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4-HYDROXY-2-QUINOLONES. 44.* SYNTHESIS OF 2-R-3-OXOMORPHOLINO[5,6-*c*]-6-R'-QUINOLIN-5-ONES

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Treatment of 1-R'-2-oxo-4-hydroxyquinolin-3-ylamides of α-halogen-substituted carboxylic acids with sodium methoxide leads to the formation of 2-R-3-oxomorpholino-[5,6-c]-6-R'-quinolin-5-ones. The antituberculosis activity of the compounds synthesized was studied.

Keywords: 4-hydroxy-2-quinolones, carbostyryl, morpholinoquinolinone, antituberculosis activity.

The universal method for the synthesis of 3-substituted 2-oxo-4-hydroxyquinolines (alkyl- [2], alkoxy-, carbalkoxyalkyl- [3], and acylamino [4]), consisting of the acylation of alkyl anthranilates by diesters or diacid chlorides of monosubstituted malonic acids and the subsequent cyclization of the products to corresponding quinolones by the action of alkali metal alcoholates, has certain limitations in practical utilization in spite of its high effectiveness. Since the formation of the quinolone ring is only accomplished under the influence of basic catalysts, the main requirement for its successful application is the stability of the substituent of the malonic ester in the alkaline medium.

One of the examples where the indicated method cannot be realized is the synthesis of 1-R'-2-oxo-4-hydroxyquinolin-3-ylamides of α-halogenocarboxylic acids **2**, since the treatment of the particular intermediate ethyl esters of 2-carbalkoxyanilides of haloacylaminomalonic acids with alkali metal alcoholates should lead inevitably to dehydrohalogenation or the substitution of the halogen atom by the alkoxy group. Therefore, the traditional synthetic scheme of introducing the required substituent into the initially synthesized quinolone should be utilized in the given case and in analogous cases. In application to the amides **2**, such a scheme includes the acylation of the 3-aminoquinolines **1** with acid chlorides of α-halogenocarboxylic acids. On account of the 4-hydroxy group, the 3-substituted 2-oxo-4-hydroxyquinolines show marked acidic properties [5]. Therefore, the subsequent treatment of the haloid derivatives **2** with sodium methylate is accompanied by the formation of the sodium salts **3**, which undergo ready cyclization in the conditions of the synthesis to form the 2-R-3-oxomorpholino[5,6-*c*]-6-R'-quinolin-5-ones **4a-l** with high yields (Table 1).

Investigation of the antituberculosis activity of the compounds synthesized was carried out in the National Institute of Allergic and Infectious Diseases of the Ministry of Health of the USA (Contract No. 01-AI-45246) by a known method [6, 7]. It was established that, from the whole group of substances, only the morpholinoquinolines **4d,e,i** at the concentration of 12.5 μg/ml produce insignificant inhibition of the growth of Mycobacterium tuberculosis H37Rv ATCC 27294. The remaining compounds were found to be inactive.

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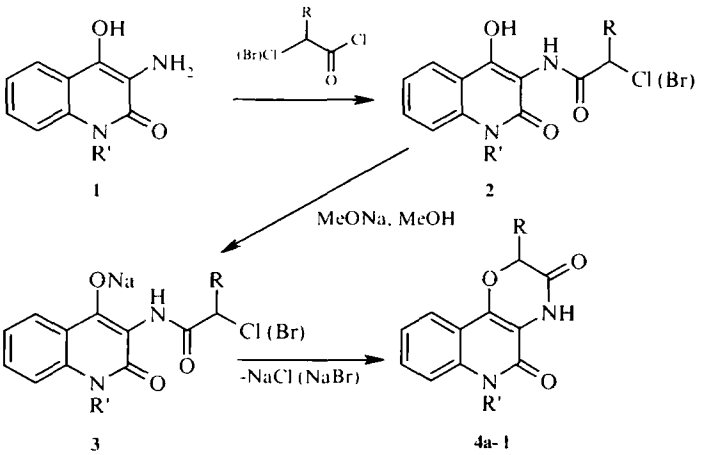
TABLE 1. Characteristics of 2-R-3-Oxomorpholino[5,6-*c*]-6-R'-quinolin-5-ones

Compound	Empirical formula	mp, °C (DMF)	Found, % / Calculated, %			Yield, %
			C	H	N	
4a	$C_{11}H_8N_2O_3$	300-304 (subl.)	61.16 / 61.11	3.70 / 3.73	12.92 / 12.96	97
4b	$C_{12}H_{10}N_2O_3$	270-272 (subl.)	62.58 / 62.61	4.42 / 4.38	12.15 / 12.17	94
4c	$C_{13}H_{12}N_2O_3$	250-254 (subl.)	63.90 / 63.93	4.97 / 4.95	11.44 / 11.47	90
4d	$C_{14}H_{14}N_2O_3$	226-230 (subl.)	65.14 / 65.11	5.42 / 5.46	10.81 / 10.85	91
4e	$C_{15}H_{16}N_2O_3$	220 (subl.)	66.11 / 66.16	5.93 / 5.92	10.34 / 10.29	89
4f	$C_{15}H_{16}N_2O_3$	240-242 (subl.)	66.18 / 66.16	5.90 / 5.92	10.26 / 10.29	86
4g	$C_{12}H_{10}N_2O_3$	256-260 (subl.)	62.65 / 62.61	4.42 / 4.38	12.11 / 12.17	92
4h	$C_{13}H_{12}N_2O_3$	226 (subl.)	63.96 / 63.93	4.92 / 4.95	11.49 / 11.47	94
4i	$C_{14}H_{14}N_2O_3$	225-226	65.14 / 65.11	5.48 / 5.46	10.81 / 10.85	90
4j	$C_{15}H_{16}N_2O_3$	210-212	66.14 / 66.16	5.94 / 5.92	10.27 / 10.29	88
4k	$C_{16}H_{18}N_2O_3$	192-194	67.15 / 67.12	6.31 / 6.34	9.80 / 9.78	91
4l	$C_{16}H_{18}N_2O_3$	228-230	67.11 / 67.12	6.36 / 6.34	9.72 / 9.78	83



4a R' = H, R = H; **b** R' = Me, R = H; **c** R' = Et, R = H; **d** R' = Pr, R = H; **e** R' = Bu, R = H; **f** R' = *i*-Bu, R = H; **g** R' = H, R = Me; **h** R' = Me, R = Me; **i** R' = Et, R = Me; **j** R' = Pr, R = Me; **k** R' = Bu, R = Me; **l** R' = *i*-Bu, R = Me

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on the Bruker WP-100 SY instrument in DMSO-d_6 using TMS as the internal standard. The 3-amino-1-R'-2-oxo-4-hydroxyquinolines **1** were synthesized by the method of the work [4].

TABLE 2. ^{1}H NMR Spectra of 2-R-3-Oxomorpholino[5,6-*c*]-6-R'-quinolin-5-ones, δ, ppm

Compound	NH of morpholine (1H, s)	H arom.		OCH(R)CO	R'
		10-H (1H, d)	9,8,7-H (3H, m)		
4a	10.22	7.69	7.58-7.11	4.79 (2H, s, CH_2)	11.95 (1H, s, NH)
4b	9.63	7.80	7.63-7.20	4.79 (2H, s, CH_2)	3.68 (3H, s, Me)
4c	9.80	7.78	7.62-7.19	4.78 (2H, s, CH_2)	4.32 (2H, q, NCH_2); 1.23 (2H, t, Me)
4d	9.70	7.81	7.62-7.21	4.79 (2H, s, CH_2)	4.28 (2H, t, NCH_2); 1.71 (2H, m, $CH_2\underline{CH_2}$); 0.96 (3H, t, Me)
4e	10.20	7.78	7.63-7.18	4.74 (2H, s, CH_2)	4.27 (2H, t, NCH_2); 1.50 (4H, m,($\underline{CH_2}$)$_2$Me); 0.92 (3H, t, Me)
4f	10.19	7.75	7.59-7.19	4.79 (2H, s, CH_2)	4.14 (2H, d, NCH_2); 2.10 (1H, m, $NCH_2\underline{CH}$); 0.88 (6H, d, 2×Me)
4g	10.13	7.71	7.57-7.13	4.90 (1H, q, CH) 1.51 (3H, d, Me)	11.92 (1H, s, NH)
4h	9.45	7.81	7.60-7.20	4.90 (1H, q, CH) 1.56 (3H, d, Me)	3.67 (3H, s, Me)
4i	10.21	7.80	7.66-7.20	4.90 (1H, q, CH) 1.50 (3H, d, Me)	4.32 (2H, q, NCH_2); 1.22 (3H, t, Me)
4j	10.21	7.81	7.64-7.19	4.92 (1H, q, CH) 1.50 (3H, d, Me)	4.25 (2H, t, NCH_2); 1.64 (2H, m, $NCH_2\underline{CH_2}$); 0.95 (3H, t, Me)
4k	10.20	7.81	7.63-7.21	4.91 (1H, q, CH) 1.52 (3H, d, Me)	4.29 (2H, t, NCH_2); 1.41 (4H, m, ($\underline{CH_2}$)$_2$Me); 0.93 (3H, t, Me)
4l	10.19	7.80	7.61-7.18	4.91 (1H, q, CH) 1.50 (3H, d, Me)	4.16 (2H, d, NCH_2); 2.14 (1H, m, $NCH_2\underline{CH}$); 0.89 (6H, d, 2×Me)

1-R'-2-Oxo-4-hydroxyquinolin-3-ylamides of α-Chloro(bromo)carboxylic Acids (2) (General Method). To the mixture of 3-aminoquinoline **1** (0.01 mol) and triethylamine (1.53 ml, 0.011 mol) in acetone (20 ml) the corresponding chloro(bromo)-substituted carboxylic acid chloride (0.011 mol) is added, and the mixture is left for 3-4 h at room temperature. The reaction mixture is diluted with water and acidified with HCl to pH 3. The residue of amide **2** is filtered off, washed with water, and dried. The amides obtained are utilized for further synthesis without additional purification.

2-R-3-Oxomorpholino[5,6-*c*]-6-R'-quinolin-5-ones (4a-l). To the solution of the corresponding amide **2** (0.01 mol) in abs. methyl alcohol (50 ml) a solution of sodium methoxide, obtained from metallic sodium (0.35 g, 0.015 mol) and abs. methyl alcohol (20 ml) is added. The mixture is boiled for 2 h, after which it is cooled and acidified with AcOH to pH ~4. The separated residue of morpholinoquinoline **4** is filtered off, washed with water, and dried.

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