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Synthesis of Derivatives of 4-Hydroxy-2-methyl-3-[2-(5-mercapto-1*H*-1,2,4-triazol-3-yl)-ethyl]quinoline and 2-[2-(4-Hydroxy-2-methyl-3-quinolyl)ethyl]-4*H*-3,1-benzoxazin-4-one

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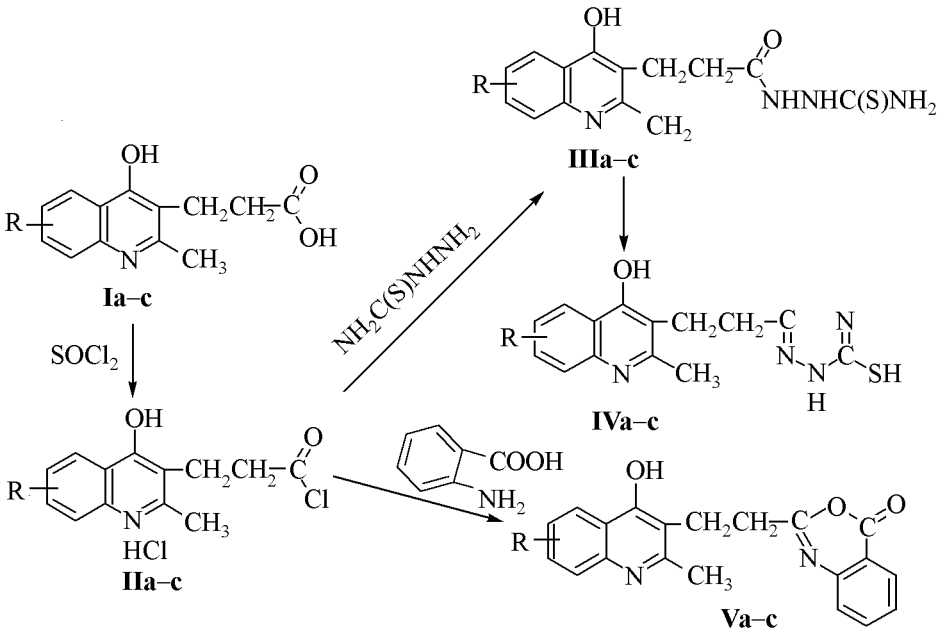
Abstract—From 4-hydroxy-2-methylquinoline-3-propionyl chlorides hydrochlorides the corresponding thiosemicarbazides were synthesized. The cyclization of the latter both in alkaline and acidic media furnished 4-hydroxy-2-methyl-3-[2-(5-mercapto-1*H*-1,2,4-triazol-3-yl)ethyl]quinolines. The reaction of the above propionyl chlorides with anthranilic acid afforded the corresponding 2-[2-(4-hydroxy-2-methyl-3-quinolyl)ethyl]-4*H*-3,1-benzoxazin-4-ones.

Among heterocycles with quinoline ring to be present are known pharmacologically active substances and dyes [1, 2]. In extension of the research aimed at the synthesis of new quinoline derivatives fuzed with the other heterocycles also possessing biological activity [3, 4] we performed in this study the synthesis of functionally substituted derivatives of mercaptotriazolyl- and benzoxazinone-4-hydroxy-2-methylquinolines. To this end the corresponding quinoline-3-propionic acids **Ia–c** [5, 6] were converted into acyl chlorides **IIa–c** with almost quantitative yield by treating with thionyl chloride in anhydrous benzene in the presence of DMF. The heating of hydrochlorides of acyl chlorides **IIa–c** with thiosemicarbazide in 1 : 1 ratio in pyridine medium gave rise to thiosemicarbazide derivatives **IIIa–c** in high yield. Intramolecular cyclization of compounds **IIIa–c** both in alkaline and acidic media resulted in 4-hydroxy-2-methyl-3[2-(5-mercapto-1*H*-1,2,4-triazol-3-yl)ethyl]-quinolines (**IVa–c**).



R = H, 6-CH_3, 6-OCH_3.

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Table 1. 4-Hydroxy-2-methyl-6R-quinoline-3-propionyl chlorides hydrochlorides (**IIa**–**c**) and [3-(4-hydroxy-2-methyl-6R-quinol-3-yl)propionyl]thiosemicarbazides (**IIIa**–**c**)

Compd. no.	R	Yield, %	mp, °C	Found, %					Formula	Calculated, %				
				C	H	Cl	N	S		C	H	Cl	N	S
IIa	H	96	290 (decomp.)	–	–	24.97	4.71	–	$C_{13}H_{12}NO_2$·HCl	–	–	24.82	4.89	–
IIb	6-CH_3	97	310 (decomp.)	–	–	23.83	4.42	–	$C_{14}H_{14}NO_2$·HCl	–	–	23.67	4.66	–
IIc	6-OCH_3	93	275 (decomp.)	–	–	22.64	4.27	–	$C_{14}H_{14}NO_3$·HCl	–	–	22.47	4.43	–
IIIa	H	87	> 350	55.11	5.34	–	18.22	10.71	$C_{14}H_{16}N_4O_2S$	55.26	5.26	–	18.42	10.53
IIIb	6-CH_3	91	> 370	56.73	5.53	–	17.75	9.89	$C_{15}H_{18}N_4O_2S$	56.60	5.66	–	17.61	10.06
IIIc	6-OCH_3	85	289 (decomp.)	53.80	5.47	–	16.88	9.44	$C_{15}H_{18}N_4O_3S$	53.89	5.39	–	16.77	9.58

Table 2. 4-Hydroxy-2-methyl-3-[2-(5-mercapto-1*H*-1,2,4-triazol-3-yl)ethyl]-6R-quinolines (**IVa**–**c**) and 2-[2-(4-hydroxy-2-methyl-6R-quinol-3-yl)ethyl]-4*H*-3,1-benzoxazin-4-ones (**Va**–**c**)

Compd. no.	R	Yield, %		mp, °C	R_f	Found, %				Formula	Calculated, %			
		method *a*	method *b*			C	H	N	S		C	H	N	S
IVa	H	88	79	269	0.58	–	–	19.67	11.62	$C_{14}H_{14}N_4OS$	–	–	19.58	11.80
IVb	6-CH_3	81	82	305	0.51	–	–	18.69	10.84	$C_{15}H_{16}N_4OS$	–	–	18.72	10.70
IVc	6-OCH_3	77	75	205	0.55	–	–	17.91	10.03	$C_{15}H_{16}N_4O_2S$	–	–	17.77	10.12
Va	H	76		205	0.58	72.51	4.73	8.40	–	$C_{20}H_{16}N_2O_3$	72.29	4.82	8.43	–
Vb	6-CH_3	71		315	0.49	72.95	5.28	8.14	–	$C_{21}H_{18}N_2O_3$	72.83	5.20	8.09	–
Vc	6-OCH_3	68		210	0.47	69.52	4.91	7.66	–	$C_{21}H_{18}N_2O_4$	69.61	4.97	7.73	–

Solvent: [a] benzene-chloroform, [b] benzene-ethanol.

Apparently the arising mesoionic 4-hydroxy-2-methyl-3-[2-(5-amino-1,2,4-thiodiazol-3-yl)ethyl]-quinolines in the acidic medium are thermodynamically and kinetically unstable, and at recrystallization from ethanol readily rearrange and afford in high yield compounds **IVa–c**.

We also carried out reactions of quinoline-3-propionyl chlorides hydrochlorides **IIa–c** with anthranilic acid and studied the effect of various factors on the course of the reaction. As a result of the study we found optimum conditions for the reaction. It readily occurred in pyridine at heating the initial components on a water bath for 8–10 h at the reagents ratio 1 : 1, and the yield of the target products **Va–c** under these conditions attained 72–75%.

The structure of compounds obtained was confirmed by ^{1}H NMR spectra.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Mercury-300 Varian NMR from solutions in DMSO. The homogeneity of compounds obtained was checked by TLC on Silufol UV-254 plates, development in iodine vapor.

3-(4-Hydroxy-2-methylquinol-3-yl)propionyl chlorides hydrochlorides (IIa–c). To a solution of 0.05 mol of an appropriate acid **Ia–c** [5, 6] in 50 ml of anhydrous benzene was added at cooling 9 g (0.075 mol) of thionyl chloride dissolved in a mixture of 20 ml of anhydrous benzene and 4 ml of DMF. The mixture was heated on a water bath for 3 h. On cooling the precipitated crystals of acyl chlorides hydrochlorides were filtered off and washed with anhydrous benzene (Table 1).

[3-(4-Hydroxy-2-methyl-6R-3-quinolyl)propionyl]thiosemicarbazides (IIIa–c). A mixture of 0.0025 mol of an appropriate acyl chloride **IIa–c** and 0.228 g (0.0025 mol) of thiosemicarbazide in 10 ml of anhydrous pyridine was heated on a water bath for 5–6 h. On cooling the precipitated crystals were filtered off and recrystallized from a mixture alcohol–water, 1 : 1 (Table 1).

4-Hydroxy-2-methyl-3-[2-(5-mercapto-1*H*-1,2,4-triazol-3-yl)ethyl]-6R-quinolines (IVa–c). (a) A mixture of 0.0025 mol of thiosemicarbazide **IIIa–c** and 10 ml of 20% solution of NaOH was heated on a water bath till the precipitate totally dissolved, and then the heating was continued for 2 h more. On cooling the solution was filtered and acidified with hydrochloric acid till pH 5–6. The separated precipitate was filtered off and recrystallized from a mixture alcohol–water, 1 : 1 (Table 2).

(b) To 0.0025 mol of thiosemicarbazide **IIIa–c** was added 3 ml of concn. H_2SO_4, and the mixture was left standing at room temperature for 24 h. Then the mixture was poured into ice water, and after neutralization till pH 5–6 the precipitate obtained was filtered off and recrystallized from a mixture alcohol–water, 1 : 1. The mixed samples of compounds **IVa–c** obtained by methods (a) and (b) melted without depression of the melting point. ^{1}H NMR spectrum of compound **IVa**, δ, ppm: 2.50 t (2H, CH_2), 2.75 s (3H, CH_3), 3.0 t (2H, CH_2), 7.70–7.90 m (4H, arom), 8.35, 8.40 s (2H, 2NH), 11.25 s (H, OH).

2-[2-(4-hydroxy-2-methyl-3-quinolyl)ethyl]-4*H*-3,1-benzoxazin-4-ones (Va–c). A mixture of 0.0025 mol of an appropriate acyl chloride hydrochloride **IIa–c** and 0.34 g (0.0025 mol) of anthranilic acid in 15 ml of anhydrous pyridine was heated at reflux for 8–10 h. Then pyridine was distilled off under reduced pressure, to the residue 20 ml of cold water was added, and the solution was acidified to pH ~4. On the next day the separated precipitate was filtered off and washed with water (Table 2). ^{1}H NMR spectrum of compound **Va**, δ, ppm: 2.45 s (3H, CH_3), 2.60 t (2H, CH_2), 2.90 t (2H, CH_2), 7.0–8.62 m (8H, arom), 11.25 s (H, OH).

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