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4-HYDROXY-2-QUINOLONES

165*. 1-R-4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBALDEHYDES AND THEIR THIOSEMICARBAZONES. SYNTHESIS, STRUCTURE, AND BIOLOGICAL PROPERTIES

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Two variants are discussed of the synthesis of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid β-N-tosylhydrazides which undergo a McFayden-Stevens reaction to give 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes in high yields. It was shown that the thiosemicarbazones prepared from them exist in the solid state exclusively in the syn-form while in solution a hydrazone ↔ enhydrazine tautomerism is observed. The results of a study of the antitubercular activity of the synthesized compounds are reported.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes, thiosemicarbazones, isomerization, antitubercular activity, X-ray structural analysis.

Thiosemicarbazones have a broad spectrum of pharmacological activities. Amongst this class of substances there are found compounds with antiproliferative [2] and antiamebal [3] activity. They are effective in the fight against malaria [4], the herpes simplex virus [5], carcinoma of the prostate gland [6], hormone dependent breast cancer [7], and other types of malignant neoplasms [8, 9]. However, the widest use of thiosemicarbazones is actually found in the treatment of various microbial infections [10-16]. There is special interest in their ability to inhibit the growth of the tubercular mycobacterium. Conditions of continuing pandemic and the appearance of multiresistant strains of pathogen in this insidious illness serve as a reason for the search for novel antimycobacterial agents in this series of compounds. The first antitubercular preparation in the group discussed (*p*-acetamidobenzaldehyde thiosemicarbazone) has been used in medical practice for more than 50 years under the trade name of *thiacetazone* (*tibon*) [17]. It shows clear bacteriostatic activity towards the tubercular mycobacterium but, in view of its relatively high toxicity, it has limited use and is usually prescribed in combination with other preparations for improving their therapeutic effect and to avoid the

* For Communication 164 see [1].

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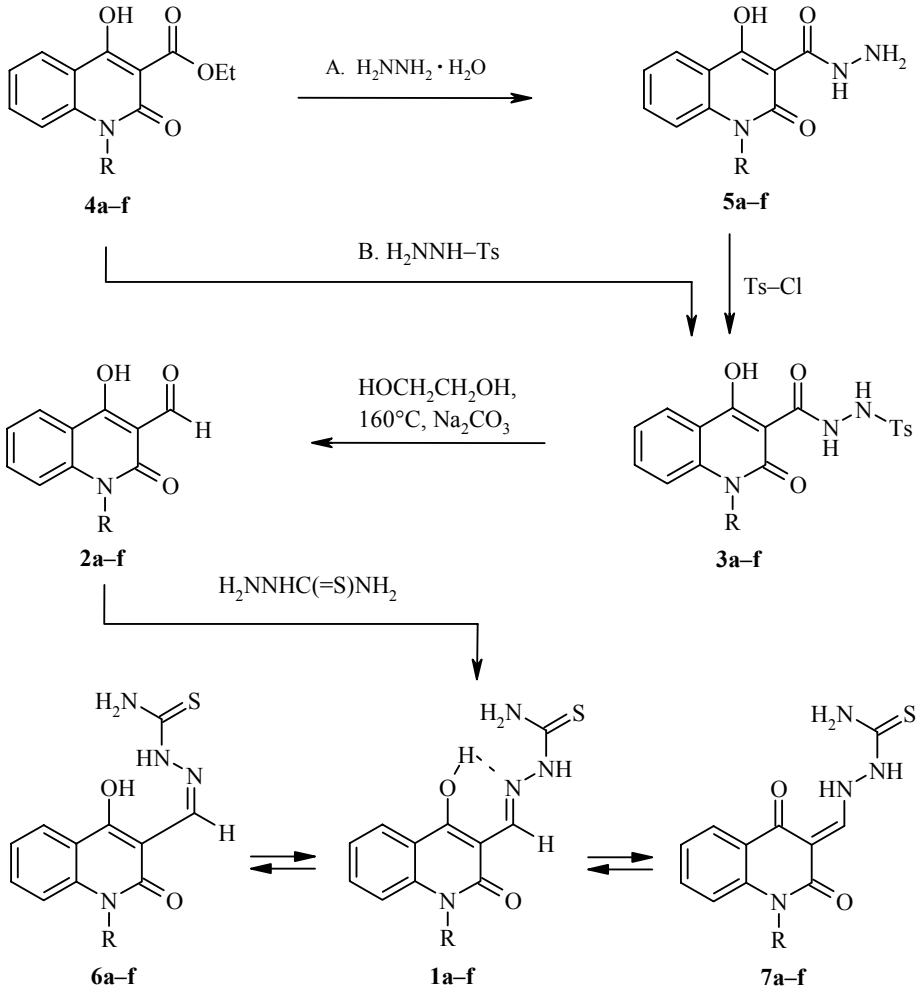
possible appearance of resistant forms [17, 18]. Chemical modification of the aldehyde part of the *thiacetazone* molecule within broad limits has been used by many synthetic chemists in a search for improved analogs of this preparation [18-22]. This was also the basic position in our work related to the synthesis and study of the antitubercular properties of the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazones **1a-f**.



1–6 a R = Me, **b** R = Et, **c** R = Pr, **d** R = Bu, **e** R = C_5H_{11}, **f** R = C_6H_{13}

The obvious route for the synthesis of the starting 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes (4-hydroxy-3-formylcarbostyrils) **2a-f** by Vilsmeier formylation of 4-hydroxy-2-quinolones is not successful [23, 24]. Hence, for a long time, they were prepared by the Reimer-Tiemann method although the yields of the target compounds did not exceed 40% [25]. More efficientl was basic hydrolysis of 3-arylaminomethylenequinoline-2,4-(1H,3H)-diones [32] which, in turn, were prepared also by reaction of 4-hydroxy-2-quinolones with triethylorthoformate and anilines [23, 26] or with formamidines [26, 27]. However, good yields were only basically achieved in this case in the final stage.

With this in mind we undertook an attempt to synthesize aldehydes **2a-f** *via* the well known McFayden-Stevens method from the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid β-N-tosylhdrazides **3a-f**. Decomposition of the tosylhydrazides **3a-f** using sodium carbonate in ethylene glycol occurs readily and the aldehydes **2a-f** can be isolated in very good yields (87-96%). As is known [28], hydrazinolysis of the

TABLE 1.Characteristics of the Compounds Synthesized **1a-f** and **3a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystallization)	Yield*, % (method)
		C	H	N		
1a	$C_{12}H_{12}N_4O_2S$	52.31 / 52.16	4.49 / 4.38	20.14 / 20.28	269-271 (DMF)	83
1b	$C_{13}H_{14}N_4O_2S$	53.90 / 53.78	4.95 / 4.86	19.42 / 19.30	233-235(DMF)	80
1c	$C_{14}H_{16}N_4O_2S$	55.18 / 55.25	5.36 / 5.30	18.34 / 18.41	238-240 (butanol)	85
1d	$C_{15}H_{18}N_4O_2S$	56.74 / 56.59	5.83 / 5.70	17.71 / 17.60	222-224 (ethanol)	82
1e	$C_{16}H_{20}N_4O_2S$	57.70 / 57.81	6.15 / 6.06	16.94 / 16.85	218-220 (ethanol)	76
1f	$C_{17}H_{22}N_4O_2S$	59.08 / 58.94	6.52 / 6.40	16.09 / 16.17	225-227 (ethanol)	77
3a	$C_{18}H_{17}N_3O_5S$	55.71 / 55.81	4.34 / 4.42	10.77 / 10.85	196-198	96 (A)
3b	$C_{19}H_{19}N_3O_5S$	56.92 / 56.85	4.70 / 4.77	10.35 / 10.47	178-180	92 (A)
3c	$C_{20}H_{21}N_3O_5S$	57.73 / 57.82	5.16 / 5.09	10.19 / 10.11	185-187	95 (A) 53 (B)
3d	$C_{21}H_{23}N_3O_5S$	58.60 / 58.73	5.31 / 5.40	9.67 / 9.78	181-183	90 (A)
3e	$C_{22}H_{25}N_3O_5S$	59.48 / 59.58	5.56 / 5.68	9.39 / 9.47	174-176	88 (A)
3f	$C_{23}H_{27}N_3O_5S$	60.45 / 60.38	6.07 / 5.95	9.26 / 9.18	153-155	93 (A)

* Yields of thiosemicarbazones **1a-f** calculated from the corresponding β-N-tosylhydrazides **3a-f**.

esters **4** occurs almost quantitatively. The hydrazides **5** formed can then be acylated very readily by tosyl chloride (method A) and this allows us to recommend the overall synthetic scheme on a preparative scale.

In principle, the preparation of the intermediate tosylhydrazides **3a-f** can be achieved in a single stage by direct reaction of esters **4** with *p*-toluenesulfonylhydrazide (method B). However, as shown in the analogous reaction for benzoic acid hydrazides [29], a temperature of around 140-160ºC is needed at which the *p*-toluenesulfonylhydrazide undergoes marked decomposition. As a result, the yields of tosylhydrazides **3a-f** by this method are comparatively low while under milder conditions (*e.g.* refluxing in ethanol for 20 h) the esters **4** do not react with *p*-toluenesulfonylhydrazide at all.

Condensation of aldehydes **2a-f** with thiosemicarbazide occurs in refluxing ethanol without the addition of any kind of catalyst and gives the thiosemicarbazones **1a-f** which are light-yellow, crystalline materials (Table 1).

Because of the relatively rigid carbon–nitrogen double bond in the thiosemicarbazones **1a-f** they can potentially exist as the two geometrical *syn*- and *anti*-isomeric forms **1↔6** which are of interest for structural investigation. According to our X-ray data (see Fig. 1 and Tables 2 and 3) the independent part of the unit cell of the thiosemicarbazone **1c** actually exists as two molecules (**A** and **B**), differentiated by certain geometrical parameters. However, it turned out that this was in no way connected with the theoretically possible *syn*↔*anti* isomerism in the compound studied but the difference is most significantly seen in the structure of the 1-N-propyl substituent. Hence in molecule **A** all of the non-hydrogen atoms with the exclusion of atoms C(13) and C(14) lie in a single plane to within 0.02 Å. It is likely that such a structure is stabilized by an intramolecular hydrogen bond O(2a)–H(2Oa)···N(2a) (H···N 1.88 Å, O–H···N 137º). In the molecule **B** the plane of the

thiosemicarbazone substituent at atom C(8) is somewhat noncoplanar with that of the quinolone fragment (torsional angle C(7)–C(8)–C(10)–N(2) 8.3(4)º despite the formation of the same hydrogen bond as in molecule **A**: O(2b)–H(2Ob)···N(2b) (H···N 1.94 Å, O–H···N 144º). Formation of the rather strong hydrogen bonds leads to

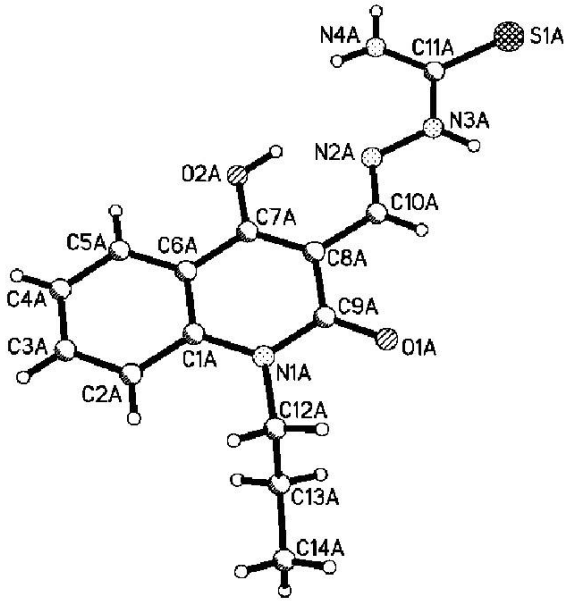


Fig. 1. Structure of the thiosemicarbazone **1c** with atomic numbering.

TABLE 2. Bond Lengths (*l*) in the Thiosemicarbazone **1c** Structure

Bond	*l*, Å	Bond	*l*, Å
S(1A)–C(11A)	1.681(3)	N(1A)–C(9A)	1.379(3)
N(1A)–C(1A)	1.403(3)	N(1A)–C(12A)	1.469(3)
N(2A)–C(10A)	1.284(3)	N(2A)–N(3A)	1.379(3)
N(3A)–C(11A)	1.349(3)	N(4A)–C(11A)	1.317(4)
O(1A)–C(9A)	1.243(3)	O(2A)–C(7A)	1.342(3)
C(1A)–C(6A)	1.397(4)	C(1A)–C(2A)	1.408(4)
C(2A)–C(3A)	1.373(4)	C(3A)–C(4A)	1.372(4)
C(4A)–C(5A)	1.375(4)	C(5A)–C(6A)	1.409(3)
C(6A)–C(7A)	1.427(4)	C(7A)–C(8A)	1.369(3)
C(8A)–C(10A)	1.449(4)	C(8A)–C(9A)	1.450(3)
C(12A)–C(13A)	1.539(1)	C(13A)–C(14A)	1.538(1)
S(1B)–C(11B)	1.670(3)	N(1B)–C(9B)	1.382(3)
N(1B)–C(1B)	1.402(3)	N(1B)–C(12B)	1.468(3)
N(2B)–C(10B)	1.282(3)	N(2B)–N(3B)	1.375(3)
N(3B)–C(11B)	1.342(3)	N(4B)–C(11B)	1.324(3)
O(1B)–C(9B)	1.236(3)	O(2B)–C(7B)	1.332(3)
C(1B)–C(2B)	1.398(4)	C(1B)–C(6B)	1.402(4)
C(2B)–C(3B)	1.372(4)	C(3B)–C(4B)	1.375(4)
C(4B)–C(5B)	1.381(4)	C(5B)–C(6B)	1.400(3)
C(6B)–C(7B)	1.432(3)	C(7B)–C(8B)	1.374(3)
C(8B)–C(10B)	1.438(3)	C(8B)–C(9B)	1.447(3)
C(12B)–C(13B)	1.536(1)	C(13B)–C(14B)	1.535(1)

TABLE 3. Valence Angles (ω) in the Thiosemicarbazone **1c** Structure

Angle	ω, deg	Angle	ω, deg
C(9A)–N(1A)–C(1A)	122.2(2)	C(9A)–N(1A)–C(12A)	117.3(2)
C(1A)–N(1A)–C(12A)	120.4(2)	C(10A)–N(2A)–N(3A)	115.9(2)
C(11A)–N(3A)–N(2A)	121.3(2)	C(6A)–C(1A)–N(1A)	119.9(2)
C(6A)–C(1A)–C(2A)	118.7(2)	N(1A)–C(1A)–C(2A)	121.3(3)
C(3A)–C(2A)–C(1A)	119.9(3)	C(4A)–C(3A)–C(2A)	121.6(3)
C(3A)–C(4A)–C(5A)	119.8(3)	C(4A)–C(5A)–C(6A)	120.1(3)
C(1A)–C(6A)–C(5A)	119.9(3)	C(1A)–C(6A)–C(7A)	118.6(2)
C(5A)–C(6A)–C(7A)	121.5(3)	O(2A)–C(7A)–C(8A)	122.0(2)
O(2A)–C(7A)–C(6A)	116.7(2)	C(8A)–C(7A)–C(6A)	121.3(3)
C(7A)–C(8A)–C(10A)	122.7(2)	C(7A)–C(8A)–C(9A)	120.0(2)
C(10A)–C(8A)–C(9A)	117.3(2)	O(1A)–C(9A)–N(1A)	120.1(2)
O(1A)–C(9A)–C(8A)	122.0(2)	N(1A)–C(9A)–C(8A)	117.9(2)
N(2A)–C(10A)–C(8A)	122.0(2)	N(4A)–C(11A)–N(3A)	118.0(3)
N(4A)–C(11A)–S(1A)	123.1(2)	N(3A)–C(11A)–S(1A)	118.9(2)
N(1A)–C(12A)–C(13A)	111.8(2)	C(14A)–C(13A)–C(12A)	111.7(3)
C(9B)–N(1B)–C(1B)	122.5(2)	C(9B)–N(1B)–C(12B)	117.6(2)
C(1B)–N(1B)–C(12B)	119.9(2)	C(10B)–N(2B)–N(3B)	116.4(2)
C(11B)–N(3B)–N(2B)	120.7(2)	C(2B)–C(1B)–C(6B)	118.6(2)
C(2B)–C(1B)–N(1B)	121.8(3)	C(6B)–C(1B)–N(1B)	119.6(2)
C(3B)–C(2B)–C(1B)	120.4(3)	C(2B)–C(3B)–C(4B)	121.6(3)
C(3B)–C(4B)–C(5B)	118.9(3)	C(4B)–C(5B)–C(6B)	120.8(3)
C(5B)–C(6B)–C(1B)	119.6(2)	C(5B)–C(6B)–C(7B)	121.6(2)
C(1B)–C(6B)–C(7B)	118.8(2)	O(2B)–C(7B)–C(8B)	122.6(2)
O(2B)–C(7B)–C(6B)	116.4(2)	C(8B)–C(7B)–C(6B)	121.1(2)
C(7B)–C(8B)–C(10B)	122.9(2)	C(7B)–C(8B)–C(9B)	120.1(2)
C(10B)–C(8B)–C(9B)	117.0(2)	O(1B)–C(9B)–N(1B)	120.7(2)
O(1B)–C(9B)–C(8B)	121.4(2)	N(1B)–C(9B)–C(8B)	117.9(2)
N(2B)–C(10B)–C(8B)	121.3(2)	N(4B)–C(11B)–N(3B)	117.7(3)
N(4B)–C(11B)–S(1B)	122.6(2)	N(3B)–C(11B)–S(1B)	119.7(2)
N(1B)–C(12B)–C(13B)	113.1(3)	C(14B)–C(13B)–C(12B)	111.4(3)

redistribution of electron density in the quinolone fragment as shown by the lengthened bond O(1)–C(9) 1.243(3) in molecule **A** and 1.236(3) Å in molecule **B** when compared with their mean value of 1.210 Å [30] and the C(7)–C(8) bond 1.369(3) in **A** and 1.374(3) Å in **B** (mean value 1.326 Å) together with the shortened bond O(2)–C(7) 1.342(3) in **A** and 1.332(3) Å in **B** (1.362 Å).

The strong repulsion between the atoms of the 1-N-propyl substituent in the quinolone fragment [shortened intramolecular contacts H(2)···C(12) 2.55 in molecule **A** and 2.54 in **B** (sum of van der Waal radii 2.87 [31], H(2)···H(12b) 2.00 in **A** and 2.14 in **B** (2.34), H(12a)···C(2) 2.55 in **A** and 2.64 in **B** (2.87) and H(12a)···O(1) 2.31 in **A** and 2.30 in **B** (2.46 Å)) lead to lengthening of the bond N(1)–C(9) 1.379(3) in **A** and 1.382(3) Å in **B** and also the bond N(1)–C(1) 1.403(3) in **A** and 1.402(3) in **B** when compared with the mean values of 1.353 and 1.371 Å respectively, as was seen in previous studies of quinolone series compounds.

The propyl substituent on the N(1) atom is placed almost perpendicularly to the heterocyclic plane (torsional angle C(1)–N(1)–C(12)–C(13) 84.0(3)º in molecule **A** and 78.7(3)º in **B**). The C(13)–C(14) bond in the **A** molecule occurs in an *ap* position relative to the N(1)–C(12) bond (torsional angle N(1)–C(12)–C(13)–C(14) = -175.0(3)º) and in molecule **B** it has *a +sc* orientation relative to this bond where the same torsional angle is 61.4(4)º despite the repulsion between the methylene group in the substituent and a benzene ring atom [shortened intramolecular contact H(2b)···H(13c) 2.25 Å (2.34Å)].

In the crystal the thiosemicarbazone **1c** molecules form dimers *via* intermolecular hydrogen bonds: N(3a)–H(3Na)···O(1b) (H···O 2.00 Å, N–H···O 166º) and N(3b)–H(3Nb)···O(1a) (H···O 2.11 Å. N–H···O 173º).

The dimer molecules do not lie in a single plane the angle between the planes of the bicyclic fragments being 13.9º. The crystal also shows intermolecular hydrogen bonds: N(4a)–H(4Na) ···S(1b)' (0.5+*x*, 1.5-*y*, 0.5+*z*) H···S 2.70 Å, N–H···S 159º; N(4a)–H(4Nb)···S(1b)' (0.5-*x*, 1.5-*y*, 1-*z*) H···S 2.84 Å, N–H···S 118º; and N(4b)–H(4Nc)···S(1a)' (-0.5+*x*, 1.5-*y*, -0.5+*z*) H···S 2.46 Å, N–H···S 164º.

The overall results of the X-ray analysis confirm that in the crystalline state the thiosemicarbazone **1c** exists exclusively in the more stable isomeric *syn* form and this is a general characteristic for hydrazones [32].

As a rule, in solution there is established an equilibrium between the configurational partners and this can usually be readily determined with the help of NMR spectroscopy [32, 33]. However, the ^{1}H NMR spectra of the thiosemicarbazones **1a-f** (Table 4) show no kind of typical doubling of signals for such examples. Hence

TABLE 4. ^{1}H NMR Spectra of the Compounds Synthesized **1a-f** and **3a-f**

Com-pound	Chemical shifts δ, ppm (*J*, Hz)
1a	11.61 (1H, s, OH); 11.43 (1H, s, NH); 8.58 (1H, s, CH=N); 8.14 (2H, s, NH_2); 8.01 (1H, dd, *J* = 8.1 and *J* = 1.6, H-5); 7.67 (1H, td, *J* = 7.8 and *J* = 1.7, H-7); 7.51 (1H, d, *J* = 8.3, H-8); 7.27 (1H, t, *J* = 7.5, H-6); 3.56 (3H, s, CH_3)
1b	11.56 (1H, s, OH); 11.44 (1H, s, NH); 8.59 (1H, s, CH=N); 8.10 (2H, s, NH_2); 8.02 (1H, dd, *J* = 8.2 and *J* = 1.5, H-5); 7.69 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.54 (1H, d, *J* = 8.4, H-8); 7.27 (1H, t, *J* = 7.5, H-6); 4.26 (2H, q, *J* = 7.2, NCH_2); 1.19 (3H, t, *J* = 7.2, $NCH_2C\underline{H}_3$)
1c	11.52 (1H, s, OH); 11.40 (1H, s, NH); 8.58 (1H, s, CH=N); 8.12 (2H, s, NH_2); 8.00 (1H, dd, *J* = 8.2 and *J* = 1.6, H-5); 7.66 (1H, td, *J* = 7.8 and *J* = 1.6, H-7); 7.52 (1H, d, *J* = 8.3, H-8); 7.28 (1H, t, *J* = 7.4, H-6); 4.13 (2H, t, *J* = 7.5, NCH_2); 1.60 (2H, m, $NCH_2C\underline{H}_2$); 0.91 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$)
1d	11.54 (1H, s, OH); 11.41 (1H, s, NH); 8.58 (1H, s, CH=N); 8.15 (2H, s, NH_2); 7.98 (1H, dd, *J* = 8.1 and *J* = 1.5, H-5); 7.65 (1H, td, *J* = 7.7 and *J* = 1.7, H-7); 7.49 (1H, d, *J* = 8.3, H-8); 7.27 (1H, t, *J* = 7.5, H-6); 4.16 (2H, t, *J* = 7.4, NCH_2); 1.54 (2H, q, *J* = 6.7, $NCH_2C\underline{H}_2$); 1.35 (2H, m, $C\underline{H}_2CH_3$); 0.91 (3H, t, *J* = 7.3, CH_3)
1e	11.53 (1H, s, OH); 11.41 (1H, s, NH); 8.59 (1H, s, CH=N); 8.12 (2H, s, NH_2); 8.01 (1H, dd, *J* = 8.0 and *J* = 1.4, H-5); 7.68 (1H, td, *J* = 7.8 and *J* = 1.5, H-7); 7.52 (1H, d, *J* = 8.4, H-8); 7.30 (1H, t, *J* = 7.5, H-6); 4.17 (2H, t, *J* = 7.3, NCH_2); 1.57 (2H, q, *J* = 6.8, $NCH_2C\underline{H}_2$); 1.32 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.85 (3H, t, *J* = 6.6, CH_3)
1f	11.46 (1H, s, OH); 11.40 (1H, s, NH); 8.59 (1H, s, CH=N); 8.06 (2H, s, NH_2); 8.02 (1H, d, *J* = 8.0, H-5); 7.67 (1H, t, *J* = 7.9, H-7); 7.51 (1H, d, *J* = 8.5, H-8); 7.30 (1H, t, *J* = 7.5, H-6); 4.18 (2H, t, *J* = 7.3, NCH_2); 1.58 (2H, q, *J* = 6.6, $NCH_2C\underline{H}_2$); 1.30 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.84 (3H, t, *J* = 6.3, CH_3)
3a	15.68 (1H, s, OH); 11.61 (1H, s, CONH); 10.27 (1H, s, SO_2NH); 8.04 (1H, d, *J* = 8.1, H-5); 7.87–7.59 (4H, m, H-7,8,2',6'); 7.44–7.32 (3H, m, H-6,3',5'); 3.58 (3H, s, NCH_3); 2.38 (3H, s, Ar–CH_3)
3b	15.65 (1H, s, OH); 11.62 (1H, s, CONH); 10.26 (1H, s, SO_2NH); 8.05 (1H, dd, *J* = 8.0 and *J* = 1.5, H-5); 7.84-7.60 (4H, m, H-7,8,2',6'); 7.46-7.29 (3H, m, H-6,3',5'); 4.24 (2H, q, *J* = 7.3, NCH_2); 2.38 (3H, s, Ar–CH_3); 1.18 (3H, t, *J* = 7.1, $NCH_2C\underline{H}_3$)
3c	15.68 (1H, s, OH); 11.60 (1H, s, CONH); 10.30 (1H, s, SO_2NH); 8.04 (1H, dd, *J* = 8.2 and *J* = 1.6, H-5); 7.86–7.61 (4H, m, H-7,8,2',6'); 7.50-7.32 (3H, m, H-6,3',5'); 4.15 (2H, t, *J* = 7.7, NCH_2); 2.37 (3H, s, Ar–CH_3); 1.59 (2H, m, $NCH_2C\underline{H}_2$); 0.91 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$)
3d	15.66 (1H, s, OH); 11.67 (1H, s, CONH); 10.26 (1H, s, SO_2NH); 8.02 (1H, dd, *J* = 8.1 and *J* = 1.6, H-5); 7.87–7.59 (4H, m, H-7,8,2',6'); 7.48-7.33 (3H, m, H-6,3',5'); 4.18 (2H, t, *J* = 7.5, NCH_2); 2.38 (3H, s, Ar–CH_3); 1.56 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.36 (2H, m, $C\underline{H}_2CH_3$); 0.90 (3H, t, *J* = 7.1, CH_3)
3e	15.66 (1H, s, OH); 11.60 (1H, s, CONH); 10.28 (1H, s, SO_2NH); 8.02 (1H, dd, *J* = 8.2 and *J* = 1.5, H-5); 7.84–7.59 (4H, m, H-7,8,2',6'); 7.48-7.29 (3H, m, H-6,3',5'); 4.17 (2H, t, *J* = 7.3, NCH_2); 2.36 (3H, s, Ar–CH_3); 1.56 (2H, q, *J* = 7.0, $NCH_2C\underline{H}_2$); 1.30 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.84 (3H, t, *J* = 6.9, CH_3)
3f	15.62 (1H, s, OH); 11.59 (1H, s, CONH); 10.31 (1H, s, SO_2NH); 8.00 (1H, dd, *J* = 8.1 and *J* = 1.6, H-5); 7.82–7.58 (4H, m, H-7,8,2',6'); 7.51-7.31 (3H, m, H-6,3',5'); 4.19 (2H, t, *J* = 7.3, NCH_2); 2.39 (3H, s, Ar–CH_3); 1.57 (2H, q, *J* = 6.8, $NCH_2C\underline{H}_2$); 1.31 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.86 (3H, t, *J* = 6.5, CH_3)

TABLE 5. Full List of $^{1}H–^{13}C$ Heteronuclear Correlations found for the Thiosemicarbazone **1d**

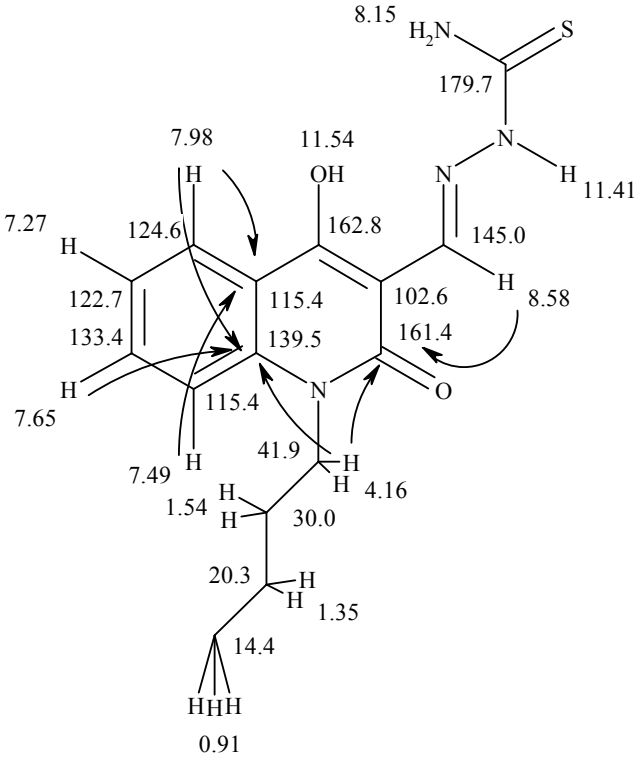
^{1}H Signal, δ, ppm	Position of cross peaks in the ^{13}C measurements	
	HMQC	HMBC
11.54	—	—
11.41	—	—
8.58	145.0	161.4; 102.6
8.15	—	—
7.98	124.6	139.5; 133.4
7.65	133.4	139.5; 124.6; 115.4
7.49	115.4	133.4; 122.7; 115.4
7.27	122.7	115.4
4.16	41.9	161.4; 139.4; 30.0; 20.3
1.54	30.0	41.9
1.35	20.3	14.4
0.91	14.4	30.3; 20.3

to identify the structural features of the synthesized compounds in solution we have measured the ^{13}C NMR spectrum of the 1-N-butyl derivative **1d**. It was found that the ^{13}C NMR spectrum of this compound recorded at room temperature did not show the signals for the two quaternary carbon atoms which must be displaced to low field. This did not allow us to carry out a safe assignment of the signals seen. Hence we also undertook heteronuclear $^{1}H–^{13}C$ correlation experiments. Table 5 shows the cross peak coordinates found in these HMQC and HMBC correlation spectra.

The assignment of the ^{13}C signals on the basis of their heteronuclear correlations demands an initial assignment of the signals in the proton spectrum. The aromatic proton signals of the thiosemicarbazone **1d** occur as an ABCD spin system and appear as two triplets and two doublets in the region 7.27-7.98 ppm. The assignment needs the position of one of the doublets to be securely established. The remaining signals can then be assigned on the basis of the spin-spin interactions occurring. Since at this step of the analysis of the spectrum we have no full picture of the spin-spin interaction it will be assumed that the signal at lower field at 7.98 ppm is the absorption of the H-5 proton signal. This assumption can be fully justified since, firstly, it agrees with numerous data for previously studied 4-hydroxyquinol-2-ones and, secondly, the strongly anisotropic oxygen atom of the 4-OH group is in a *peri* position to the proton indicated. We can subsequently confirm this hypothesis through the heteronuclear spin-spin interactions. The scheme below shows the proton and carbon signal assignments made.

The chemical shifts of the protonated carbon atoms follow from the presence of their correlation through one chemical bond in the HMQC spectrum with the corresponding proton signal. The signals of the nodal carbon atoms in the quinolone ring can be assigned on the basis of the 2-3 chemical bonds correlations in the HMBC spectrum. Hence the assignment for the signal at 139.5 ppm to the C(8a) atom follows from its correlation with the signal for the $N–CH_2$ group protons of the butyl fragment at 4.16 ppm and also with the signals for the H-5 and H-7 aromatic protons. Similarly, the signal at 115.4 ppm corresponds to the C(4a) atom because it correlates with the H-5, H-6, and H-8 aromatic proton signals. It should be noted that the signals for atoms C(4a) and C(8) coincide but in the spectrum recorded upon raising the temperature they appear separately. Assignment of the signal at 161.4 ppm to the carbonyl C(2) atom follows from its correlation with the signal for the $1\text{-}CH_2$ group of the N-butyl substituent and the exocyclic proton with chemical shift of 8.58 ppm assigned to the hydrazone fragment in the molecule. From the scheme it follows that the assignments we have made for the proton signals are indeed valid.

The conventional ^{13}C NMR spectrum of the thiosemicarbazone **1d** shows the absence of signals corresponding to the C(4) atom and the carbon atom of the thiourea fragment. To reveal these we have measured the carbon spectrum on heating to 90ºC. Under these conditions the spectrum shows two further carbon signals with chemical shifts of 179.7 and 162.8 ppm which, from their chemical shift values must be assigned to the carbon atom of the thiourea fragment and the quinolone C(4) atom respectively.



Based on the observed broadening of the signal for the C(4) atom we can conclude that there exists in a DMSO solution of the thiosemicarbazone **1d** not the *syn*↔*anti* isomerism for **1**↔**6** we expected but rather a hydrazone↔enhydrazine tautomerism **1**↔**7**. Participation of the C(2)=O carbonyl in the tautomerism is very unlikely since its signal is virtually unbroadened. As regards the carbon atom of the thio group, considering the distance from the quinolone ring, the broadening of its signal is most likely caused by a totally independent type of tautomerism, in fact typical of thiosemicarbazide derivatives [34].

Study of the antitubercular properties of the compounds synthesized showed that, against expectations, both the thiosemicarbazones **1a-f** and their synthetic precursor tosylhydrazides **3a-f** were totally unable to inhibit the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of the thiosemicarbazone **1d**, the 2D ^{1}H COSY NMR spectroscopic experiments, the NOESY-2D Overhauser effect homonuclear, and HMQC and HMBC heteronuclear correlations were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All of the 2D experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequences corresponded $^{1}J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The number of increments in the COSY and HMQC experiments was 128 and in the HMBC spectra 400. The mixing time in the NOESY-2D experiment was 500 ms.

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

1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazides **5a-f** were prepared using the method in the report [28]. For the synthesis of the β-N-tosylhydrazides **3a-f** commercial *p*-toluenesulfonyl chloride was used from Merck, anhydrous DMF for peptide synthesis from Fluka, and *p*-toluenesulfonylhydrazide from Aldrich.

4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid β-N-Tosylhydrazide (3c). A. Triethylamine (1.54 ml, 11 mmol) followed, with stirring, by *p*-toluenesulfonyl chloride (2.1 g, 11 mmol) were added to a solution of the hydrazide **5c** (2.61 g, 10 mmol) in dry DMF (20 ml) and the product was left for 10-12 h at room temperature. The reaction mixture was treated with cold water and acidified to pH 5 using dilute HCl. The precipitated β-N-tosylhydrazide **3c** was filtered off, washed with water, dried, and crystallized from a mixture of DMF and ethanol.

B. A mixture of the ester **4c** (2.75 g, 10 mmol) and p-toluenesulfonylhydrazide (1.86 g, 10 mmol) in DMF (1 ml) was vigorously stirred and held for 3-5 min at 140ºC. The still hot mixture was carefully treated with ethanol (10-15 ml) and triturated. The precipitate was filtered off, washed with alcohol, and dried.

A mixed sample of the β-N-tosylhydrazide **3c** prepared by the different methods did not show a depressed melting point and their ^{1}H NMR spectra were identical.

4-Hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carbaldehyde Thiosemicarbazide (1c). Anhydrous Na_2CO_3 (3.18 g, 30 mmol) was added in one aliquot to a solution of the β-N-tosylhydrazide **3c** (4.15 g, 10 mmol) in ethylene glycol (20 ml) heated to 160ºC (with care !, vigorous frothing). After several minutes the gas evolution ceased. The reaction mixture was cooled, diluted with water, and acidified with diluted 1:1 HCl to pH ~ 4. The aldehyde **2c** formed was extracted with chloroform (3×20 ml). Solvent was distilled off (finally under reduced pressure). Ethanol (10 ml) and thiosemicarbazide (0.83 g, 9.1 mmol) were added to the technical aldehyde **2c** (2.1 g, 9.1 mmol) and refluxed for 30 min. The yellow crystalline precipitate of the thiosemicarbazone **1c** formed on cooling was filtered off and dried.

Thiosemicarbazones 1a,b,d-f (Table 1) were prepared by a similar method.

X-ray Structural Investigation. Crystals of the thiosemicarbazone **1c** are monoclinic (butanol), at 20ºC: a = 27.266(1), b = 13.057(1), c = 17.293(1) Å, β = 108.15(1)º, V = 5849.9(3) Å^3, M_r = 304.37, Z = 16, space group $C2/c$, d_{calc} = 1.382 g/cm^3, μ(MoKα) = 0.231 mm^{-1}, F(000) = 2560. The unit cell parameters and intensities of 16147 reflections (5047 independent, R_{int} = 0.034) 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 the direct method using the SHELXTL program package [35]. The positions of the hydrogen atoms were revealed using 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 remaining hydrogen atoms). Hydrogen atoms taking part in the formation of hydrogen bonds were refined in the isotropic approximation. In the refinement of the structure limits were set on the length of the bonds in the propyl substituent (Csp^3–Csp^3 = 1.54 Å). The structure was refined in F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.124 for 4983 reflections (R_1 = 0.046 for 2637 reflections with $F > 4\sigma(F)$, S = 0.869). The full crystallographic information has been deposited in the Cambridge structural database (deposit No. CCDC 717533). Interatomic distances and valence angles are given in Tables 2 and 3.

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