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4-HYDROXY-2-QUINOLONES. 149*. SYNTHESIS, CHEMICAL TRANSFORMATIONS, AND BIOLOGICAL PROPERTIES OF β-N-ACYLHYDRAZIDES OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-4-CARBOXYLIC ACIDS

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Two methods of preparation have been proposed and the synthesis has been effected of a large series of β-N-acylhydrazides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids. The possibility of using various condensing agents for converting them into the corresponding 1,3,4-oxadiazoloquinolines has been studied. Results are given of an investigation of the antitubercular activity of the synthesized compounds.

Keywords: acylhydrazines, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, 1,3,4-oxadiazoles, antitubercular activity.

A characteristic feature of the search for new medicinal agents under modern conditions is purpose-directed synthesis based on developing, accumulating, and systematizing empirical data on the relation between chemical structure and the biological properties of substances. It is impossible in principle to develop rules of such a type from the example of any one compound. It is necessary to study a series of related structures [2]. The present communication is the investigation of just such a series, the aim of which is the definition in the structure of previously described benzylidenehydrazides of 1-R-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acids [3-5] of functional groups strengthening or, on the other hand, weakening the antitubercular activity of these substances.

To carry out the projected aim we obtained, and then subjected to microbiological screening, β-N-acylhydrazides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **1-4**, which are formally derivatives of the acylhydrazones indicated above. The subjects of the investigation were synthesized by the two methods given in the scheme: by hydrazinolysis of the ethyl esters of quinoline-3-carboxylic acids **5** with subsequent acylation of the intermediate hydrazides **6** (method A) or by the direct reaction of esters **5** with previously obtained benzoylhydrazines (method B). Both methods are fairly simple in use, are readily reproduced, and give good yields of the desired 1,2-diacylhydrazines **1-4** (see Table 1). At first sight method B appears preferable since it is possible to form the final compounds in one step. At the same time each of the reactions in method A is distinguished by high

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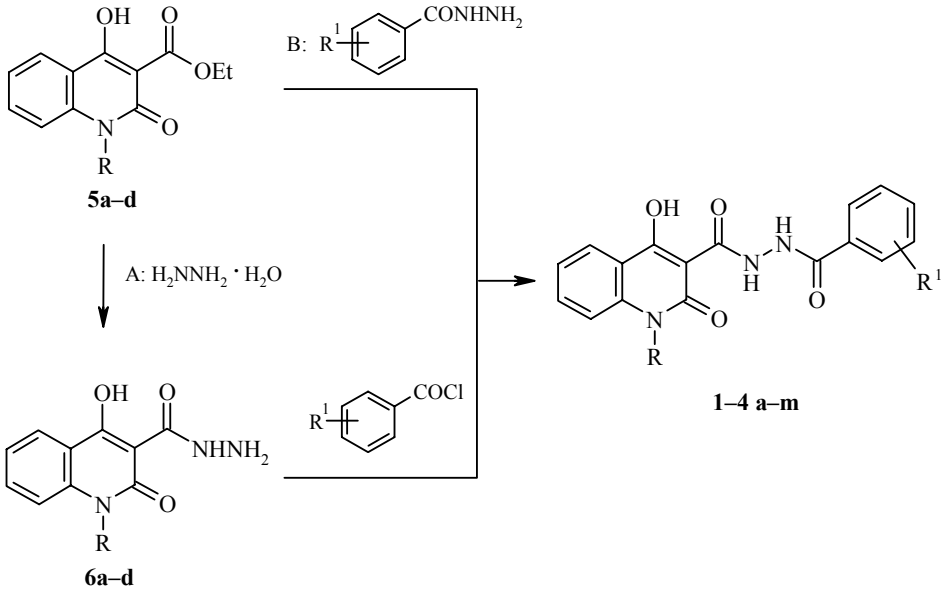
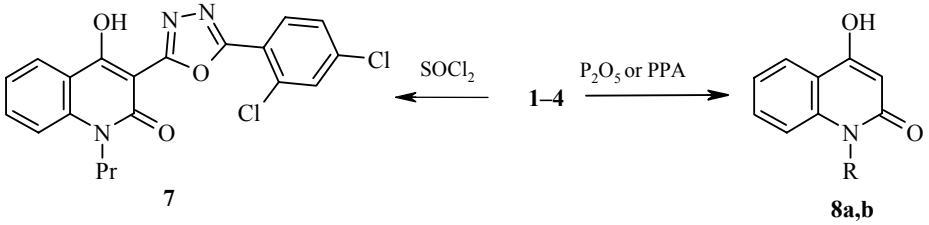
efficiency. In fact the main criterion when selecting one or other of the methods of obtaining 1,2-diacylhydrazines **1-4** in each actual case is the availability of the respective reactants, *viz.* the presence of the prepared hydrazides of aromatic carboxylic acids using method B, or in the absence of them using the linear synthetic scheme A.



1a–m, 5,**6 a** R = H, **2a–m, 5**,**6 b** R = Me, **3a–m, 5**,**6 c** R = Et, **4a–m, 5**,**6 d** R = Pr;
1–4 a R^1 = H, **b** R^1 = 2-F, **c** R^1 = 2-Cl, **d** R^1 = 3-Cl, **e** R^1 = 2-Br, **f** R^1 = 4-Br, **g** R^1 = 2,4-Cl_2,
h R^1 = 2-NO_2, **i** R^1 = 3-NO_2, **j** R^1 = 4-NO_2, **k** R^1 = 3,5-$(NO_2)_2$, **l** R^1 = 3-Me, **m** R^1 = 4-Me

All the synthesized 1,2-diacylhydrazines **1-4** (Table 1) were colorless crystalline substances practically insoluble in water and weakly soluble in alcohols. In their ^{1}H NMR spectra (Table 2) signals of 7-9 protons close in properties were concentrated in the fairly narrow section from 7.25 to 8.18 ppm in the "aromatic" region of the spectrum. Consequently precise assignment was difficult if not impossible in the majority of cases without using special NMR procedures. Only in the spectra of the 3,5-dinitrobenzoyl derivatives **1k-4k**, thanks to the two possessing the powerful magnetic anisotropy nitro groups, were the signals of the protons of the β-N-acyl residues strongly displaced towards low field and overlap with the signals of the quinolone protons was not observed.

The microbiological testing carried out showed that *in vitro* none of the obtained 1,2-diacylhydrazines **1-4** at a concentration of 6.25 μg/ml was capable of inhibiting to a significant degree the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294. The negative effect on antitubercular activity of replacing the azomethine grouping in benzylidenehydrazines of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids by an amide fragment similar in structure has therefore been confirmed experimentally.



8 a R = Et, **b** R = Pr

TABLE 1. Characteristics of 1,2-Diacylhydrazines **1-4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	
		C	H	N		A	B
1	2	3	4	5	6	7	8
1a	$C_{17}H_{13}N_3O_4$	63.21 / 63.16	4.12 / 4.05	13.08 / 13.00	323-325		90
1b	$C_{17}H_{12}FN_3O_4$	59.75 / 59.83	3.47 / 3.54	12.41 / 12.31	295-297		93
1c	$C_{17}H_{12}ClN_3O_4$	57.00 / 57.08	3.29 / 3.38	11.83 / 11.75	326-328	91	
1d	$C_{17}H_{12}ClN_3O_4$	57.03 / 57.08	3.33 / 3.38	11.81 / 11.75	318-320	95	
1e	$C_{17}H_{12}BrN_3O_4$	50.85 / 50.77	3.11 / 3.01	10.54 / 10.45	330-332	84	
1f	$C_{17}H_{12}BrN_3O_4$	50.82 / 50.77	3.08 / 3.01	10.51 / 10.45	392-394		92
1g	$C_{17}H_{11}Cl_2N_3O_4$	52.01 / 52.06	2.89 / 2.83	10.83 / 10.71	376-378	85	
1h	$C_{17}H_{12}N_4O_6$	55.51 / 55.44	3.20 / 3.28	15.17 / 15.21	339-341	82	
1i	$C_{17}H_{12}N_4O_6$	55.49 / 55.44	3.36 / 3.28	15.15 / 15.21	321-323	88	
1j	$C_{17}H_{12}N_4O_6$	55.53 / 55.44	3.32 / 3.28	15.28 / 15.21	355-357	87	
1k	$C_{17}H_{11}N_5O_8$	49.35 / 49.40	2.60 / 2.68	17.03 / 16.94	220 (dec.)	90	
1l	$C_{18}H_{15}N_3O_4$	64.17 / 64.09	4.54 / 4.48	12.53 / 12.46	334-336	93	
1m	$C_{18}H_{15}N_3O_4$	64.16 / 64.09	4.41 / 4.48	12.55 / 12.46	328-330		91
2a	$C_{18}H_{15}N_3O_4$	64.13 / 64.09	4.56 / 4.48	12.40 / 12.46	137-139		88
2b	$C_{18}H_{14}FN_3O_4$	60.94 / 60.85	4.03 / 3.97	11.89 / 11.83	192-194		91
2c	$C_{18}H_{14}ClN_3O_4$	58.08 / 58.15	3.71 / 3.80	11.37 / 11.30	170-172	90	
2d	$C_{18}H_{14}ClN_3O_4$	58.17 / 58.15	3.83 / 3.80	11.39 / 11.30	153-155	93	
2e	$C_{18}H_{14}BrN_3O_4$	51.98 / 51.94	3.46 / 3.39	10.04 / 10.10	189-191	87	
2f	$C_{18}H_{14}BrN_3O_4$	51.87 / 51.94	3.44 / 3.39	10.17 / 10.10	197-199		90
2g	$C_{18}H_{13}Cl_2N_3O_4$	53.15 / 53.22	3.19 / 3.23	10.41 / 10.34	279-281	86	
2h	$C_{18}H_{14}N_4O_6$	56.63 / 56.55	3.74 / 3.69	14.70 / 14.65	243-245	83	
2i	$C_{18}H_{14}N_4O_6$	56.61 / 56.55	3.77 / 3.69	14.62 / 14.65	234-236	87	
2j	$C_{18}H_{14}N_4O_6$	56.50 / 56.55	3.62 / 3.69	14.57 / 14.65	215-217	88	
2k	$C_{18}H_{13}N_5O_8$	50.55 / 50.59	3.01 / 3.07	16.47 / 16.39	218 (dec.)	85	
2l	$C_{19}H_{17}N_3O_4$	64.86 / 64.95	4.80 / 4.88	12.03 / 11.96	224-226	89	
2m	$C_{19}H_{17}N_3O_4$	64.88 / 64.95	4.82 / 4.88	11.90 / 11.96	205-207		90
3a	$C_{19}H_{17}N_3O_4$	64.87 / 64.95	4.80 / 4.88	12.04 / 11.96	102-104	94	92
3b	$C_{19}H_{16}FN_3O_4$	61.85 / 61.79	4.32 / 4.37	11.46 / 11.38	188-190		86
3c	$C_{19}H_{16}ClN_3O_4$	59.13 / 59.15	4.22 / 4.18	10.94 / 10.89	174-176	95	
3d	$C_{19}H_{16}ClN_3O_4$	59.23 / 59.15	4.27 / 4.18	10.97 / 10.89	115-117	96	
3e	$C_{19}H_{16}BrN_3O_4$	53.11 / 53.04	3.80 / 3.75	9.83 / 9.77	196-198	89	

TABLE 1 (continued)

1	2	3	4	5	6	7	8
3f	$C_{19}H_{16}BrN_3O_4$	53.09 53.04	3.82 3.75	9.85 9.77	222-224		91
3g	$C_{19}H_{15}Cl_2N_3O_4$	54.24 54.30	3.52 3.60	10.11 10.00	227-229	88	
3h	$C_{19}H_{16}N_4O_6$	57.51 57.58	4.00 4.07	14.05 14.14	243-245	85	
3i	$C_{19}H_{16}N_4O_6$	57.68 57.58	4.16 4.07	14.19 14.14	271-273	90	
3j	$C_{19}H_{16}N_4O_6$	57.63 57.58	4.14 4.07	14.10 14.14	188-190	92	
3k	$C_{19}H_{15}N_5O_8$	51.65 51.71	3.36 3.43	15.80 15.87	223 (dec.)	87	
3l	$C_{20}H_{19}N_3O_4$	65.83 65.74	5.31 5.24	11.62 11.50	190-192	88	
3m	$C_{20}H_{19}N_3O_4$	65.81 65.74	5.27 5.24	11.55 11.50	182-184		91
4a	$C_{20}H_{19}N_3O_4$	65.70 65.74	5.19 5.24	11.45 11.50	96-98		86
4b	$C_{20}H_{18}FN_3O_4$	62.74 62.66	4.79 4.73	11.03 10.96	172-174		89
4c	$C_{20}H_{18}ClN_3O_4$	60.15 60.08	4.50 4.54	10.53 10.51	161-163	85	
4d	$C_{20}H_{18}ClN_3O_4$	60.02 60.08	4.47 4.54	10.58 10.51	120-122	90	
4e	$C_{20}H_{18}BrN_3O_4$	54.13 54.07	4.16 4.08	9.51 9.46	184-186	87	
4f	$C_{20}H_{18}BrN_3O_4$	54.10 54.07	4.13 4.08	9.55 9.46	205-207		84
4g	$C_{20}H_{17}Cl_2N_3O_4$	55.25 55.31	3.86 3.95	9.74 9.68	209-211	86	
4h	$C_{20}H_{18}N_4O_6$	58.47 58.54	4.34 4.42	13.60 13.65	231-233	80	
4i	$C_{20}H_{18}N_4O_6$	58.48 58.54	4.47 4.42	13.58 13.65	217-219	85	
4j	$C_{20}H_{18}N_4O_6$	58.62 58.54	4.49 4.42	13.73 13.65	166-168	90	
4k	$C_{20}H_{17}N_5O_8$	52.67 52.75	3.66 3.76	15.29 15.38	222 (dec.)	85	
4l	$C_{21}H_{21}N_3O_4$	66.55 66.48	5.64 5.58	11.13 11.07	151-153	87	
4m	$C_{21}H_{21}N_3O_4$	66.57 66.48	5.65 5.58	11.02 11.07	144-146		89

The most convenient method of obtaining 2,5-disubstituted 1,3,4-oxadiazoles is the intramolecular cyclization of 1,2-diacylhydrazines. Closing of the oxadiazole ring may be effected thermally or even by the action of acid catalysts [6, 7]. For some time past a great number of new dehydrating agents have appeared [8-11]. However the already well-known agents have not lost their value. Moreover $POCl_3$, P_2O_5, and $SOCl_2$ are inexpensive and available [7, 12]. Treatment of diacylhydrazines **1-4** with $POCl_3$ assuredly leads to the formation of 4-chloro (or 2,4-dichloro in the case of derivatives unsubstituted at position 1) quinolines. For this reason $POCl_3$ was not considered by us as a possible condensing agent for converting 1,2-diacylhydrazines **1-4** into the corresponding 4-hydroxy-3-(1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydroquinolines **7**. The use of phosphorus pentoxide in anhydrous carbon tetrachloride and also PPA was not justified. As it turned out, on interaction with these reagents 1,2-diacylhydrazines **1-4** were readily decomposed and form 1-R-4-hydroxy-2-oxo-1,2-dihydroquinolines **8**. It is interesting that under such conditions 2-sulfamylanilides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids behave in an analogous manner [13]. But here in thionyl chloride 1,3,4-oxadiazolylquinolines **7** are formed without any complications. The high yield of the desired compounds, the simplicity of carrying out the experiment, the ease of separating the excess of cyclodehydrating reagent, and its accessibility on the whole enable this method to be recommended as preparative.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)*	
	H arom.	N- quinolone substituent
1	2	3
1a	8.03-7.25 (9H)	12.06 (1H, s, NH)
1b	8.04-7.26 (8H)	12.07 (1H, s, NH)
1c	8.03-7.28 (8H)	12.00 (1H, s, NH)
1d	8.02-7.26 (8H)	12.09 (1H, s, NH)
1e	8.04-7.27 (8H)	11.98 (1H, s, NH)
1f	8.03-7.24 (8H)	12.02 (1H, s, NH)
1g	8.04-7.28 (7H)	12.04 (1H, s, NH)
1h	8.02-7.24 (8H)	12.01 (1H, s, NH)
1i	8.74 (1H, s, H-2'); 8.48-7.25 (7H, m)	12.08 (1H, s, NH)
1j	8.26 (2H, d, *J* = 8.8, H-3',5'); 8.15-8.09 (3H, m, H-2',6',5); 7.80 (1H, td, *J* = 7.9 and *J* = 1.3, H-7); 7.67 (1H, d, *J* = 8.4, H-8); 7.36 (1H, td, *J* = 7.5 and *J* = 1.3, H-6)	12.06 (1H, s, NH)
1k	9.09 (2H, d, *J* = 2.3, H-2',6'); 8.99 (1H, t, *J* = 2.3, H-4'); 7.94 (1H, dd, *J* = 8.4 and *J* = 1.5, H-5); 7.66 (1H, td, *J* = 7.9 and *J* = 1.8, H-7); 7.35 (1H, d, *J* = 8.5, H-8); 7.25 (1H, t, *J* = 7.7, H-6)	12.10 (1H, s, NH)
1l	8.03-7.25 (8H)	12.05 (1H, s, NH)
1m	8.00 (1H, dd, *J* = 8.1 and *J* = 1.4, H-5); 7.86-7.75 (3H, m, H-2',6',7); 7.44 (1H, d, *J* = 8.5, H-8); 7.31 (1H, t, *J* = 7.4, H-6); 7.23 (2H, d, *J* = 8.3, H-3',5')	12.08 (1H, s, NH)
2a	8.11-7.30 (9H)	3.66 (3H, s, CH_3)
2b	8.12-7.27 (8H)	3.67 (3H, s, CH_3)
2c	8.14-7.35 (8H)	3.66 (3H, s, CH_3)
2d	8.13-7.22 (8H)	3.67 (3H, s, CH_3)
2e	8.17-7.35 (8H)	3.66 (3H, s, CH_3)
2f	8.15-7.32 (8H)	3.67 (3H, s, CH_3)
2g	8.16-7.34 (7H)	3.67 (3H, s, CH_3)
2h	8.16-7.36 (8H)	3.68 (3H, s, CH_3)
2i	8.80 (1H, s, H-2'); 8.51-7.30 (7H, m)	3.66 (3H, s, CH_3)
2j	8.38 (2H, d, *J* = 8.9, H-3',5'); 8.19-8.13 (3H, m, H-2',6',5); 7.87 (1H, td, *J* = 7.8 and *J* = 1.3, H-7); 7.73 (1H, d, *J* = 8.3, H-8); 7.41 (1H, td, *J* = 7.6 and *J* = 1.2, H-6)	3.67 (3H, s, CH_3)
2k	9.10 (2H, d, *J* = 2.3, H-2',6'); 9.01 (1H, t, *J* = 2.3, H-4'); 8.11 (1H, dd, *J* = 8.2 and *J* = 1.4, H-5); 7.80 (1H, td, *J* = 7.8 and *J* = 1.7, H-7); 7.67 (1H, d, *J* = 8.4, H-8); 7.38 (1H, t, *J* = 7.7, H-6)	3.68 (3H, s, CH_3)
2l	8.15-7.28 (8H)	3.67 (3H, s, CH_3)
2m	8.10 (1H, dd, *J* = 8.1 and *J* = 1.4, H-5); 7.89-7.78 (3H, m, H-2',6',7); 7.64 (1H, d, *J* = 8. 5, H-8); 7.39 (1H, t, *J* = 7.4, H-6); 7.30 (2H, d, *J* = 8.3, H-3',5')	3.66 (3H, s, CH_3)
3a	8.17-7.34 (9H)	4.34 (2H, q, *J* = 7.0, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)
3b	8.16-7.28 (8H)	4.34 (2H, q, *J* = 7.1, CH_2); 1.24 (3H, t, *J* = 7.1, CH_3)
3c	8.15-7.33 (8H)	4.33 (2H, q, *J* = 7.1, NCH_2); 1.25 (3H, t, *J* = 7.1, CH_3)
3d	8.16-7.26 (8H)	4.35 (2H, q, *J* = 7.0, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)
3e	8.18-7.36 (8H)	4.35 (2H, q, *J* = 7.1, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)
3f	8.17-7.33 (8H)	4.34 (2H, q, *J* = 7.0, NCH_2); 1.26 (3H, t, *J* = 7.0, CH_3)
3g	8.18-7.33 (7H)	4.34 (2H, q, *J* = 7.0, NCH_2); 1.24 (3H, t, *J* = 7.0, CH_3)
3h	8.15-7.32 (8H)	4.33 (2H, q, *J* = 7.1, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)

TABLE 2 (continued)

1	2	3
3i	8.81 (1H, s, H-2'); 8.52-7.33 (7H, m)	4.34 (2H, q, *J* = 7.0, NCH_2); 1.26 (3H, t, *J* = 7.0, CH_3)
3j	8.37 (2H, d, *J* = 8.9, H-3',5'); 8.18-8.10 (3H, m, H-2',6',5); 7.85 (1H, td, *J* = 7.8 and *J* = 1.4, H-7); 7.71 (1H, d, *J* = 8.5, H-8); 7.40 (1H, td, *J* = 7.6 and *J* = 1.3, H-6)	4.35 (2H, q, *J* = 7.0, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)
3k	9.08 (2H, d, *J* = 2.3, H-2',6'); 9.00 (1H, t, *J* = 2.3, H-4'); 8.08 (1H, dd, *J* = 8.3 and *J* = 1. 3, H-5); 7.77 (1H, td, *J* = 7.7 and *J* = 1.6, H-7); 7.65 (1H, d, *J* = 8.5, H-8); 7.38 (1H, t, *J* = 7.6, H-6)	4.36 (2H, q, *J* = 7.1, NCH_2); 1.24 (3H, t, *J* = 7.1, CH_3)
3l	8.16-7.27 (8H)	4.34 (2H, q, *J* = 7.1, NCH_2); 1.25 (3H, t, *J* = 7.0, CH_3)
3m	8.13 (1H, dd, *J* = 8.0 and *J* = 1.2, H-5); 7.90-7.79 (3H, m, H-2',6',7); 7.70 (1H, d, *J* = 8.6, H-8); 7.41 (1H, t, *J* = 7.6, H-6); 7.31 (2H, d, *J* = 8.2, H-3',5')	4.34 (2H, q, *J* = 6.8, NCH_2); 1.25 (3H, t, *J* = 6.9, CH_3)
4a	8.18-7.31 (9H)	4.26 (2H, t, *J* = 7.4, NCH_2); 1.65 (2H, m, $C\underline{H}_2CH_3$); 0.97 (3H, t, *J* = 7.4, CH_3)
4b	8.17-7.26 (8H)	4.26 (2H, t, *J* = 7.5, NCH_2); 1.67 (2H, m, $C\underline{H}_2CH_3$); 0.99 (3H, t, *J* = 7.4, CH_3)
4c	8.18-7.35 (8H)	4.25 (2H, t, *J* = 7.5, NCH_2); 1.66 (2H, m, $C\underline{H}_2CH_3$); 0.97 (3H, t, *J* = 7.5, CH_3)
4d	8.13-7.29 (8H)	4.27 (2H, t, *J* = 7.4, NCH_2); 1.69 (2H, m, $C\underline{H}_2CH_3$); 0.99 (3H, t, *J* = 7.4, CH_3)
4e	8.15-7.34 (8H)	4.25 (2H, t, *J* = 7.4, NCH_2); 1.66 (2H, m, $C\underline{H}_2CH_3$); 0.97 (3H, t, *J* = 7.5, CH_3)
4f	8.17-7.32 (8H)	4.24 (2H, t, *J* = 7.3, NCH_2); 1.65 (2H, m, $C\underline{H}_2CH_3$); 0.98 (3H, t, *J* = 7.4, CH_3)
4g	8.16-7.36 (7H)	4.27 (2H, t, *J* = 7.5, NCH_2); 1.66 (2H, m, $C\underline{H}_2CH_3$); 0.99 (3H, t, *J* = 7.4, CH_3)
4h	8.17-7.35 (8H)	4.26 (2H, t, *J* = 7.6, NCH_2); 1.67 (2H, m, $C\underline{H}_2CH_3$); 0.98 (3H, t, *J* = 7.5, CH_3)
4i	8.79 (1H, s, H-2'); 8.53-7.36 (7H, m)	4.25 (2H, t, *J* = 7.5, NCH_2); 1.66 (2H, m, $C\underline{H}_2CH_3$); 0.98 (3H, t, *J* = 7.4, CH_3)
4j	8.40 (2H, d, *J* = 8.8, H-3',5'); 8.19-8.10 (3H, m, H-2',6',5); 7.86 (1H, td, *J* = 7.7 and *J* = 1.4, H-7); 7.70 (1H, d, *J* = 8.4, H-8); 7.42 (1H, td, *J* = 7.7 and *J* = 1.3, H-6)	4.27 (2H, t, *J* = 7.4, NCH_2); 1.68 (2H, m, $C\underline{H}_2CH_3$); 0.97 (3H, t, *J* = 7.4, CH_3)
4k	9.09 (2H, d, *J* = 2.3, H-2',6'); 9.00 (1H, t, *J* = 2.3, H-4'); 8.13 (1H, dd, *J* = 8.3 and *J* = 1.5, H-5); 7.84 (1H, td, *J* = 7.9 and *J* = 1.9, H-7); 7.70 (1H, d, *J* = 8. 3, H-8); 7.39 (1H, t, *J* = 7.6, H-6)	4.26 (2H, t, *J* = 7.2, NCH_2); 1.67 (2H, m, $C\underline{H}_2CH_3$); 0.98 (3H, t, *J* = 7.3, CH_3)
4l	8.15-7.29 (8H)	4.25 (2H, t, *J* = 7.3, NCH_2); 1.66 (2H, m, $C\underline{H}_2CH_3$); 0.99 (3H, t, *J* = 7.3, CH_3)
4m	8.16 (1H, dd, *J* = 8.2 and *J* = 1.3, H-5); 7.89-7.77 (3H, m, H-2',6',7);7.70 (1H, d, *J* = 8.6, H-8); 7.39 (1H, t, *J* = 7.5, H-6); 7.30 (2H, d, *J* = 8.1, H-3',5')	4.25 (2H, t, *J* = 7.4, NCH_2); 1.67 (2H, m, $C\underline{H}_2CH_3$); 0.96 (3H, t, *J* = 7.5, CH_3)

* Signals of the protons of the 4-OH groups are displayed as singlets at 16.27-16.05, of the NH groups of hydrazine fragments as two singlets at 12.31-11.87 and 11.63-10.93, and of the methyl groups in β-N-acyl residues of 1,3-diacylhydrazines **1l,m-4l,m** as singlets of intensity 3H at 2.37-2.36 ppm respectively.

EXPERIMENTAL

The ^{1}H NMR spectra of all the synthesized compounds were recorded on a Varian Mercury-VX-200 (200 MHz) spectrometer, solvent was DMSO-d_6, and internal standard TMS. The chromato-mass spectrum of 1,3,4-oxadiazolylquinolone **7** was recorded on a Hewlett Packard 5890/5972 instrument in total scanning mode over the range 35-700 *m/z*, ionization by electron impact 70 eV; the chromatographic column was a Hewlett Packard-5MS, length 25 m, internal diameter 0.2 mm, stationary phase was a polysiloxane film (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μ, carrier gas was helium. Hydrazides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **6a-d** were obtained by the procedure of [14].

β-N-Benzoylhydrazide of 1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (3a). A. Triethylamine (1.54 ml, 0.011 mmol) was added to a solution of hydrazide **6c** (2.47 g, 0.01 mol) in dry dioxane (20 ml), and then benzoyl chloride (1.28 g, 0.011 mol) was added with cooling and stirring. The mixture was left for 4 h at room temperature. The reaction mixture was diluted with cold water, and acidified with dilute HCl to pH 5. The precipitated solid diacylhydrazine **3a** was filtered off, washed with water, and dried.

B. A mixture of ester **5c** (2.61 g, 0.01 mol), benzoic acid hydrazide (1.36 g, 0.01 mol), and DMF (1 ml) was stirred and maintained at 160°C for 3-5 min. Initially the reactants dissolved, and then after violent evolution of ethanol the final diacylhydrazine **3a** crystallized out. Ethanol (10-15 ml) was carefully added to the still hot reaction mixture, which was thoroughly triturated. The solid was filtered off, washed with alcohol, and dried. A mixing test of samples of diacylhydrazine **3a** obtained by the different methods gave no depression of melting point, and their ^{1}H NMR spectra were identical.

3-[5-(2,4-Dichlorophenyl)-1,3,4-oxadiazol-2-yl]-4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline (7). A solution of 2,4-dichlorobenzoylhydrazide **4g** (4.34 g, 0.01 mol) in $SOCl_2$ (50 ml) was boiled for 3.5 h. The reflux condenser was changed for distillation and the $SOCl_2$ was removed from the reaction mixture (in vacuum at the end). The residue was treated with cold water, the isolated solid oxadiazoloquinolone **7** was filtered off, washed with water, and dried. Yield was 3.78 g (91%); mp 170-172°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.06 (1H, br. s, OH); 8.20-7.54 (6H, m, H arom); 7.34 (1H, t, *J* = 7.6, H-6 quinolone); 4.23 (2H, t, *J* = 7.3, NCH_2); 1.67 (2H, m, $C\underline{H}_2CH_3$); 0.97 (3H, t, *J* = 7.3, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 415 $[M]^+$ (27), 373 $[M-C_3H_6]^+$ (77), 188 (42), 173 (58), 132 (100), 77 (22), *m/z* values are given for the ^{35}Cl isotope only. Found, %: C 57.79; H 3.72; N 10.02. $C_{20}H_{15}Cl_2N_3O_3$. Calculated, %: C 57.71; H 3.63; N 10.09.

1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline (8a). Phosphorus pentoxide (4.2 g, 0.03 mol) was added to a solution of diacylhydrazine **3a** (3.51 g, 0.01 mol) in anhydrous CCl_4 (50 ml) and the mixture boiled with a $CaCl_2$ tube fitted to protect from moisture of the air for 3h. The reaction mixture was cooled, the organic layer separated from the solid by decantation, after which the CCl_4 was distilled off in vacuum. The residue was treated with cold water, and then Na_2CO_3 was added to pH 5. The solid was filtered off, washed with water, and dried. Yield was 1.56 g (83%); mp 274-276°C (ethanol).

A mixing test with an authentic sample of 3H-quinolone **8a** [15, 16] gave no depression of melting point, and the ^{1}H NMR spectra of these compounds were identical.

4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline (8b). A mixture of diacylhydrazine **4a** (3.65 g, 0.01 mol) and PPA (polyphosphoric acid) (20 g) was maintained at 100°C for 2 h. The mixture was cooled, an ice-water mixture was added, and carefully stirred. The reaction mixture was then treated as in the previous experiment. Yield was 1.50 g (74%); mp 221-222°C (ether).

A mixing test with an authentic sample of the 1-propyl substituted 3H-quinoline **8b** [13] gave no depression of melting point, the ^{1}H NMR spectra of these compounds were identical.

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