Chemistry of Heterocyclic Compounds, Vol. 37, No. 2, 2001

4-HYDROXY-2-QUINOLONES. 47*. SYNTHESIS AND DIURETIC ACTIVITY OF (2H-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDE-3-YL)METHYLAMIDES OF 1R-4-HYDROXY-2-OXOQUINOLINE-3-CARBOXYLIC ACIDS

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With the aim of investigating the relationship between chemical structure and biological activity we have synthesized and studied the effect of (2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)methylamides of 1-R-4-hydroxy-2-oxoquinoline-3-carboxylic acids on kidney urinary output.

Keywords: benzothiadiazine, diuretics, carbostyril, 4-hydroxy-2-quinolone.

Following the introduction into medicinal usage of chlorothiazide (the first representative of the benzothiadiazine diuretics) and with its structural analog hypothiazide in mind, we have carried out a search for novel and more active compounds through a broad investigation of changes to the parent structures. In this way we have revealed the influence of the specific substitutents both in the benzene and in the heterocyclic ring on the strength of the urinary effect. In particular, the highest diuretic activity was found for benzothiadiazines which have alkyl or aralkyl substituents at position 3 [2]. Bearing this in mind, and with the aim of establishing a structure–activity relationship, we have synthesized (2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)methylamides of 1-R-4-hydroxy-2-oxoquinoline-3-carboxylic acids (**1**) as analogs of 1-R-3-(2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-4-hydroxy-2-oxoquinolines [3] and studied their effect on kidney urinary output.

(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)methylamine (**2**) was prepared by acylation of *o*-aminobenzenesulfonamide (**3**) by phthaloylaminoacetyl chloride (**4**) and subsequent cyclization of anilide **5** using an aqueous solution of potassium carbonate to give benzothiadiazine (**6**). Hydrazinolysis [4] of the latter in the final step gives amine **2**. Under thermolysis conditions (170-190°C) amine **2** readily reacts with ethyl esters of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids **7** to give the target amides **1** (Tables 1, 2).

* For Communication 46 see [1].

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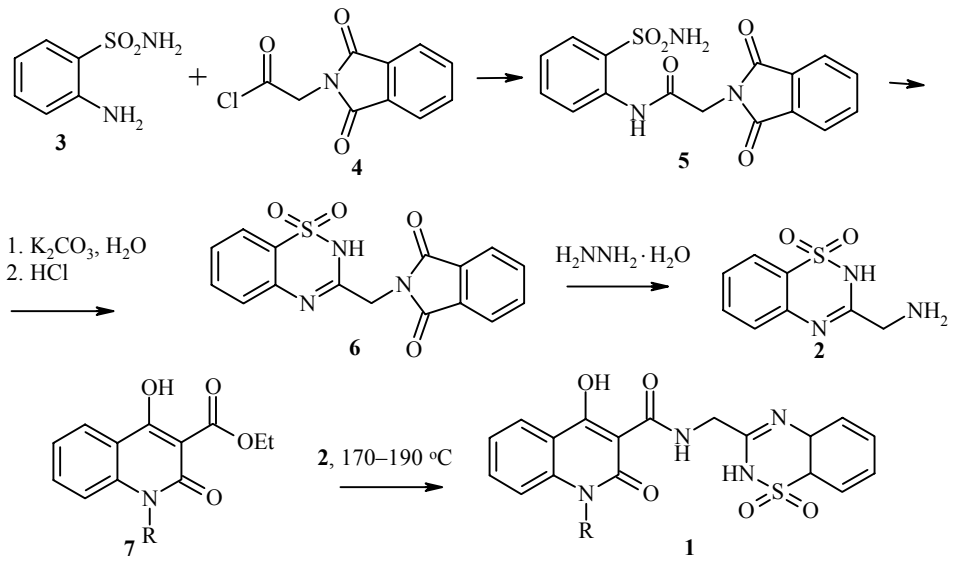
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 262-265, February, 2001. Original article submitted February 10, 1999.

0009-3122/01/3702-0237$25.00©2001 Plenum Publishing Corporation



1, 7 a R = Me; **b** R = Et; **c** R = $CH_2CH{=}CH_2$; **d** R = Pr; **e** R = Bu; **f** R = *i*-Bu; **g** R = C_5H_{11}; **h** R = C_6H_{13}; **i** R = C_7H_{15}

The effect of the synthesized compounds on diuresis in white rats was studied by the method proposed earlier [3]. 1-N-Methyl derivative **1a** was found to show antidiuretic activity (21% inhibition of diuresis when compared with control data).

Lengthening of the hydrocarbon chain in the N-alkyl substituent is accompanied by strengthening of the urinary effect, gradually approaching a maximum at (2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)methylamide of 1-hexyl-4-hydroxy-2-oxoquinoline-3-carboxylic acid (**1h**) whose activity approaches that of hypothiazide. As a whole, the comparative analysis of diuretic properties of amides **1a-i** and their structural analogs – 1-R-3-(2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)-4-hydroxy-2-oxoquinolines [3] – allows us to conclude that the introduction of methylaminocarbonyl bridge between the quinoline and benzothiadiazine rings in compounds **1** leads to a decrease in the diuretic activity.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (DMF–EtOH)	Yield, %
		C	H	N	S		
1a	$C_{19}H_{16}N_4O_5S$	55.41 / 55.33	3.84 / 3.91	13.66 / 13.58	7.68 / 7.77	279-281	84
1b	$C_{20}H_{18}N_4O_5S$	56.25 / 56.33	4.33 / 4.25	13.21 / 13.14	7.45 / 7.52	254-256	80
1c	$C_{21}H_{18}N_4O_5S$	57.44 / 57.53	4.20 / 4.14	12.71 / 12.78	7.37 / 7.31	242-244	78
1d	$C_{21}H_{20}N_4O_5S$	57.32 / 57.26	4.51 / 4.58	12.70 / 12.72	7.25 / 7.28	257-259	83
1e	$C_{22}H_{22}N_4O_5S$	58.07 / 58.14	4.96 / 4.88	12.25 / 12.33	7.13 / 7.05	228-230	75
1f	$C_{22}H_{22}N_4O_5S$	58.19 / 58.14	4.93 / 4.88	12.40 / 12.33	7.00 / 7.05	234-236	78
1g	$C_{23}H_{24}N_4O_5S$	58.90 / 58.96	5.23 / 5.16	11.99 / 11.96	6.76 / 6.84	229-231	71
1h	$C_{24}H_{26}N_4O_5S$	59.85 / 59.74	5.49 / 5.43	11.52 / 11.61	6.58 / 6.64	225-227	76
1i	$C_{25}H_{28}N_4O_5S$	60.55 / 60.47	5.60 / 5.68	11.33 / 11.28	6.54 / 6.46	189-191	75

TABLE 2. ^{1}H NMR Spectral Characteristics of (2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)methylamides of 1-R-4-Hydroxy-2-oxoquinoline-3-carboxylic Acids, ppm

Com-pound	OH (1H, s)	SO_2NH (1H, t)	CONH (1H, t)	H_{arom} (8H, m)	NCH_2 (2H, d)	R
1a	16.70	12.28	10.75	8.11-7.27	4.59	3.63 (3H, s, Me)
1b	16.68	12.22	10.75	8.26-7.29	4.57	4.33 (2H, quartet, CH_2); 1.25 (3H, t, Me)
1c	16.61	12.16	10.70	8.19-7.26	4.57	5.95 (1H, m, CH=); 5.17 (2H, d, NCH_2); 4.95 (2H, d, CH_2=)
1d	16.69	12.21	10.75	8.18-7.28	4.54	4.24 (2H, t, NCH_2); 1.65 (2H, m, $C\underline{H}_2$Me); 0.97 (3H, t, Me)
1e	16.72	12.26	10.75	8.19-7.27	4.55	4.28 (2H, t, NCH_2); 1.51 (4H, m, $(C\underline{H}_2)_2$Me); 0.94 (3H, t, Me)
1f	16.70	12.26	10.76	8.18-7.29	4.56	4.18 (2H, d, NCH_2); 2.14 (1H, m, $C\underline{H}Me_2$); 0.92 (6H, d, Me_2)
1g	16.74	12.21	10.74	8.16-7.28	4.56	4.26 (2H, t, NCH_2); 1.74 (2H, quintet, $NCH_2C\underline{H}_2$); 1.39 (4H, m, $(C\underline{H}_2)_2$Me); 0.88 (3H, t, Me)
1h	16.73	12.21	10.74	8.14-7.25	4.55	4.25 (2H, t, NCH_2); 1.76 (2H, quintet, $NCH_2C\underline{H}_2$); 1.32 (6H, m, $(C\underline{H}_2)_3$Me); 0.85 (3H, t, Me)
1i	16.71	12.26	10.76	8.17-7.28	4.55	4.24 (2H, t, NCH_2); 1.75 (2H, quintet, $NCH_2C\underline{H}_2$); 1.29 (8H, m, $(C\underline{H}_2)_4$Me); 0.85 (3H, t, Me)

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WP-100 SY instrument using DMSO-d_6 solvent and TMS as internal standard. The mass spectrum of amine **2** was recorded on a Finnigan MAT Incos 50 quadrupole spectrometer over the *m/z* range of 33-700 and electron impact ionization of 70 eV with direct introduction and heating rate of ~5°C / sec.

General Method for Preparing of (2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)methylamides of 1-R-4-Hydroxy-2-oxoquinoline-3-carboxylic Acids (1a-i). Mixture of (2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)methylamine **2** (2.11 g, 0.01 mol) and the corresponding ester **7** (0.01 mol) was held for 5-10 min on a metal bath at 170-190°C. The residue was dissolved in refluxing DMF (20 ml), filtered, ethanol (50 ml) added, and the residue was left for several hours at room temperature. The precipitated amide **1** was filtered, washed with alcohol, and dried.

(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)methylamine (2). Triethylamine (14 ml, 0.1 mol) was added to solution of *o*-aminobenzenesulfonamide (17.22 g, 0.1 mol) in acetone (100 ml). Phthaloylaminoacetyl chloride (22.36 g, 0.1 mol) was added under cooling and stirring. After 5 h the reaction mixture was diluted with water and acidified with HCl to pH 4. The precipitated anilide 5 was filtered, transferred to a flask, solution of K_2CO_3 (15 g) in water (100 ml) added, the product was stirred until the precipitate dissolved, and then acidified with HCl to pH 4. The precipitated benzothiadiazine **6** was filtered off, washed with water, and dried to give 24.0 g (81%). Benzothiadiazine **6** was suspended in water (50 ml), hydrazine hydrate (8.5 ml) was added, and

the mixture was refluxed for 3 h. After cooling it was acidified with HCl to pH 3 and filtered. The filtrate was neutralized with an aqueous solution of NaOH and left for 10-12 h at 8-10°C. The precipitate was filtered off, washed with cold water, and dried. Yield of amine **2** 10.12 g (48% calculated on the starting *o*-aminobenzenesulfonamide). Mp 258-260°C (ethanol). Mass spectrum, *m/z* (I_{rel}, %): 211 (100) $[M]^+$, 183 (31), 155 (17), 146 (60), 131 (27), 118 (86), 91 (90), 64 (78), 52 (31). Found, %: C 45.57; H 4.18; N 19.92; S 15.13. $C_8H_9N_3O_2S$. Calculated, %: C 45.49; H 4.29; N 19.89; S 15.18.

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