Chemistry of Heterocyclic Compounds, Vol. 41, No. 4, 2005

SYNTHESIS OF 4-HYDROXY- AND 4-AMINO-2-METHYL-3-(2-METHYLINDOL-3-YL)METHYLQUINOLINES AND THEIR 6- AND 8- SUBSTITUTED DERIVATIVES

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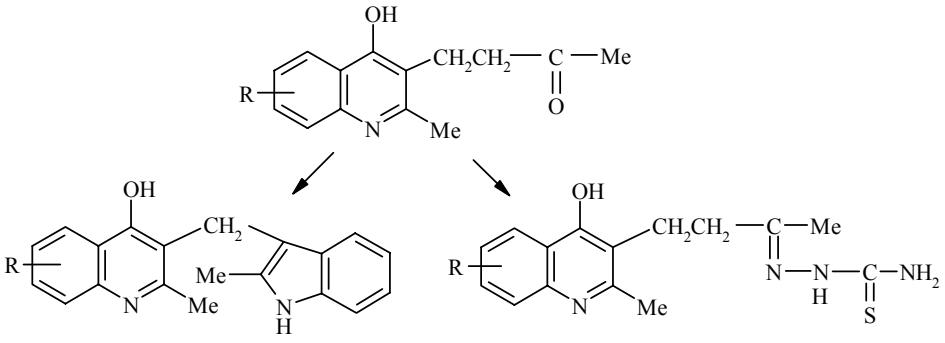
A method has been developed for the synthesis of substituted 4-hydroxy- and 4-amino-2-methyl-3-(2-methylindol-3-yl)methylquinolines by treating the corresponding 4-hydroxy(chloro)-2-methyl-3-(3-oxobutyl)quinolines with phenylhydrazine hydrochloride. It was found that nucleophilic substitution occurred in the case of the 4-chloroquinolines together with subsequent rearrangement to give the 4-amino derivatives. The thiosemicarbazones of the corresponding 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines were also obtained.

Keywords: 4-hydroxy(amino)-2-methyl-3-(2-methylindol-3-yl)methylquinolines, 4-hydroxy(chloro)-2-methyl-3-(3-oxobutyl)quinolines, 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines thiosemicarbazones.

We have previously developed a convenient method for the synthesis of differently structured 3-(3-oxobutyl)quinolines [1, 2] as suitable starting materials for conversion to different novel heterocyclic systems. In continuing these investigations of the synthesis of quinolines also containing an indole ring we have studied the reaction of the corresponding 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines with phenylhydrazine hydrochloride.

Optimum conditions for the reaction have been developed. It was found that the reaction indicated can be brought about by heating equimolar mixtures of the starting components in alcoholic solution in the presence of H_2SO_4 for 7-8 h. Evidently the reaction takes place with the formation of an intermediate phenylhydrazone and a subsequent Fischer type rearrangement to give high yields of the corresponding indolylquinolines **1a-e**.



1a–e **2a–e**

1, 2 a R = H, **b** R = 6-Me, **c** R = 8-Me, **d** R = 6-OMe, **e** R = 8-OMe

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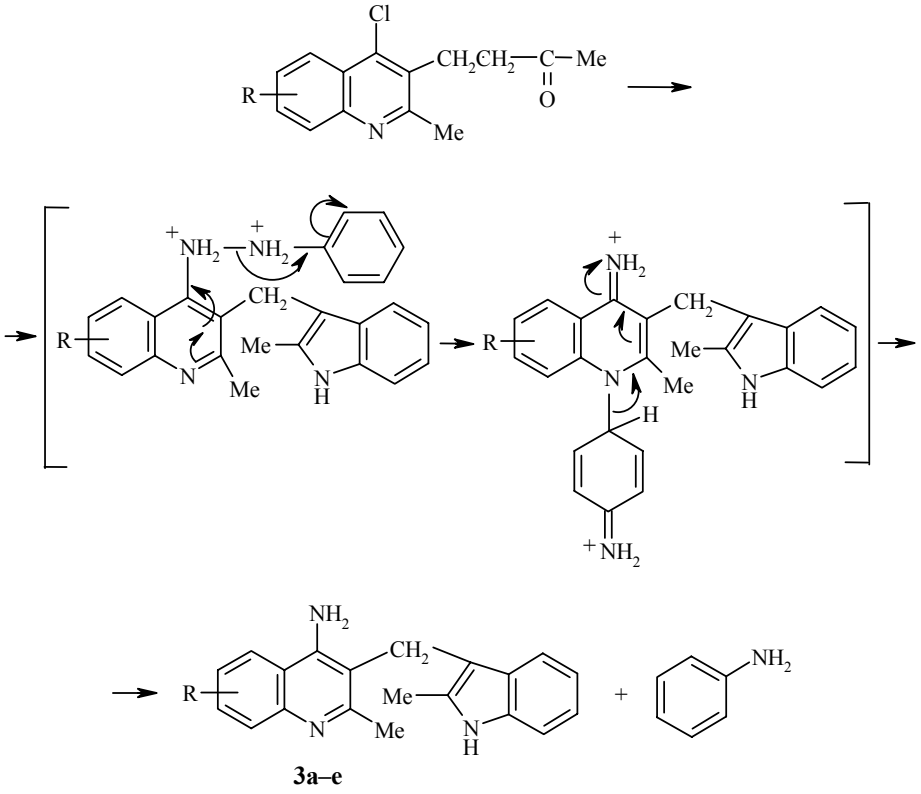
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 554-557, April, 2005. Original article submitted July 23, 2002.

We have also obtained the thiosemicarbazones of the corresponding 4-hydroxy-2-methyl-3-(3-oxobutyl)quinolines **2a-e** by treating the latter with thiosemicarbazide in aqueous alcoholic solution in the presence of acetic or sulfuric acid.

It was of interest to follow the reaction of the 4-chloro-2-methyl-3-(3-oxobutyl)quinolines with phenylhydrazine for different ratios of components. Hence a 1:1 ratio of components gave the phenylhydrazones of 4-chloro-2-methyl-3-(3-oxobutyl)quinolines while in the presence of sulfuric acid the formation of the expected indolyl derivatives, as in the case of 4-hydroxyquinolines, was not observed. It was found that a 1:2 ratio of components gave the corresponding 4-amino-2-methyl-3-(2'-methylindol-3'-yl)methylquinolines **3a-e** in place of the expected 2-methyl-3-(2'-methylindol-3'-yl)methyl-4-phenylhydrazinoquinolines. In all probability the 4-phenylhydrazinoquinolines formed as a result of the reaction, similarly to hydrazo compounds [3, 4], undergo disproportionation in accordance with a [5,5]-sigmatropic shift mechanism to give *para*-quinoid intermediates which decompose to the corresponding 4-aminoquinolines and aniline.



3a–e

3 a R = H, **b** R = 6-Me, **c** R = 8-Me, **d** R = 6-OMe, **e** R = 8-OMe

EXPERIMENTAL

^{1}H NMR spectra were taken on a Varian Mercury-300 spectrometer (300 MHz) using DMSO and with TMS internal standard. IR spectra were taken on a UR-20 spectrometer for vaseline oils. The purity of the compounds obtained was monitored using TLC on Silufol UV-254 plates with the systems: EtOH–CCl_4 (1:4.5) (**1a-e**) or 1:6.0 (**3a-e**) and EtOH–H_2O (6:1) (**2a-e**) and were revealed using iodine vapor. The characteristics of compounds **1-3** are given in Table 1.

TABLE 1. Physicochemical Characteristics for Compounds **1-3**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f	Yield, %
		C	H	N	S			
1a	$C_{20}H_{18}N_2O$	79.36 / 79.47	5.87 / 5.96	9.31 / 9.27		192	0.58	72
1b	$C_{21}H_{20}N_2O$	79.82 / 79.74	6.41 / 6.32	8.78 / 8.86		250	0.42	68
1c	$C_{21}H_{20}N_2O$	79.68 / 79.74	6.27 / 6.32	8.94 / 8.86		191	0.66	71
1d	$C_{21}H_{20}N_2O_2$	75.84 / 75.90	6.11 / 6.02	8.51 / 8.43		195	0.50	78
1e	$C_{21}H_{20}N_2O_2$	75.82 / 75.90	6.13 / 6.02	8.39 / 8.43		220	0.60	70
2a	$C_{15}H_{18}N_4OS$	47.79 / 47.68	5.85 / 5.96	18.50 / 18.54	10.39 / 10.59	215	0.51	90
2b	$C_{16}H_{20}N_4OS$	60.69 / 60.75	6.42 / 6.33	17.65 / 17.72	10.28 / 10.12	220	0.48	95
2c	$C_{16}H_{20}N_4OS$	60.82 / 60.75	6.40 / 6.33	17.68 / 17.72	10.30 / 10.12	206	0.50	91
2d	$C_{16}H_{20}N_4O_2S$	57.92 / 57.83	6.09 / 6.02	16.79 / 16.86	9.41 / 9.63	200	0.49	92
2e	$C_{16}H_{20}N_4O_2S$	57.91 / 57.83	5.97 / 6.02	16.90 / 16.86	9.43 / 9.63	158	0.53	89
3a	$C_{20}H_{19}N_3$	79.85 / 79.73	6.17 / 6.31	13.87 / 13.95		125	0.55	70
3b	$C_{21}H_{21}N_3$	80.11 / 80.00	6.71 / 6.66	13.28 / 13.33		155	0.41	65
3c	$C_{21}H_{21}N_3$	80.09 / 80.00	6.70 / 6.66	13.31 / 13.33		115	0.65	76
3d	$C_{21}H_{21}N_3O$	76.18 / 76.13	6.39 / 6.34	12.70 / 12.68		126	0.51	75
3e	$C_{21}H_{21}N_3O$	76.21 / 76.13	6.31 / 6.34	12.59 / 12.68		110	0.56	69

4-Hydroxy-2-methyl-3-(2-methylindol-3-yl)methylquinolines 1a-e. The corresponding 4-hydroxy-2-methyl-3-(3-oxobutyl)quinoline [1, 2] (5 mmol), phenylhydrazine hydrochloride (0.72 g, 5 mmol), EtOH (2.5 ml), and conc. H_2SO_4 (0.3 ml) were placed in a round-bottomed flask. The mixture was heated on a water bath for 7-8 h, cooled, and diluted with water. The acid solution was filtered and basified to pH 7-8. The precipitate was washed with water and recrystallized from a mixture of ethanol and water (1:1). ^{1}H NMR spectrum for **1d**, δ, ppm: 2.20 (3H, s, CH_3); 2.50 (3H, s, CH_3); 3.95 (3H, s, OCH_3); 4.40 (2H, s, CH_2); 6.7-7.2 (4H, m, H_{arom}); 7.3-7.8 (3H, m, H_{arom}); 10.5 (1H, s, NH).

4-Hydroxy-2-methyl-3-(3-oxobutyl)methylquinoline Thiosemicarbazones 2a-e. Thiosemicarbazide (0.5 g, 5.5 mmol) and acetic acid (0.5 ml) or conc. H_2SO_4 (2 drops) were added to a solution of the corresponding 4-hydroxy-2-methyl-3-(3-oxobutyl)quinoline [1, 2] (5 mmol) in EtOH (10 ml) and water (10 ml). The mixture was heated on a water bath for 2 h. The product was cooled, diluted with water and the precipitate was filtered off and washed with a mixture of alcohol and water (1:1). IR spectrum, ν, cm^{-1}: 1615 (–C=N); 3250-3175 (NH, NH_2). ^{1}H NMR spectrum for **2c**, δ, ppm: 2.35 (3H, s, CH_3); 2.45 (2H, s, NH_2); 3.2-3.3 (4H, m, 2 CH_2); 7.75-7.95 (3H, m, H_{arom}); 9.6 (1H, s, NH); 11.0 (1H, s, OH).

4-Amino-2-methyl-3-(2-methylindol-3-yl)methylquinolines 3a-e. A mixture of the corresponding 4-chloro-2-methyl-3-(3-oxobutyl)quinoline [5] (5 mmol), phenylhydrazine hydrochloride (1.44 g, 10 mmol), EtOH (2.5 ml), and conc. H_2SO_4 (0.6 ml) was heated on a water bath for 12 h, cooled, diluted with water, and the acid solution was filtered and basified. The precipitated solid was filtered off, washed with water, and recrystallized from a mixture of alcohol and water (1:1). ^{1}H NMR spectrum for **3a**, δ, ppm: 2.20 (3H, s, CH_3); 2.55 (3H, s, CH_3); 4.40 (2H, s, CH_2); 5.65 (2H, s, NH_2); 6.8-8.2 (8H, m, H_{arom}); 10.45 (1H, s, NH); for **3c** 2.25

(3H, s, CH_3); 2.60 (3H, s, CH_3); 2.80 (3H, s, CH_3); 4.55 (2H, s, CH_2); 5.60 (2H, s, NH_2); 6.8-7.3 (4H, m, H_{arom}); 7.4-7.9 (3H, m, H_{arom}); 10.75 (1H, s, NH); for **3d** 2.20 (3H, s, CH_3); 2.50 (3H, s, CH_3); 3.95 (3H, s, OCH_3); 4.40 (2H, s, CH_2); 5.60 (2H, s, NH_2); 6.7-7.2 (4H, m, H_{arom}); 7.3-7.8 (3H, m, H_{arom}); 10.50 (1H, s, NH).

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