Brief Communications

Synthesis of (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides and their effect on blood coagulation system

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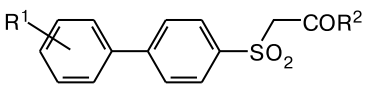
(4-Methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides were obtained by either amidation of the respective acid with anilines or the reaction of *N*-aryl-2-chloroacetamide with 4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfinic acid. Screening of the synthesized compounds revealed their hemostatic activity *in vitro*.

Key words: (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides, sulfones, hemostatic action.

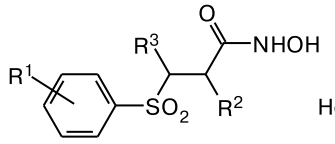
Functional derivatives of (Het)arylsulfonylalkanecarboxylic acids **I**—**III** are biologically active and interesting starting structures as regards the search for new biologically active substances.[1—6]



I

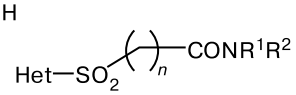
(antiviral activity, inhibitors of metalloprotein kinases)

R^2 = OH, NH_2, OMe



II

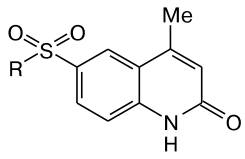
(antiinflammatory activity)



n = 1, 2 **III**

(inhibitors of protein kinases)

In continuation of investigations into the chemistry of sulfoquinoline derivatives, we synthesized (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides and studied their effect on the blood coagulation system. The choice of the subjects was caused by the fact that earlier[7] we have synthesized 6-alkylsulfonyl-4-methyl-1,2-dihydroquinolin-2-ones **IV** among which compounds that manifested hemostatic activity were found. In addition, some aryl sulfone derivatives possess anticoagulant activity.[8—10]



IV

R = Alk, Bn, All

In this connection it was reasonable to extend the range of radicals in sulfones **IV** by different substituents, in particular, acetanilide fragments.

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Sulfinic acid **1** was used as the starting compound for the synthesis of the target (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides (Scheme 1).[7] The corresponding ethyl (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetate (**2**) was obtained by the S-alkylation of its sulfinic fragment with ethyl chloroacetate in the system DMSO—K_2CO_3.

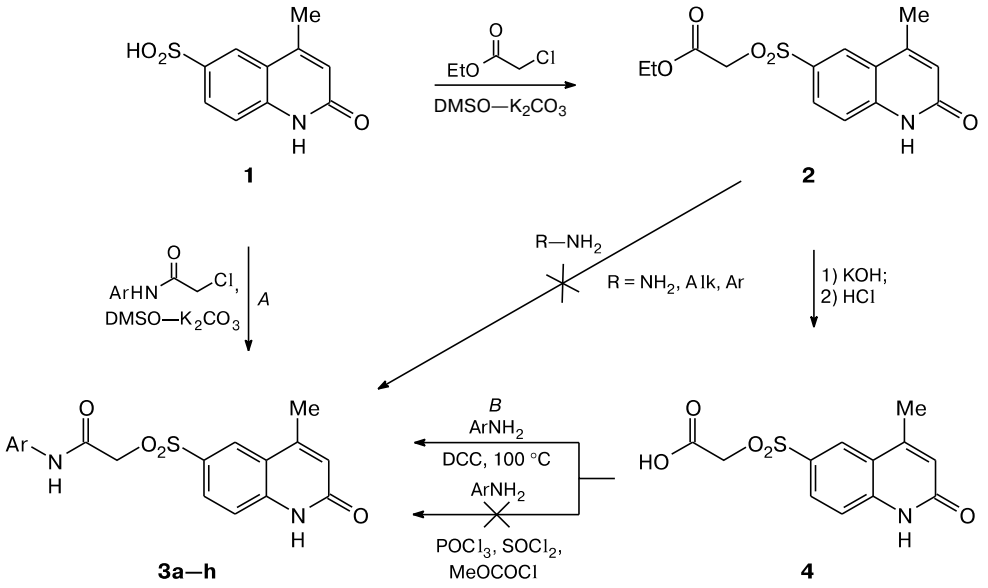
Esters of acetic acids with electron-withdrawing substituents are good acylating agents and easily react with diverse amines.[11] Therefore, we expected ethyl ester **2** to be easily converted to amides **3** due to the strong electron-withdrawing effect of the sulfonyl group. However, ester **2** proved to be completely inactive with respect to arylamines. We tried to accomplish this reaction by varying the temperature range (up to thermolysis), by using different solvents (alcohols, DMF, glacial acetic acid, pyridine, xylene, nitrobenzene), and by varying of the reactant ratio. In order to determine the reactivity of ethyl ester **2** with respect to other N-nucleophiles, we tried to carry out functionalization with ammonia, primary amines (butylamine, benzylamine), and hydrazine. In all cases, only the starting substance was isolated from the reaction mixture.

The target amides **3** were obtained from compound **1** by two alternative methods (see Scheme 1). First, the sulfinic fragment of compound **1** was directly S-alkylated with chloroacetanilides (method *A*). The second method was based on the use of (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetic acid (**4**) (method *B*) obtained by alkaline hydrolysis of ethyl ester **2**. It is of interest that acid **4**, like ester **2**, has low reactivity in coupling with arylamines. The attempts to obtain (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetyl chloride, as well as to accomplish the amidation in the presence of inorganic halogenating agents ($POCl_3$ or $SOCl_2$), unfortunately were unsuccessful. The method of mixed carboxylic acid anhydrides involving methyl chloroformate did not lead to the desired result. Therefore we used the other known methods of activation of the carboxylic group in sulfonylacetic acid **4**. The reactions with arylamines in the presence of dicyclohexylcarbodiimide (DCC) did not occur at low temperatures, but under more drastic conditions, *viz.*, on heating of the reaction mixture at 100—110 °C in DMF (method *B*), the target compounds **3a**—**h** were synthesized.

A comparison of the two methods of synthesis of (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides **3a—h** showed the method *B* to be preferable, because it allows preparation of the target products in higher yields and higher purity. According to the ^{1}H NMR spectroscopy data, an admixture of a quinolone ring alkylation by-product (5—15%) was present in the samples synthesized by the method *A*.

In vitro study of the effect of several obtained compounds on blood coagulation system showed that (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides **3** and ethyl ester **2** possess hemostatic activity. It is important that this effect for some of these compounds exceeds that of the reference agent, ε-aminocaproic acid, by 14—23%. Thus, the modification of alkyl substituents in sulfonyl group of the earlier studied sulfones **IV** with the acetic acid derivatives results in the enhancement of hemostatic activity.

Scheme 1



3: Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 2-$MeOC_6H_4$ (**d**), 4-$MeOC_6H_4$ (**e**), 2-ClC_6H_4 (**f**), 2-FC_6H_4 (**g**), 2,4-$Me_2C_6H_3$ (**h**)

Experimental

^{1}H NMR spectra of the synthesized compounds were recorded for solutions in DMSO-d_6 on a Varian Mercury VX-200 instrument (200 MHz) with Me_4Si as the internal standard.

Ethyl (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)-acetate (2). A mixture of 4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfinic acid (**1**) (2.23 g, 10 mmol) and K_2CO_3 (1.52 g, 11 mmol) was heated at 50—60 °C in DMSO (15 mL) until dissolution of sulfinic acid. Then ethyl chloroacetate (1.35 g, 11 mmol) was added, and the mixture was stirred for 1.5—2 h at 80 °C. The reaction mixture was diluted with water. The precipitate that obtained was filtered off and recrystallized from ethanol. The product (2.52 g, 81%) was obtained in a form of colorless crystals, m.p. 194—195 °C. Found (%): C, 54.25; H, 4.77;

Table 1. Yields, elemental analysis data, physicochemical and spectral characteristics of (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilides **3a—h**

Compound	Yield (%) (method)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)
3a	72 (*A*), 79 (*B*)	256—258	60.51 / 60.66	4.49 / 4.53	7.79 / 7.86	$C_{18}H_{16}N_2O_4S$	2.42 (s, 3 H, C(4)Me); 4.47 (s, 2 H, CH_2); 6.52 (s, 1 H, C(3)H); 7.06 (t, 1 H, Ar, *J* = 7.9); 7.29 (t, 2 H, Ar, *J* = 7.9); 7.40—7.50 (m, 3 H, C(8)H, Ar); 7.94 (dd, 1 H, C(7)H, *J* = 8.5, *J* = 1.8); 8.13 (d, 1 H, C(5)H, *J* = 1.8); 10.26 (s, 1 H, NHCO); 12.03 (s, 1 H, NH)
3b	74 (*A*), 81 (*B*)	253—255	61.50 / 61.61	4.82 / 7.90	7.69 / 7.56	$C_{19}H_{18}N_2O_4S$	2.43 (s, 3 H, C(4)Me); 2.10 (s, 3 H, C(2′)Me); 4.55 (s, 2 H, CH_2); 6.53 (s, 1 H, C(3)H); 7.01—7.31 (m, 4 H, Ar); 7.43 (d, 1 H, C(8)H, *J* = 8.6); 7.95 (dd, 1 H, C(7)H, *J* = 8.6, *J* = 1.8); 8.15 (d, 1 H, C(5)H, *J* = 1.8); 9.61 (s, 1 H, NHCO); 12.03 (s, 1 H, NH)
3c	68 (*A*), 79 (*B*)	240—242	61.55 / 61.61	7.87 / 7.90	7.61 / 7.56	$C_{19}H_{18}N_2O_4S$	2.27 (s, 3 H, C(3′)Me); 2.43 (s, 3 H, C(4)Me); 4.45 (s, 2 H, CH_2); 6.54 (s, 1 H, C(3)H); 6.88 (d, 1 H, Ar, *J* = 7.0); 7.06—7.36 (m, 3 H, Ar); 7.37 (d, 1 H, C(8)H, *J* = 8.8); 7.94 (dd, 1 H, C(7)H, *J* = 8.8, *J* = 1.8); 8.12 (d, 1 H, C(5)H, *J* = 1.8); 10.20 (s, 1 H, NHCO); 12.05 (s, 1 H, NH)
3d	60 (*A*), 67 (*B*)	242—244	58.99 / 59.06	4.74 / 4.70	7.40 / 7.25	$C_{19}H_{18}N_2O_5S$	2.39 (s, 3 H, C(4)Me); 3.74 (s, 3 H, C(2′)OMe); 4.69 (s, 2 H, CH_2); 6.52 (s, 1 H, C(3)H); 6.80—7.12 (m, 3 H, Ar); 7.43 (d, 1 H, C(8)H, *J* = 8.4); 7.83—7.97 (m, 2 H, C(7)H, Ar); 8.11 (d, 1 H, C(5)H, *J* = 1.8); 9.40 (s, 1 H, NHCO); 12.02 (s, 1 H, NH)
3e	64 (*A*), 71 (*B*)	283—285	58.92 / 59.06	7.66 / 7.70	7.45 / 7.25	$C_{19}H_{18}N_2O_5S$	2.44 (s, 3 H, C(4)Me); 3.70 (s, 3 H, C(4′)OMe); 4.44 (s, 2 H, CH_2); 6.54 (s, 1 H, C(3)H); 6.85, 7.35 (both d, 2 H each, Ar, *J* = 9.2); 7.42 (d, 1 H, C(8)H, *J* = 8.8); 7.94 (dd, 1 H, C(7)H, *J* = 8.8, *J* = 1.8); 8.12 (d, 1 H, C(5)H, *J* = 1.8); 10.13 (s, 1 H, NHCO); 12.02 (s, 1 H, NH)
3f	63 (*A*), 75 (*B*)	222—224	55.43 / 55.32	3.90 / 3.87	7.35 / 7.17	$C_{18}H_{15}ClN_2O_4S$	2.42 (s, 3 H, C(4)Me); 4.66 (c, 2 H, CH_2); 6.52 (s, 1 H, C(3)H); 7.11—7.35 (m, 4 H, Ar); 7.45 (d, 1 H, C(8)H, *J* = 8.4); 7.94 (dd, 1 H, C(7)H, *J* = 8.4, *J* = 0.7); 8.14 (d, 1 H, C(5)H, *J* = 0.7); 9.76 (s, 1 H, NHCO); 12.02 (s, 1 H, NH)
3g	62 (*A*), 69 (*B*)	218—219	57.80 / 57.75	4.16 / 4.07	7.60 / 7.48	$C_{18}H_{15}FN_2O_4S$	2.42 (s, 3 H, C(4)Me); 4.67 (s, 2 H, CH_2); 6.52 (s, 1 H, C(3)H); 7.00—7.26 (m, 4 H, Ar); 7.45 (d, 1 H, C(8)H, *J* = 8.9); 7.94 (dd, 1 H, C(7)H, *J* = 8.9, *J* = 1.2); 8.14 (d, 1 H, C(5)H, *J* = 1.2); 9.77 (s, 1 H, NHCO); 12.02 (s, 1 H, NH)
3h	72 (*A*), 79 (*B*)	245—247	62.41 / 62.48	5.15 / 5.24	7.31 / 7.29	$C_{20}H_{20}N_2O_4S$	2.10 (s, 6 H, C(2′)Me, C(5′)Me); 2.43 (s, 3 H, C(4)Me); 4.55 (s, 2 H, CH_2); 6.55 (s, 1 H, C(3)H); 7.00—7.10 (m, 3 H, Ar); 7.45 (d, 1 H, C(8)H, *J* = 8.6); 7.94 (dd, 1 H, C(7)H, *J* = 1.8, *J* = 8.6); 8.15 (d, 1 H, C(5)H, *J* = 1.8); 9.52 (s, 1 H, NHCO); 12.02 (s, 1 H, NH)

N, 4.67. $C_{14}H_{15}NO_5S$. Calculated (%): C, 54.36; H, 4.89; N, 4.53. ^{1}H NMR, δ: 1.04 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1 Hz); 2.48 (s, 3 H, C(4)Me); 4.03 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1 Hz); 4.64 (s, 2 H, CH_2); 6.52 (s, 1 H, C(3)H); 7.43 (d, 1 H, C(8)H, J = 8.6 Hz); 7.94 (dd, 1 H, C(7)H, J = 8.6 Hz, J = 1.9 Hz); 8.16 (d, 1 H, C(5)H, J = 1.9 Hz); 12.05 (s, 1 H, NH).

(4-Methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetanilide (3a). ***A.*** This was obtained analogously using chloroacetanilide (1.69 g, 10 mmol). The product was crystallized from butan-1-ol, the yield was 2.57 g (72%), white crystals.

B. A mixture of (4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetic acid (**4**) (2.81 g, 10 mmol), aniline (0.91 mL, 10 mmol), and DCC (2.1 g, 10 mmol) was heated for 1 h at 100—110 °C in DMF (15 mL) with periodic stirring, then diluted with water. The precipitate was filtered off, the substance obtained was vigorously shaken with aqueous NaOH (100 ml, 0.1 *M*), the insoluble residue was filtered off. The filtrate was acidified with 0.1 *M* HCl to pH 7, the precipitate was filtered off and recrystallized from butan-1-ol. The yield was 2.81 g (79%).

Anilides **3b—h** were obtained analogously, by the methods *A* and *B* using the respective chloroacetanilides or arylamines. The products were crystallized from butan-1-ol or DMF. The yields, physicochemical and spectral characteristics of the obtained compounds are listed in Table 1.

(4-Methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl)acetic acid (4). A mixture of ester **2** (3.11 g, 10 mmol) and KOH (1.70 g, 30 mmol) in 50 mL of water was refluxed for 2.5 h. The solution was acidified with HCl to pH 7, the precipitate was filtered off and recrystallized from water. The product (2.62 g, 93%) was obtained in a form of fine white crystals, m.p. 270—271 °C. Found (%): C, 51.08; H, 3.82; N, 4.86. $C_{12}H_{11}NO_5S$. Calculated (%): C, 51.24; H, 3.94; N, 4.98. ^{1}H NMR, δ: 2.46 (s, 3 H, C(4)Me); 4.50 (s, 2 H, CH_2); 6.53 (s, 1 H, C(3)H); 7.44 (d, 1 H, C(8)H, J = 8.9 Hz); 7.95 (dd, 1 H, C(7)H, J = 8.9 Hz, J = 1.8 Hz); 8.16 (d, 1 H, C(5)H, J = 1.8 Hz); 12.03 (br.s, 1 H, NH).

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