according to the known methods [15]. 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 recorded on a Bruker AM-300 spectrometer operating at 300.13 MHz or 75.46 MHz working frequencies in $CDCl_3$ or $(CD_3)_2SO$ solutions with TMS as an internal standard. For the assignment of signals in the ^{13}C NMR spectra DEPT and semiselective INEPT techniques were used. (*Note*: Comma index refers to the positions of 2-hydroxypropyl grouping; positions in the benzene ring are two-comma indexed). Elemental analyses were obtained on a Perkin—Elmer 240 analyzer.

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*
III	100	1000	1000	1000	1000	1000	1000
IV	1000	1000	1000	1000	1000	1000	1000
V	10	<10	100	1000	1000	1000	1000
VI	<10	<10	10	100	1000	100	100
VII	10	10	10	1000	1000	1000	1000
VIII	100	100	100	1000	1000	1000	1000
IX	1000	1000	1000	1000	1000	1000	1000
X	100	1000	1000	1000	1000	1000	1000
XI	1000	1000	1000	1000	1000	1000	1000
XII	100	100	1000	1000	1000	1000	1000
XIII	100	1000	1000	1000	1000	1000	1000
XIV	100	100	100	1000	1000	1000	100
XV	1000	1000	1000	1000	1000	1000	1000
XVI	10	10	100	1000	1000	1000	1000
XVII	10	10	100	1000	1000	1000	100
XVIII	10	10	100	1000	1000	1000	100
XIX	100	100	1000	1000	1000	1000	1000
XX	100	100	1000	1000	1000	1000	100
XXI	1000	1000	1000	1000	1000	1000	1000
XXII	10	10	100	1000	1000	100	100
XXIII	<10	10	100	1000	1000	100	100
XXIV	<10	<10	100	1000	1000	100	100
XXV	100	100	100	1000	1000	1000	100
XXVI	1000	1000	1000	1000	1000	1000	1000
XXVII	100	100	1000	1000	1000	100	1000
XXVIII	1000	1000	1000	1000	1000	1000	1000

MIC was determined by using the suspension method on solid cultivation media [13].

1-(3-Octylthio-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*VII*)

Method A. Into a solution of sodium ethoxide (0.03 mol) in dry ethanol (60 cm^3) 1-octanethiol (0.03 mol) was added and the solution was heated under reflux for 30 min. Then 1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*I*) (0.03 mol) was added and the mixture was stirred at room temperature for an additional 1 h. Solid was filtered off, ethanolic solution was concentrated at reduced pressure to a half of its volume and poured onto crushed ice (200 cm^3). Separated product was filtered, dissolved in ether and decolourized with charcoal. After filtration and evaporation of solvent, crude product was recrystallized from a mixture of ether and hexane.

^{1}H NMR spectrum ($CDCl_3$), δ: 7.88 (s, 1H, H-4), 4.63 (dd, 1H, H_a-1′, J = 13.3 Hz and 1.2 Hz), 4.10 (dd, 1H, H_b-1′, J = 13.3 Hz and 9.0 Hz), 4.05 (m, 1H, H-2′), 3.40 (br, 1H, OH), 2.85 (dd, 1H, H_a-3′, J = 13.7 Hz and 3.8 Hz), 2.59 (dd, 1H, H_b-3′, J = 13.7 Hz and 7.2 Hz), 2.56 (m, 2H, the first CH_2 in octyl), 2.53 (s, 3H, CH_3 in imidazole), 1.60 (m, 2H, the second CH_2 in octyl), 1.27 (br, 8H, 10H, the other CH_2 in octyl), 0.88 (t, 3H, CH_3 in octyl). ^{13}C NMR spectrum ($CDCl_3$), δ: 151.8 (C-2), 138.3 (C-5), 132.9 (C-4), 69.0 (C-2′), 51.0 (C-1′), 37.3 (C-3′), 32.4 (the first CH_2 in octyl), 31.8, 29.5, 29.1, 29.0, 28.8, 22.6 (the other CH_2 in octyl), 14.7 (CH_3 in imidazole), 14.1 (CH_3 in octyl).

1-(3-Phenylthio-2-hydroxypropyl)-2-methyl-5-nitroimidazole (*IX*)

Method B. To a solution of benzenethiol (0.01 mol) in methanol (50 cm^3) triethylamine (0.01 mol) was added at 50 °C. 1-(2,3-Epoxypropyl)-2-methyl-5-nitroimidazole (*II*) (0.01 mol) was added and the mixture was heated under reflux for 3 h. Then the solvent was removed under reduced pressure, product redissolved in methanol (20 cm^3) and poured onto crushed ice (200 cm^3), followed by the same work-up as in the case of method *A*.

^{1}H NMR spectrum ($CDCl_3$), δ: 7.65 (s, 1H, H-4), 7.16—7.38 (m, 5H, H_{arom}), 4.58 (d, 1H, H_a-1′, J = 18.4 Hz), 4.04 (dd, 1H, H_b-1′, J = 18.4 Hz and 9.3 Hz), 4.02 (m, 1H, H-2′), 3.20 (dd, 1H, H_a-3′, J = 13.8 Hz and 4.3 Hz), 3.01 (dd, 1H, H_b-3′, J = 13.8 Hz and 6.9 Hz), 2.37 (s, 3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 151.5 (C-2), 138.0 (C-5), 134.6 (C-1″), 132.1 (C-4), 129.4 (C-2″ and C-6″), 129.0 (C-3″ and C-5″), 126.6 (C-4″), 68.8 (C-2′), 50.7 (C-1′), 38.8 (C-3′), 14.3 (CH_3).

Methods *A* and *B* are general for the preparation of sulfides *III*—*XV*. Reaction time varied from 2 to 5 h (monitored by TLC on Silufol plates with ethyl acetate—hexane (φ_r = 3 : 2) as an eluent).

1-(3-R-Sulfonyl-2-hydroxypropyl)-2-methyl-5-nitroimidazoles *XX*—*XXVIII*

To a solution of corresponding sulfide (0.01 mol) in acetic acid (50 cm^3) hydrogen peroxide (30 %, 7 cm^3) was added dropwise under stirring. Then the mixture was heated at 70 °C for 3—8 h (monitored by TLC) and left to stand overnight at room temperature. Resulting solution was poured onto crushed ice (200 cm^3) and the product extracted by ethyl acetate. After drying over $MgSO_4$, filtration and evaporation of solvents, corresponding sulfones were recrystallized from hexane—ethyl acetate (for compounds *XXII*—*XXV*) or ethyl acetate—ethanol (for compounds *XX*, *XXI*, *XXVI*—*XXVIII*).

Compound *XXVI*: ^{1}H NMR spectrum ($CDCl_3$), δ: 7.54—7.94 (m, 5H, H_{arom}), 7.92 (s, 1H, H-4), 4.52 (dd, 1H, H_a-1′, J = 13.8 Hz and 2.5 Hz), 4.46 (m, 1H, H-2′), 4.26 (dd, 1H, H_b-1′, J = 13.8 Hz and 8.4 Hz), 3.41 (dd, 1H, H_a-3′, J = 14.1 Hz and 2.7 Hz), 3.32 (dd, 1H, H_b-3′, J = 14.1 Hz and 8.3 Hz), 2.52 (s, 3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 151.2 (C-2), 148.1 (C-1″), 137.4 (C-5), 134.5 (C-4″), 133.3 (C-4), 129.7 (C-3″ and C-5″), 127.9 (C-2″ and C-6″), 66.4 (C-2′), 59.5 (C-3′), 50.5 (C-1′), 14.8 (CH_3).

1-(3-R-Sulfinyl-2-hydroxypropyl)-2-methyl-5-nitroimidazoles *XVI*—*XIX*

These compounds were prepared essentially by the same method as given above for the preparation of sulfones excepting that the reaction temperature was kept at 0 °C for 5—10 h (monitored by TLC). The ^{1}H and ^{13}C NMR spectra of these compounds were very similar to those of corresponding sulfones excepting that the signals of H_a-3′ and H_b-3′ were shifted upfield by δ = 0.1 and those of C-3′ by about δ = 10.0.

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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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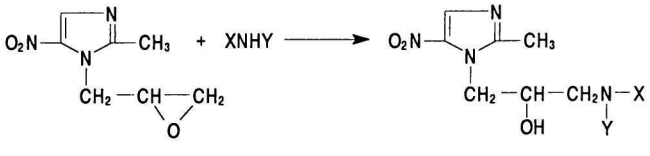
Several 1-(3-alkylamino-2-hydroxypropyl)-2-methyl-5-nitroimidazoles were prepared by the ring-opening displacement reaction of 1-(2,3-epoxypropyl)-2-methyl-5nitroimidazole with some amines. The structure of the prepared compounds was confirmed on the basis of IR, mass, NMR spectral data and elemental 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