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4-HYDROXY-2-QUINOLONES 171*. SYNTHESIS, ISOMERISM, AND ANTITUBERCULAR ACTIVITY OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACID ALKYLIDENEHYDRAZIDES

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Alkylidenehydrazides have been synthesized by the reaction of 1-R-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid hydrazides with lower dialkyl ketones in order to reveal a structure-antitubercular activity relationship. It was shown by ^{1}H NMR spectroscopy that hydrazones obtained from the unsymmetrical ketone – methyl ethyl ketone – exist primarily in the E-isomer form. It was found that the presence of two aliphatic substituents in the alkylidene fragment of the compounds investigated leads to a marked lowering of antimicrobacterial properties.

Keywords: hydrazones, 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, isomerism, antitubercular activity.

The chemical modification of known medicines is one of the most widely used procedures at this time for the elimination of particular limitations [2]. One of the most significant examples of the success and promise of this route for resolving problems in the discovery and development of more efficient medicines for treating tuberculosis is *isoniazid* which has been well known for a long time. For more than 50 years this preparation has remained as one of the main chemotherapeutic agents for treatment of different forms of tuberculosis. Additionally, numerous hydrazones were synthesized on its basis by reactions with different aldehydes and ketones, which successfully are used in medical practice [2, 3] and which are characterized by improved pharmaceutical and/or pharmacokinetic properties. What is particularly importantly that new hydrazones are continuosly designed [4-14].

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* For Communication 170 see [1].

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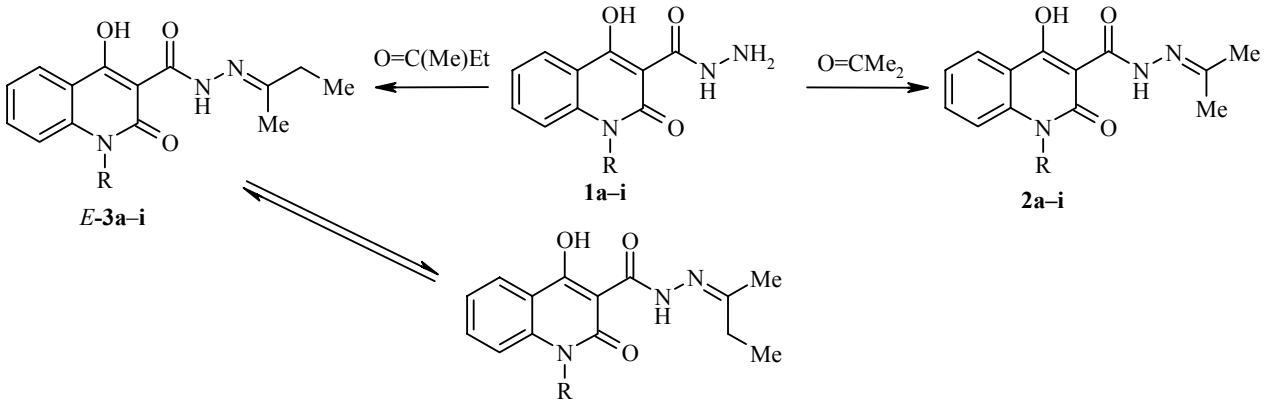


1–3 a R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = C_3H_7, **f** R = C_4H_9, **g** R = C_5H_{11}, **h** R = C_6H_{13}, **i** R = C_7H_{15}

TABLE 1. Characteristics of the 1-R-4-Hydroxy-2-oxo-1,2-dihydroxy-quinoline-3-carboxylic acids alkylidenehydrazides **2** and **3**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Antitubercular activity. Inhibition of the growth of *M. tuberculosis*, %*
		C	H	N			
2a	$C_{13}H_{13}N_3O_3$	60.36 / 60.23	5.16 / 5.05	16.08 / 16.21	316 (decomp.)	97	2
2b	$C_{14}H_{15}N_3O_3$	61.68 / 61.53	5.62 / 5.53	15.50 / 15.38	216-218	92	9
2c	$C_{15}H_{17}N_3O_3$	62.59 / 62.71	6.08 / 5.96	14.71 / 14.62	192-194	90	7
2d	$C_{16}H_{17}N_3O_3$	64.27 / 64.20	5.80 / 5.72	13.92 / 14.04	170-172	87	8
2e	$C_{16}H_{19}N_3O_3$	63.64 / 63.77	6.47 / 6.36	14.08 / 13.94	155-157	85	16
2f	$C_{17}H_{21}N_3O_3$	64.87 / 64.74	6.83 / 6.71	13.47 / 13.32	141-143	82	12
2g	$C_{18}H_{23}N_3O_3$	65.76 / 65.63	7.13 / 7.04	12.63 / 12.76	132-134	81	4
2h	$C_{19}H_{25}N_3O_3$	66.36 / 66.45	7.45 / 7.34	12.38 / 12.24	89-91	83	9
2i	$C_{20}H_{27}N_3O_3$	67.06 / 67.20	7.50 / 7.61	11.64 / 11.76	83-85	85	5
3a	$C_{14}H_{15}N_3O_3$	61.65 / 61.53	5.62 / 5.53	15.49 / 15.38	292 (decomp.)	93	21
3b	$C_{15}H_{17}N_3O_3$	62.82 / 62.71	5.87 / 5.96	14.52 / 14.62	177-179	87	15
3c	$C_{16}H_{19}N_3O_3$	63.63 / 63.77	6.25 / 6.36	14.08 / 13.94	168-170	84	14
3d	$C_{17}H_{19}N_3O_3$	65.28 / 65.16	6.20 / 6.11	13.55 / 13.41	110-112	87	9
3e	$C_{17}H_{21}N_3O_3$	64.63 / 64.74	6.84 / 6.71	13.22 / 13.32	96-98	84	7
3f	$C_{18}H_{23}N_3O_3$	65.75 / 65.63	7.13 / 7.04	12.89 / 12.76	93-95	81	13
3g	$C_{19}H_{25}N_3O_3$	66.33 / 66.45	7.48 / 7.34	12.37 / 12.24	90-92	79	27
3h	$C_{20}H_{27}N_3O_3$	67.35 / 67.20	7.52 / 7.61	11.64 / 11.76	74-76	84	12
3i	$C_{21}H_{29}N_3O_3$	68.03 / 67.90	7.98 / 7.87	11.45 / 11.31	69-71	83	5

* Concentration of substances studied = 6.25 μg/ml.

TABLE 2. ^{1}H NMR Spectra of the 1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids alkylidenehydrazides **2** and **3**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*									
	Isomer ratio, *Z*:*E*	NH–N= (1H, s)	Quinolone ring				Alkylidene fragment			R
			H-5 (1H, d)	H-7 (1H, t)	H-8 (1H, d)	H-6 (1H, t)	CH_3 (3H, s)	C_2H_5		
								CH_2 (2H, q, *J* = 7.5)	CH_3 (3H, t, *J* = 7.5)	
1	2	3	4	5	6	7	8	9	10	11
2a	—	12.97	7.96 (*J* = 8.1)	7.69 (*J* = 7.8)	7.37 (*J* = 8.3)	7.28 (*J* = 7.5)	2.02; 1.95	—	—	11.96 (1H, s, NH)
2b	—	12.98	8.09 (*J* = 8.0)	7.82 (*J* = 7.8)	7.64 (*J* = 8.5)	7.39 (*J* = 7.5)	2.04; 1.97	—	—	3.63 (3H, s, NCH_3)
2c	—	12.98	8.09 (*J* = 8.1)	7.81 (*J* = 7.7)	7.68 (*J* = 8.5)	7.37 (*J* = 7.5)	2.03; 1.97	—	—	4.30 (2H, q, *J* = 7.1, NCH_2); 1.21 (3H, t, *J* = 7.1, CH_3)
2d	—	12.92	8.11 (*J* = 8.1)	7.78 (*J* = 7.8)	7.53 (*J* = 8.6)	7.38 (*J* = 7.5)	2.03; 1.96	—	–	5.94 (1H, m, C<u>H</u>=CH_2); 5.12 (1H, d, *J* = 10.7, NCH_2CH=C<u>H</u>-*cis*); 4.98 (1H, d, *J* = 14.5, NCH_2CH=C<u>H</u>-*trans*); 4.91 (2H, s, NCH_2)
2e	—	12.94	8.06 (*J* = 8.0)	7.77 (*J* = 7.7)	7.63 (*J* = 8.6)	7.34 (*J* = 7.6)	2.02; 1.95	—	—	4.17 (2H, t, *J* = 7.6, NCH_2); 1.60 (2H, m, $NCH_2C\underline{H}_2$); 0.94 (3H, t, *J* = 7.5, CH_3)
2f	—	12.97	8.09 (*J* = 8.0)	7.81 (*J* = 7.8)	7.65 (*J* = 8.7)	7.37 (*J* = 7.5)	2.03; 1.97	—	—	4.24 (2H, t, *J* = 7.5, NCH_2); 1.58 (2H, q, *J* = 7.4, $C\underline{H}_2CH_2CH_3$); 1.39 (2H, m, $C\underline{H}_2CH_3$); 0.92 (3H, t, *J* = 7.1, CH_3)
2g	—	12.98	8.10 (*J* = 8.0)	7.81 (*J* = 7.7)	7.64 (*J* = 8.7)	7.38 (*J* = 7.5)	2.02; 1.98	—	—	4.23 (2H, t, *J* = 7.5, NCH_2); 1.62 (2H, q, *J* = 7.4, $NCH_2C\underline{H}_2$); 1.33 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.86 (3H, t, *J* = 6.8, CH_3)
2h	—	12.97	8.09 (*J* = 8.1)	7.82 (*J* = 7.8)	7.63 (*J* = 8.6)	7.37 (*J* = 7.5)	2.03; 1.97	—	—	4.22 (2H, t, *J* = 7.6, NCH_2); 1.58 (2H, q, *J* = 7.3, $NCH_2C\underline{H}_2$); 1.41-1.22 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.84 (3H, t, *J* = 6.8, CH_3)
2i	—	12.96	8.08 (*J* = 8.0)	7.79 (*J* = 7.8)	7.62 (*J* = 8.6)	7.35 (*J* = 7.5)	2.02; 1.96	—	—	4.20 (2H, t, *J* = 7.3, NCH_2); 1.57 (2H, q, *J* = 7.1, $NCH_2C\underline{H}_2$); 1.40-1.18 (8H, m, $(C\underline{H}_2)_4CH_3$); 0.83 (3H, t, *J* = 6.7, CH_3)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
3a	0.24:0.76	13.10 (*Z*); 12.97 (*E*)	7.97 (*J* = 8.1)	7.69 (*J* = 7.7)	7.38 (*J* = 8.3)	7.29 (*J* = 7.6)	2.01 (*Z*); 1.95 (*E*)	2.33	1.12 (*Z*); 1.07 (*E*)	11.96 (1H, s, NH)
3b	0.22:0.78	13.03 (*Z*); 12.93 (*E*)	8.10 (*J* = 8.0)	7.75 (*J* = 7.6)	7.55 (*J* = 8.4)	7.33 (*J* = 7.5)	2.07(*Z*); 2.01 (*E*)	2.39	1.21 (*Z*); 1.17 (*E*)	3.65 (3H, s, NCH_3)
3c	0.23:0.77	13.09 (*Z*); 12.98 (*E*)	8.10 (*J* = 8.0)	7.81 (*J* = 7.8)	7.68 (*J* = 8.4)	7.38 (*J* = 7.5)	2.01 (*Z*); 1.96 (*E*)	2.34	1.09 (*Z*); 1.06 (*E*)	4.30 (2H, q, *J* = 7.0, NCH_2); 1.21 (3H, t, *J* = 7.0, CH_3)
3d	0.22:0.78	13.01 (*Z*); 12.92 (*E*)	8.11 (*J* = 8.0)	7.77 (*J* = 7.8)	7.52 (*J* = 8.5)	7.37 (*J* = 7.6)	2.01 (*Z*); 1.95 (*E*)	2.33	1.11 (*Z*); 1.07 (*E*)	5.93 (1H, m, C<u>H</u>=CH_2); 5.12 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); .97 (1H, d, *J* = 14.3, NCH_2CH=C<u>H</u>-*trans*); 4.91 (2H, s, NCH_2)
3e	0.22:0.78	13.07 (*Z*); 12.98 (*E*)	8.09 (*J* = 8.0)	7.80 (*J* = 7.7)	7.66 (*J* = 8.6)	7.37 (*J* = 7.5)	2.02 (*Z*); 1.96 (*E*)	2.34	1.12 (*Z*); 1.07 (*E*)	4.20 (2H, t, *J* = 7.6, NCH_2); 1.62 (2H, m, NCH_2C<u>H_2</u>); 0.94 (3H, t, *J* = 7.4, CH_3)
3f	0.20:0.80	13.09 (*Z*); 12.98 (*E*)	8.11 (*J* = 8.0)	7.82 (*J* = 7.8)	7.66 (*J* = 8.6)	7.38 (*J* = 7.5)	2.02 (*Z*); 1.97 (*E*)	2.34	1.12 (*Z*); 1.07 (*E*)	4.25 (2H, t, *J* = 7.5, NCH_2); 1.59 (2H, q, *J* = 7.4, C<u>H_2</u>CH_2CH_3); 1.41 (2H, m, C<u>H_2</u>CH_3); 0.91 (3H, t, *J* = 7.2, CH_3)
3g	0.19:0.81	13.27 (*Z*); 13.18 (*E*)	8.11 (*J* = 7.9)	7.76 (*J* = 7.8)	7.59 (*J* = 8.7)	7.33 (*J* = 7.5)	2.01 (*Z*); 1.96 (*E*)	2.33	1.11 (*Z*); 1.07 (*E*)	4.22 (2H, t, *J* = 7.4, NCH_2); 1.59 (2H, q, *J* = 7.3, NCH_2C<u>H_2</u>); 1.33 (4H, m, (C<u>H_2</u>$)_2CH_3$); 0.86 (3H, t, *J* = 6.6, CH_3)
3h	0.20:0.80	13.09 (*Z*); 12.99 (*E*)	8.11 (*J* = 8.0)	7.82 (*J* = 7.7)	7.65 (*J* = 8.7)	7.38 (*J* = 7.5)	2.02 (*Z*); 1.96 (*E*)	2.34	1.12 (*Z*); 1.07 (*E*)	4.25 (2H, t, *J* = 7.3, NCH_2); 1.60 (2H, q, *J* = 7.2, NCH_2C<u>H_2</u>); 1.30 (6H, m, (C<u>H_2</u>$)_3CH_3$); 0.84 (3H, t, *J* = 6.6, CH_3)
3i	0.23:0.77	13.08 (*Z*); 12.98 (*E*)	8.10 (*J* = 8.0)	7.81 (*J* = 7.8)	7.64 (*J* = 8.6)	7.37 (*J* = 7.5)	2.02 (*Z*); 1.97 (*E*)	2.34	1.12 (*Z*); 1.07 (*E*)	4.24 (2H, t, *J* = 7.2, NCH_2); 1.59 (2H, q, *J* = 7.1, NCH_2C<u>H_2</u>); 1.40-1.18 (8H, m, (C<u>H_2</u>$)_4CH_3$); 0.83 (3H, t, *J* = 6.6, CH_3)

* The signals for the 4-OH group protons appear as a singlet in the range 16.95-17.14 ppm.

This same principle stands as the basis of our investigation, the aim of which was to follow how a change from using benzaldehydes to lower aliphatic ketones impacts the biological properties of the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids benzylidenehydrazides which are well regarded as potential anti-tubercular agents [15-19].

Reaction of the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids hydrazides **1a-i** with acetone or methyl ethyl ketone (which simultaneously acted as solvents) gave the corresponding isopropylidene and *sec*-butylidene derivatives **2a-i** and **3a-i** in preparatively high yields (Table 1).

All of the compounds obtained are colorless, crystalline substances, readily soluble in the majority of organic solvents and virtually insoluble in water.

All of the protons contained in the functional groups of the isopropylidenehydrazides **2a-i** are readily identified from the corresponding signals in the ^{1}H NMR spectra (Table 2). The unsymmetrical methyl ethyl ketone is used in the synthesis of the *sec*-butylidenehydrazides **3a-i** and their spectra show both signals for the main material and clear evidence for an admixture of minor components. In freshly prepared solutions in DMSO the amount of the admixture in each case is near to 10%. However, even after several hours the content of the minor component in the mixture increases approximately twofold to reach a mean of 20-22% and stays almost unchanged for several months. The most likely reason for the observed effect is the potential for different orientations of the methyl and ethyl group of the alkylidene fragment in the *sec*-butylidenehydrazides **3a-i** with respect to the carbon–nitrogen double bond thus forming *Z*- and *E*-isomers and these are of interest for a more detailed structural investigation.

The structures of the main and minor components were demonstrated in the case of the *sec*-butylidene-hydrazide **3b**. Besides the ^{1}H NMR spectrum we have additionally recorded its ^{13}C NMR spectrum and also carried out homonuclear (COSY, NOESY) and heteronuclear ^{1}H–^{13}C (HMQC, HMBC) correlation experiments to deduce the geometric structure of the molecule.

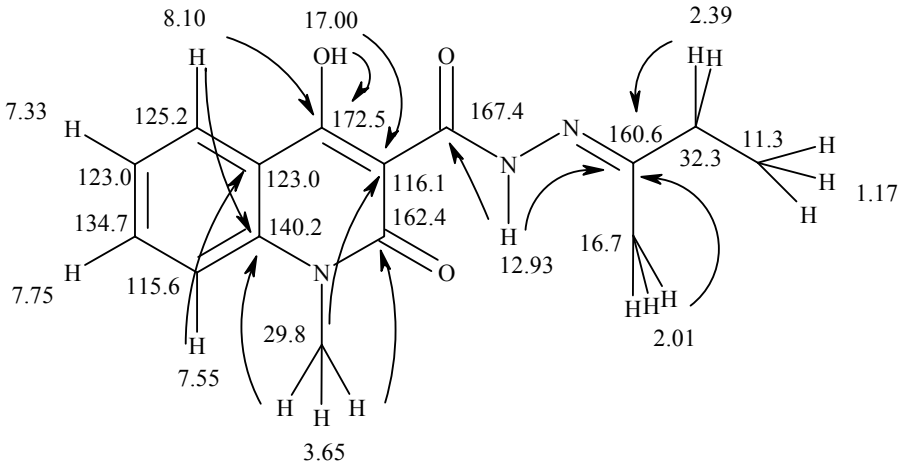
Determination of the structure of this compound is based on which of the aliphatic groups in the alkylidene part of the molecule is close in space to the NH proton signal, but it was necessary first to establish its location in the spectrum. The data obtained in the heteronuclear correlation of signals was employed. The cross peaks found in the HMQC and HMBC spectra of the *sec*-butylidenehydrazide **3b** are given in Table 3.

With the help of the HMQC correlations found and the signal assignments made in the proton spectrum all of the carbon signals bound to these protons can be located. The signals for the quaternary carbon atoms were interpreted on the basis of the long range correlations in the HMBC spectrum. The same spectrum permits assignment of the values of the OH and NH proton signal chemical shifts. In particular, one of the signals (which has a chemical shift of 12.93 ppm) correlates with two quaternary carbon atoms with chemical shifts of

TABLE 3. Full List of ^{1}H–^{13}C Heteronuclear Correlations found for the Main Isomer of the *sec*-Butylidenehydrazide **3b**

^{1}H NMR signal, δ, ppm	Position of the cross peaks in the ^{13}C measurement	
	HMQC	HMBC
17.00	—	172.6; 116.1
12.93	—	167.4; 160.6
8.10	125.2	172.6; 140.2; 134.7
7.75	134.7	140.2; 125.2; 115.6
7.55	115.6	172.6; 134.7; 123.0; 115.6
7.33	123.0	140.2; 134.7; 125.2; 115.6
3.65	29.8	162.4; 140.2; 116.1
2.39	32.3	160.6; 16.6; 11.3
2.01	16.7	160.6; 32.3
1.17	11.3	160.6; 116.1; 32.3

167.4 and 160.6 ppm. The signal at 160.6 ppm also correlates with the signals of the aliphatic protons of the alkylidene fragment. This gives a confirmation that the proton signal at 12.93 ppm is due to the NH proton. The lowest field protons signal is seen at 17.00 ppm and correlates in the HMBC spectrum with carbon atoms of the quinolone fragment and so corresponds to the 4-OH group. The scheme below shows the full assignment of the signals in the ^{1}H and ^{13}C NMR spectra of the *sec*-butylidenehydrazide **3b**. The curved arrows show the most important HMBC correlations and served as the basis for the signal assignments.



Clarification of the orientation of the alkyl substituents in the main and minor isomers of the *sec*-butylidenehydrazide **3b** comes from the presence of a correlation in the NOESY spectrum between these substituents and the NH proton. The NOESY spectrum of this compound clearly shows that the minor component of the isomer mixture has a cross peak with the methylene proton signal in the ethyl substituent and that the main component correlates with the methyl group signal. It therefore follows that the main component of the *sec*-butylidenehydrazide **3b** has an *E*-configuration.

A study of the antitubercular activity of the acylhydrazones **2** and **3** was carried out radiometrically [20, 21] within the scope of the international TAACF program (Tuberculosis Antimicrobial Acquisition and Coordinating Facility). The microbiological work was carried out *in vitro* relative to *Mycobacterium tuberculosis* H37Rv ATCC 27294. The experimental data in Table 1 clearly shows that exchange of the benzaldehydes for lower aliphatic ketones causes a very marked fall in the antimicobacterial activity of the 1-R-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinoyl hydrazones derived from them. In addition, the much lower activity for the high solubility acylhydrazones **2** and **3** when compared with their extremely poorly soluble structural analogs (prepared using 3-acetyl-4-hydroxy-2-oxo-1,2-dihydroquinoline [22] as the ketone component) once more confirms the conclusion we have reached before that the antitubercular activity of 4-hydroxy-2-quinolones does not, in practice, depend on solubility.

EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra of the *sec*-butylidenehydrazide **3b**, COSY 2D ^{1}H NMR experiments, the NOESY-2D homonuclear spectroscopy, and the heteronuclear HMQC and HMBC spectra 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 were respectively $^{1}J_{CH}$ = 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 spectrum 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). In all cases DMSO-d_6 was used as solvent and TMS as internal standard. The 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazides **1a-i** were synthesized by our reported method [23].

1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids Alkylidenehydrazides 2 and 3 (General Method). A mixture of the corresponding 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazide (0.01 mol) and acetone or methyl ethyl ketone (30 ml) was refluxed for 1 h. The reflux condenser was removed and downward distillation was used to remove about 20 ml of solvent. The remaining solution was purified using carbon, filtered, and placed in a freezer at -20ºC for 10-12 h. The crystals of the isopropylidene hydrazide **2** or the *sec*-butylidenehydrazide **3** were filtered off and dried. For separation of the *sec*-butylidene hydrazides **3d-i** the methyl ethyl ketone was fully distilled from the reaction mixture. The residue was crystallized from diethyl ether.

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REFERENCES

1. I. V. Ukrainets, N. L. Bereznyakova, O. V. Gorokhova, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 1546 (2009). [*Chem. Heterocycl. Comp.*, **45**, 1241 (2009)].
2. S. G. Kuznetsov, S. M. Chigareva, and S. M. Ramsh, in: *Summaries Sources of Science and Technology. Organic Chemistry* [in Russian], Vol. 19, VINITI, Moscow (1991), p. 25.
3. M. V. Rubtsov and A. G. Baichikov, *Synthetic Chemico-Pharmaceutical Preparations* [in Russian], Meditsina, Moscow (1971), p. 190.
4. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 2, Novaya Volna, Moscow (2002), p. 306.
5. F. V. Bagrov and T. V. Vasil'eva, *Zh. Org. Khim.*, **38**, 1364 (2002).
6. T. Scior and S. J. Garcés-Eisele, *Curr. Med. Chem.*, **13**, 2205 (2006).
7. R. Maccari, R. Ottanà, and M. G. Vigorita, *Bioorg. Med. Chem. Lett.*, **15**, 2509 (2005).
8. A. De Logu, V. Onnis, B. Saddi, C. Congiu, M. L. Schivo, and M. T. Cocco, *J. Antimicrob. Chemother.*, **49**, 275 (2002).
9. B. N. Swamy, T. K. Suma, G. V. Rao, and G. C. Reddy, *Eur. J. Med. Chem.*, **42**, 420 (2007).
10. D. Sriram, P. Yogeeswari, and K. Madhu, *Bioorg. Med. Chem. Lett.*, **15**, 4502 (2005).
11. A. Bijev, *Arzneimit.-Forsch.*, **56**, 96 (2006).
12. A. Bijev, *Letters in Drug Design & Discovery*, **3**, 506 (2006).
13. D. Sriram, P. Yogeeswari, and K. Madhu, Bioorg. *Med. Chem. Lett.*, **16**, 876 (2006).
14. L. I. Petrukh, M. M. Kovalenko, and O. I. Mikhalik, *Farmakom*, No. 2, 9 (1999).
15. I. V. Ukrainets, Jaradat Nidal Amin, P. O. Bezugly, O. V. Gorokhova, and L. V. Sidorenko, *Visnyk Farmatsii*, No. 1 (21), 13 (2000).
16. I. V. Ukrainets, O. S. Prokopenko, L. V. Sidorenko, and O. V. Gorokhova, *Visnyk Farmatsii*, No. 3 (39), 3 (2004).
17. I. V. Ukrainets, L. V. Sidorenko, O. S. Prokopenko, V. B. Rybakov, and V. V. Chernyshev, *Zh. Org. Farm. Khim.*, **2**, No. 4 (8), 17 (2004).
18. A. O. Tkach, O. S. Golovchenko, I. V. Ukrainets, and L. O. Petrushova, *Zh. Org. Farm. Khim.*, **5**, No. 4 (20), 36 (2007).
19. L. V. Sidorenko, O. S. Golovchenko, I. V. Ukrainets, and T. V. Alekseeva, *Visnyk Farmatsii*, No. 2 (54), 3 (2008).

20. L. B. Heifets, in: L. B. Heifets (editor), *Drug Susceptibility in the Chemotherapy of Mycobacterial Infections*, CRC Press, Boca Raton (1991), p. 89.
21. C. B. Inderleid and K. A. Nash, in: V. Lorian (editor), *Antibiotics in Laboratory Medicine*, Williams and Wilkins, Baltimore (1996), p. 127.
22. I. V. Ukrainets, A. A. Tkach, and Liu Yangyang, *Khim. Geterotsikl. Soedin.*, 214 (2009). [*Chem. Heterocycl. Comp.*, **45**, 169 (2009)].
23. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, M. Yu. Kornilov, A. V. Turov, A. I. Maslennikov, S. V. Gladchenko, and V. I. Krivobok, *Khim. Geterotsikl. Soedin.*, 1086 (1992). [*Chem. Heterocycl. Comp.*, **28**, 912 (1992)].