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4-HYDROXY-2-QUINOLONES. 42*. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-R-2-OXO-3-(2H-1,2,4-BENZOTHIADIAZINE-1,1-DIOXID-3-YL)-4-HYDROXYQUINOLINES

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A preparative method for the synthesis of 1-R-2-oxo-3-(2H-1,2,4-benzothiadiazine-1,1-dioxid-3-yl)-4-hydroxyquinolines has been developed. The diuretic and antitubercular activity of the obtained compounds have been studied.

Keywords: benzothiadiazine, diuretic, carbostyryl, 4-hydroxy-2-quinolone.

Amongst the multitude of classes of organic compounds in which substances show diuretic activity, special attention is merited by benzothiadiazine derivatives since one of their representatives (hypothiazide), along with furosemide has a high relative importance in a listing of the international market for current diuretics [2]. A marked diuretic action is also noted for derivatives of 2-oxo-4-hydroxyquinoline [3].

The aim of this work is the synthesis of 1-R-2-oxo-3-(2H-1,2,4-benzothiadiazine-1,1-dioxid-3-yl)-4-hydroxyquinolines (**1**) and a study of their biological behavior.

Synthesis of the starting 2-sulfamylanilides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids (**2**) was carried out by thermolysis of the corresponding ethyl esters **3** with an equimolar amount of *o*-aminobenzenesulfonamide (Table 1). Like the 2-carbamylanilides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids [4], these compounds readily cyclize in high yield to the corresponding 1-R-2-oxo-3-(2H-1,2,4-benzothiadiazine-1,1-dioxid-3-yl)-4-hydroxyquinolines (**1a-k**) in aqueous basic solution (Table 2). At the same time the N-alkylsulfamoyl derivatives **2** (R^1 = Alk) are not susceptible to heterocyclization under the same conditions. Attempts to use polyphosphoric acid (PPA) or phosphorus pentoxide as condensing agents also did not give positive results and unexpectedly gave 1-R-2-oxo-3H-4-hydroxyquinolines (**4**), the structure of which was confirmed by an alternative synthesis *via* thermolysis of 1-R-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (**5**). Evidently, anilides **2** are deacetylated under these conditions and quinoline-3-carboxylic acids formed in this way in acid medium are (as is known [5]) quite readily decarboxylated, thus bringing about the result we obtained.

Analysis of the pharmacological investigation has shown that the sulfamylanilides **2** have almost no effect upon the urinary function of the kidneys while compounds with a closed benzothiadiazine ring are characterized by marked diuretic activity. In the case of a number of examples (e.g. compound **1c**) this exceeds the activity of

* For Communication 41 see [1].

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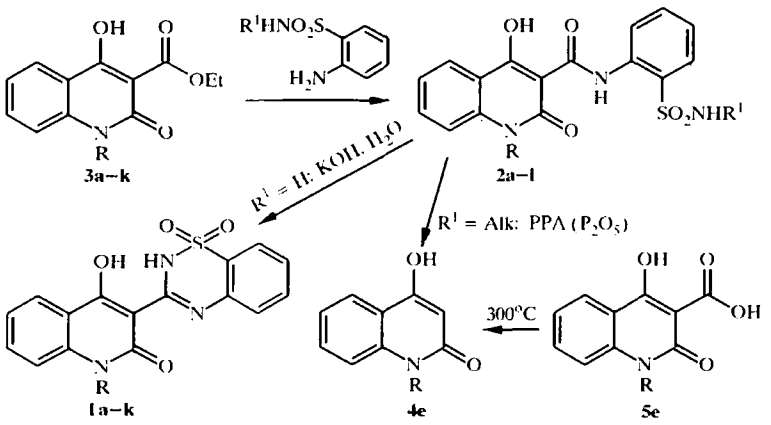

1–5 a R = H; b R = CH_3; c R = C_2H_5; d R = $CH_2CH=CH_2$; e R = C_3H_7; f R = C_4H_9;

g R = *i*-C_4H_9; h R = C_5H_{11}; i R = *i*-C_5H_{11}; j R = C_6H_{13}; k R = C_7H_{15};

2a–k R^1 = H; 2l R^1 = CH_3, R = C_3H_7

hypothiazide by a factor of two. Upon introduction of alkyl substituents the diuretic activity of benzothiadiazinequinolines **1** is gradually increased, reaching a maximum at the N-ethyl derivative **1c**. With further increase of the hydrocarbon chain of the alkyl substituent at position 1 in the quinolone ring, the activity decreases and virtually disappears at the N-heptyl substituent derivative **1k**.

The high antimicrobial activity of 2-oxo-4-hydroxyquinoline derivatives [7, 8] serves as a theoretical basis for studying the antitubercular activity of the compounds synthesized by us. Investigations were carried out by known methods [9, 10] at the National Institute of Allergic and Infectious Diseases, Ministry of Public Health, USA (contract 01-AI-45246). They showed that neither the sulfamylanilides **2** nor the benzothiadiazinequinolines **1**, at concentrations of 12.5 micrograms / ml, showed antimicrobial activity towards *Mycobacterium tuberculosis* H37Rv ATCC 27294.

TABLE 1. 2-Sulfamylanilides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (aqueous DMF)	Yield, %
		C	H	N	S		
2a	$C_{16}H_{13}N_3O_5S$	53.63 / 53.48	3.74 / 3.65	11.55 / 11.69	8.81 / 8.92	257-259	91
2b	$C_{17}H_{15}N_3O_5S$	54.50 / 54.69	4.00 / 4.05	11.27 / 11.25	8.68 / 8.59	214-216	87
2c	$C_{18}H_{17}N_3O_5S_2$	55.96 / 55.81	4.49 / 4.42	10.72 / 10.85	8.20 / 8.28	233-235	90
2d	$C_{19}H_{17}N_3O_5S$	57.00 / 57.13	4.42 / 4.29	10.43 / 10.52	8.18 / 8.03	192-194	83
2e	$C_{19}H_{19}N_3O_5S$	56.68 / 56.85	4.80 / 4.77	10.33 / 10.47	8.09 / 7.99	195-197	86
2f	$C_{20}H_{21}N_3O_5S$	57.94 / 57.82	5.01 / 5.09	10.24 / 10.11	7.85 / 7.72	183-185	78
2g	$C_{20}H_{21}N_3O_5S$	57.90 / 57.82	5.13 / 5.09	10.19 / 10.11	7.79 / 7.72	217-219	85
2h	$C_{21}H_{23}N_3O_5S$	58.60 / 58.73	5.34 / 5.40	9.89 / 9.78	7.50 / 7.47	196-198	82
2i	$C_{21}H_{23}N_3O_5S$	58.78 / 58.73	5.56 / 5.40	9.67 / 9.78	7.33 / 7.47	168-170	88
2j	$C_{22}H_{25}N_3O_5S$	59.33 / 59.58	5.79 / 5.68	9.28 / 9.47	7.20 / 7.23	191-193	87
2k	$C_{23}H_{27}N_3O_5S$	60.44 / 60.38	5.80 / 5.95	9.25 / 9.18	7.13 / 7.01	170-172	83

TABLE 2. 1-R-2-Oxo-3-(2H-1,2,4-benzothiadiazine-1,1-dioxid-3-yl)-4-hydroxyquinolines

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (aqueous DMF)	Yield, %
		C	H	N	S		
1a	$C_{16}H_{11}N_3O_4S$	56.21 / 56.30	3.34 / 3.25	12.09 / 12.31	9.44 / 9.39	> 330	94
1b	$C_{17}H_{13}N_3O_4S$	57.64 / 57.46	3.78 / 3.69	11.80 / 11.82	9.11 / 9.02	289-291	96
1c	$C_{18}H_{15}N_3O_4S$	58.47 / 58.53	4.17 / 4.09	11.30 / 11.38	8.59 / 8.68	274-276	82
1d	$C_{19}H_{15}N_3O_4S$	59.76 / 59.83	3.83 / 3.96	11.14 / 11.02	8.38 / 8.41	243-245	87
1e	$C_{19}H_{17}N_3O_4S$	59.68 / 59.52	4.37 / 4.47	10.89 / 10.96	8.33 / 8.36	254-256	90
1f	$C_{20}H_{19}N_3O_4S$	60.40 / 60.44	4.81 / 4.82	10.62 / 10.57	8.05 / 8.07	234-236	81
1g	$C_{20}H_{19}N_3O_4S$	60.49 / 60.44	4.77 / 4.82	10.64 / 10.57	8.00 / 8.07	240-242	85
1h	$C_{21}H_{21}N_3O_4S$	61.19 / 61.30	5.11 / 5.14	10.32 / 10.21	7.85 / 7.79	223-225	80
1i	$C_{21}H_{21}N_3O_4S$	61.22 / 61.30	5.18 / 5.14	10.20 / 10.21	7.76 / 7.79	202-204	76
1j	$C_{22}H_{23}N_3O_4S$	62.18 / 62.10	5.44 / 5.45	9.82 / 9.88	7.64 / 7.54	197-199	74
1k	$C_{23}H_{25}N_3O_4S$	62.80 / 62.85	5.80 / 5.73	9.60 / 9.56	7.22 / 7.29	179-181	81

TABLE 3. ^{1}H NMR Spectra of 2-Sulfamylanilides of 1R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids (δ, ppm)

Compound	OH (1H, s)	NH (1H, s)	H_{arom} + SO_2NH_2 (10H, m)	R
2a	14.60	12.71	8.21-7.24	11.81 (1H, s, NH)
2b	14.49	12.58	8.19-7.21	3.72 (3H, s, CH_3)
2c	16.43	12.60	8.20-7.30	4.38 (2H, q, NCH_2); 1.31 (3H, t, CH_3)
2d	16.50	12.52	8.18-7.23	6.00 (1H, m, CH=); 5.21 (2H, d, NCH_2); 4.09 (2H, d, CH_2=)
2e	14.49	12.55	8.27-7.21	4.32 (2H, t, NCH_2); 1.76 (2H, m, CH_2CH_3); 1.07 (3H, t, CH_3)
2f	14.51	12.58	8.22-7.24	4.34 (2H, t, NCH_2); 1.73 (2H, quintet, CH_2CH_2); 1.50 (2H, m, CH_2CH_3); 1.01 (3H, t, CH_3)
2g	14.54	12.59	8.23-7.25	4.22 (2H, t, NCH_2); 2.24 (1H, m, CH); 0.99 (6H, d, $2CH_3$)
2h	14.50	12.58	8.19-7.20	4.33 (2H, t, NCH_2); 1.71 (2H, quintet, NCH_2CH_2); 1.43 (4H, m, $(CH_2)_2CH_3$); 0.95 (3H, t, CH_3)
2i	14.58	12.60	8.21-7.23	4.24 (2H, t, NCH_2); 1.72 (1H, m, CH); 1.50 (2H, q, NCH_2CH_2); 0.97 (6H, d, $2CH_3$)
2j	14.55	12.59	8.20-7.24	4.32 (2H, t, NCH_2); 1.70 (2H, quintet, NCH_2CH_2); 1.42 (6H, m, $(CH_2)_3CH_3$); 0.99 (3H, t, CH_3)
2k	14.52	12.56	8.21-7.22	4.31 (2H, t, NCH_2); 1.73 (2H, quintet, NCH_2CH_2); 1.40 (8H, m, $(CH_2)_4CH_3$); 0.98 (3H, t, CH_3)

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker AC 300 instrument in DMSO-d_6 solutions using TMS as internal standard. Ethyl esters of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids **3** and 1-propyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (**5e**) were prepared by the method [11].

TABLE 4. ^{1}H NMR Spectra of Benzothiadizinequinolines (δ, ppm)

Compound	OH (1H, s)	NH (1H, s)	H_{arom} (8H, m)	R
1a	15.23	14.33	8.11-7.17	11.91 (1H, s, NH)
1b	15.18	14.32	8.24-7.34	3.71 (3H, s, CH_3)
1c	15.12	14.35	8.20-7.18	4.34 (2H, q, NCH_2); 1.26 (3H, t, CH_3)
1d	15.20	14.23	8.22-7.29	6.06 (1H, m, CH=); 5.19 (2H, d, NCH_2); 4.96 (2H, d, CH_2=)
1e	15.29	14.36	8.24-7.27	4.27 (2H, t, NCH_2); 1.70 (2H, m, CH_2CH_3); 0.99 (3H, t, CH_3)
1f	15.18	14.26	8.21-7.39	4.34 (2H, t, NCH_2); 1.70 (2H, quintet, NCH_2CH_2); 1.48 (2H, m, CH_2CH_3); 0.97 (3H, t, CH_3)
1g	15.27	14.35	8.25-7.30	4.21 (2H, t, NCH_2); 2.21 (1H, m, CH); 0.94 (6H, d, $2CH_3$)
1h	15.19	14.31	8.22-7.39	4.33 (2H, t, NCH_2); 1.70 (2H, q, NCH_2CH_2); 1.41 (4H, m, $(CH_2)_2CH_3$); 0.90 (3H, t, CH_3)
1i	15.24	14.33	8.24-7.40	4.25 (2H, t, NCH_2); 1.73 (1H, m, CH); 1.48 (2H, q, NCH_2CH_2); 0.93 (6H, d, $2CH_3$)
1j	15.25	14.31	8.21-7.38	4.34 (2H, t, NCH_2); 1.71 (2H, q, NCH_2CH_2); 1.49-1.23 (6H, m, $(CH_2)_3CH_3$); 0.94 (3H, t, CH_3)
1k	15.24	14.30	8.22-7.34	4.33 (2H, t, NCH_2); 1.69 (2H, q, NCH_2CH_2); 1.40 (4H, m, $N(CH_2)_2CH_2CH_2$); 1.28 (4H, s, $(CH_2)_2CH_3$); 0.87 (3H, t, CH_3)

2-Sulfamylanilides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids (2a-k). (General Method). A mixture of the corresponding ethyl ester of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acid **3** (0.01 mol) and 2-aminobenzenesulfonamide (1.72 g, 0.01 mol) was vigorously stirred and held on a metal bath at 180-190°C for 10 min. The product was cooled, ethyl alcohol (20 ml) was added, and the product was stirred, the precipitate filtered off and washed on the filter funnel with alcohol. The residue was recrystallized from aqueous DMF.

2-Methylsulfonamidoanilide of 1-Propyl-2-oxo-4-hydroxyquinoline-3-carboxylic Acid (2l) was obtained similarly. Yield 87%; mp 167-169°C (aqueous DMF). ^{1}H NMR spectrum: 16.42 (1H, s, OH); 12.60 (1H, s, CONH); 8.21-7.28 (9H, m, H_{arom} + SO_2NH); 4.23 (2H, t, NCH_2); 2.45 (3H, d, NCH_3); 1.66 (2H, m, NCH_2CH_2); 0.98 ppm (3H, t, CH_3). Found, %: C 57.73; H 5.19; N 10.00; S 7.88. $C_{20}H_{21}N_3O_5S$. Calculated, %: C 57.82; H 5.09; N 10.11; S 7.72.

1-R-2-Oxo-3-(2H,-1,2,4-benzothiadiazine-1,1-dioxid-3-yl)-4-hydroxyquinolines (1a-k) (General Method). A mixture of 2-sulfamylanilide **2** (0.01 mol) and an aqueous solution of KOH (10%, 100 ml) was refluxed for 5 h (in the case of the lipophilic anilides **2** (R = C_4 to C_7, ethanol (20-30 ml) had been added to the reaction mixture). After cooling it was acidified with HCl to pH 3 and the precipitated benzothiadiazinequinolone **1** was filtered off, washed with water, and dried.

1-Propyl-2-oxo-4-hydroxyquinoline (4e). A. A mixture of 2-methylsulfonamidoanilide **2l** (4.15 g, 0.01 mol) and PPA (20 g) was held at 100-105°C for 2 h. After cooling, ice and water (200 ml) were added to the reaction mixture. The product was stirred vigorously and Na_2CO_3 was added to pH 5. The precipitate was filtered off, washed with water, and dried. Yield 1.03 g (51%); mp 221-222°C (diethyl ether). ^{1}H NMR spectrum: 11.34 (1H, s, OH); 7.90 (1H, d, 5-H); 7.61 (1H, t, 7-H); 7.46 (1H, d, 8-H); 7.20 (1H, t, 6-H); 5.88 (1H, s, 3-H); 4.11(2H, t, NCH_2); 1.57 (2H, m, NCH_2CH_2); 0.91 ppm (3H, t, CH_3). Found, %: C 70.84; H 6.58; N 6.72. $C_{12}H_{11}NO_2$. Calculated, %: C 70.92; H 6.45; N 6.89.

A similar product was obtained by treatment of 2-methylsulfonamidoanilide **2l** with P_2O_5 in carbon tetrachloride.

B. 1-Propyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (**5e**) (2.47 g, 0.01 mol) was held in a metal bath at 290-300°C until evolution of CO_2 ceased (~10 min). The product was cooled. Recrystallization from diethyl ether gave quinolone **4e** (1.83 g, 90%). A mixture of the samples prepared by the different methods did not show melting point depression. Their ^{1}H NMR spectra were identical.

Pharmacological Investigations of Compounds 1 and 2. The effect of the synthesized compounds on kidney urinary function was studied by the method of E. N. Berkhin [6] using non-pedigree, white, male rats of weight 260-300 g. Animals of the control group were prepared by aqueous dosing at a loading of 3 ml per 100 g. Rats of the other group were treated with the synthesized compounds in the form of a finely dispersed aqueous suspension stabilized by Tween-80 over 30 min by aqueous, oral loading. The dose was 50 mg/kg which corresponds to the ED_{50} of hypothiazide and the investigation was carried out in parallel and by comparison with the latter. The amount of urea produced by the animals during 4 h was used to measure the degree of urination.

REFERENCES

1. I. V. Ukrainets, S. G. Taran, L. V. Sidorenko, and O. V. Gorokhova, *Khim. Geterotsikl. Soedin.*, No. 11, 1542 (1997).
2. A. K. Matveeva, V. G. Voronin, I. D. Muravskaya, and M. G. Pleshakov, *Synthetic Diuretics: Medicinal Substances, Economics, Technology, and Preparative Aspects*, All Union Science and Technology Research Institute SÉNTI, Minmedbioprom USSR, Mosow (1988), Issue 2.
3. I. V. Ukrainets, P. A. Bezuglyi, O. V. Gorokhova, V. I. Treskach, V. A. Georgiyants, A. V. Turov, and I. L. Dikii, *Khim. Geterotsikl. Soedin.*, No. 1, 100 (1993).
4. I. V. Ukrainets, S. G. Taran, P. A. Bezuglyi, S. N. Kovalenko, A. V. Turov, and N. A. Marusenko, *Khim. Geterotsikl. Soedin.*, No. 9, 1223 (1993).
5. R. E. Lutz, G. Ashburn, J. A. Freek, R. N. Jordan, N. H. Leake, T. A. Martin, K. J. Rowlett, and R. J. Wilson, *J. Am. Chem. Soc.*, **68**, 1285 (1946).
6. E. B. Berkhin, *Khim. -Farm. Zh.*, **11**, No. 5, 3 (1977).
7. N. I. Filimonova, *Dis. Kand. Med. Nauk*, Khar'kov (1994).
8. O. V. Gorokhova, *Dis. Kand. Khim. Nauk*, Khar'kov (1993).
9. K. S. Collins and S. G. Franzblau, *Antimicr. Agents and Chemother.*, **41**, 1004 (1997).
10. C. B. Inderleid and M. Salfinger, in: *Manual of Clinical Microbiology*, Editors P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Yolken, ASM Press, Washington D. C. (1995), p. 1385.
11. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, *Khim. Geterotsikl. Soedin.*, No. 7, 958 (1994).