Russian Journal of Organic Chemistry, Vol. 40, No. 6, 2004, pp. 889–891. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 6, 2004, pp. 926–928.

New Quinoline Derivatives on the Basis of (4-Hydroxy-2-methylquinolin-3-yl)acetic Acid

A. A. Avetisyan, I. L. Aleksanyan, and A. A. Pivazyan

Erevan State University, ul. A. Manukyana 1, Erevan, 375025 Armenia
e-mail: organkim@sun.ysu.am

Received April 21, 2003

Abstract—A procedure was developed for the synthesis of (4-hydroxy-2-methylquinolin-3-yl)acetic acid and the corresponding acyl chloride. Reactions of the latter with *o*-aminobenzenethiol, *o*-phenylenediamine, *o*-aminophenol, anthranilic acid, and thiosemicarbazide gave, respectively, 2-(4-hydroxy-2-methylquinolin-3-ylmethyl)-1,3-benzothiazole, -benzoxazole, -benzimidazole, 2-(4-hydroxy-2-methylquinolin-3-ylmethyl)-4*H*-3,1-benzoxazin-4-one, and 4-hydroxy-2-methyl-3-(5-sulfanyl-1*H*-1,2,4-triazol-3-ylmethyl)quinoline.

Quinolines are widely spread in nature, and many biologically active substances include a quinoline fragment [1–3]. Both natural and synthetic quinoline derivatives exhibit antiallergic, spasmodic, psychotropic, neurotropic, and antiphlogistic activity, and they attract interest from the practical viewpoint, specifically for the preparation of medicines [4, 5].

We have developed a convenient procedure for the synthesis of (4-hydroxy-2-methylquinolin-3-yl)acetic acid (**II**) and -acetyl chloride (**III**). The procedure is based on thermal cyclization of ethyl α-ethoxycarbonylmethyl-β-phenylaminocrotonate which is obtained by reaction of diethyl acetylsuccinate [6] with aniline at room temperature. Alkaline hydrolysis of the cyclization product, ethyl (4-hydroxy-2-methylquinolin-3-yl)acetate (**I**) gave (4-hydroxy-2-methylquinolin-3-yl)acetic acid (**II**). Treatment of the latter with thionyl chloride in anhydrous benzene in the presence of DMF afforded acyl chloride hydrochloride **III** in almost quantitative yield. We examined reactions of **III** with some nucleophilic reagents, in particular *o*-aminobenzenethiol, *o*-phenylenediamine, *o*-aminophenol, anthranilic acid, and thiosemicarbazide. These reactions smoothly occurred on heating equimolar amounts of the reactants in anhydrous pyridine on a water bath, and the yield of the target products ranged from 68 to 96%. By reaction of **III** with thiosemicarbazide we obtained compound **VIII** which underwent intramolecular cyclization in acidic or basic medium, leading to 4-hydroxy-2-methyl-3-(5-sulfanyl-1*H*-1,2,4-triazol-3-ylmethyl)quinoline (**IX**) (Scheme 1).

EXPERIMENTAL

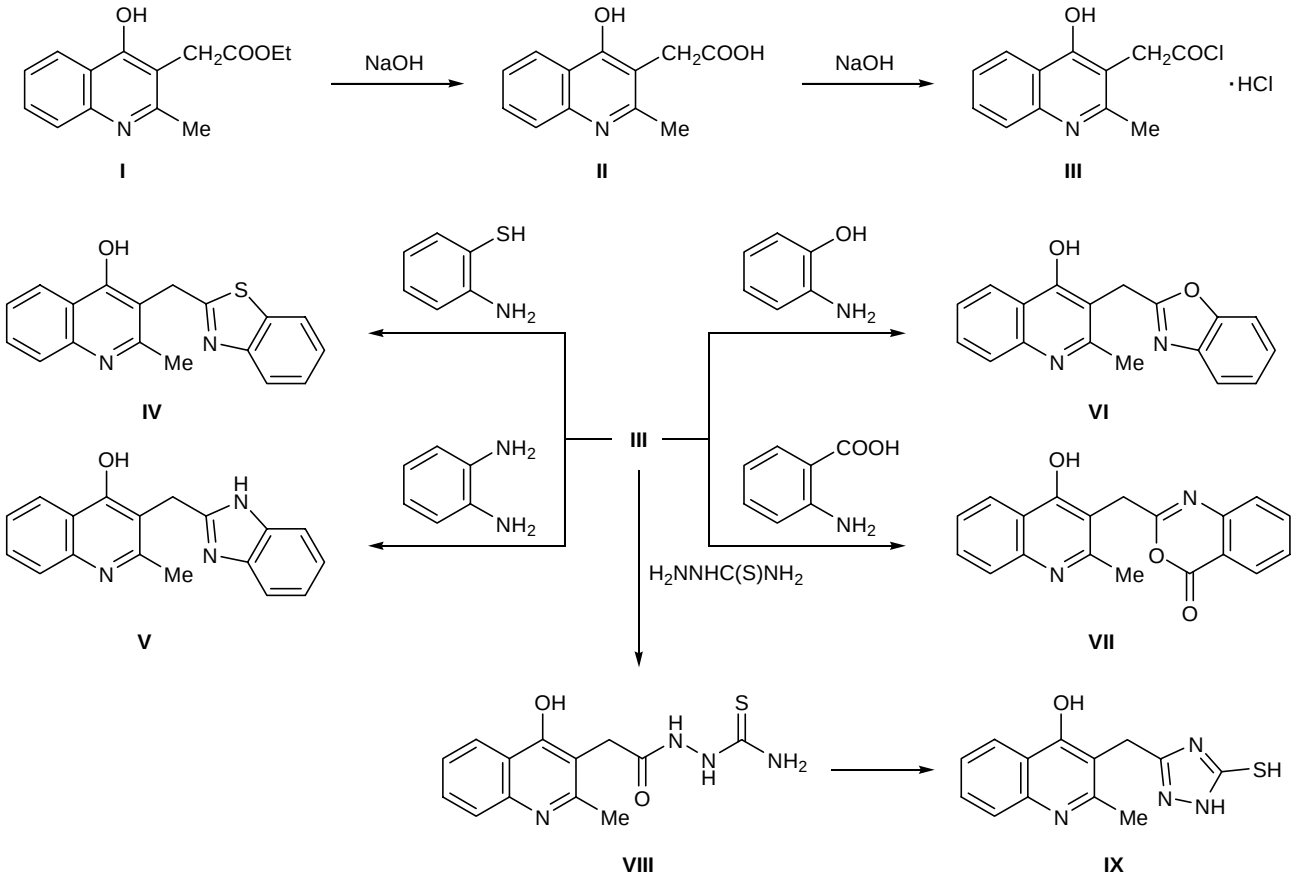
The ^{1}H NMR spectra were obtained on a Varian Mercury-300 instrument in DMSO-d_6. The IR spectrum of acid **II** was recorded on a UR 20 spectrometer in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates (development with iodine vapor). The yields and elemental analyses of compounds **I**–**IX** are given in table.

Ethyl (4-hydroxy-2-methylquinolin-3-yl)acetate (I). A mixture of 21.6 g (0.1 mol) of diethyl acetylsuccinate [6] and 9.3 g (0.1 mol) of freshly distilled aniline was left to stand at room temperature in a desiccator charged with phosphorus(V) oxide until a required amount of water (1.8 ml) was separated. The resulting material was then washed with strongly dilute hydrochloric acid and with water, dried over $MgSO_4$, and subjected to heterocyclization. For this purpose, 14.55 g (0.05 mol) of ethyl α-ethoxycarbonylmethyl-β-phenylaminocrotonate was added dropwise under vigorous stirring in a stream of nitrogen to 200 ml of mineral oil heated to 250°C. The mixture was cooled, and the precipitate was filtered off, washed with benzene, and recrystallized from acetic acid. ^{1}H NMR spectrum, δ, ppm: 1.3 s (3H, CH_3), 2.5 s (3H, CH_3), 3.5 t (2H, CH_2), 4.1 s (2H, CH_2), 7.2–8.0 m (4H, H_{arom}), 11.25 s (1H, OH).

(4-Hydroxy-2-methylquinolin-3-yl)acetic acid (II). A mixture of 2.45 g (0.01 mol) of ethyl ester **I**, 1.2 g (0.03 mol) of NaOH dissolved in 50 ml of water, and 30 ml of ethyl alcohol was heated for 4 h on

1070-4280/04/4006-0889 © 2004 MAIK "Nauka/Interperiodica"

Scheme 1.



a water bath. The alcohol was distilled off, the residue was diluted with 20 ml of cold water, the mixture was filtered, the filtrate was acidified to pH 4–5, and the precipitate was filtered off. IR spectrum, ν, cm^{-1}: 1730 (C=O, acid), 2700–3000 (OH, acid). ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 3.60 s (2H, CH_2), 7.2–8.1 m (4H, H_{arom}), 11.15 s (2H, OH).

(4-Hydroxy-2-methylquinolin-3-yl)acetyl chloride hydrochloride (III). A solution of 9 g (0.075 mol) of thionyl chloride in a mixture of 20 ml of anhydrous benzene and 4 ml of DMF was added on cooling to a solution of 2.17 g (0.05 mol) of acid **II** in 50 ml of anhydrous benzene. The mixture was heated for 3 h on a water bath and cooled, and the precipitate of **III** was filtered off and washed with anhydrous benzene.

2-(4-Hydroxy-2-methylquinolin-3-ylmethyl)-1,3-benzothiazole (IV). A mixture of 0.68 g (0.0025 mol) of acyl chloride **III** and 0.3125 g (0.0025 mol) of *o*-aminobenzenethiol in 10 ml of anhydrous pyridine was heated for 5–6 h on a water bath. Pyridine was distilled off under reduced pressure, 30 ml of cold water was added to the residue, and the mixture was left overnight. The precipitate of **IV** was filtered off, washed with water, and recrystallized from aqueous alcohol. ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 3.00 s (2H, CH_2), 6.6–8.1 m (8H, H_{arom}), 11.20 s (1H, OH).

2-(4-Hydroxy-2-methylquinolin-3-ylmethyl)-1,3-benzimidazole (V) was synthesized in a similar way from 0.68 g (0.0025 mol) of compound **III** and 0.27 g (0.0025 mol) of *o*-phenylenediamine. ^{1}H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 2.90 s (2H, CH_2), 6.6–8.0 m (8H, H_{arom}), 9.6 s (1H, NH), 11.05 s (1H, OH).

2-(4-Hydroxy-2-methylquinolin-3-ylmethyl)-1,3-benzoxazole (VI) was synthesized in a similar way from 0.68 g (0.0025 mol) of compound **III** and 0.2725 g (0.0025 mol) of *o*-aminophenol. ^{1}H NMR spectrum, δ, ppm: 2.54 s (3H, CH_3), 2.9 t (2H, CH_2), 6.6–7.1 m (4H, H_{arom}), 7.4–8.0 m (4H, H_{arom}), 11.2 s (1H, OH).

2-(4-Hydroxy-2-methylquinolin-3-yl)methyl)-4*H*-3,1-benzoxazin-4-one (VII). A mixture of 0.68 g (0.0025 mol) of compound **III** and 0.34 g (0.0025 mol) of anthranilic acid in 15 ml of anhydrous pyridine was

Yields, melting points, R_f values, and elemental analyses of compounds **I**–**IX**

Comp. no.	Yield, %	mp, °C	R_f	Found,%				Formula	Calculated,%			
				C	H	N	S		C	H	N	S
I	61	245	–	68.40	6.20	5.65	–	$C_{14}H_{15}NO_3$	68.57	6.12	5.71	–
II	95	300	0.7[a]	66.50	5.20	6.60	–	$C_{12}H_{11}NO_3$	66.36	5.07	6.45	–
III	88	–	–	53.20	3.85	5.25	–	$C_{12}H_{10}ClNO_2 \cdot HCl$	52.94	4.04	5.15	–
IV	72	196	0.61[b]	67.90	4.42	9.54	10.30	$C_{18}H_{14}N_2OS$	68.35	4.57	9.15	10.45
V	68	285	0.67[c]	75.05	5.42	14.66	–	$C_{18}H_{15}N_3O$	74.74	5.19	14.53	–
VI	96	240	0.44[a]	74.60	4.72	9.45	–	$C_{18}H_{14}N_2O_2$	74.48	4.82	9.65	–
VII	75	300	0.46[b]	71.20	4.55	8.92	–	$C_{19}H_{14}N_2O_3$	71.70	4.40	8.80	–
VIII	75	282	–	53.97	4.68	19.12	11.25	$C_{13}H_{14}N_4O_2S$	53.79	4.82	19.31	11.03
IX	91 (*a*) 89 (*b*)	230	0.40[a]	57.15 56.90	4.66 4.55	20.87 20.45	11.55	$C_{13}H_{12}N_4OS$	57.35	4.41	20.58	11.76

[a] Eluent chloroform–acetone, 10:1.
[b] Eluent benzene–acetone, 6:1.
[c] Eluent benzene–acetone, 3:1.

heated for 8–10 h under reflux. The solvent was distilled off under reduced pressure, 20 ml of cold water was added to the residue, and the mixture was acidified to pH 4 and was left overnight. The precipitate of **VII** was filtered off and washed with water. ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 2.90 s (2H, CH_2), 7.0–8.0 (8H, H_{arom}), 11.20 s (1H, OH).

***N*^{1}-[(4-Hydroxy-2-methylquinolin-3-yl)acetyl]-thiosemicarbazide (VIII).** A mixture of 0.68 g (0.0025 mol) of chloride **III** and 0.228 g (0.0025 mol) of thiosemicarbazide in 10 ml of anhydrous pyridine was heated for 9–10 h on a water bath. After cooling, the precipitate was filtered off and recrystallized from aqueous alcohol.

4-Hydroxy-2-methyl-3-(5-sulfanyl-1*H*-1,2,4-triazol-3-ylmethyl)quinoline (IX). *a*. A mixture of 0.725 g (0.0025 mol) of thiosemicarbazide **VIII** and 10 ml of a 20% solution of NaOH was heated on a water bath until it became homogeneous and was then heated for an additional 2 h. The solution was cooled and filtered, and the filtrate was acidified to pH 5–6. The precipitate was filtered off and recrystallized from aqueous alcohol.

b. Concentrated sulfuric acid, 3 ml, was added to 0.725 g (0.0025 mol) of thiosemicarbazide **VIII**, and the mixture was left to stand for 24 h at room temperature. It was then poured into ice water and neutralized to pH 5–6, and the precipitate was filtered off and recrystallized from aqueous alcohol (1:1). Samples of **IX** prepared as described in *a* and *b* showed no depression of the melting point on mixing. ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, CH_3), 3.10 s (2H, CH_2), 7.50–7.9 m (4H, H_{arom}), 8.35 s and 8.40 s (2H, NH), 11.5 s (1H, OH).

REFERENCES

1. Michael, J.P., *Nat. Prod. Rep.*, 1997, vol. 14, p. 11.
2. Bellino, A. and Venturella, P., *Heterocycles*, 1986, vol. 24, p. 1821.
3. Ramesh, C.A. and Selvapalam, N., *J. Chem. Res., Synop.*, 1998, no. 6, p. 531.
4. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2002, vol. 2, p. 289.
5. Aleksanyan, I.L., *Cand. Sci. (Chem.) Dissertation*, Erevan, 1985.
6. *Organic Syntheses*, Blatt, A.H., Ed., New York: Wiley, 1943, collect. vol. 2. Translated under the title *Sintezy organicheskikh preparatov*, Moscow: Inostrannaya Literatura, 1957, vol. 2, p. 580.