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4-HYDROXY-2-QUINOLONES 132*. SYNTHESIS, CHEMICAL, AND BIOLOGICAL PROPERTIES OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACIDS 2-NITROBENZYLIDENEHYDRAZIDES

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1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids 2-nitrobenzylidenehydrazides are reduced to the corresponding quinoline-3-carboxamides by zinc in glacial acetic acid but in refluxing triethylphosphite they are converted to the symmetrical N,N'-di(4-hydroxy-2-oxo-1,2-dihydro-3-quinolinoyl)hydrazines. A study of the antitubercular activity of the synthetic compounds has been carried out.

Keywords: hydrazides, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, amidation, reduction, antitubercular activity.

In carrying out a systematic search for novel, potential medicinal preparations suitable for treatment of microbacterial infections we have repeatedly noted the high antitubercular activity of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids benzylidenehydrazides [2-4]. The 2-nitrobenzylidene derivatives **1** are interesting objects of study in this area. Such compounds can also serve as the basis for the synthesis of different heterocyclic compounds through reactions of the *ortho*-positioned nitro groups.

The starting 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids 2-nitrobenzylidene-hydrazides **1** were prepared by reaction of the corresponding quinoline-3-carboxylic acid hydrazides **2** with *ortho*-nitrobenzaldehyde in refluxing ethanol. They are light yellow, crystalline materials with sharp melting points (Table 1), soluble in DMF and DMSO, of low solubility in ethanol, and virtually insoluble in water, ether, and hexane.

A reliable confirmation of the formation of the acylhydrazones **1** is the singlet signal for the methine protons in the ^{1}H NMR spectra (Table 2). The assignment of the signals of each of the eight aromatic protons without special NMR experiments is made difficult or, in the extreme, impossible because they are localized in a narrow spectral range and frequently overlapped.

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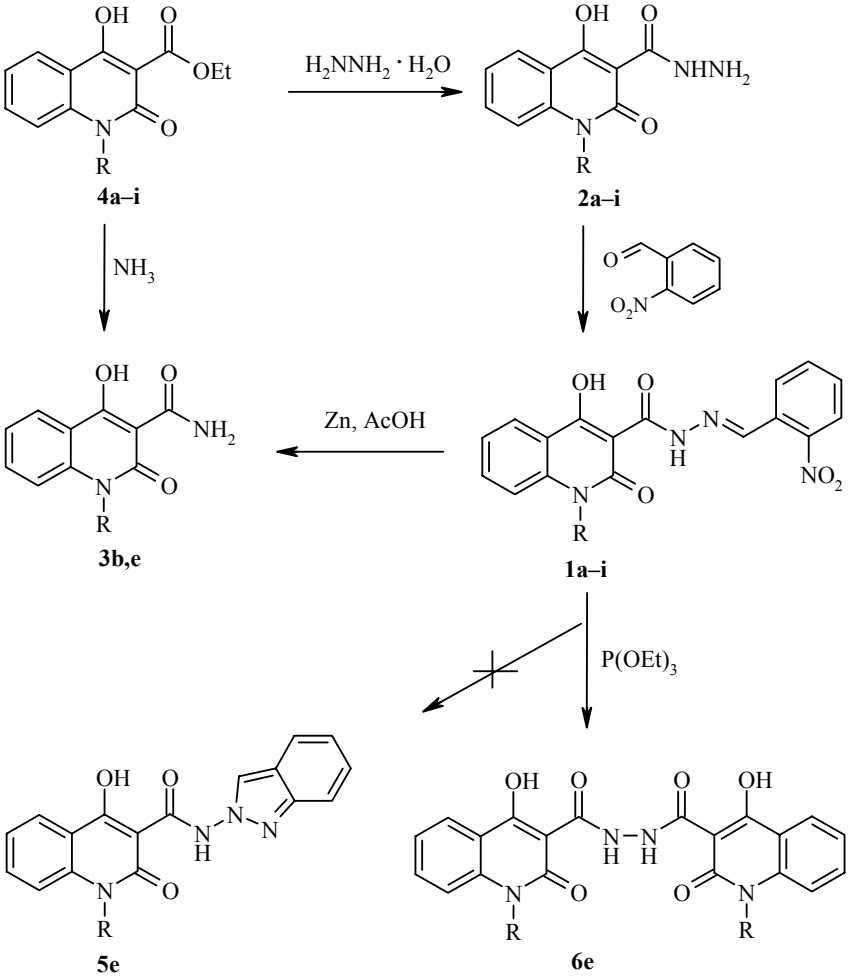
As is known, carboxylic acids hydrazides are reduced with somewhat greater difficult than derivatives with a C=N bond [5]. This feature opens up the possibility of a selective hydrogenation of acylhydrazones with retention of the acyl group and this is often used in the pharmaceutical industry in the synthesis of medicinal compounds [6, 7].



a R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = Pr, **f** R = Bu, **g** R = *i*-Bu, **h** R = C_5H_{11}, **i** R = C_6H_{13}

Reducing agents used are hydrogen, hydrides, complex hydrides, metals, organometallic compounds etc. As a rule, this type of reaction occurs without particular difficulty and gives good results [6-8]. Only in certain examples is a partial fission of the N–N bond observed [5]. However, in the reduction of the acylhydrazones **1** using zinc dust in glacial acetic acid this process becomes predominant and gives high yields of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides **3** in the end, even though the preparation of the amine derivatives from hydrazines normally needs catalytic hydrogenation under pressure over Raney nickel or platinum catalysts [5].

The structure of the amides **3** obtained was confirmed by a counter synthesis *via* the amidation of the ethyl esters **4** (readily soluble in alcohols). At first glance this may be a trivial reaction but it proved also to have specific features.

Thus when solutions of esters **4** in methanol or ethanol were saturated with gaseous ammonia the corresponding quinoline-3-carboxamides **3** were formed with unexpectedly high difficulty and occurred to no more than 20% over 24 h despite a large excess of the amine. It was of interest that, in methanol, the strongly

predominating process is that of trans esterification and not amidation. However, in the case of 2-propanol, immediately after addition of ammonia to the reaction mixture white precipitates formed which proved, after filtering and drying, to be the unexpected starting esters **4**. It is likely that the initial products of this reaction are the ammonium 1-R-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolin-4-olates. Their formation may account for the extremely low rate of amidation, completion of which could not be achieved in the poorly solvating 2-propanol, even after increasing the reaction time to 10 days.

TABLE 1. Characteristics of 2-Nitrobenzylidenehydrazides **1a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{17}H_{12}N_4O_5$	57.87 / 57.96	3.36 / 3.43	15.97 / 15.90	310-312	90
1b	$C_{18}H_{14}N_4O_5$	59.12 / 59.02	3.95 / 3.85	15.20 / 15.29	274-276	91
1c	$C_{19}H_{16}N_4O_5$	59.94 / 60.00	4.28 / 4.24	14.81 / 14.73	249-251	87
1d	$C_{20}H_{16}N_4O_5$	61.16 / 61.22	4.16 / 4.11	14.35 / 14.28	204-206	83
1e	$C_{20}H_{18}N_4O_5$	60.97 / 60.91	4.52 / 4.60	14.17 / 14.21	177-179	88
1f	$C_{21}H_{20}N_4O_5$	61.66 / 61.76	4.85 / 4.94	13.82 / 13.72	151-153	85
1g	$C_{21}H_{20}N_4O_5$	61.80 / 61.76	4.88 / 4.94	13.79 / 13.72	170-172	90
1h	$C_{22}H_{22}N_4O_5$	62.50 / 62.55	5.33 / 5.25	13.20 / 13.26	191-193	86
1i	$C_{23}H_{24}N_4O_5$	63.35 / 63.29	5.59 / 5.54	12.93 / 12.84	185-187	82

TABLE 2. ^{1}H NMR Spectra of the 2-Nitrobenzylidenehydrazides **1a-i**

Compound	Chemical shifts, δ, ppm. (*J*,Hz)				
	4-OH (1H, s)	NH–N (1H, s)	N=CH (1H, s)	H arom. (8H, m)	R
1a	16.33	13.47	8.75	8.12-7.26	12.06 (1H, s, NH)
1b	16.45	13.50	8.81	8.19-7.35	3.69 (3H, s, CH_3)
1c	16.37	13.53	8.82	8.19-7.36	4.32 (2H, q, *J* = 7.2, NCH_2); 1.03 (3H, t, *J* = 7.2, CH_3)
1d	16.39	13.45	8.76	8.14-7.29	5.97 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, dd, *J* = 10.8 and *J* = 1.3, NCH_2CH=C<u>H</u>-*cis*); 5.03 (1H, dd, *J* = 17.3 and *J* = 1.3, NCH_2CH=C<u>H</u>-*trans*); 4.94 (2H, d, *J* = 4.8, NCH_2)
1e	16.44	13.42	8.80	8.17-7.34	4.18 (2H, t, *J* = 7.1, NCH_2); 1.62 (2H, m, $NCH_2C\underline{H}_2$); 0.97 (3H, t, *J* = 7.0, CH_3)
1f	16.40	13.49	8.82	8.17-7.35	4.28 (2H, t, *J* = 7.3, NCH_2); 1.63 (2H, m, $NCH_2C\underline{H}_2$); 1.42 (2H, m, $C\underline{H}_2CH_3$); 0.93 (3H, t, *J* = 7.2, CH_3)
1g	16.47	13.50	8.82	8.18-7.35	4.19 (2H, d, *J* = 7.5, NCH_2); 2.16 (1H, m, CH); 0.92 (6H, d, *J* = 6.7, $2CH_3$)
1h	16.36	13.44	8.81	8.16-7.30	4.25 (2H, t, *J* = 7.2, NCH_2); 1.65 (2H, m, $NCH_2C\underline{H}_2$); 1.36 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.90 (3H, t, *J* = 7.1, CH_3)
1i	16.30	13.48	8.81	8.17-7.29	4.26 (2H, t, *J* = 7.2, NCH_2); 1.66 (2H, m, $NCH_2C\underline{H}_2$); 1.33 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.87 (3H, t, *J* = 7.0, CH_3)

A similar inertness towards nucleophiles, including amines, has also been demonstrated in sodium and potassium 1-R-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolin-4-olates [9]. The ammonium salts differ in their formation from a weak acid and weak bases (the 4-OH group in the ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **4** having a p*K*a of about 8.6 [10]), their separation from the reaction mixture occurring with rapid decomposition by the action of atmospheric moisture and carbon dioxide (as observed experimentally). The high reactivity of the ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **4** has often been noted. However, only with ammonia (one of about 200 aliphatic, aromatic, and heterocyclic amines used by us to this time in the synthesis of the corresponding quinoline-3-carboxamides) do they take part in the reaction with such difficulty. It is possible that the unique steric structure of the ammonia molecule has an importance in this case and thanks to which they can form stable adducts in solution with 3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines. As a result, the approach to the quinolone reaction center (in particular the ester carbonyl carbon atom) is blocked to a marked extent. A similar selective inertness towards ammonia has already been discussed by us in the case of ethyl 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylates [11]. Meanwhile, amidation of esters **4** by ammonia can also be brought about by carrying out the synthesis in refluxing DMF to give the amides **3** in good yields.

The 2-nitrobenzylidenehydrazides **1** also behave unusually in reaction with triethylphosphite, at least the expected [12] reductive cyclization to the indazolyl-2-amides proved to be impossible. Under experimentally similar conditions to the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids ethoxymethylidene-hydrazides [13] the acylhydrazones **1** gave the symmetrical N,N'-di(1-R-4-hydroxy-2-oxo-1,2-dihydro-3-quinoinoyl)hydrazines **6**. In this case it is most likely that the triethylphosphite merely behaves as a high boiling solvent since, for example, such a conversion can be brought about in the inert bromobenzene.

The antimicrobial activity of all of the synthesized 2-nitrobenzylidenehydrazides **1** was studied radiometrically [14, 15]. It was quite clear that the single 1-N-amyl derivative **1h** inhibits the *in vitro* growth of *Mycobacterium tuberculosis* H37RvATCC27294 by 99% at a concentration of 12.5 μg/ml. In the following step of microbial screening where the minimum inhibitory concentration (MIC) is determined it was found that, in terms of antitubercular properties, the 2-nitrobenzylidenehydrazide **1h** and its 2-fluoro substituted analog [3] were identical (for both compounds the MIC was 3.13 μg/ml). In all other examples, fluoro derivatives have proved much more active.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX-200 (200 MHz) instrument for DMSO-d_6 solutions with TMS as internal standard.

1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids Hydrazides 2 were prepared by the method in [16].

1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids 2-Nitrobenzylidenehydrazides 1a-i (General Method). The 2-nitrobenzaldehyde (1.66 g, 0.011 mol) was added to a solution of the corresponding quinoline-3-carboxylic acid hydrazide **2** (0.01 mol) in ethanol (50 ml) and refluxed for 30 min (in the preparation of the 1-H and 1-CH_3 derivatives the solvents used were respectively DMF and DMF–ethanol (1:1)). The reaction mixture was cooled, and the target 2-nitrobenzylidenehydrazide **1** was filtered off, washed with ether or ethanol, dried, and crystallized from DMF or ethanol.

4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxamide (3e). A. A refluxing solution of the 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-nitrobenzylidenehydrazide (**1e**) (3.94 g, 0.01 mol) in glacial acetic acid (70 ml) with intensive stirring was treated with zinc powder (5 g) added in small portions at such a rate that that the evolution of hydrogen was not too vigorous. After addition of all of the zinc it was stirred with heating for 3 h. The reaction mixture was cooled, filtered, and the residue on the filter

washed several times with ethanol. The solvent from the filtrate was distilled *in vacuo* to a volume of about 15 ml. The residue was diluted with cold water. The precipitated solid amide **3e** was filtered off, washed with water, and dried. Yield 2.02 g (82%); mp 189-191ºC (aqueous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.11 (1H, s, OH); 9.67 (1H, s, NH); 8.58 (1H, s, NH); 8.09 (1H, dd, *J* = 7.9, 1.5, H-5); 7.79 (1H, td, *J* = 6.9, 1.7, H-7); 7.63 (1H, d, *J* = 8.0, H-8); 7.34 (1H, td, *J* = 7.0, 1.5, H-6); 4.19 (2H, t, *J* = 7.1, NCH_2); 1.62 (2H, m, $NCH_2C\underline{H}_2$); 0.95 (3H, t, *J* = 7.1, CH_3). Found, %: C 63.46; H 5.80; N 11.29. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.40; H 5.73; N 11.38.

B. A solution of ethyl 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylate (**4e**) in DMF (15 ml) was saturated, with ammonia and refluxed for 30 min. After cooling, the operation was repeated. The reaction mixture was diluted with cold water and acidified with dilute HCl to pH 5.0. The precipitated amide **3e** was filtered off, washed with water, and dried. Yield 2.06 g (84%). A mixed sample with that from that obtained by method A did not give a melting point depression and their ^{1}H NMR spectra were identical.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxamide (3b) was prepared as in the previous experiment (method A). Yield 80%; mp 207-209ºC (aqueous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.07 (1H, s, OH); 9.65 (1H, s, NH); 8.54 (1H, s, NH); 8.06 (1H, dd, *J* = 7.9, 1.6, H-5); 7.77 (1H, td, *J* = 7.0, 1.8, H-7); 7.56 (1H, d, *J* = 8.2, H-8); 7.33 (1H, td, *J* = 7.0, 1.6, H-6); 3.59 (3H, s, NCH_3). Found, %: C 60.48; H 4.57; N 12.75. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

N,N'-Di(4-hydroxy-2-oxo-1-propyl-1,2-dihydro-3-quinolinoyl)hydrazine (6e). A solution of the 2-nitrobenzylidenehydrazide **1e** (3.94 g, 0.01 mol) in triethylphosphite (50 ml) was refluxed for 2 h and the triethylphosphite distilled off *in vacuo*. The residue was treated with ethanol (30 ml). The precipitate was filtered off, washed with ethanol and then water, and dried. Yield 1.83 g (75%); mp 326-328ºC (DMF). The ^{1}H NMR spectra of the diacylhydrazine **6e** obtained and a known sample [13] are identical.

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