Russian Journal of Organic Chemistry, Vol. 40, No. 12, 2004, pp. 1813–1818. From Zhurnal Organicheskoi Khimii, Vol. 40, No. 12, 2004, pp. 1861–1865.

Synthesis and Biological Activity of New 2-Amino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazole Derivatives*

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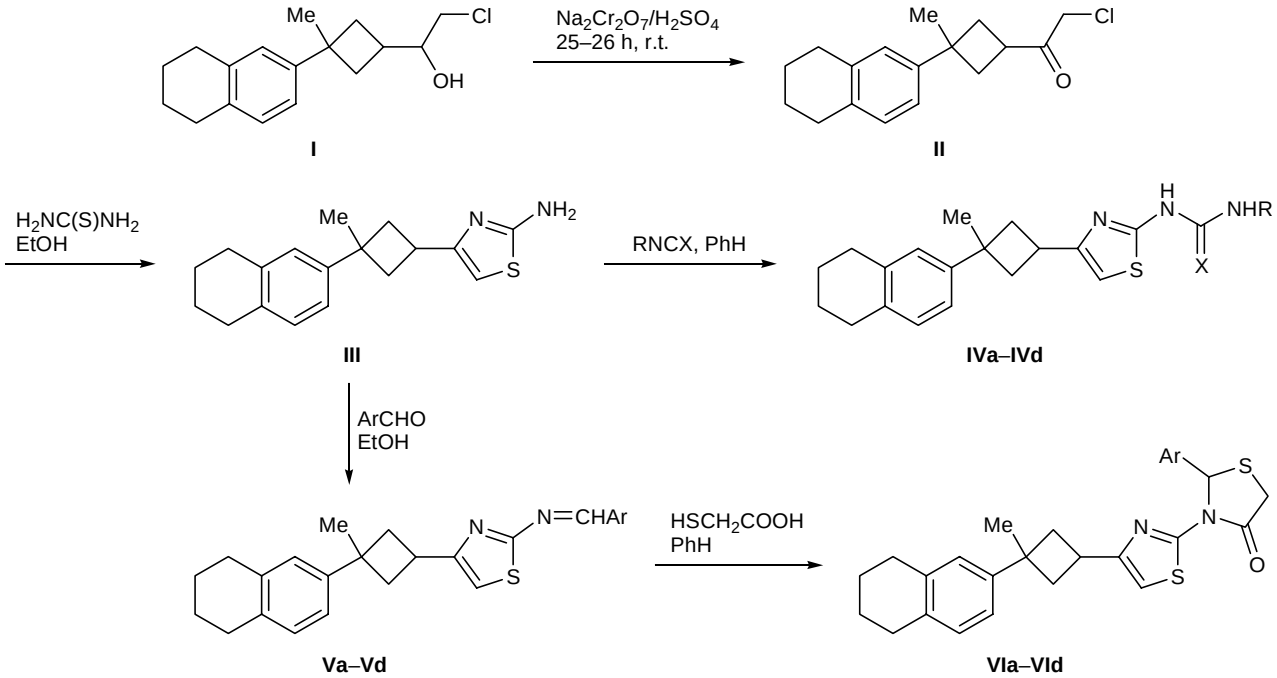
Received September 23, 2003

Abstract—2-Amino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazole was synthesized by reaction of 1-methyl-1-(5,6,7,8-tetrahydro-2-naphthyl)-3-chloroacetylcyclobutane with thiourea in ethanol, and its subsequent transformations afforded new derivatives which were tested *in vitro* for antibacterial activity against some bacteria using the disk diffusion technique.

The formation of substituted cyclobutanes in reactions of 6-chloro-4,5-epoxy-2-methyl-1-hexene with aromatic hydrocarbons, such as benzene, toluene, naphthalene, and mesitylene, has been reported [1–3]. Thiazole and its derivatives are biologically important compounds. For example, molecules of vitamin B_1 and cocarboxylase coenzyme contain thiazole fragments [4]; penicillin molecule includes a thiazolidine ring. 2-Aminothiazoles are known as biologically active compounds with a broad range of activity, and they are also used as intermediate products in the synthesis of antibiotics and dyes [5]. Derivatives of 3-substituted cyclobutanecarboxylic acid exhibit antiinflammatory and antidepressant activity [6, 7], as well as liquid

Scheme 1.



IV, R = Et, X = O (**a**); R = *i*-Pr, X = O (**b**); R = Me, X = S (**c**); R = Ph, X = S (**d**); **V**, **VI**, Ar = 4-ClC_6H_4 (**a**), 4-$O_2NC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**), 2-hydroxy-1-naphthyl (**d**).

* The original article was submitted in English.

1070-4280/04/4012-1813

Table 1. Yields, melting points, and elemental analyses of compounds **IVa**–**IVd**, **Va**–**Vd**, and **VIa**–**VId**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IVa	65	232	68.23	7.12	11.34	$C_{21}H_{27}N_3OS$	68.26	7.36	11.37
IVb	73	240	68.89	7.78	10.75	$C_{22}H_{29}N_3OS$	68.89	7.62	10.96
IVc	57	245	64.90	6.96	11.19	$C_{20}H_{25}N_3S_2$	64.65	6.78	11.31
IVd	80	299	69.50	6.47	09.33	$C_{25}H_{27}N_3S_2$	69.24	6.28	09.69
Va	55	227	71.16	5.72	06.44	$C_{25}H_{25}ClN_2S$	71.38	5.99	06.65
Vb	70	219	69.52	6.16	09.45	$C_{25}H_{25}N_3O_2S$	69.58	5.84	09.74
Vc	65	205	75.66	6.49	06.69	$C_{26}H_{28}N_2OS$	74.96	6.77	06.72
Vd	70	233	76.83	6.45	05.99	$C_{29}H_{28}N_2OS$	76.96	6.24	06.19
VIa	58	176	65.25	5.90	05.36	$C_{27}H_{27}ClN_2OS_2$	65.50	5.50	05.66
VIb	62	193	64.27	5.48	08.41	$C_{27}H_{27}N_3O_3S_2$	64.13	5.38	08.31
VIc	55	217	68.01	6.37	05.25	$C_{28}H_{30}N_2O_2S_2$	68.54	6.16	05.71
VId	65	211	70.35	5.91	05.17	$C_{31}H_{30}N_2O_2S_2$	70.69	5.74	05.32

Table 2. ^{1}H NMR spectra of compounds **IVa**–**IVd**, **Va**–**Vd**, and **VIa**–**VId**

Comp. no.	Chemical shifts δ, ppm					
	H_{arom}, m	CH_2, m (naphthalene + cyclobutane)	CH, m (1H) (cyclobutane)	CH_3, s (3H)	5-H, s (1H)	other protons
IVa	6.86–7.06 (3H)	1.81–1.84 (4H) 2.76–2.80 (4H) 2.33–2.55 (4H)	3.38–3.50	1.51	5.96	1.56 t (3H, C**H**$_3$CH$_2$), 3.61 q (2H, CH$_3$C**H**$_2$), 5.30–5.41 br.s (1H, N**H**CH$_2$); 5.52 s (1H, NH)
IVb	6.85–7.05 (3H)	1.82–1.86 (4H) 2.31–2.81 (8H)	3.37–3.52	1.49	5.97	1.55–1.59 d (6H, CH$_3$), 5.31–5.40 br.s (1H, N**H**CH), 5.50 s (1H, NH)
IVc	6.85–7.05 (3H)	1.82–1.86 (4H) 2.31–2.81 (8H)	3.37–3.52	1.51	5.97	3.02 d (3H, CH$_3$), 5.30–5.40 br.s (1H, N**H**CH$_3$), 5.50 s (1H, NH)
IVd	6.85–8.12 (8H)	1.82–1.86 (4H) 2.31–2.81 (8H)	3.37–3.52	1.50	5.97	9.60–10.41 br.s (2H, NH)[a]
Va	6.80–7.55 (7H)	1.82–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	8 06 s (1H, N=CH)
Vb	6.81–7.61 (7H)	1.82–1.86 (4H) 2.33–2.81 (8H)	3.37–3.52	1.50	5.91	8.00 s (1H, N=CH)
Vc	6.80–7.55 (7H)	1.82–1.86 (4H) 2.33–2.81 (8H)	3.37–3.52	1.50	5.91	3.33 s (3H, OCH$_3$), 7.99 s (1H, N=CH)
Vd	6.82–7.56 (9H)	1.82–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	7 99 s (1H, N=CH), 13.61 s (1H, OH)
VIa	6.81–7.55 (7H)	1.81–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	4 10 s (2H, CH$_2$S)
VIb	6.81–7.43 (7H)	1.81–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	3.81 s (3H, OCH$_3$), 4.10 s (2H, CH$_2$S)
VIc	6.81–7.55 (7H)	1.81–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	4 10 s (2H, CH$_2$S)
VId	6.82–7.56 (9H)	1.82–1.85 (4H) 2.33–2.81 (8H)	3.37–3.52	1.53	5.91	4.10 s (2H, CH$_2$S), 13.58 s (1H, OH)

[a] Exchanges with D_2O.

crystal properties [8]. Various thiazole derivatives were shown to exert herbicidal [9], antiinflammatory [10, 11], antimicrobial [12], and antiparasitic action [13]. Schistosomiasis is a chronic and debilitating disease which infects about 300 millions people in tropical and subtropical regions [14].

In mammalian systems, molecular oxygen is directly incorporated into naphthalene metabolism [15]. Tetrahydronaphthalene may undergo biological oxidation to a quinoid structure which is reponsible for reduction of the rate of schistosoma glycolysis [16]. In addition, tetrahydronaphthalene is capable of binding molecular oxygen under mild conditions with formation of peroxy compounds [17]. Bushby *et al*. [18] reported that some thiazoles and thiazolidin-4-ones are biologically important as antimetabolites and schistosomicides.

The present communication describes the synthesis of 2-amino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazole (**III**) from 2-chloro-1-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]-ethanol (**I**). Compound **I** was oxidized to 3-chloroacetylcyclobutane **II** which was brought into condensation with thiourea to obtain 4-cyclobutyl-2-aminothiazole **III**. On the basis of compound **III** we synthesized a number of derivatives **IV**–**VI** having urea, thiourea, Schiff base, and thiazolidin-4-one fragments (Scheme 1). The structure of the products was confirmed by elemental analysis and ^{1}H NMR spectroscopy (Tables 1, 2). Compound **III** characteristically showed in the IR spectrum absorption bands at 3285 and 3310 (NH_2), 1604 (C=N), and 685 cm^{-1} (C–S–C); no absorption assignable to C–Cl or carbonyl vibrations was present.

Table 3 contains the results of testing compounds **III**–**VI** for antibacterial activity against some bacteria.

EXPERIMENTAL

The melting points were determined in open capillaries using a Gallenkamp digital melting point apparatus and were not corrected. The IR spectra were recorded in KBr on a Mattson 1000 FT-IR spectrometer. The ^{1}H NMR spectra were obtained on JEOL FX 90 (90 MHz) and Bruker (200 MHz) instruments from solutions in $CDCl_3$–DMSO-d_6 using TMS as internal reference. The elemental compositions were determined on a LECO-CHNS-938 analyzer.

1,2,3,4-Tetrahydronaphthalene (Aldrich) was dried over anhydrous magnesium sulfate prior to use. Diethyl ether, anhydrous $CaCl_2$, KOH (Aldrich), anhydrous $AlCl_3$ (Riedel), $Na_2Cr_2O_7$, and H_2SO_4 (Merck) were used without additional purification. 6-Chloro-4,5-epoxy-2-methyl-1-hexene was received from organic chemists at the Department of Chemistry, University of Fırat; it was distilled just before use. 2-Chloro-1-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]-ethanol (**I**) was synthesized as described in [1].

2-Chloro-1-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]ethanone (II). A 1000-ml four-necked flask was charged with 0.29 mol of $Na_2Cr_2O_7$, 0.52 mol of compound **I**, and 50 ml of water, and 75 ml of 68% (by volume) sulfuric acid was added dropwise under stirring over a period of 7–8 h, maintaining the mixture at room temperature. The mixture was stirred for about 18 h at room temperature, the precipitate was filtered off, and the filtrate was extracted with several portions of diethyl ether. The extract was dried over anhydrous $CaCl_2$, the solvent was distilled off, and the residue was distilled under reduced pressure (1 mm) at 186°C. The distillate was passed through a column charged with silica gel using benzene–ethyl acetate (20:1) as eluent; R_f 0.48. Yield of **II** ~75%. IR spectrum, ν, cm^{-1}: 1730 (C=O), 736 (C–Cl); no OH absorption was present.

2-Amino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazole (III). A solution of 2.76 g (10 mmol) of compound **II** in 30 ml of anhydrous ethanol was added dropwise under continuous stirring to a solution of 0.76 g (10 mmol) of thiourea in 50 ml of anhydrous ethanol, heated to 50–60°C. The progress of the reaction was monitored by IR spectroscopy, following the disappearance of the carbonyl absorption band of initial ketone **II**. The mixture was made alkaline by adding 5% aqueous ammonia, and the colorless precipitate was filtered off, washed with aqueous ammonia and several portions of water, dried in air, and recrystallized from aqueous ethanol (1:3). Yield 74%. Colorless crystals, mp 222–223°C. IR spectrum (KBr), ν, cm^{-1}: 3285–3310 (NH_2), 1604 (C=N), 685 (C–S–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.86–7.06 m (3H, $H_{arom.}$), 5.95 s (1H, 5-H, thiazole), 5.48 s (2H, NH_2), 3.52 quint (1H, CH, cyclobutane, J = 8.80 Hz), 2.76–2.80 m (4H, CH_2, tetralin), 2.33–2.55 m (4H, CH_2, cyclobutane), 1.81–1.84 m (4H, CH_2, tetralin), 1.54 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 170.60 (C^1), 157.85 (C^2), 152.09 (C^3), 42.55 (C^4), 40.18 (C^5), 32.66 (C^6), 31.50 (C^7), 31.05 (C^8), 138.87 (C^9), 136.18 (C^{10}), 131.04 (C^{11}), 127.52 (C^{12}), 124.30 (C^{13}), 102.27 (C^{14}), 25.35

Table 3. Antibacterial activity of thiazole derivatives **IVa**–**IVd**, **Va**–**Vd**, and **VIa**–**VId** (inhibition zone, mm)[a]

Comp. no.	Concentration, μg	*Salmonella thypimurium*	*Kluyveromyces fragilis*	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Rhodotorula rubrum*	*Aeromonas hydrophila*	*Enterococcus faecalis*	*Corynebacterium xerosis*	*Enterobacter aerogenes*	*Bacillus megaterium*	*Listeria monocytogenes*	*Proteus vulgaris*	*Mycobacterium smegmatis*	*Bacillus subtilis*	*Staphylococcus aureus*	*Escherichia coli*
IVa	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	400	1	5	6	5	5	7	9	1	9	6	6	1	8	8	9	5
IVb	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	400	8	5	7	6	6	6	1	8	9	7	6	9	7	8	1	5
IVc	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	400	7	6	6	5	5	7	8	6	8	7	7	9	8	7	1	6
IVd	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	400	6	5	7	5	6	7	7	7	9	6	7	8	9	8	1	5
Va	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	5	–	–	–	–	–	5	–	6	–	–	–	–	–
	400	11	7	13	11	7	12	11	10	13	12	12	12	11	11	10	7
Vb	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	6	–	–	–	5	–	7	–	7	–	–	5	–	–
	400	14	6	13	14	7	14	16	15	14	13	16	15	15	16	15	9
Vc	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	5	–	–	–	6	–	6	–	6	–	–	–	–	–
	400	12	6	11	10	7	11	12	12	14	12	13	12	14	13	12	5
Vd	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	6	–	–	–	5	–	5	–	6	–	–	–	–	–
	400	10	5	12	9	5	10	12	10	12	11	11	11	12	12	10	6
VIa	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	7	–	–	–	5	–	6	–	6	–	–	–	–	–
	400	12	6	13	13	6	10	12	12	13	12	13	11	11	13	12	6
VIb	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	5	–	–	–	5	–	6	–	5	–	–	–	–	–
	400	11	5	12	11	5	11	12	13	13	12	12	10	11	10	10	6
VIc	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	5	–	–	–	5	–	–	–	5	–	–	–	–	–
	400	9	5	13	10	6	11	12	11	9	9	10	9	9	10	9	6
VId	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	200	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	400	6	4	7	7	5	6	8	8	7	7	9	7	8	8	9	5
Standards:																	
Ampicillin (10 μg)		12	NP	13	10	NP	13	12	9	16	20	34	14	19	17	12	10
Nystatin (30 μg)		NP	18	NP	NP	15	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP

[a] Dash denotes the absence of inhibition zone, and NP stands for "not performed."

(C^{15}), 25.31 (C^{16}). Found, %: C 72.10; H 7.41; N 8.93; S 10.68. $C_{18}H_{22}N_2S$. Calculated, %: C 72.44; H 7.43; N 9.39; S 10.74.

4-[3-Methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)-cyclobutyl]-2-ureido(thioureido)thiazoles IVa–IVd (*general procedure***).** A mixture of 2.98 g (0.01 mol) of compound **III** and 0.01 mol of the corresponding isocyanate or isothiocyanate in anhydrous benzene was heated for 6 h under reflux. After cooling, the precipitate was filtered off and recrystallized from methanol.

2-Arylmethyleneamino-4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazoles Va–Vd (*general procedure***).** A solution of 2.98 g (0.01 mol) of compound **III** in 40 ml of anhydrous ethanol was added dropwise under continuous stirring to a solution of 0.01 mol of the corresponding aromatic aldehyde in 20 ml of anhydrous ethanol. The mixture was stirred for 10 h at 60–70°C, cooled, and poured into ice water. The precipitate was filtered off and recrystallized from ethanol.

2-Aryl-3-{4-[3-methyl-3-(5,6,7,8-tetrahydro-2-naphthyl)cyclobutyl]thiazol-2-yl}tetrahydrothiazol-4-ones VIa–VId (*general procedure***).** A solution of 0.1 ml (0.01 mol) of sulfanylacetic acid in 10 ml of anhydrous benzene was added under vigorous stirring to a solution of 0.01 mol of compound **Va**–**Vd** in 60 ml of anhydrous benzene. The mixture was heated for 6 h under reflux, the solvent was removed under reduced pressure, and the residue was treated with warm petroleum ether. The precipitate was filtered off and recrystallized from ethanol.

The yields, melting points, and analytical data of compounds **IVa**–**IVd**, **Va**–**Vd**, and **VIa**–**VId** are given in Table 1, and their ^{1}H NMR spectra, in Table 2.

Preparation of microorganism cultures. All samples to be tested and standard antibiotics were injected into empty sterilized antibiotic disks (6 mm in diameter; Schleicher & Shull No. 2668, Germany) in an amount of 100, 200, or 400 μg. Disks injected with chloroform were used as control. All the bacteria listed below were incubated at 30±0.1°C over a period of 24 h by inoculation into Nutrient Broth (Difco), and the yeasts were incubated in Sabourand Dextrose Broth (Difco) over a period of 24 h. Mueller Hinton Agar (oxoid) and Sabourand Dextrose Agar were sterilized in a flask, cooled to 45–50°C, and distributed over sterilized Petri dishes (9 cm in diameter) in an amount of 15 ml using a pipette in 24 h after injecting cultures of bacteria and yeasts in an amount of 0.1 ml (10^5 bacteria per ml or 10^4 yeast cells per ml), ensuring homogeneous distribution of the food medium over Petri dishes. The disks injected with the extracts were placed on the solid agar medium and were slightly pressed [19–23].

The Petri dishes prepared as described above were kept for 2 h at 4°C; samples inoculated with yeasts were incubated for 24–36 h at 25±0.1°C, and bacteria were incubated for 18–20 h at 35°C. The inhibition zones formed on the food medium were evaluated in millimeters. Each experiment was performed in three parallel runs.

The newly synthesized thiazole derivatives were tested *in vitro* for antimicrobial activity against the following bacteria: *Salmonella thypimurium* TA 100 hi, *Kluyveromyses fragilis*, *Serratia marcescens* NRRL 3284, *Pseudomonas aeruginosa* ATCC 27, *Rhodotorula rubrum*, *Aeromonas hydrophila* ATCC 7966, *Enterococcus faecalis* ATCC 15, *Corynebacterium xerosis* UC 9165, *Enterobacter aerogenes* RA 2971, *Bacillus megaterium* DSM 32, *Listeria monocytogenes* Scoot A, *Proteus vulgaris* FMC 1, *Mycobacterium smegmatis* CCM 2067, *Bacillus subtilis* IMG 22, *Staphylococcus aureus* Cowan 1, and *Escherichia coli* DM. The diameters of the inhibition zones were measured at doses of 100, 200, and 400 μg; the results are summarized in Table 3. No antibacterial effect was observed for all the examined compounds at a dose of 100 μg. At 200 μg, only compounds **Va**–**Vd** and **VIa**–**VIc** showed antimicrobial effect against some microorganisms. The best effect was observed for all compounds at a dose of 400 μg (Table 3).

This study was supported by FUNAF (grant no. 477; Elazığ, Turkey). The authors are thankful to Assoc. Prof. Dr. Metin Dığrak for his help in the determination of biological activity.

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