Synthesis and Antihistaminic Activity of 1-[(4-Substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines

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Received June 18, 1979, from the *Department of Chemistry, College of Pharmacy, and the ‡Department of Experimental Medicine and Pharmacology, Faculty of Medicine, Tehran University, Tehran, Iran. Accepted for publication December 20, 1979.

Abstract □ Starting with readily available aryl 4-substituted-1,2,3-thiadiazol-5-yl ketones, a series of 1-[(4-substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines was synthesized and tested for antihistaminic and anticholinergic activities. Four compounds were potent antihistamines, and two of these compounds displayed moderate anticholinergic activity.

Keyphrases □ Antihistaminic activity—1-[(4-substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines, synthesis, IR, NMR, and mass spectral analyses □ Anticholinergic activity—1-[(4-substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines, synthesis, IR, NMR, and mass spectral analyses □ 1-[(4-Substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines—synthesis, antihistaminic and anticholinergic activity

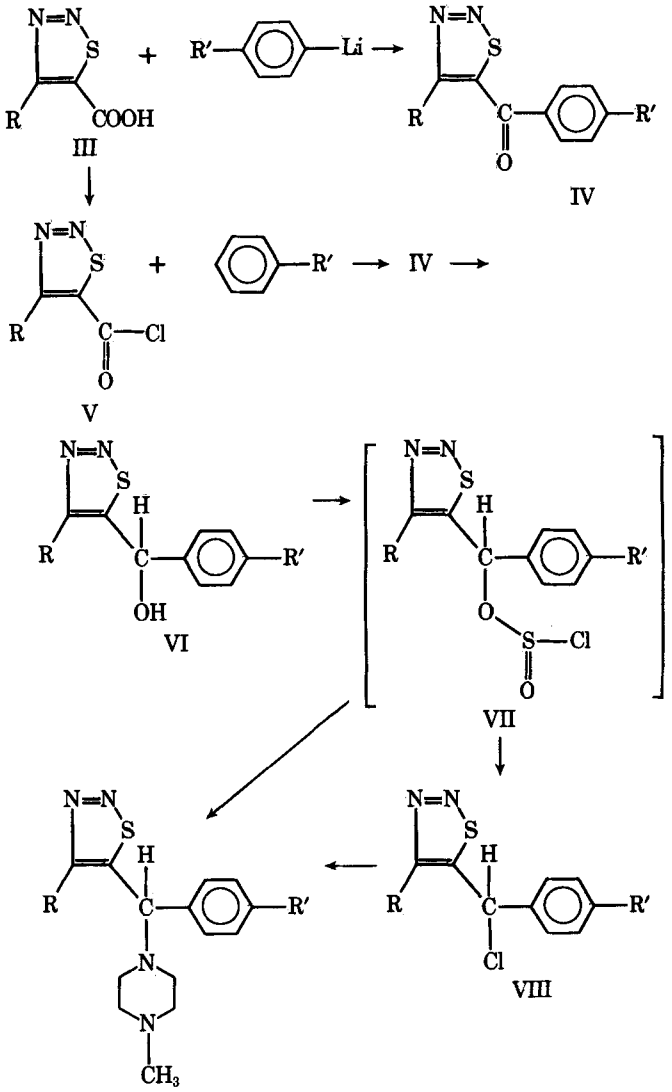
It was reported that piperazine derivatives such as chlorcyclizine (I) and meclizine (II) have significant antihistaminic activity (1). 1,2,3-Thiadiazole derivatives of benzimidazole, benzoxazole, and benzothiazole were reported to be anthelmintics (2). Some phosphorus compounds having the 1,2,3-thiadiazole ring system showed insecticide activity (3), and 4-amino-1,2,3-thiadiazolesulfonamides exhibited antibacterial properties (4). The synthesis and antibacterial activity of 4-substituted-(1,2,3-thiadiazol-5-yl)carbamic acid esters were reported recently (5).

In a continuing effort to find a potent antihistamine with low toxicity (6), a series of 1-[(4-substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines was prepared, and efficacy was determined.

RESULTS AND DISCUSSION

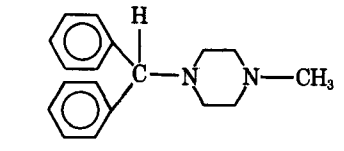
Chemistry—Ethyl 4-substituted-1,2,3-thiadiazole-5-carboxylates were prepared by an oxidative cyclization of methyl or methylene ketone semicarbazones with thionyl chloride (7).

Aryl 4-phenyl-1,2,3-thiadiazol-5-yl ketones (IV, R = C_6H_5) were prepared from the reaction of aryllithium (8) with 4-phenyl-1,2,3-thiadiazole-5-carboxylic acid (III, R = C_6H_5), and aryl 4-methyl-1,2,3-thiadiazol-5-yl ketones (IV, R = CH_3) were prepared from the Friedel–Crafts reaction of 4-methyl-1,2,3-thiadiazole-5-carboxyl chloride (V, R = CH_3) with aromatic hydrocarbones. Reduction of IV with sodium borohydride gave (4-substituted-1,2,3-thiadiazol-5-yl)arylcarbinol (VI). Reaction of VI with thionyl chloride in benzene at room temperature gave VII as an intermediate, which was transformed to VIII at 80°. The latter compound afforded IX through reaction with *N*-methylpiperazine. Transformation of VII (R = CH_3, R′ = OCH_3) to VIII could not be achieved under different experimental conditions. In all cases, a mixture of products was obtained. However, VII (R = CH_3, R′ = OCH_3) could be converted directly to IX (R = CH_3, R′ = OCH_3) through the reaction with *N*-methylpiperazine (Scheme I).



a: R = CH_3, R′ = H
b: R = CH_3, R′ = CH_3
c: R = CH_3, R′ = CH_3O
d: R = CH_3, R′ = Br
e: R = CH_3, R′ = Cl
f: R = C_6H_5, R′ = H
g: R = C_6H_5, R′ = CH_3
h: R = C_6H_5, R′ = Cl

Scheme I



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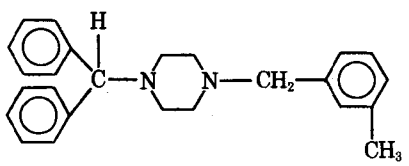

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Table I—Aryl 4-Substituted-1,2,3-thiadiazol-5-yl Ketones [a]

Compound	R	R′	Yield, %	Melting Point [b]	Formula	Analysis, %	Calc.	Found
IV*a*	CH_3	H	70	180–182° [c]	$C_{10}H_8N_2OS$	C	58.82	58.66
						H	3.92	3.74
						N	13.73	13.64
IV*b*	CH_3	CH_3	87	170–172° [c]	$C_{11}H_{10}N_2OS$	C	60.55	60.72
						H	4.59	4.75
						N	12.84	12.99
IV*c*	CH_3	OCH_3	66	53–55°	$C_{11}H_{10}N_2O_2S$	C	56.41	56.60
						H	4.27	4.39
						N	11.97	11.81
IV*d*	CH_3	Br	71	82–84°	$C_{10}H_7BrN_2OS$	C	42.40	42.35
						H	2.47	2.65
						N	9.89	9.72
IV*e*	CH_3	Cl	64	55–57°	$C_{10}H_7ClN_2OS$	C	50.31	50.50
						H	2.94	2.75
						N	11.74	11.86
IV*f*	C_6H_5	H	66	130–132° [c]	$C_{15}H_{10}N_2OS$	C	67.67	67.48
						H	3.76	3.89
						N	10.53	10.65
IV*g*	C_6H_5	CH_3	68	88–90°	$C_{16}H_{12}N_2OS$	C	68.57	68.71
						H	4.29	4.12
						N	10.0	10.15
IV*h*	C_6H_5	Cl	50	137–139°	$C_{15}H_9ClN_2OS$	C	59.90	59.98
						H	2.99	3.15
						N	9.32	9.51

[a] IR, NMR, and mass spectra of all compounds were as expected. [b] Unless otherwise indicated, the recrystallization solvent was ether. [c] The boiling point was obtained at 4 mm Hg.

Table II—(4-Substituted-1,2,3-thiadiazol-5-yl)arylcarbinols [a]

Compound	R	R′	Yield, %	Melting Point [b]	Formula	Analysis, %	Calc.	Found
VI*a*	CH_3	H	90	94–96°	$C_{10}H_{10}N_2OS$	C	58.25	58.44
						H	4.85	4.98
						N	13.59	13.74
VI*b*	CH_3	CH_3	84	113–115°	$C_{11}H_{12}N_2OS$	C	60.00	59.85
						H	5.45	5.63
						N	12.73	12.91
VI*c*	CH_3	OCH_3	96	111–113°	$C_{11}H_{12}N_2O_2S$	C	55.93	55.98
						H	5.08	5.24
						N	11.86	11.98
VI*d*	CH_3	Br	72	102–104°	$C_{10}H_9BrN_2OS$	C	42.11	42.29
						H	3.16	3.28
						N	9.82	9.67
VI*e*	CH_3	Cl	86	108–110°	$C_{10}H_9ClN_2OS$	C	49.90	49.75
						H	3.74	3.61
						N	11.64	11.46
VI*f*	C_6H_5	H	91	58–60° [c]	$C_{15}H_{12}N_2OS$	C	67.16	67.02
						H	4.48	4.29
						N	10.45	10.31
VI*g*	C_6H_5	CH_3	86	63–64° [c]	$C_{16}H_{14}N_2OS$	C	68.09	68.22
						H	4.96	4.78
						N	9.93	9.75
VI*h*	C_6H_5	Cl	94	86–88° [c]	$C_{15}H_{11}ClN_2OS$	C	59.50	59.28
						H	3.64	3.82
						N	9.26	9.42

[a] IR, NMR, and mass spectra of all compounds were as expected. [b] Unless otherwise indicated, the recrystallization solvent was ether. [c] This compound was crystallized from petroleum ether.

The physical data for the intermediates IV, VI, and VIII and the final compound IX are summarized in Tables I–IV.

Pharmacological Assay—The compounds listed in Table IV were screened for antihistaminic and anticholinergic activities. Isolated guinea pig ileum was prepared according to the method of Magnus (9) and suspended in a 10-ml bath filled with Tyrode solution, which was aerated at 36°. The isotonic concentrations were recorded through an isotonic transducer on a polygraph[1]. The pA_2 values were determined by a literature method (10).

Histamine and acetylcholine were used as agonists, and promethazine was tested for comparison. The results are presented in Table V.

Compounds IX*e*–IX*h* were the most potent antihistamines. However, only IX*e* and IX*h* displayed moderate anticholinergic activity. The LD_{50} value of IX*h* in mice, estimated by the moving average method (11), was 155.5 (141.2–171.4) mg/kg.

[1] Narco Biosystems.

EXPERIMENTAL[2]

4-Phenyl-1,2,3-thiadiazole-5-carboxylic Acid (III, R = C_6H_5)—A solution of ethyl 4-phenyl-1,2,3-thiadiazole-5-carboxylate (23.4 g, 0.1 mole) and sodium hydroxide (4.4 g, 1.1 moles) in ethanol–water (150 ml) was refluxed for 2 hr. The solvent was evaporated, and the residue was crystallized from ethanol to give 15.5 g (75% yield) of III, mp 152–153°.

Anal.—Calc. for $C_9H_6N_2O_2S$: C, 52.43; H, 2.91; N, 13.59. Found: C, 52.61; H, 2.74; N, 13.76.

Phenyl 4-Phenyl-1,2,3-thiadiazol-5-yl Ketone (IV*f*)—To a solution of phenyllithium (0.1 mole) in 150 ml of dry ether (12) was added III (R = C_6H_5, 4.12 g, 0.02 mole) at 0°. The mixture was stirred for 36 hr at room

[2] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded using a Perkin-Elmer 267 spectrometer. Mass spectra were recorded on a Varian Mat III instrument. NMR spectra were determined with a Varian T-60A instrument.

Table III—5-(α-Chlorobenzyl)-4-methyl-1,2,3-thiadiazoles

Compound	R	R′	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
VIII*a*	CH_3	H	76	138–140° [a]	$C_{10}H_9ClN_2S$	C	53.45	53.28
						H	4.01	4.18
						N	12.47	12.65
VIII*b*	CH_3	CH_3	60	144–146° [a]	$C_{11}H_{11}ClN_2S$	C	55.35	55.52
						H	4.61	4.80
						N	11.74	11.92
VIII*d*	CH_3	Br	98	Oil	$C_{10}H_8BrClN_2S$	C	39.54	39.72
						H	2.64	2.46
						N	9.23	9.05
VIII*e*	CH_3	Cl	98	140–142° [a]	$C_{10}H_8Cl_2N_2S$	C	46.33	46.48
						H	3.09	3.25
						N	10.81	10.96
VIII*f*	C_6H_5	H	86	104–106° [b]	$C_{15}H_{11}ClN_2S$	C	62.83	62.95
						H	3.84	3.68
						N	9.77	9.59
VIII*g*	C_6H_5	CH_3	94	Oil	$C_{16}H_{13}ClN_2S$	C	63.89	63.71
						H	4.33	4.18
						N	9.32	9.48
VIII*h*	C_6H_5	Cl	95	56–57° [c]	$C_{15}H_{10}Cl_2N_2S$	C	56.07	56.19
						H	3.12	3.24
						N	8.72	8.91

[a] The boiling point was obtained at 4 mm Hg. [b] This compound was crystallized from petroleum ether. [c] This compound was crystallized from ether.

Table IV—[(4-Substituted-1,2,3-thiadiazol-5-yl)arylmethyl]-4-methylpiperazines

Compound	R	R′	Yield, %	Melting Point[a]	Formula	Analysis, %	Calc.	Found
IX*a*	CH_3	H	62	217–218°	$C_{15}H_{20}N_4S$	C	62.50	62.68
						H	6.94	6.99
						N	19.44	19.62
IX*b*	CH_3	CH_3	65	152–155°	$C_{16}H_{22}N_4S$	C	63.58	63.74
						H	7.28	7.45
						N	18.54	18.72
IX*c*	CH_3	OCH_3	65	145–148°	$C_{16}H_{22}N_4OS$	C	60.38	60.19
						H	6.92	6.98
						N	17.61	17.43
IX*d*	CH_3	Br	62	156–160°	$C_{15}H_{19}BrN_4S$	C	49.05	49.22
						H	5.18	5.34
						N	15.26	15.08
IX*e*	CH_3	Cl	68	160–163°	$C_{15}H_{19}ClN_4S$	C	55.81	55.69
						H	5.89	5.95
						N	17.36	17.18
IX*f*	C_6H_5	H	75	226–230°	$C_{20}H_{22}N_4S$	C	68.57	68.74
						H	6.29	6.18
						N	16.0	16.18
IX*g*	C_6H_5	CH_3	70	251–255°	$C_{21}H_{24}N_4S$	C	69.23	69.18
						H	6.59	6.74
						N	15.38	15.24
IX*h*	C_6H_5	Cl	86	192–196°	$C_{20}H_{21}ClN_4S$	C	62.42	62.31
						H	5.46	5.29
						N	14.56	14.38

[a] All compounds were crystallized from absolute ethanol as the hydrochloride.

temperature under nitrogen, water was added, and the ether was evaporated. The residue was distilled to give 3.5 g (66% yield) of IV*f*, bp 130–132° (4 mm); IR (KBr): 1660 (C=O) cm^{-1}; mass spectrum: *m/z* (relative intensity) 266 (M^+, 45), 208 (45), 207 (68), 195 (41), 194 (64), 167 (43), 99 (61), 56 (100), and 44 (23).

Anal.—Calc. for $C_{15}H_{10}N_2OS$: C, 67.67; H, 3.76; N, 10.53. Found: C, 67.48; H, 3.89; N, 10.65.

p-Chlorophenyl 4-Phenyl-1,2,3-thiadiazol-5-yl Ketone (IV*h*)—To a stirring solution of *p*-chlorophenyllithium, prepared from *p*-chlorobromobenzene (9.575 g, 0.05 mole) and *n*-butyllithium (32 ml of 10% solution in hexane, 0.05 mole) according to the literature (8), was added III (R = C_6H_5, 2.06 g, 0.01 mole). The mixture was stirred overnight under nitrogen at room temperature. Ice water was added to the mixture, followed by extraction with ether. The ether was dried, filtered, and evaporated. The residue was purified by TLC (silica gel, chloroform–petroleum ether, 50:50) and crystallized from ether to give 10.5 g (50% yield) of IV*h*, mp 137–139°; IR (KBr): 1650 (C=O) cm^{-1}.

Anal.—Calc. for $C_{15}H_9ClN_2OS$: C, 59.90; H, 2.99; N, 9.32. Found: C, 59.98; H, 3.15; N, 9.51.

Compound IV*g* was prepared similarly.

4-Methyl-1,2,3-thiadiazol-5-carboxyl Chloride (V, R = CH_3)—A mixture of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (14.4 g, 0.1 mole) (13) and thionyl chloride (40 ml) was refluxed for 4 hr. The solvent was evaporated, and the residue was distilled to give 15.5 g (95% yield) of V (R = CH_3), bp 102–104° (20 mm).

Anal.—Calc. for $C_4H_3ClN_2OS$: C, 29.54; H, 1.85; N, 17.23. Found: C, 29.72; H, 1.98; N, 17.41.

Phenyl 4-Methyl-1,2,3-thiadiazol-5-yl Ketone (IV*a*)—A stirring mixture of V (R = CH_3, 3.25 g, 0.02 mole) and aluminum chloride (5.34 g, 0.04 mole) in 30 ml of dry benzene was refluxed for 8 hr. After cooling, the complex was decomposed with ice water and dilute hydrochloric acid. The organic layer was separated, and the mother liquor was extracted once more with benzene. The combined organic solvent was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried, filtered, and evaporated, and the residue was distilled to give 2.9 g (71% yield) of IV*a*, bp 180–182° (4 mm); IR (KBr): 1660 (C=O) cm^{-1}; NMR ($CDCl_3$): 8.0–7.53 (m, 5H, aromatic) and 2.8 (s, 3H, CH_3) ppm; mass spectrum: *m/z* (relative intensity) 204 (M^+, 2), 186 (38), 105 (28), and 77 (100).

Anal.—Calc. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.73. Found: C, 58.66; H, 3.74; N, 13.64.

Compounds IV*b*–IV*e* were prepared similarly at the boiling point of the respective solvent, except IV*c* which was prepared at 100° (Table I).

(4-Methyl-1,2,3-thiadiazol-5-yl)phenylcarbinol (VI*a*)—To a stirring solution of IV*a* (2.04 g, 0.01 mole) in 50 ml of methanol was added

Table V—Antihistaminic and Anticholinergic Activities of 1,2,3-Thiadiazole Derivatives

Compound	pA_2 Values: Antihistaminic Activity	pA_2 Values: Anticholinergic Activity
IX*a*	5.37	NT[a]
IX*b*	4.59	NT[a]
IX*c*	5.02	—[b]
IX*d*	5.22	—[b]
IX*e*	6.69	4.94
IX*f*	6.92	—[b]
IX*g*	6.67	—[b]
IX*h*	7.72 ± 0.26 (5)	4.6
Promethazine	10.47	6.9

[a] Not tested. [b] Inactive up to the concentration of 2×10^{-5} *M*.

sodium borohydride (0.38 g, 0.01 mole). The mixture was stirred 30 min. Water (100 ml) was added to the mixture, which then was extracted with chloroform (3 × 100 ml). The chloroform was dried, filtered, and evaporated, and the residue was crystallized from ether to give 1.85 g (90% yield) of VI*a*, mp 94–96°; IR (KBr): 3250 (OH) cm^{-1}; NMR ($CDCl_3$): 7.36 (s, 5H, C_6H_5), 6.11 (s, 1H, HCO), 3.56 (broad s, 1H, OH), and 2.41 (s, 3H, CH_3) ppm; mass spectrum: *m/z* (relative intensity) 206 (M^+, 1), 177 (22), 107 (100), 79 (99), 77 (99), 51 (66), and 45 (65).

Anal.—Calc. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.44; H. 4.98; N, 13.74.

Compounds VI*b*–VI*h* were prepared similarly (Table II).

5-(α-Chlorobenzyl)-4-methyl-1,2,3-thiadiazole (VIIIa)—A solution of VI*a* (2.06 g, 0.01 mole) and thionyl chloride (4 ml) in 120 ml of dry benzene was stirred overnight. The mixture was filtered, and the solvent was evaporated. The residue was distilled to give 1.70 g (76% yield) of VIII*a*, bp 138–140° (4 mm); NMR ($CDCl_3$): 7.40 (s, 5H, C_6H_5), 6.25 (s, 1H, HCCl), and 2.55 (s, 3H, CH_3) ppm; mass spectrum: *m/z* (relative intensity) 224 (M^+, 2), 195 (56), 161 (56), 125 (68), and 59 (100).

Anal.—Calc. for $C_{10}H_9ClN_2S$: C, 53.45; H, 4.01; N, 12.47. Found: C, 53.28; H, 4.18; N, 12.65.

Compounds VIII*b*–VIII*h* were prepared similarly (Table III).

1-[(4-Methyl-1,2,3-thiadiazol-5-yl)phenylmethyl]-4-methylpiperazine (IXa)—A solution of VIII*a* (2.245 g, 0.01 mole) and *N*-methylpiperazine (2.0 g, 0.02 mole) in 30 ml of pyridine was refluxed under nitrogen overnight. The solvent was evaporated. Water (15 ml) was added to the residue and then extracted with ether. The ether was evaporated, and the residue was purified by TLC (chloroform–methanol, 95:5) to give 1.73 g (60% yield) of IX*a*; NMR ($CDCl_3$): 7.33 (s, 5H, C_6H_5), 4.7 (s, 1H, HCN), 2.56 (s, 3H, CH_3), 2.46 (s, 8H, CH_2N), and 2.3 (s, 3H, CH_3) ppm.

Anal.—Calc. for $C_{15}H_{20}N_4S$: C, 62.50; H, 6.94; N, 19.44. Found: C, 62.68; H, 6.99; N, 19.62.

This compound was crystallized as the hydrochloride (mp 217–218°) from absolute ethanol.

Compounds IX*b* and IX*d*–IX*h* were prepared similarly (Table IV).

1-[(4-Methyl-1,2,3-thiadiazol-5-yl)-*p*-methoxyphenylmethyl]-4-methylpiperazine (IXc)—A solution of VI*c* (2.36 g, 0.01 mole) and thionyl chloride (4 ml) in 120 ml of benzene was stirred overnight. The solvent was evaporated under reduced pressure at 0° to give VII*c* as an oil; IR (KBr): 1250 and 1180 (SO_2) cm^{-1}; NMR ($CDCl_3$): 7.14 (q, 4H, aromatic), 6.26 (s, 1H, HCOSOCl), 3.8 (s, 3H, CH_3O), and 2.55 (s, 3H, CH_3) ppm. This compound was not purified further. To the residue were added pyridine (25 ml) and *N*-methylpiperazine (2 g, 0.02 mole). The mixture was refluxed under nitrogen and treated as was IX*a* to give 2.1 g (66% yield) of IX*c*; NMR ($CDCl_3$): 7.0 (q, 4H, aromatic), 4.65 (s, 1H, HCN), 3.73 (s, 3H, CH_3O), 2.53 (s, 3H, CH_3), 2.43 (s, 8H, CH_2N), and 2.23 (s, 3H, CH_2N) ppm.

Anal.—Calc. for $C_{16}H_{22}N_4OS$: C, 60.38; H, 6.92; N, 17.61. Found: C, 60.19; H, 6.98; N, 17.43.

This compound was crystallized from absolute ethanol as the hydrochloride, mp 145–148°.

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ACKNOWLEDGMENTS

Supported by Grant 400-7-35/2 from the Ministry of Culture and Higher Education.