Chemistry of Heterocyclic Compounds, Vol. 45, No. 2, 2009

4-HYDROXY-2-QUINOLONES. 152*. 3-ACETYL-4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE AND ITS BIOLOGICALLY ACTIVE DERIVATIVES

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A synthesis and study of the spatial structure of 3-acetyl-4-hydroxy-2-oxo-1,2-dihydroquinoline have been carried. 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [1-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene]hydrazides were prepared from this compound by two routes. A comparative analysis of the antitubercular properties of the synthesized compounds and of the closely structurally related N,N'-di(1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)hydrazines has been performed.

Keywords: 3-acetyl-4-hydroxy-2-oxo-1,2-dihydroquinolines, acetoacetic ester, hydrazides, hydrazones, 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, antitubercular activity, X-ray structural analysis.

In a study of the biological properties of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids hydrazides it was found that their high antitubercular activity almost totally disappeared in their thermolysis products, i.e. the symmetrical N,N'-di(1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)hydrazines. It was proposed that the main reason for this effect was basically the sharp lowering of the solubility of the N,N'-di-acylhydrazines in water and in organic solvents [2]. Attempts to confirm or to contradict this proposal are the subject of this publication.

For a proper resolution of the stated problem it would be necessary to investigate substances which, on the one hand, were close in structure to the reported N,N'-diacylhydrazines while (at the same time) not belonging to them and, on the other hand, differing significantly from them in solubility (in a worse direction). In our view, one rather readily achieved practical route for reaching this target may be a change from diacylhydrazines to acylhydrazones. As a rule such compounds are poorly soluble in the majority of organic solvents and this property is frequently used in analytical chemistry. However, in order to adhere to the second requirement of structural similarity one of the acyl fragments in the N,N'-diacylhydrazines should not simply be exchanged with any kind of aldehyde or ketone but needs to contain a 4-hydroxy-2-oxoquinoline ring. In particular an extremely suitable example of such ketones is the 3-acetyl-4-hydroxy-2-oxo-1,2-dihydroquinoline (**1**).

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* For Communication 151 see [1].

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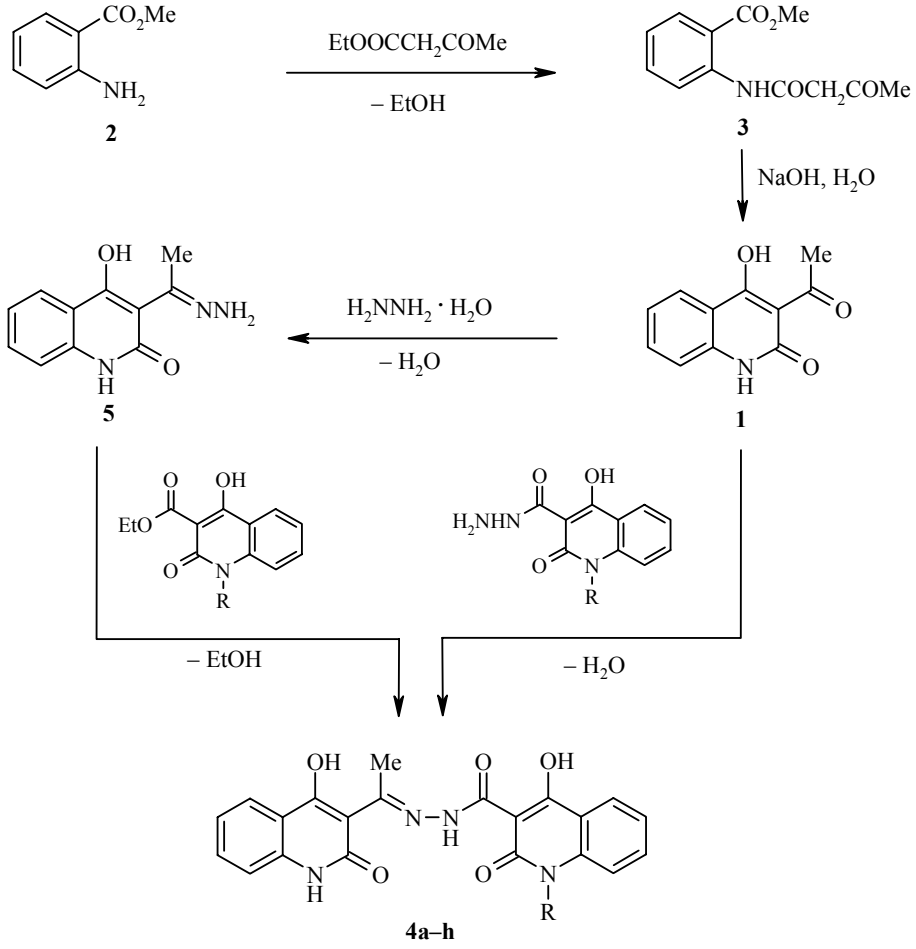
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 214-222, February, 2009. Original article submitted September 28, 2007.

The synthesis of the 3-acyl substituted 4-hydroxyquinol-2-ones uses different synthetic schemes i.e. the Friedel-Crafts acylation of the previously prepared 4-hydroxy-2-oxo-1,2-dihydroquinolines using acyl halides, the thermal conversion or Fries rearrangement of the corresponding 4-O-acyl derivatives, and also hydrolytic cleavage and simultaneous decarboxylation of pyrano[3,2-*c*]quinoline-2,5(6H)-diones [3, 4]. Regarding the acetylquinoline **1** unsubstituted at position 1 this is much more conveniently prepared by acylation of the methyl anthranilate **2** using acetoacetic ester with subsequent Dieckmann [5] intramolecular cyclization of the intermediate 2-methoxycarbonylanilide **3**. It should be noted here that the most convenient preparative synthetic method for anilides using acetoacetic ester has been reported in [6].



4 a R = Me, **b** R = Et, **c** R = All, **d** R = Pr, **e** R = Bu, **f** R = C_5H_{11},
g R = *i*-C_5H_{11}, **h** R = *c*-Hex

In order to confirm the chemical structure of the acetylquinoline **1** prepared in this way we have used ^{1}H NMR spectroscopy and X-ray structural analysis (see Fig. 1 and Tables 1 and 2). In this way it was shown that all of the non-hydrogen atoms in the molecule of the compound studied lie in one plane to an accuracy of 0.02 Å, this likely through formation of a strong intramolecular hydrogen bond O(3)–H(3O)···O(2) (H···O 1.41 Å, O–H···O 157º). This is also responsible for the redistribution of electronic charge within the molecule as seen in the lengthening of the O(2)–C(10) 1.255(2) and C(7)–C(8) bonds 1.393(2) when compared with their mean values [7] of 1.210 and 1.322 Å respectively and in the shortening of the O(3)–C(7) bond to 1.313(2) Å

(mean value 1.333 Å). A marked repulsion between the methyl group and atom O(1) [shortened intramolecular contact O(1)···C(11) 2.80 Å (sum of van der Waal radii [8] 3.00 Å)] leads to an increase in the valence angles O(1)–C(9)–C(8) and C(8)–C(10)–C(11) to 124.5(2) and 123.1(2)º respectively.

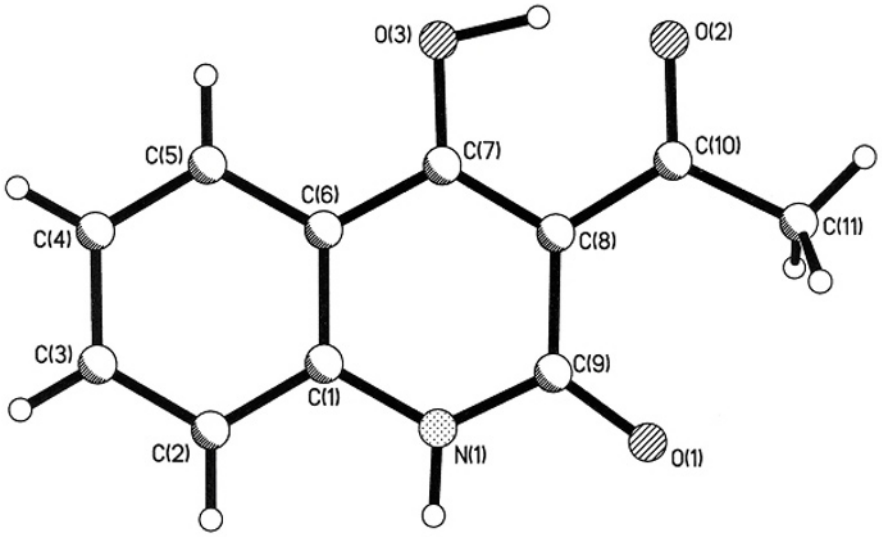


Fig. 1. Structure of the acetylquinoline **1** molecule with atomic numbering.

In the crystal, the acetylquinoline **1** molecules form dimers *via* an intermolecular hydrogen bond N(1)–H(1N)···O(1)' [(1-*x*), -*y*, -*z*], H···O 1.93 Å, N–H···O 173º] which also contributes to lengthening of the O(1)–C(9) bond to 1.237(2) Å when compared to the mean value of 1.210 Å.

TABLE 1. Bond Lengths (*l*) in the Acetylquinoline **1** Structure

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(9)	1.352(2)	N(1)–C(1)	1.381(2)
O(1)–C(9)	1.237(2)	O(2)–C(10)	1.255(2)
O(3)–C(7)	1.313(2)	C(1)–C(2)	1.382(2)
C(1)–C(6)	1.397(2)	C(2)–C(3)	1.364(2)
C(3)–C(4)	1.387(2)	C(4)–C(5)	1.361(2)
C(5)–C(6)	1.401(2)	C(6)–C(7)	1.429(2)
C(7)–C(8)	1.393(2)	C(8)–C(10)	1.451(2)
C(8)–C(9)	1.459(2)	C(10)–C(11)	1.476(2)

TABLE 2. Valence Angles (ω) in the Acetylquinoline **1** Structure

Angle	ω, deg	Angle	ω, deg
C(9)–N(1)–C(1)	125.6(1)	N(1)–C(1)–C(2)	120.8(1)
N(1)–C(1)–C(6)	119.2(2)	C(2)–C(1)–C(6)	120.0(2)
C(3)–C(2)–C(1)	119.7(2)	C(2)–C(3)–C(4)	121.2(2)
C(5)–C(4)–C(3)	119.8(2)	C(4)–C(5)–C(6)	120.3(2)
C(1)–C(6)–C(5)	119.1(2)	C(1)–C(6)–C(7)	118.0(1)
C(5)–C(6)–C(7)	123.0(2)	O(3)–C(7)–C(8)	122.1(2)
O(3)–C(7)–C(6)	116.3(1)	C(8)–C(7)–C(6)	121.6(1)
C(7)–C(8)–C(10)	118.5(1)	C(7)–C(8)–C(9)	119.1(1)
C(10)–C(8)–C(9)	122.4(1)	O(1)–C(9)–N(1)	118.9(1)
O(1)–C(9)–C(8)	124.5(2)	N(1)–C(9)–C(8)	116.5(1)
O(2)–C(10)–C(8)	119.5(2)	O(2)–C(10)–C(11)	117.4(2)
C(8)–C(10)–C(11)	123.1(2)		

Further synthesis of the target 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [1-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene]hydrazides **4a-h** is theoretically possible by several routes. We have studied two of these which are the clearest and simplest to achieve. The first is carried out in a single stage with good yields by condensation of the starting acetylquinoline **1** with 1-R-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acids hydrazides (method A). However a second variant involving initial reaction of acetylquinoline **1** to the 3-(1-hydrazonoethyl)-4-hydroxy-1H-quinolin-2-one (**5**) and subsequent acylation using ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates (method B) is also very efficient. In the synthesis of the acylhydrazones **4a-h** presented in this study both methods proved of approximately equal value although for other 4-hydroxyquinol-2-ones specific limitations can certainly appear. One such example concerns the hydrazide of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*if*]quinoline-2-carboxylic acid, the use of which for preparation of the corresponding acylhydrazone *via* method A is known to be impossible due to its instability in refluxing DMF [9].

All of the acylhydrazones **4a-h** prepared (Table 3) are light-yellow, crystalline materials with high melting points. As expected, their solubility is so low that it was not possible to record even a qualitative ^{1}H NMR spectrum hence confirmation of the composition and structure of the compounds prepared used elemental analysis and mass spectrometry.

Molecular ion peaks for the acylhydrazones **4a-h** were seen in the mass spectra in all cases but their intensities were quite low and rarely exceeded 10% and this is explained by their large molecular weight (Table 4). The primary fragmentation under electron impact occurs similarly and, judged by the presence of a maximum intensity peak with *m/z* 201 in all of the spectra, first involves fission of the N–N bond. In hydrazine derivatives this is similarly weak [10]. Along with this, the corresponding "amide" type decomposition fragments can only be recorded for the acylhydrazones with higher alkyl substituents, starting at butyl.

A second important fragmentation route for the molecular ions of the acylhydrazones **4a-h** can involve cleavage of the hydrazide CO–NHN bond. The intensity of the corresponding peaks is comparatively low but is seen in all of the examples quoted without exception. As is known, isomeric compounds often give spectra which are virtually identical in ion composition as a result of which the potential of mass spectrometry to

TABLE 3. Characteristics of the 1-R-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acids [1-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene]hydrazides **4a-h**

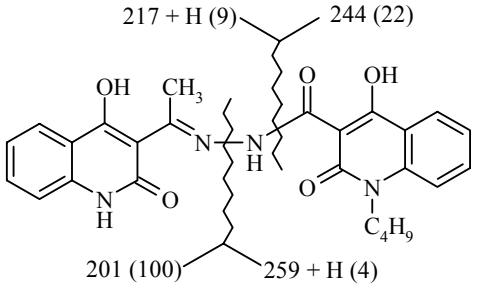
Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield*,%	Antitubercular activity. Inhibition of the growth of *M. Tuberculosis*, %
		C	H	N			
4a	$C_{22}H_{18}N_4O_5$	63.23 / 63.15	4.44 / 4.34	13.28 / 13.39	438-440	92	15
4b	$C_{23}H_{20}N_4O_5$	63.79 / 63.88	4.73 / 4.66	13.07 / 12.96	430-432	90	19
4c	$C_{24}H_{20}N_4O_5$	64.76 / 64.86	4.48 / 4.54	12.53 / 12.61	407-409	87	31
4d	$C_{24}H_{22}N_4O_5$	64.65 / 64.57	5.08 / 4.97	12.65 / 12.55	381-383	85	0
4e	$C_{25}H_{24}N_4O_5$	65.30 / 65.21	5.33 / 5.25	12.09 / 12.17	325-327	88	56
4f	$C_{26}H_{26}N_4O_5$	65.90 / 65.81	5.61 / 5.52	11.72 / 11.81	343-345	93	24
4g	$C_{26}H_{26}N_4O_5$	65.92 / 65.81	5.47 / 5.52	11.74 / 11.81	352-354	90	37
4h	$C_{27}H_{28}N_4O_5$	66.30 / 66.38	5.89 / 5.78	11.56 / 11.47	336-338	94	0

* Yield using method A; yield of compound **4a** by method B = 89%.

TABLE 4. Mass Spectra of the Acylhydrazones **4a-h**

Compound	*m/z* ($I_{отн}$, %)
4a	418 $[M]^+$ (5), 218 (9), 202 (40), 201 (100), 188 (11), 146 (18), 134 (23), 120 (25), 104 (24), 92 (28), 77 (43)
4b	432 $[M]^+$ (4), 218 (6), 216 (27), 201 (100), 188 (9), 146 (10), 134 (16), 120 (16), 104 (20), 92 (22), 77 (17)
4c	444 $[M]^+$ (6), 228 (7), 217 (4), 201 (100), 188 (20), 146 (13), 134 (8), 120 (26), 104 (19), 92 (40), 77 (52)
4d	446 $[M]^+$ (4), 230 12), 218 (6), 201 (100), 188 (17), 146 (10), 134 (19), 120 (51), 104 (17), 92 (56), 77 (51)
4e	460 $[M]^+$ (8), 260 (4), 244 (22), 218 (9), 201 (100), 188 (48), 146 (14), 134 (10), 120 (50), 104 (16), 92 (35), 77 (42)
4f	474 $[M]^+$ (11), 274 (2), 258 (6), 218 (5), 201 (100), 188 (25), 146 (10), 134 (11), 120 (61), 104 (13), 92 (32), 77 (50)
4g	474 $[M]^+$ (32), 274 (5), 258 (13), 218 (54), 201 (100), 188 (40), 146 (21), 134 (33), 120 (82), 104 (17), 92 (29), 77 (31)
4h	488 $[M]^+$ (4), 288 (4), 272 (5), 218 (8), 201 (100), 188 (55), 146 (12), 134 (10), 120 (44), 104 (14), 92 (28), 77 (33)

establish the structure of the alky substituents in compounds of one series has certain limitations [11]. In fact the differences in the spectra of the amyl **4f** and isoamyl **4g** derivatives are very small and seen only in the lowering of the intensity of molecular ion and some fragmentation ion peaks in compounds with an alkyl chain of normal structure.



4e

The antitubercular properties of the acylhydrazones **4a-h** were studied *in vitro* by a radiometric method [12, 13] at a concentration of 12.5 μg/ml. The results of primary microbiological screening obtained in this way showed the most active of the compounds synthesized was able to inhibit the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294 in all by only 56% (Table 3). None the less, when compared with the N,N'-di(1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)hydrazines (which at the same dose generally had no effect on the tubercular mycobacterium [2]) the acylhydrazones **4a-h** showed a much clearer antimicrobacterial effect even though they were markedly inferior in solubility. Hence, based on the study reported it can be confirmed that the absence of antitubercular activity we reported previously for N,N'-diacylhydrazines is to a first degree due to their chemical structure and not to their poor solubility. In other words, we have obtained a further experimental confirmation of the previously reported conclusion [14] that the introduction of a second acyl residue in 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazide molecules uniformly leads to loss of activity while the preparation of hydrazones based on them can be identified as an extremely promising route for creating novel, potentially antimicrobacterial medicinal compounds.

EXPERIMENTAL

The ^{1}H NMR spectra of the acetylquinoline **1** and hydrazone **5** were recorded on a Varian Mercury VX-200 spectrometer (200 MHz) using DMSO-d_6 solvent and TMS internal standard. Mass spectra for the acylhydrazones **4a-h** were obtained on a Varian 1200L instrument in full scanning mode in the range 45-550 *m/z* with 70 eV EI ionization and direct introduction of the sample. The ethyl esters and hydrazides of the 1-R-4-hydroxy-2-oxo-1,2 dihydroquinoline-3-carboxylic acids were prepared by the methods reported in [15] and [16] respectively.

3-Acetyl-4-hydroxy-2-oxo-1,2-dihydroquinoline (1). A mixture of freshly distilled acetoacetic ester (13.9 ml, 0.11 mol), xylene (20 ml, commercial mixture of isomers), and triethanolamine (1 g) was heated to reflux. A solution of methyl anthranilate **2** (12.9 ml, 0.1 mol) in xylene (30 ml) was added dropwise to the refluxing solution not allowing a marked fall in temperature. The ethanol formed in the reaction was removed *via* a fractionating column. After addition of all of the methyl anthranilate the refluxing was continued for about 1 h while distilling from it a mixture of xylene and alcohol (20 ml). The solution of the 2-carbomethoxyanilde **3** in xylene obtained was cooled and a solution of NaOH (12.0 g, 0.3 mol) in water (100 ml) was added to it with stirring. Cyclization occurred with a marked evolution of heat and required much external cooling ! Stirring was continued for 1 h, the organic layer was separated, and the aqueous was purified using carbon and then acidified using dilute (1:1) HCl to pH 4-5. The precipitated acetylquinoline **1** produced was filtered off, washed with cold water, and dried. Yield 18.5 g (91%); mp 252-254ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.81 (1H, s, OH); 11.52 (1H, s, NH); 7.96 (1H, d, *J* = 8.0, H-5); 7.66 (1H, td, *J* = 7.8 and *J* = 1.5, H-7); 7.27 (1H, d, *J* = 8.0, H-8); 7.21 (1H, t, *J* =7.5, H-6); 2.70 (3H, s, CH_3).

X-ray Crystallographic Investigation. Crystals of the acetylquinoline **1** are monoclinic (DMF), at 20ºC: *a* = 9.309(2), *b* = 5.209(2), *c* = 18.505(6) Å, β = 91.53(2)º, *V* = 897.0(5) Å^3, M_r = 203.19, *Z* = 4, space group $P2_1/n$, d_{calc} = 1.505 g/cm^3, μ(MoKα) = 0.111 mm^{-1}, *F*(000) = 424. Unit cell parameters and intensities of 4955 reflections (1564 independent, R_{int} = 0.023) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 50º). The structure was solved by a direct method using the SHELXTL package [17]. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ (*n* = 1.5 for a methyl group and *n* = 1.2 for other hydrogen atoms). The positions of the hydrogen atoms taking part in hydrogen bonding were refined in the isotropic approximation. The structure was refined by F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.083 for 1541 reflections (R_1 = 0.033 for 994 reflections with $F > 4\sigma(F)$, *S* = 0.860). The full crystallographic information has been placed in the Cambridge structural database (reference No. CCDC 672206). Interatomic distances and valence angles are given in Tables 1 and 2.

3-(1-Hydrazonoethyl)-4-hydroxy-1H-quinolin-2-one (5). An 80% aqueous solution of hydrazine hydrate (2 ml) was added to a solution of the acetylquinoline **1** (2.03 g, 0.01 mol) in ethanol (50 ml) and refluxed for 2 h. The product was cooled and the precipitated hydrazone **5** was filtered, washed with cold water, and dried. Yield 1.87 g (86%); mp 291-293ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.12 (1H, s, OH); 10.60 (1H, s, NH); 7.90 (1H, dd, *J* = 8.1 and *J* = 1.5, H-5), 7.41 (1H, td, *J* = 7.7 and *J* = 1.6, H-7); 7.11 (1H, d, *J* = 8.2, H-8); 7.03 (1H, td, *J* = 7.5 and *J* = 1.0, H-6); 6.00 (1H, s, NH_2); 2.66 (3H, s, CH_3). Found, %: C 60.71; H 5.02; N 19.45. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.82; H 5.10; N 19.34.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylc Acid [1-(4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)ethylidene]hydrazide (4a). A. 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazide (2.33 g, 0.01 mol) was added to a solution of the acetylquinoline **1** (2.03 g, 0.01 mol) in DMF (30 ml) and refluxed for 30 min. The acylhydrazone **4a** was formed as a bulky light-yellow precipitate. It was filtered, washed several times with alcohol, and dried.

B. Ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (2.47 g, 0.01 mol) was added to a solution of the hydrazone **5** (2.17 g, 0.01 mol) in DMF (30 ml) and refluxed for 1 h. The target compound was separated by the method described above.

A mixed sample of the acylhydrazone **4a** prepared by the different methods did not show a depression of melting point. Their mass spectra were identical.

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