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4-HYDROXY-2-QUINOLONES. 90.* SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF 4-METHYL-2-THIAZOLYLAMIDES OF HALO-SUBSTITUTED 4-HYDROXY-2-OXO-1,2-DIHYDRO-3-QUINOLINECARBOXYLIC ACIDS

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Several variants were studied for the synthesis of esters of halogen derivatives of 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acids, whose reaction with 2-amino-4-methylthiazole gives the corresponding hetarylamides. Results are given for a study of the antitubercular activity of these products.

Keywords: amides, 2-amino-4-methylthiazole, 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acids, antitubercular activity.

Since the first fluoroquinolone antibiotics appeared on the market, extensive studies have been carried out worldwide on the synthesis and biological properties of their numerous structural analogs. This work has led to the steady introduction of new safer and more efficient drugs from this group [2]. It has been repeatedly noted that the halogen atom in the benzene part of the quinolone molecule, especially at $C_{(6)}$, always facilitates the antimicrobial activity [3]. The 6-fluoro derivatives were long thought to be the most active molecules in this class but it was later convincingly shown that the presence of a fluorine atom at $C_{(6)}$ is not necessary to obtain highly active compounds. The analogous effect may be obtained for other halogens [4] and even without halogen [5].

Hence, we have modified the previously described methyl derivatives of 2-thiazolylamides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, which display strong *in vitro* antitubercular activity [6], by introducing halogen atoms into the quinoline fragment.

The synthesis of 4-methyl-2-thiazolylamides of halogen derivatives of 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acids **1a-f** is possible using several approaches. The major differences between these approaches lies in the method of obtaining the starting esters of the corresponding 3-quinolinecarboxylic acids **2**, which may then be readily converted into the desired hetarylamides. The traditional method entails the esterification of anthranilic acids **3**, acylation of the resultant alkyl anthranilates **4** using ethoxymalonyl chloride, and cyclization of the ethyl esters of 2-carbalkoxymalonanilic acids **5** to give quinolones **2** under conditions for the Dieckmann reaction (method A). This method is highly reproducible and gives

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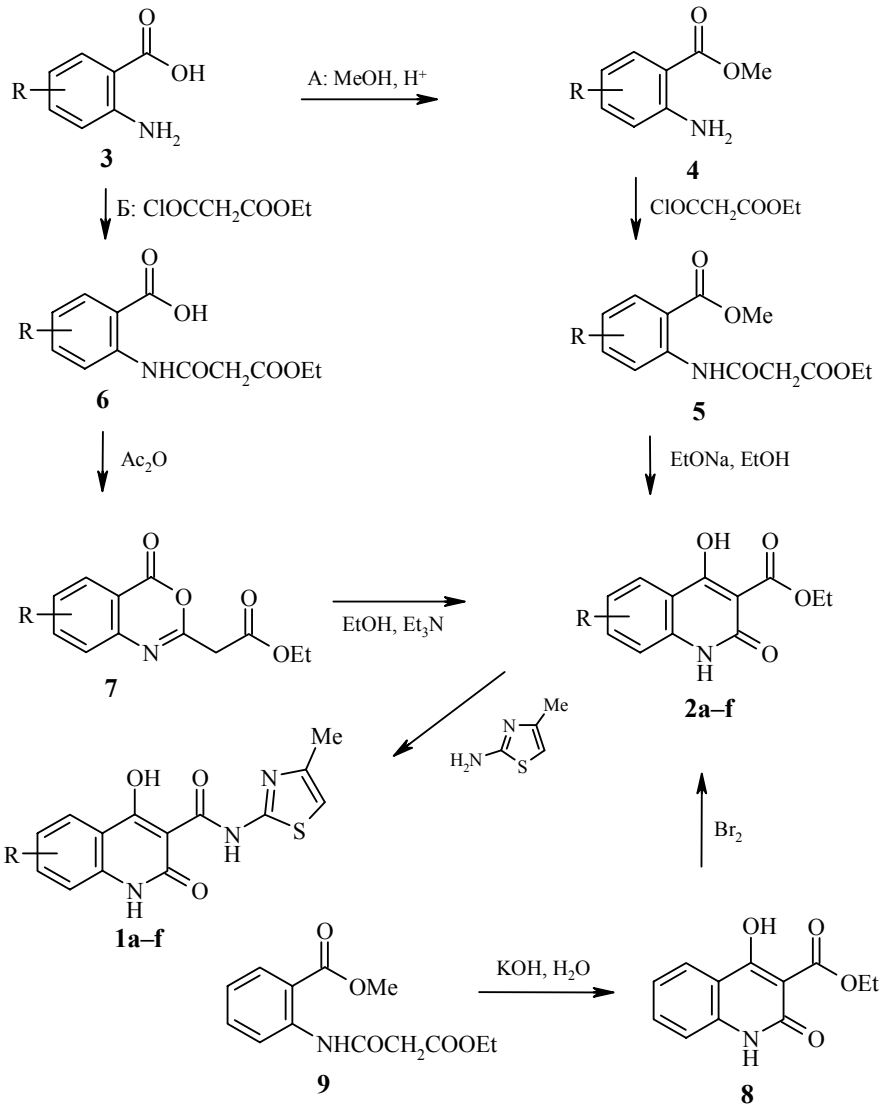
3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines **2** with satisfactory yields. However, the laborious esterification of anthranilic acids, which rarely gives high yields, along with the high cost of the halogen derivatives, significantly lowers the usefulness of this method on the whole.



1, 2 a R = 6-F, **b** R = 6,7-F_2, **c** R = 6-Cl, **d** R = 7-Cl, **e** R = 6-Br, **f** R = 6-I

In order to avoid this disadvantage, we employed another synthetic scheme, in which the anthranilic acids are directly acylated by ethoxymalonyl chloride. The resultant ethyl esters of 2-carboxymalonanilic acids **6** are condensed with 2-ethoxycarbonylmethyl-3,1-benzoxazin-4-ones **7** by the action of acetic anhydride. In turn, benzoxazinones **7** are recyclized by treatment with triethylamine in absolute methanol to give esters of 3-quinolinecarboxylic acids **2** (method B). The entire chain of these chemical transformations can be carried out in high yield without separation of the intermediates, which recommends this approach as a preparative method.

Still another variant is possible for the synthesis of esters 2. This method involves halogenation of previously prepared unsubstituted ethyl ester of 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (**8**). A significant advantage of this method lies in the possibility of heterocyclization of diester **9** using aqueous alkali hydroxide [7], while analogs **5**, which are substituted in the benzene ring, undergo hydrolysis under these

TABLE. 1. Characteristics of Ethyl Esters of Halogen Derivatives of 4-Hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acids **2a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C* (dec.)	Yield, % (method
		C	H	N		
2a	$C_{12}H_{10}FNO_4$	57.44 / 57.37	4.17 / 4.01	5.42 / 5.58	~200	80 (B)
2b	$C_{12}H_9F_2NO_4$	53.69 / 53.54	3.35 / 3.37	5.28 / 5.20	~200	78 (B)
2c	$C_{12}H_{10}ClNO_4$	53.80 / 53.85	3.71 / 3.77	5.31 / 5.23	~200	57 (A), 83 (B)
2d	$C_{12}H_{10}ClNO_4$	53.93 / 53.85	3.76 / 3.77	5.16 / 5.23	~200	80 (B)
2e	$C_{12}H_{10}BrNO_4$	46.11 / 46.18	3.30 / 3.23	4.61 / 4.49	~200	85 (B)
2f	$C_{12}H_{10}INO_4$	40.27 / 40.14	2.66 / 2.81	3.78 / 3.90	~200	82 (B)

* All esters **2** are converted without melting at about 200°C into compounds with mp >320°C, which are probably halogen analogs of 6,7,8-trioxodiquinolino[3,4-b;3',4'-e]-4H-pyrans [12].

conditions. Nevertheless, this advantage is lost in the final step since the halogenation of esters **8** at $C_{(6)}$ of the quinoline system is possible only in thoroughly dried solvents and has been studied so far only for the bromination [1]. Thus, this method was not examined as an alternative to methods A and B.

Upon fusion with an equimolar amount of 4-methyl-2-thiazolylamine, ethyl esters **2** give the desired hetarylamides of halogen derivatives of 4-hydroxy-2-oxo-dihydro-3-quinolinecarboxylic acids **1a-f** in high yields. Carboxylic acids **1a-f** are colorless crystalline compounds virtually insoluble in water (Table 2). The structures of all these products were supported by their ^{1}H NMR spectra (Table 3).

TABLE 2. Characteristics of 4-Methyl-2-thiazolylamides of 4-Hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acids **1a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (dec.)	Yield, %	Growth delay *M. tuberculosis* at *c* 6.25 μg/ml, %	MIC*, %, at *c* 6.25 μg/ml
		C	H	N				
1a	$C_{14}H_{10}FN_3O_3S$	52.50 / 52.66	3.24 / 3.16	13.25 / 13.16	296	91	100	0.39
1b	$C_{14}H_9F_2N_3O_3S$	49.77 / 49.85	2.80 / 2.69	12.40 / 12.46	253	90	100	0.39
1c	$C_{14}H_{10}ClN_3O_3S$	50.19 / 50.08	3.08 / 3.00	12.62 / 12.51	285	92	99	0.39
1d	$C_{14}H_{10}ClN_3O_3S$	50.22 / 50.08	3.13 / 3.00	12.45 / 12.51	294	95	100	0.78
1e	$C_{14}H_{10}BrN_3O_3S$	44.17 / 44.23	2.59 / 2.65	11.16 / 11.05	306	94	99	0.39
1f	$C_{14}H_{10}IN_3O_3S$	39.44 / 39.36	2.28 / 2.36	9.75 / 9.84	313	87	100	0.78

* MIC – minimal inhibition concentration.

TABLE 3. ^{1}H NMR Spectra of Synthesized Compounds

Compounds	Chemical shifts, δ, ppm (*J*, Hz)									
	4-OH (1H, s)	NH (1H, s)	NH (1H, s)	H arom. quinolone			H arom thiazole (1H, s)	CH_3 (3H, s)	$COOCH_2CH_3$	
				H-5 (1H)	H-7 (1H)	H-8 (1H)			CH_2 (2H, q, *J* = 7.0)	CH_3 (3H, t, *J* = 7.0)
2a	13.20	11.33	—	7.76-7.34 (3H, m)			—	—	4.33	1.30
2b	13.30	11.62	—	7.87 (m)	—	7.19 (m)	—	—	4.30	1.27
2c	13.28	11.46	—	7.88 (d, *J* = 2.6)	7.65 (dd, *J* = 9.0, *J* = 2.6)	7.27 (d, *J* = 9.0)	—	—	4.31	1.30
2d	13.15	11.25	—	7.75 (d, *J* = 8.9)	7.17 (dd, *J* = 8.9, *J* = 2.4, H-6)	7.26 (d, *J* = 2.4)	—	—	4.30	1.29
2e	13.22	11.67	—	8.01 (d, *J* = 2.4)	7.74 (dd, *J* = 9.0, *J* = 2.4)	7.22 (d, *J* = 9.0)	—	—	4.36	1.37
2f	13.24	11.56	—	8.18 (d, *J* = 2.2)	7.87 (dd, *J* = 8.8, *J* = 2.2)	7.08 (d, *J* = 8.8)	—	—	4.32	1.30
1a	15.00	13.67	12.24	7.78-7.35 (3H, m)			6.91	2.25	—	—
1b	14.76	13.45	12.34	7.90 (m)	—	7.22 (m)	6.88	2.24	—	—
1c	14.87	13.50	12.37	7.92 (s)	7.72 (dd, *J* = 8.7, *J* = 2.4)	7.40 (d, *J* = 9.0)	6.90	2.30	—	—
1d	14.96	13.49	12.25	7.94 (d, *J* = 8.7)	7.33 (d, *J* = 8.7, H-6)	7.27 (s)	6.87	2.25	—	—
1e	15.07	13.53	12.33	8.08 (s)	7.85 (dd, *J* =9.0, *J* = 2.7)	7.35 (d, *J* = 9.0)	6.91	2.30	—	—
1f	14.92	13.41	12.28	8.23 (s)	7.95 (dd, *J* = 8.9, *J* = 2.2)	7.20 (d, *J* = 8.9)	6.87	2.30	—	—

The antitubercular properties of amides **1a-f** were studied at the National Allergy and Infectious Diseases Institute of the United States according to a program of the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) using a radiometric method [8-11]. These results given in Table 2 indicate that 4-methyl-2-thiazolylamides of halogen derivatives of 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acids **1a-f** are capable of effecting 99-100% inhibition of the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294 at *c* 6.25 μg/ml independent of the nature of the halogen atom in the quinoline system, while their actual MIC is lower than the value for the unsubstituted analog [6] by a factor of 2-4.

EXPERIMENTAL

The ^{1}H NMR spectra of the products were recorded on a Varian Mercury-VX-200 spectrometer at 200 MHz in DMSO-d_6 using TMS as the internal standard.

4-Methyl-2-thiazolylamides of Halogen Derivatives of 4-Hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic Acids 1a-f (General Method). A mixture of (0.01 mol) ethyl ester of the corresponding 4-hydroxy-2-oxo-1,2-dihydroquinolinecarboxylic acid **2** , 2-amino-4-methylthiazole (1.14 g, 0.01 mol) and DMF (1-2 ml) was stirred and maintained for 3 min in a metal bath at 160-180°C. The mixture was cooled and ethanol (30 ml) was added. The mixture was thoroughly stirred and filtered to give amide **1**, which was washed on a filter with ethanol, dried, and crystallized from DMF.

Ethyl Ester of 6-Chloro-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (2c). A. A sample of concentrated sulfuric acid (17 ml) was added carefully to a solution of 5-chloroanthranilic acid **3** (17.15 g, 0.1 mol) in methanol (100 ml). The reaction mixture was maintained for 15 h on a steam bath. Excess methanol was removed and the residue was cooled. Then, cold water (200 ml) was added, followed by sodium carbonate to bring the pH of the aqueous layer to 8. The precipitate of methyl 5-chloroanthranilate **4** was extracted with three 50-ml portions of CH_2Cl_2. The organic extracts were combined and the solvent was removed to give 12.8 g (69%) technical-grade methyl anthranilate **4**, which was acylated without further purification as follows. The sample was dissolved in CH_2Cl_2 and triethylamine (10.6 ml, 0.076 mol) was added. Then, ethoxymalonyl chloride (11.44 g, 0.076 mol) was added with stirring to the cooled solution and left at room temperature for 4-5 h. The reaction mixture was diluted with water. The organic layer was separated and dried over anhydrous calcium chloride. The solvent was removed, initially at normal pressure and, finally, at reduced pressure. A solution of sodium ethylate obtained by adding metallic sodium (2.3 g, 0.1 mol) to absolute ethanol (150 ml) was added to the residual 2-carbomethoxyanilide **5** and heated at reflux for 30 min on a steam bath. Heating was discontinued and the mixture was left for 7-8 h at room temperature. The reaction mixture was diluted with water and made acidic by adding a solution composed of one part concentrated hydrochloric acid and one part water to pH 4.5-5.0. The residue was filtered off, washed with water, and dried to give 15.25 g **2c** (57% relative to 5-chloroanthranilic acid **3**).

B. A sample of 5-chloroanthranilic acid **5** (17.15 g, 0.1 mol) was acylated using ethoxymalonyl chloride using the method described in the preceding experiment. After removal of the solvent, the residue of 2-carboxyanilide **6** was heated at reflux for 3 h in acetic anhydride (150 ml). The excess condensing agent was distilled off and absolute ethanol (100 ml) was added to the resultant 4-benzoxazinone **7**, followed by triethylamine (20 ml). The reaction mixture was heated at reflux for 10 h, cooled, and treated analogously to method A to give 22.21 g (83%) **2c**.

The melting point of a mixed probe of samples of **2c** obtained by the different methods was undepressed. The ^{1}H NMR spectra of these products were identical.

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