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4-HYDROXY-2-QUINOLONES. 26.* BROMINATION OF 3-SUBSTITUTED 2-OXO-4-HYDROXYQUINOLINES

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The bromination of 3-alkyl- and 3-ethoxycarbonyl-2-oxo-4-hydroxyquinolines by molecular bromine gave 3-bromo-3-R-2,4-dioxoquinolines. Under analogous conditions, 1-R-2,4-dioxo-3H-quinoline-3-carboxylic acids form 1-R-3-bromo-2-oxo-4-hydroxyquinolines. The results of the study of the antimicrobial activity of the compounds synthesized are presented.

The given communication is the continuation of our investigations in the search for potential antimicrobial medicinal agents among halogen-substituted quinolines [2], and is dedicated to the study of the behavior of 3-substituted 2-oxo-4-hydroxyquinolines under conditions of bromination with molecular bromine. It was established that 3-alkyl-substituted 2-oxo-4-hydroxyquinolines (I), previously described by us [3], in glacial acetic acid readily form 3-bromo-3-alkyl-2,4-dioxoquinolines (II) with high yields. Treatment of the last with sodium methoxide gives the 3-methoxy derivatives (III), whereas potassium tert,-butoxide brings about rapid dehydrobromination with the formation of the initial 3-alkylquinolines (I). The interesting behavior of the 1-R-2,4-dioxo-3H-quinoline-3-carboxylic acids (IV) under the conditions of the reaction studied should be noted. If the ethyl esters (V), similarly to the 3-alkylquinolones (I), form the corresponding 3-bromo-2,4-dioxo derivatives (VI), then the treatment of the acids (IV) with bromine led to the isolation, from the reaction mixture, of the 1-R-3-bromo-2-oxo-4-hydroxyquinolines (VII), the structure of which was confirmed by direct synthesis using the acid hydrolysis of the esters (VI). The strongly marked acidic properties and, consequently, also the ease of decarboxylation [4] of the initially formed 3-bromo-2,4-dioxoquinoline-3-carboxylic acids (VIII) can be explained by several factors. Firstly, by the possibility of the stabilization of anions of the acids (IV) due to delocalization of their charges by means of the formation of intramolecular hydrogen bonds of the ortho-effect type in the o-hydroxy- and, especially, o-dihydroxybenzoic acids [4]. These factors evidently explain the ease of the amidation of the 1-R-2,4-3H-quinoline-3-carboxylic acids [5]. Secondly, the introduction of the electron-acceptor substituent (the bromine atom) in the α-position relative to the carboxyl group determines the significant increase in the acidity even more [4]. The summation of the effects indicated probably also leads to the fact that the bromine-substituted acids (VIII) are already decarboxylated at room temperature. Taking into account the simple synthesis of the 1-R-2,4-3H-quinoline-3-carboxylic acids (IV) [6] and the smooth course of their bromination, the given method can be recommended as a preparative method for the synthesis of 1-R-3-bromo-2-oxo-4-hydroxyquinolines (VII).

The antibacterial activity of the compounds synthesized was determined by the method of twofold serial dilutions [7] in Khottinger beef–peptone broth (pH 7.2-7.4). The test cultures utilized were *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (ATCC 6633), and *Pseudomonas aeruginosa* (ATCC 78857). Of all the substances studied, the most active were found to be the methyl (IIa), (VIIa) and hexyl (VIIc) derivatives, which show a universal bacteriostatic effect toward all the investigated test strains of the microorganisms at the dose of 60 μg/ml. The activity of the other quinolines is less marked, and is absent, in general, for the bromine-substituted ester (VIa). It is interesting that this compound completely inhibits the antibacterial action of the solvent — ethyl alcohol.

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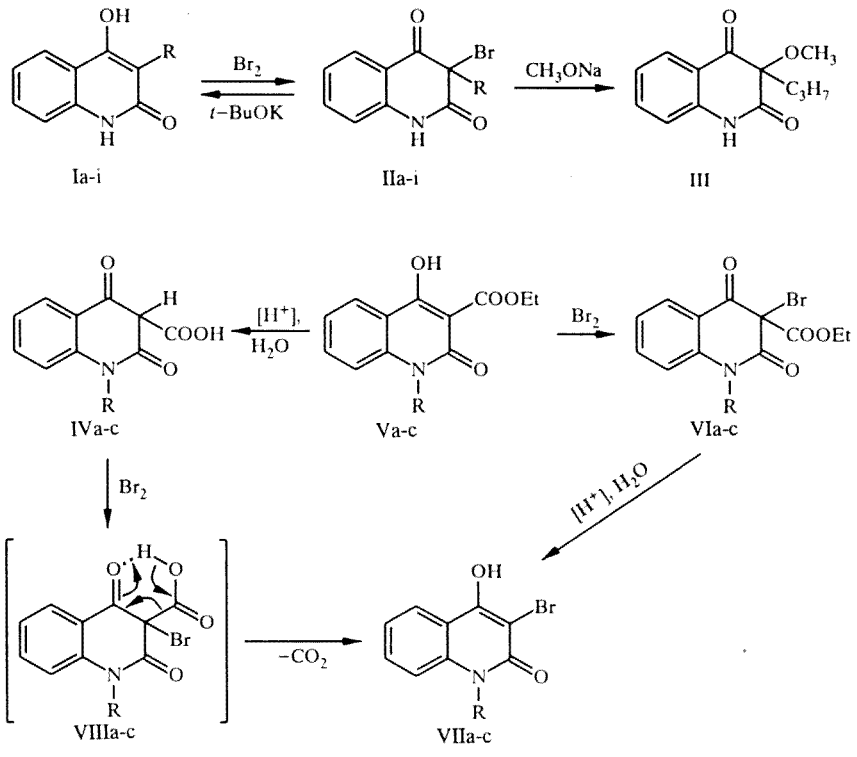

I, II a R = CH_3, b R = C_2H_5, c R = C_3H_7, d R = C_4H_9, e R = C_5H_{11}, f R = C_6H_{13}, g R = C_7H_{15}, h R = C_8H_{17}, i R = CH_2—C_6H_5; V, VI a R = H, b R = CH_3, c R = C_2H_5; IV, VII a R = CH_3, d R = C_2H_5, e R = C_6H_{13}

EXPERIMENTAL

The PMR spectra of the compounds synthesized were recorded on the Bruker WP-100 SY instrument in DMSO-D_6; the internal standard was TMS.

The data of the elemental analysis for C, H, N, and Br correspond with the calculated data.

General Method for the Isolation of 3-Bromo-3-alkyl-2,4-dioxoquinolines (IIa-i). To the solution of 0.01 mole of the corresponding 3-alkylquinoline (I) in 10 ml of glacial acetic acid is added 0.52 ml (0.01 mole) of bromine, and the mixture is stirred and left for 30-40 min at room temperature. The reaction mixture is diluted with 100 ml of water. The precipitated residue of the 3-bromine-substituted quinoline (II) is filtered off, washed with water, and dried.

3-Methoxy-3-propyl-2,4-dioxoquinoline (III) ($C_{13}H_{15}NO_3$). To the solution of 2.82 g (0.01 mole) of 3-bromo-3-propyl-2,4-dioxoquinoline (IIc) in 15 ml of absolute methanol is added the solution of sodium methoxide [from 0.25 g (0.011 mole) of metallic sodium and 10 ml of absolute methanol], and the mixture is boiled for 30 min. The mixture is cooled and acidified with HCl to the pH 4. The precipitated residue of the methoxy derivative (III) is filtered off, washed with water, and dried. The yield is 2.19 g (94%). The mp is 158-160°C (methanol). The PMR spectrum is as follows: 10.97 ppm (1H, s, NH), 7.76 ppm (1H, d, J = 7.8 Hz, 5-H), 7.62 ppm (1H, td, J = 7.0 and 1.8 Hz, 7-H), 7.21-7.00 ppm (2H, m, 6,8-H), 3.17 ppm (3H, s, OCH_3), 1.71 ppm (2H, t, $CH_2CH_2CH_3$), 1.22 ppm (2H, m, $\underline{CH_2}CH_3$), and 0.75 ppm (3H, t, $CH_2\underline{CH_3}$).

Ethyl 1H-2,4-Dioxo-3-bromoquinoline-3-carboxylate (VIa) ($C_{12}H_{10}BrNO_4$). This compound was obtained from the ester (Va) by the method of the bromination of the 3-alkylquinolines (I). The yield is 87%. The mp is 82-84°C (ethanol). The PMR spectrum is as follows: 11.64 ppm (1H, s, NH), 7.89 ppm (1H, d, J = 7.9 Hz, 5-H), 7.76 ppm (1H, td, J = 7.0 and 1.8 Hz, 7-H), 7.25 ppm (2H, t, J = 7.3 Hz, 6,8-H), 4.27 ppm (2H, q, J = 6.8 Hz, OCH_2), and 1.17 ppm (3H, t, J = 6.8 Hz, CH_3).

Ethyl 1-Ethyl-2,4-dioxo-3-bromoquinoline-3-carboxylate (VIc) ($C_{14}H_{14}BrNO_4$). This compound was obtained analogously. The yield is 73%. The mp is 44-45°C (ethanol). The PMR spectrum is as follows: 7.90 ppm (1H, d, J = 7.9

TABLE 1. Characteristics of the 3-Bromo-3-alkyl-2,4-dioxoquinolines (IIa-i)

Compound	Empirical formula	mp, °C (ethanol)	PMR spectral parameters. δ, ppm					Yield, %
			NH (1H,S,)	H_{arom}			R	
				5-H, (1H, dd, J, Hz)	7-H (1H, td, J, Hz)	6,8-H (2H, t, J, hz)		
IIa	$C_{10}H_8BrNO_2$	168...170	11,02	7,89 (8,0, 2,0)	7,61 (7,9, 1,7)	7,14 (7,9)	1,95 (3H, s, CH_3)	89
IIb	$C_{11}H_{10}BrNO_2$	140...142	11,27	7,86 (8,1, 2,0)	7,67 (8,0, 2,0)	7,19 (9,0)	2,44 (2H, q, CH_2), 0,83 (3H, t, CH_3)	91
IIc	$C_{12}H_{12}BrNO_2$	76...78	11,42	8,00 (8,0, 2,0)	7,81 (7,3, 1,8)	7,32 (8,0)	2,45 (2H, t, CH_2), 1,34 (2H, m, CH_2CH_3), 0,82 (3H, t, CH_3)	84
IId	$C_{13}H_{14}BrNO_2$	111...113	11,30	7,87 (8,0, 2,0)	7,69 (7,0, 1,7)	7,19 (7,6)	2,41 (2H, t, CH_2), 1,20 (4H, m, $(CH_2)_2CH_3$), 0,84 (3H, t, CH_3)	87
IIe	$C_{14}H_{16}BrNO_2$	118...120	11,30	7,86 (7,8, 1,8)	7,69 (7,0, 1,7)	7,19 (8,0)	2,40 (2H, t, CH_2), 1,24 (6H, m, $(CH_2)_3CH_3$), 0,83 (3H, t, CH_3)	90
IIf	$C_{15}H_{18}BrNO_2$	74...76	11,29	7,86 (8,1, 2,0)	7,68 (7,2, 1,8)	7,19 (7,8)	2,38 (2H, t, CH_2), 1,22 (8H, s, $(CH_2)_4CH_3$), 0,83 (3H, t, CH_3)	84
IIg	$C_{16}H_{20}BrNO_2$	72...74	11,47	8,04 (8,0, 2,0)	7,85 (7,2, 1,8)	7,36 (8,0)	2,47 (2H, t, CH_2), 1,35 (1 OH, s, $(CH_2)_5CH_3$), 1,01 (3H, t, CH_3)	82
IIh	$C_{17}H_{22}BrNO_2$	68...70	11,27	7,85 (8,0, 1,8)	7,68 (7,0, 1,7)	7,19 (7,9)	2,40 (2H, t, CH_2), 1,21 (12H, s, $(CH_2)_6CH_3$), 0,84 (3H, t, CH_3)	80
IIi	$C_{16}H_{12}BrNO_2$	156...158	11,36	7,86 (8,0, 2,0)	7,61 (7,1, 1,8)	7,30...6,97 (7H, m, 6,8-H + Ph)	3,84 (2H, s, CH_2), Ph s m. 6,8-H	94

Hz, 5-H), 7.79 ppm (1H, td, J = 7.0 and 1.9 Hz, 7-H), 7.27 ppm (2H, t, J = 7.3 Hz, 6,8-H), 4.29 ppm (2H, q, CH_2), 3.25 ppm (2H, q, CH_2), 1.31 ppm (3H, t, CH_3), and 1.11 ppm (3H, t, CH_3).

1-Methyl-2-oxo-3-bromo-4-hydroxyquinoline (VIIa) ($C_{10}H_8BrNO_2$). A. This compound was obtained by the bromination of the acid (IVa) according to the general method. The yield is 93%. The mp is 158-160°C (ethanol). The PMR spectrum is as follows: 14.60 ppm (1H, s, OH), 8.15 ppm (1H, d, J = 8.0 Hz, 5-H), 7.94 ppm (1H, t, J = 7.4 Hz, 7-H), 7.77 ppm (1H, d, J = 8.1 Hz, 8-H), 7.51 ppm (1H, t, J = 7.3 Hz, 6-H), and 3.72 ppm (3H, s, CH_3).

B. To the solution of 2.47 g (0.01 mole) of the ester (Vb) in 30 ml of chloroform is added 0.52 g (0.01 mole) of bromine, and the mixture is stirred and left for 30 min. Then, to the reaction mixture containing the bromine-substituted ester (VIb) are added 100 ml of water prior to the boiling with the simultaneous distillation of the chloroform (the HBr released in the process of bromination is sufficient for the hydrolysis). The residue of the bromoquinoline (VIIa) is filtered off, washed with water, and dried. The yield is 2.11 g (83%).

The mixed test with the sample obtained according to the method A does not give a depression of the melting temperature.

1-Ethyl-2-oxo-3-bromo-4-hydroxyquinoline (VIIb) ($C_{11}H_{10}BrNO_2$). This compound was obtained by the method B of the preceding experiment. The yield is 86%. The mp is 163-164° (ethanol). The PMR spectrum is as follows: 14.39 ppm (1H, s, OH), 8.21 ppm (1H, d, J = 8 Hz, 5-H), 7.92 ppm (1H, t, J = 7.5 Hz, 7-H), 7.74 ppm (1H, d, J = 8.1 Hz, 8-H), 7.53 ppm (1H, t, J = 7.3 Hz, 6-H), 4.40 ppm (2H, q, CH_2), and 1.28 ppm (3H, t, CH_3).

1-Hexyl-2-oxo-3-bromo-4-hydroxyquinoline (VIIc) ($C_{15}H_{18}BrNO_2$). This compound was obtained by the method A. The yield is 84%. The mp is 70-72°C (ethanol). The PMR spectrum is as follows: 14.15 ppm (1H, s, OH), 8.02 ppm (1H, d, J = 8.0 Hz, 5-H), 7.69 ppm (1H, t, J = 7.4 Hz, 7-H), 7.52 ppm (1H, d, J = 8.1 Hz, 8-H), 7.28 ppm (1H, t, J = 7.3 Hz, 6-H), 4.20 ppm (1H, t, N−CH_2), 1.54 ppm (2H, q, $NCH_2\underline{CH_2}$), 1.31 ppm [6H, s, $(\underline{CH_2})_3CH_3$], and 0.87 ppm (3H, t, CH_3).

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