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4-HYDROXY-2-QUINOLONES. 95*. SYNTHESIS, STRUCTURE, AND ANTITUBERCULAR PROPERTIES OF HETARYLAMIDES OF 4-HYDROXY-2-OXO-1,2,5,6,7,8-HEXAHYDROQUINOLINE-3-CARBOXYLIC ACID

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The optimal conditions for obtaining hetarylamides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid are suggested on the basis of derivatographic investigations. The ^{1}H NMR spectra of the synthesized compounds, their spatial structure, and also the results of a study of their antitubercular properties are discussed.

Keywords: amides, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, antitubercular activity, X-ray structural analysis, thermolysis.

More recently tuberculosis was considered to be an illness already finally conquered, but today it has become the most widespread infectious disease in the world. The reason for the position established now is concealed in the reduction of the set of antitubercular measures in the majority of developing and economically highly developed countries. As a result tuberculosis has emerged from being under control and at the beginning of the nineties of the last century approached a crisis point, in place of an annual fall in morbidity an impetuous deterioration in the epidemiological situation began [2, 3]. In addition, seriously complicating the problem, the ability of *Mycobacterium tuberculosis* to mutate actively, has given it the possibility of producing resistance (frequently multiple) against many well-known antitubercular preparations. As a result there are now in the world several million people for whom classical medical treatment is no help. In connection with this the search for new medicinal agents with antimycobacterial action is a problem of paramount importance in contemporary international public health.

Of undoubted interest in this project are anilides [4], hetarylamides [5-7], and hydrazides [8] of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, which show, in experiments *in vitro*, high activity in relation not only to *Mycobacterium tuberculosis*, but also to inducers of nontubercular mycobacterial disease, the *Mycobacterium avium* complex. With the aim of clarifying the rules of the chemical structure–antitubercular action in the series of compounds being studied we have effected the synthesis and carried out microbiological screening of hydrogenated analogs of the compounds described previously and of the hetaryl-amides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acids **1a-u**.

* For Part 94 see [1].

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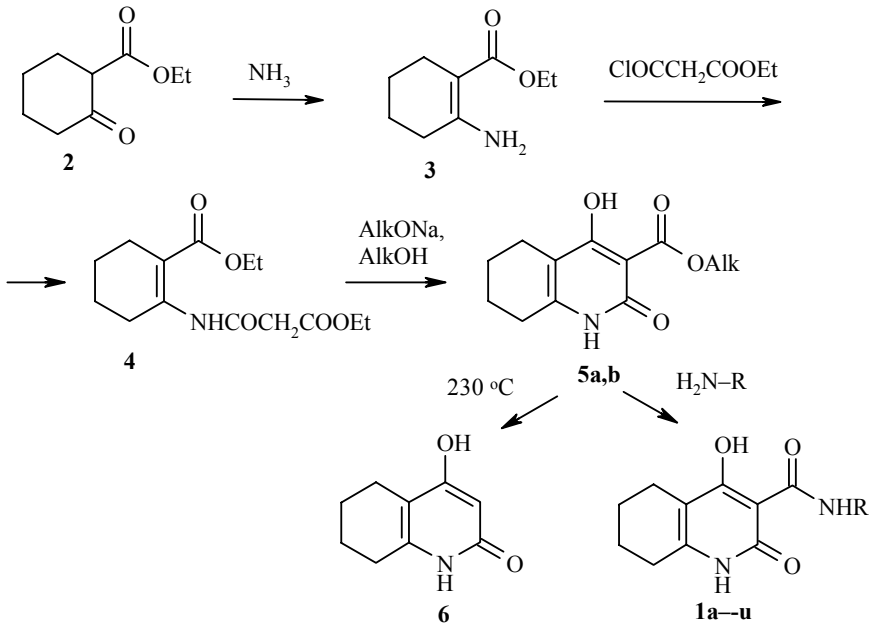

1 a R = Py-4, **b** R = Py-3, **c** R = Py-2, **d** R = 3-Me-Py-2, **e** R = 4-Me-Py-2, **f** R = 5-Me-Py-2, **g** R = 6-Me-Py-2, **h** R = 4-picolyl, **i** R = 3-picolyl, **j** R = 2-picolyl, **k** R = 3-OH-Py-2, **l** R = 2-thiazolyl, **m** R = 4-(1-adamantyl)-2-thiazolyl, **n** R = 2-benzothiazolyl, **o** R = 6-Me-2-benzothiazolyl, **p** R = 6-Br-2-benzothiazolyl, **q** R = 1,3,4-thiadiazol-2-yl, **r** R = 5-Me-1,3,4-thiadiazol-2-yl, **s** 5-Et-1,3,4-thiadiazol-2-yl, **t** 5-Pr-1,3,4-thiadiazol-2-yl, **u** 5-Isopropyl-1,3,4-thiadiazol-2-yl; **5 a** Alk = Me; **b** Alk = Et

The ethyl ester of cyclohexanone-2-carboxylic acid (**2**) served as starting material for obtaining amides **1a-u**, and is readily converted on treatment with gaseous ammonia into enamine **3**. Subsequent acylation with the ethyl ester of chlorocarbonylacetic acid, and then intramolecular cyclization of the resulting diester **4** under the action of alkali metal alcoholates gave the esters of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid **5a,b**.

It was shown previously that thermolysis at 160-200°C is most rational for the amidation of esters of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with anilines or hetarylamines [4-7]. Evidently such a method is also right for their hydrogenated analogs. Consequently to select optimum conditions for obtaining amides **1a-u** we studied the thermal behavior of ester **5a**. From the derivatograms shown in Fig. 1 it follows that methyl ester **5a** is stable to 175°C. On further increase of temperature a smooth loss of mass begins, which sharply increases from 185°C. A break is observed at this temperature on curve 4 changing into a peak at 220°C. The rapid loss of mass stops at 250°C and then only a uniform volatilization of the compound occurs. The overall loss of mass in the temperature range 180 to 230°C was 25% of the initial, which calculated on each molecule of ester **5a** corresponds to 56 atomic mass units. In other words, under conditions of dry heat the ester group of compound **5a** decomposes (as indicated by the endothermal peak at 220°C on curve 2) with the formation of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline (**6**), the structure of which was confirmed by ^{1}H NMR and mass spectra. It is interesting that under analogous conditions esters of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids behave differently. They are practically quantitatively condensed into 5,9-di-R-6,7,8-trioxodiquinolino[3,4-*b*;3',4'-*e*]-4H-pyranes [9].

The derivatographic investigation therefore shows that amidation of esters **5** with hetarylamines under thermolysis conditions must be carried out at a temperature no greater than 175°C. In addition we noted that carrying out the synthesis in the presence of a small amount of a high-boiling solvent (DMF or bromobenzene)

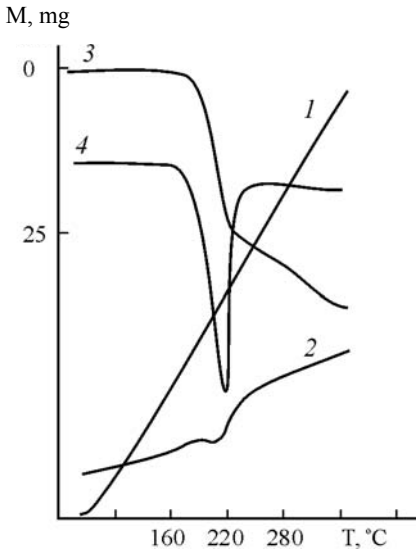

Fig. 1. Derivatograms of methyl ester **5a**: 1) thermal analysis curve; 2) differential thermal analysis curve; 3) thermogravimetric curve; 4) differential thermogravimetric curve. Sample weight 100 mg.

gives the best results, which provides better mixing of reactants and prevents local overheating of the reaction mixture. The hetarylamides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid **1a-u** obtained in this way contain less contaminants while retaining high yields (Table 1).

All of the proton-containing functional groups of the synthesized compounds were identified in the ^{1}H NMR spectra fairly simply (Table 2). Difficulties arose only on assigning signals for the hydroquinolone methylene groups. In all cases they were displayed by three multiplets of intensity 2, 2, and 4H. It is apparent that the last of the signals mentioned is caused by the similar CH_2 groups in positions 6 and 7 together. The methylene groups in positions 5 and 8 are magnetically non-equivalent and for the precise assignment of their signals we used the nuclear Overhauser effect (NOE) [10]. In ester **5b** the only protons which may help in the assignment of the signals of the cyclohexene fragment by the NOE method are the protons of the NH and OH groups. Their assignment follows from comparison with the spectrum of the N-alkyl-substituted analog of esters **5** [11] in which the signal of the NH group is displayed at higher field (at 11.20 ppm). Saturation of this signal in the NOE experiment led to an increase of 2% for the signal at 2.45 ppm. Consequently this signal corresponds to the proton at $C_{(8)}$ and the remaining signal at 2.30 ppm to the methylene proton at $C_{(15)}$. The small size of the NOE is linked most likely with the presence of a fairly rapid exchange of the NH group proton of the quinoline with water, which also reduces the size of the effect.

Interesting features of the spatial structure of amides **1a-u** became apparent in the X-ray structural investigation of one of these compounds. In the symmetrically independent portion of the unit cell of the crystal of 4-(1-adamantyl)-2-thiazolylamide **1m** two molecules were detected (**A** and **B**) differing in the conformation of the cyclohexene ring. In the molecule it was possible to distinguish two fragments planar to a precision of 0.02 Å. One of them includes the pyridine ring and the $O_{(1)}$, $O_{(2)}$, $O_{(3)}$, and $C_{(10)}$ atoms. The second contains the thiazole ring and the $N_{(2)}$ and $C_{(14)}$ atoms. The two planar fragments are folded somewhat relative to one another by an angle of 11.9 (molecule **A**) and 15.8° (**B**), which is probably caused by the shortened intramolecular contact $O_{(3)}\cdots S_{(1)}$ 2.81 in **A** and 2.86 Å in molecule **B** (the sum of the van der Waals radii is 3.09 Å [12]). The repulsion between these atoms also leads to an increase in the valence angle $C_{(11)}$–$N_{(2)}$–$C_{(10)}$ to 125.0(5) **A**, 127.3(4)° **B**. The adamantyl substituent is disposed in such a way that one of the C–C bonds is practically in the plane of the thiazole nucleus [torsion angle $C_{(13)}$–$C_{(12)}$–$C_{(14)}$–$C_{(15)}$ is 9(1) in **A** and 17(1)° in **B**]. The cyclohexene

TABLE 1. Characteristics of N-R-Amides of 4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acids (**1a-u**)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (dec.)	Antitubercular activity*	Yield, %
		C	H	N			
1a	$C_{15}H_{15}N_3O_3$	63.22 / 63.15	5.41 / 5.30	14.60 / 14.73	307-309	0	90
1b	$C_{15}H_{15}N_3O_3$	63.25 / 63.15	5.39 / 5.30	14.78 / 14.73	270-272	1	93
1c	$C_{15}H_{15}N_3O_3$	63.06 / 63.15	5.40 / 5.30	14.80 / 14.73	277-279	14	85
1d	$C_{16}H_{17}N_3O_3$	64.11 / 64.20	5.62 / 5.72	14.00 / 14.04	225-227	13	76
1e	$C_{16}H_{17}N_3O_3$	64.15 / 64.20	5.75 / 5.72	14.16 / 14.04	262-264	14	87
1f	$C_{16}H_{17}N_3O_3$	64.33 / 64.20	5.84 / 5.72	14.13 / 14.04	293-295	0	90
1g	$C_{16}H_{17}N_3O_3$	64.10 / 64.20	5.80 / 5.72	14.02 / 14.04	303-305	0	92
1h	$C_{16}H_{17}N_3O_3$	64.14 / 64.20	5.78 / 5.72	14.15 / 14.04	222-224	33	88
1i	$C_{16}H_{17}N_3O_3$	64.32 / 64.20	5.66 / 5.72	14.17 / 14.04	241-243	21	84
1j	$C_{16}H_{17}N_3O_3$	64.30 / 64.20	5.81 / 5.72	14.14 / 14.04	232-234	6	83
1k	$C_{15}H_{15}N_3O_4$	59.92 / 59.80	5.13 / 5.02	13.88 / 13.95	271-273	33	78
1l	$C_{13}H_{13}N_3O_3S$	53.55 / 53.60	4.63 / 4.50	14.51 / 14.42	302-304	19	86
1m	$C_{23}H_{27}N_3O_3S$	64.98 / 64.92	6.54 / 6.40	9.76 / 9.87	331-333	10	89
1n	$C_{17}H_{15}N_3O_3S$	59.73 / 59.81	4.34 / 4.43	12.40 / 12.31	325-327	14	90
1o	$C_{18}H_{17}N_3O_3S$	60.89 / 60.83	4.95 / 4.82	11.72 / 11.82	318-320	29	87
1p	$C_{17}H_{14}BrN_3O_3S$	48.60 / 48.58	3.47 / 3.36	10.14 / 10.00	310-312	36	92
1q	$C_{12}H_{12}N_4O_3S$	49.45 / 49.31	4.26 / 4.14	19.25 / 19.17	283-285	8	80
1r	$C_{13}H_{14}N_4O_3S$	50.84 / 50.97	4.70 / 4.61	18.38 / 18.29	297-299	24	82
1s	$C_{14}H_{16}N_4O_3S$	52.40 / 52.49	5.15 / 5.03	17.40 / 17.49	288-290	4	77
1t	$C_{15}H_{18}N_4O_3S$	53.97 / 53.88	5.55 / 5.43	16.64 / 16.75	274-276	8	81
1u	$C_{15}H_{18}N_4O_3S$	53.94 / 53.88	5.50 / 5.43	16.79 / 16.75	255-257	98	80

* Depression of growth (%) of *Mycobacterium tuberculosis H37Rv* ATCC 27294 at a concentration of 6.25 μg/ml.

ring is randomized with two equally probable conformations. In the case of molecule **A** this is an asymmetric half-chair. The deviation of the $C_{(3)}$ and $C_{(4)}$ atoms from the plane of the remaining atoms of the ring was 0.15, -0.56 Å for one conformer (**C**), and -0.44, 0.28 Å for the other (**D**). In molecule **B** the tetrahydro ring is randomized with a half-chair (deviations of atoms $C_{(3)}$ and $C_{(4)}$ were 0.41 and -0.53 Å) and a *sofa* conformation (atom $C_{(4)}$ deviates from the plane of the remaining atoms by 0.54 Å).

Molecules **A** and **B** also differ in the character of their intramolecular hydrogen bonds. In both molecules bonds $N_{(2)}$–H···$O_{(1)}$ are formed with close geometric characteristics (H···O 1.90 Å in **A** and **B**, N–H···O 140 in **A**, 141° in **B**). This leads to a significant lengthening of the $C_{(9)}$=$O_{(1)}$ bond to 1.257(8) (**A**) and

TABLE 2. ^{1}H NMR Spectra of N-R-Amides of 4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid **1a-u**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)					
	OH (1H, s)	NH (1H, s)	NH quinoline (1H, s)	CH_2 quinoline*		R
				5-CH_2 (2H, m)	6,7-CH_2 (4H, m)	
1	2	3	4	5	6	7
1a	14.86	12.90	11.74	2.33	1.66	8.56 (2H, d, *J* = 5.8, H-2,6); 8.47 (2H, d, *J* = 5.8, H-3,5)
1b	15.12	12.74	11.78	2.33	1.67	8.75 (1H, d, *J* = 2.0, H-2); 8.33 (1H, dd, *J* = 4.4 and *J* = 1.5, H-6); 8.06 (1H, dt , *J* = 8.6 and *J* = 1.7, H-4); 7.39 (1H, t, *J* = 7.4, H-5)
1c	15.11	12.90	11.64	2.36	1.70	8.35 (1H, d, *J* = 4.2, 6-H); 8.11 (1H, d, *J* = 8.2, H-3); 7.82 (1H, td, *J* = 7.8 and *J* = 2.1, H-4); 7.12 (1H, t, *J* = 6.0, H-5)
1d	15.41	12.44	11.77	2.34	1.68	8.27 (1H, dd, *J* = 5.1 and *J* = 1.4, H-6); 7.72 (1H, d, *J* = 7.9, H-4); 7.22 (1H, t, *J* = 5.9, H-5); 2.23 (3H, s, CH_3)
1e	15.17	12.87	11.80	Cm. R	1.66	8.19 (1H, d, *J* = 5.0, H-6); 7.97 (1H, c, H-3); 6.99 (1H, d, *J* = 4.7, H-5); 2.33 (5H, m, 5-CH_2 + CH_3)
1f	15.23	12.85	11.79	2.33	1.66	8.17 (1H, s, H-6); 8.01 (1H, d, *J* = 8.1, H-3); 7.64 (1H, dd, *J* = 8.2 and *J* = 2.4, H-4); 2.25 (3H, s, CH_3)
1g	15.21	12.78	11.77	2.32	1.66	7.92 (1H, d, *J* = 7.9, H-3); 7.70 (1H, t, *J* = 7.7, H-4); 7.01 (1H, d, *J* = 7.4, H-5); 2.40 (3H, s, CH_3)
1h	15.75	10.71 (t, *J* = 5.5)	11.54	2.31	1.67	8.50 (2H, d, *J* = 4.0, H-2,6); 7.28 (2H, d, *J* = 4.3, H-3,5); 4.56 (2H, d, *J* = 5.8, NCH_2)
1i	15.83	10.66 (t, *J* = 5.4)	11.50	2.29	1.65	8.55 (1H, s, H-2); 8.50 (1H, d, *J* = 4.3, H-6); 7.72 (1H, dt , *J* = 8.0 and *J* = 2.0, H-4); 7.35 (1H, t, *J* = 6.0, H-5); 4.57 (2H, d, *J* = 6.4, NCH_2)
1j	15.95	10.81 (t, *J* = 5.4)	11.47	2.31	1.66	8.52 (1H, d, *J* = 4.9, H-6); 7.77 (1H, td, *J* = 7.6 and *J* = 2.0, H-4); 7.30 (2H, m, H-3,5); 4.63 (2H, d, *J* = 5.8, NCH_2)

TABLE 2 (continued)

1	2	3	4	5	6	7
1k	15.32	12.60	11.65	2.33	1.67	10.19 (1H, s, OH-Py); 7.85 (1H, dd, *J* = 4.3 and *J* = 1.7, H-6); 7.25 (1H, d, *J* = 7.6, H-4); 7.07 (1H, t, *J* = 4.1, H-5)
1l	14.40	13.55	11.84	2.34	1.66	7.44 (1H, d, *J* = 4.1, H-4); 7.08 (1H, d, *J* = 3.6, H-5)
1m	14.23	13.62	11.93	2.35	See R	6.80 (1H, s, H-5); 2.02 (3H, s, H-γ adamantane); 1.90 (6H, s, H-δ adamantane); 1.74 (10H, m, 6,7-CH_2 + H-β adamantane)
1n	14.18	13.69	11.90	2.38	1.68	8.00 (1H, d, *J* = 8.2, H-7); 7.76 (1H, d, *J* = 8.0, H-4); 7.45 (1H, t, *J* = 7.5, H-6); 7.29 (1H, t, *J* = 7.9, H-5)
1o	14.10	13.43	11.80	See R	1.67	7.74 (1H, s, H-7); 7.65 (1H, d, *J* = 7.0, H-4); 7.25 (1H, d, *J* = 7.0, H-5); 2.40 (5H, m, 5-CH_2 + CH_3)
1p	14.06	13.60	11.94	2.36	1.68	8.21 (1H, s, H-7); 7.80 (1H, d, *J* = 8.0, H-4); 7.60 (1H, d, *J* = 8.0, H-5)
1q	14.00	13.45	12.12	2.35	1.67	9.18 (1H, s, H-5)
1r	14.15	13.42	12.03	2.38	1.68	2.69 (3H, s, CH_3)
1s	14.17	13.35	12.00	2.34	1.66	3.05 (2H, q, *J* = 7.7, C<u>H</u>$_2$$CH_3$); 1.41 (3H, t, *J* = 7.6, CH_3)
1t	14.03	13.84	12.06	2.34	1.66	2.97 (1H, t, *J* = 7.3, C<u>H</u>$_2$$CH_2CH_3$); 1.74 (2H, m, CH_2C<u>H</u>$_2$$CH_3$); 0.94 (3H, t, *J* = 7.3, CH_3)
1u	14.12	13.65	12.10	2.33	1.69	3.38 (1H, m, C<u>H</u>$(CH_3)_2$); 1.33 (6H, d, *J* = 6.3, 2CH_3)

* The multiplet signal of the 8-CH_2 group protons of quinoline in amides **1a-u** coincide with the signals of the residual protons of the solvent.

1.254(5) Å (**B**) in comparison with a mean value of 1.210 Å [13]. In molecule **B** a hydrogen bond is also formed at $O_{(2)}$–H···$O_{(3)}$ (H···O 1.80 Å, O–H···O 147°). In molecule **A** such a bond is very weak (H···O 1.98 Å, O–H···O 122°), which is also confirmed by the absence of lengthening of the $C_{(10)}$=$O_{(3)}$ bond at 1.219(8) Å, in comparison with molecule **B** [1.250(6) Å].

In the crystal of the **1m** amide molecule centrosymmetric dimers are formed as a result of hydrogen bonds $N_{(1)}$–H···$O_{(1)}$, (*-x*, *-y*, *-z*): H···O 1.90 (**A**), 1.94 Å (**B**), N–H···O 177 (**A**), 169° (**B**).

The antitubercular properties of the hetarylamides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid **1a-u** were studied by the radiometric method of [14]. From the data of the first microbiological screening (Table 1) it follows that hydrogenation of the benzene portion of the quinolone is accompanied by a significant fall in activity. From all the groups of substances investigated only 5-isopropyl-1,3,4-thiadiazolyl-2-amide **1u** deserves attention. At a concentration of 6.25 μg/ml it was able to suppress the

TABLE 3. Bond Lengths (*l*) in the Structure of Amide **1m**

Bond	*l*, Å	Bond	*l*, Å
$S_{(1A)}$–$C_{(11A)}$	1.698(6)	$S_{(1A)}$–$C_{(13A)}$	1.723(5)
$O_{(1A)}$–$C_{(9A)}$	1.257(8)	$O_{(2A)}$–$C_{(7A)}$	1.29(1)
$O_{(3A)}$–$C_{(10A)}$	1.219(8)	$N_{(1A)}$–$C_{(9A)}$	1.381(7)
$N_{(1A)}$–$C_{(1A)}$	1.388(8)	$N_{(2A)}$–$C_{(10A)}$	1.358(8)
$N_{(2A)}$–$C_{(11A)}$	1.432(6)	$N_{(3A)}$–$C_{(11A)}$	1.293(7)
$N_{(3A)}$–$C_{(12A)}$	1.391(6)	$C_{(1A)}$–$C_{(6A)}$	1.31(1)
$C_{(1A)}$–$C_{(2A)}$	1.476(9)	$C_{(2A)}$–$C_{(3C)}$	1.498(9)
$C_{(2A)}$–$C_{(3D)}$	1.524(9)	$C_{(3C)}$–$C_{(4C)}$	1.52(1)
$C_{(4C)}$–$C_{(5A)}$	1.53(1)	$C_{(3D)}$–$C_{(4D)}$	1.53(1)
$C_{(4D)}$–$C_{(5A)}$	1.513(8)	$C_{(5A)}$–$C_{(6A)}$	1.48(1)
$C_{(6A)}$–$C_{(7A)}$	1.45(1)	$C_{(7A)}$–$C_{(8A)}$	1.43(1)
$C_{(8A)}$–$C_{(9A)}$	1.39(1)	$C_{(8A)}$–$C_{(10A)}$	1.489(8)
$C_{(12A)}$–$C_{(13A)}$	1.336(7)	$C_{(12A)}$–$C_{(14A)}$	1.521(7)
$C_{(14A)}$–$C_{(19A)}$	1.501(9)	$C_{(14A)}$–$C_{(15A)}$	1.504(8)
$C_{(14A)}$–$C_{(20A)}$	1.54(1)	$C_{(15A)}$–$C_{(16A)}$	1.59(1)
$C_{(16A)}$–$C_{(17A)}$	1.46(1)	$C_{(16A)}$–$C_{(22A)}$	1.53(2)
$C_{(17A)}$–$C_{(18A)}$	1.49(1)	$C_{(18A)}$–$C_{(23A)}$	1.49(1)
$C_{(18A)}$–$C_{(19A)}$	1.594(8)	$C_{(20A)}$–$C_{(21A)}$	1.60(1)
$C_{(21A)}$–$C_{(22A)}$	1.51(2)	$C_{(21A)}$–$C_{(23A)}$	1.51(1)
$S_{(1B)}$–$C_{(13B)}$	1.721(5)	$S_{(1B)}$–$C_{(11B)}$	1.726(5)
$O_{(1B)}$–$C_{(9B)}$	1.254(5)	$O_{(2B)}$–$C_{(7B)}$	1.351(6)
$O_{(3B)}$–$C_{(10B)}$	1.250(6)	$N_{(1B)}$–$C_{(9B)}$	1.357(6)
$N_{(1B)}$–$C_{(1B)}$	1.378(6)	$N_{(2B)}$–$C_{(10B)}$	1.363(6)
$N_{(2B)}$–$C_{(11B)}$	1.395(6)	$N_{(3B)}$–$C_{(11B)}$	1.300(6)
$N_{(3B)}$–$C_{(12B)}$	1.387(7)	$C_{(1B)}$–$C_{(6B)}$	1.361(7)
$C_{(1B)}$–$C_{(2B)}$	1.502(8)	$C_{(2B)}$–$C_{(3E)}$	1.54(1)
$C_{(2B)}$–$C_{(3F)}$	1.544(9)	$C_{(3E)}$–$C_{(4E)}$	1.54(1)
$C_{(4E)}$–$C_{(5B)}$	1.538(9)	$C_{(3F)}$–$C_{(4F)}$	1.54(1)
$C_{(4F)}$–$C_{(5B)}$	1.56(1)	$C_{(5B)}$–$C_{(6B)}$	1.546(8)
$C_{(6B)}$–$C_{(7B)}$	1.417(8)	$C_{(7B)}$–$C_{(8B)}$	1.396(7)
$C_{(8B)}$–$C_{(9B)}$	1.428(7)	$C_{(8B)}$–$C_{(10B)}$	1.479(7)
$C_{(12B)}$–$C_{(13B)}$	1.356(7)	$C_{(12B)}$–$C_{(14B)}$	1.509(6)
$C_{(14B)}$–$C_{(20B)}$	1.477(9)	$C_{(14B)}$–$C_{(19B)}$	1.480(9)
$C_{(14B)}$–$C_{(15B)}$	1.59(1)	$C_{(15B)}$–$C_{(16B)}$	1.61(1)
$C_{(16B)}$–$C_{(17B)}$	1.46(2)	$C_{(16B)}$–$C_{(23B)}$	1.50(1)
$C_{(17B)}$–$C_{(18B)}$	1.47(2)	$C_{(18B)}$–$C_{(22B)}$	1.58(2)
$C_{(18B)}$–$C_{(19B)}$	1.62(1)	$C_{(20B)}$–$C_{(21B)}$	1.582(9)
$C_{(21B)}$–$C_{(23B)}$	1.45(1)	$C_{(21B)}$–$C_{(22B)}$	1.49(1)

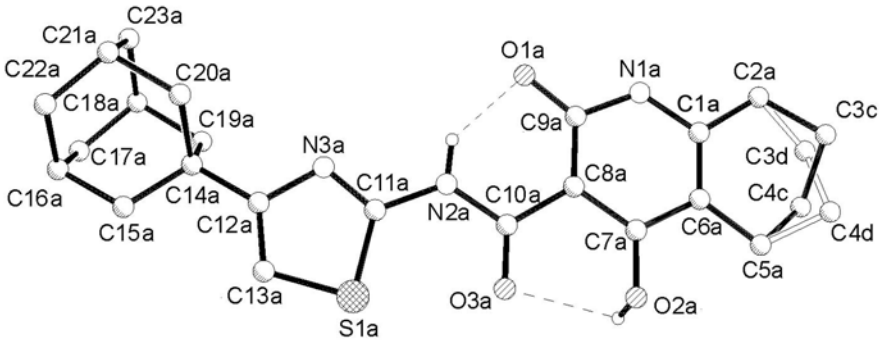

Fig. 2. Structure of amide **1m** molecule with atom numbering.

growth of Mycobacterium tuberculosis *H37Rv* ATCC 27294 by 98%. All the remaining hetarylamides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid **1a-t** in antimycobacterial properties were surpassed by their nonhydrogrenated analogs [5-7] and consequently such a structural modification must be acknowledged to be inexpedient.

TABLE 4. Valence Angles (ω) in the Structure of Amide **1m**

Valence angle	ω, deg	Valence angle	ω, deg
1	2	3	4
$C_{(11A)}$–$S_{(1A)}$–$C_{(13A)}$	87.3(3)	$C_{(9A)}$–$N_{(1A)}$–$C_{(1A)}$	125.1(7)
$C_{(10A)}$–$N_{(2A)}$–$C_{(11A)}$	125.0(5)	$C_{(11A)}$–$N_{(3A)}$–$C_{(12A)}$	109.2(4)
$C_{(6A)}$–$C_{(1A)}$–$N_{(1A)}$	121.4(6)	$C_{(6A)}$–$C_{(1A)}$–$C_{(2A)}$	122.6(6)
$N_{(1A)}$–$C_{(1A)}$–$C_{(2A)}$	115.8(7)	$C_{(1A)}$–$C_{(2A)}$–$C_{(3C)}$	120(1)
$C_{(2A)}$–$C_{(3C)}$–$C_{(4C)}$	101(2)	$C_{(3C)}$–$C_{(4C)}$–$C_{(5A)}$	117(2)
$C_{(2A)}$–$C_{(3D)}$–$C_{(4D)}$	118(2)	$C_{(5A)}$–$C_{(4D)}$–$C_{(3D)}$	102(1)
$C_{(6A)}$–$C_{(5A)}$–$C_{(4D)}$	120(1)	$C_{(6A)}$–$C_{(5A)}$–$C_{(4C)}$	105(1)
$C_{(1A)}$–$C_{(6A)}$–$C_{(5A)}$	123.2(6)	$C_{(7A)}$–$C_{(6A)}$–$C_{(5A)}$	119.3(8)
$O_{(2A)}$–$C_{(7A)}$–$C_{(8A)}$	122.1(6)	$O_{(2A)}$–$C_{(7A)}$–$C_{(6A)}$	117.9(7)
$C_{(8A)}$–$C_{(7A)}$–$C_{(6A)}$	119.9(8)	$C_{(9A)}$–$C_{(8A)}$–$C_{(7A)}$	120.7(6)
$C_{(9A)}$–$C_{(8A)}$–$C_{(10A)}$	122.9(6)	$C_{(7A)}$–$C_{(8A)}$–$C_{(10A)}$	116.3(7)
$O_{(1A)}$–$C_{(9A)}$–$N_{(1A)}$	119.4(6)	$O_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	125.5(5)
$N_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	115.1(6)	$O_{(3A)}$–$C_{(10A)}$–$N_{(2A)}$	121.8(5)
$O_{(3A)}$–$C_{(10A)}$–$C_{(8A)}$	122.7(7)	$N_{(2A)}$–$C_{(10A)}$–$C_{(8A)}$	115.5(7)
$N_{(3A)}$–$C_{(11A)}$–$N_{(2A)}$	118.4(5)	$N_{(3A)}$–$C_{(11A)}$–$S_{(1A)}$	117.6(4)
$N_{(2A)}$–$C_{(11A)}$–$S_{(1A)}$	124.0(4)	$C_{(13A)}$–$C_{(12A)}$–$N_{(3A)}$	114.0(5)
$C_{(13A)}$–$C_{(12A)}$–$C_{(14A)}$	127.3(5)	$N_{(3A)}$–$C_{(12A)}$–$C_{(14A)}$	118.6(5)
$C_{(12A)}$–$C_{(13A)}$–$S_{(1A)}$	111.9(4)	$C_{(19A)}$–$C_{(14A)}$–$C_{(15A)}$	113.1(7)
$C_{(19A)}$–$C_{(14A)}$–$C_{(12A)}$	111.8(4)	$C_{(15A)}$–$C_{(14A)}$–$C_{(12A)}$	112.6(5)
$C_{(19A)}$–$C_{(14A)}$–$C_{(20A)}$	104.4(6)	$C_{(15A)}$–$C_{(14A)}$–$C_{(20A)}$	105.4(7)
$C_{(12A)}$–$C_{(14A)}$–$C_{(20A)}$	109.0(6)	$C_{(14A)}$–$C_{(15A)}$–$C_{(16A)}$	112.0(5)
$C_{(17A)}$–$C_{(16A)}$–$C_{(22A)}$	113.3(8)	$C_{(17A)}$–$C_{(16A)}$–$C_{(15A)}$	110.2(6)
$C_{(22A)}$–$C_{(16A)}$–$C_{(15A)}$	100(1)	$C_{(16A)}$–$C_{(17A)}$–$C_{(18A)}$	112.8(8)
$C_{(23A)}$–$C_{(18A)}$–$C_{(17A)}$	114.6(6)	$C_{(23A)}$–$C_{(18A)}$–$C_{(19A)}$	105.5(6)
$C_{(17A)}$–$C_{(18A)}$–$C_{(19A)}$	104.9(5)	$C_{(14A)}$–$C_{(19A)}$–$C_{(18A)}$	111.8(4)
$C_{(14A)}$–$C_{(20A)}$–$C_{(21A)}$	112.7(8)	$C_{(22A)}$–$C_{(21A)}$–$C_{(23A)}$	111(1)
$C_{(22A)}$–$C_{(21A)}$–$C_{(20A)}$	106.5(8)	$C_{(23A)}$–$C_{(21A)}$–$C_{(20A)}$	102.1(6)

TABLE 4 (continued)

1	2	3	4
$C_{(21A)}$–$C_{(22A)}$–$C_{(16A)}$	113.6(6)	$C_{(18A)}$–$C_{(23A)}$–$C_{(21A)}$	113.2(6)
$C_{(13B)}$–$S_{(1B)}$–$C_{(11B)}$	87.8(2)	$C_{(9B)}$–$N_{(1B)}$–$C_{(1B)}$	125.1(4)
$C_{(10B)}$–$N_{(2B)}$–$C_{(11B)}$	127.3(4)	$C_{(11B)}$–$N_{(3B)}$–$C_{(12B)}$	110.7(4)
$C_{(6B)}$–$C_{(1B)}$–$N_{(1B)}$	120.9(5)	$C_{(6B)}$–$C_{(1B)}$–$C_{(2B)}$	123.3(5)
$N_{(1B)}$–$C_{(1B)}$–$C_{(2B)}$	115.7(5)	$C_{(1B)}$–$C_{(2B)}$–$C_{(3E)}$	107(1)
$C_{(4E)}$–$C_{(3E)}$–$C_{(2B)}$	111(1)	$C_{(3E)}$–$C_{(4E)}$–$C_{(5B)}$	103(1)
$C_{(4F)}$–$C_{(3F)}$–$C_{(2B)}$	113(1)	$C_{(3F)}$–$C_{(4F)}$–$C_{(5B)}$	117(1)
$C_{(6B)}$–$C_{(5B)}$–$C_{(4F)}$	110(1)	$C_{(1B)}$–$C_{(6B)}$–$C_{(7B)}$	116.5(5)
$C_{(1B)}$–$C_{(6B)}$–$C_{(5B)}$	123.2(5)	$C_{(7B)}$–$C_{(6B)}$–$C_{(5B)}$	120.3(5)
$O_{(2B)}$–$C_{(7B)}$–$C_{(8B)}$	121.7(4)	$O_{(2B)}$–$C_{(7B)}$–$C_{(6B)}$	116.0(4)
$C_{(8B)}$–$C_{(7B)}$–$C_{(6B)}$	122.3(4)	$C_{(7B)}$–$C_{(8B)}$–$C_{(9B)}$	119.6(4)
$C_{(7B)}$–$C_{(8B)}$–$C_{(10B)}$	118.6(4)	$C_{(9B)}$–$C_{(8B)}$–$C_{(10B)}$	121.7(4)
$O_{(1B)}$–$C_{(9B)}$–$N_{(1B)}$	119.3(4)	$O_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	125.0(5)
$N_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	115.6(4)	$O_{(3B)}$–$C_{(10B)}$–$N_{(2B)}$	120.9(5)
$O_{(3B)}$–$C_{(10B)}$–$C_{(8B)}$	122.2(4)	$N_{(2B)}$–$C_{(10B)}$–$C_{(8B)}$	116.9(4)
$N_{(3B)}$–$C_{(11B)}$–$N_{(2B)}$	120.0(4)	$N_{(3B)}$–$C_{(11B)}$–$S_{(1B)}$	115.9(4)
$N_{(2B)}$–$C_{(11B)}$–$S_{(1B)}$	124.1(3)	$C_{(13B)}$–$C_{(12B)}$–$N_{(3B)}$	113.6(4)
$C_{(13B)}$–$C_{(12B)}$–$C_{(14B)}$	128.2(5)	$N_{(3B)}$–$C_{(12B)}$–$C_{(14B)}$	118.1(4)
$C_{(12B)}$–$C_{(13B)}$–$S_{(1B)}$	111.9(4)	$C_{(20B)}$–$C_{(14B)}$–$C_{(19B)}$	118.6(7)
$C_{(20B)}$–$C_{(14B)}$–$C_{(12B)}$	111.7(4)	$C_{(19B)}$–$C_{(14B)}$–$C_{(12B)}$	111.3(4)
$C_{(20B)}$–$C_{(14B)}$–$C_{(15B)}$	103.6(6)	$C_{(19B)}$–$C_{(14B)}$–$C_{(15B)}$	103.9(7)
$C_{(12B)}$–$C_{(14B)}$–$C_{(15B)}$	106.3(6)	$C_{(14B)}$–$C_{(15B)}$–$C_{(16B)}$	107(1)
$C_{(17B)}$–$C_{(16B)}$–$C_{(23B)}$	110(1)	$C_{(17B)}$–$C_{(16B)}$–$C_{(15B)}$	110(1)
$C_{(23B)}$–$C_{(16B)}$–$C_{(15B)}$	103.9(7)	$C_{(16B)}$–$C_{(17B)}$–$C_{(18B)}$	114(1)
$C_{(17B)}$–$C_{(18B)}$–$C_{(22B)}$	114(1)	$C_{(17B)}$–$C_{(18B)}$–$C_{(19B)}$	101(1)
$C_{(22B)}$–$C_{(18B)}$–$C_{(19B)}$	108.4(8)	$C_{(14B)}$–$C_{(19B)}$–$C_{(18B)}$	110.1(5)
$C_{(14B)}$–$C_{(20B)}$–$C_{(21B)}$	112.9(6)	$C_{(23B)}$–$C_{(21B)}$–$C_{(22B)}$	115(1)
$C_{(23B)}$–$C_{(21B)}$–$C_{(20B)}$	104.2(8)	$C_{(22B)}$–$C_{(21B)}$–$C_{(20B)}$	104.9(6)
$C_{(21B)}$–$C_{(22B)}$–$C_{(18B)}$	109(1)	$C_{(21B)}$–$C_{(23B)}$–$C_{(16B)}$	116(1)

EXPERIMENTAL

The derivatographic investigation of ester **5a** was carried out on a Derivatograf Q-1500 D complex thermochemical instrument in a platinum crucible with a lid, rate of heating was 5°C/min. The ^{1}H NMR spectrum of ester **5b** and the NOE experiment were carried out on a Varian Mercury 400 (400 MHz) spectrometer by the standard 1D-NOE procedure with the mathematical provision for this problem. The ^{1}H NMR spectra of the remaining compounds were recorded on a Varian Mercury VX 200 (200 MHz) instrument. In all cases the solvent was DMSO-d_6, internal standard was TMS. The mass spectrum of 3-H quinolone **6** was recorded on a Varian 1200L spectrometer in total scanning mode for the range 45-550 *m/z*, ionization was by electron impact at 70 eV, with direct insertion of samples. Commercial cyclohexanone-2-carboxylic acid from Fluka was used in the work.

2-Aminocyclohex-1-enecarboxylic Acid Ethyl Ester (3). Gaseous ammonia was passed for 3.5-4 h into cyclohexanone-2-carboxylic acid ethyl ester (68.9 ml, 0.5 mol), heated to 50°C. The reaction mixture was left at room temperature for 8-10 h, and was then diluted with cold water. The crystalline solid of amino ester **3** was filtered off, washed with water, and dried. Yield 79.4 g (94%); mp 73-75°C (diethyl ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.04 (2H, br. s, NH_2); 4.04 (2H, q, *J* = 7.0, OCH_2); 2.15 (4H, m, 3,6-CH_2); 1.51 (4H, m, 4,5-CH_2); 1.16 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$). Found, %: C 63.72; H 8.80; N 8.41. $C_9H_{15}NO_2$. Calculated, %: C 63.88; H 8.93; N 8.28.

4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid Methyl Ester (5a). Triethylamine (14.4 ml, 0.11 mol) was added to a solution of amino ester **3** (16.9 g, 0.1 mol) in CH_2Cl_2 (100 ml), and then (chlorocarbonyl)acetic acid ethyl ester (16.56 g, 0.11 mol) was added dropwise with stirring and cooling. The mixture was left at room temperature for 4-5 h. The reaction mixture was diluted with water, the organic layer separated, and dried over anhydrous $CaCl_2$. The solvent was distilled (under reduced pressure at the end), and to the residue (diester **4**) was added a solution of sodium methylate [from metallic sodium (3.45 g, 0.15 mol) and absolute methyl alcohol (150 ml)]. The mixture was boiled on a water bath for 30 min, after which the heating was stopped and the mixture left for 7-8 h at room temperature. The reaction mixture was diluted with water and acidified with dilute 1:1 HCl to pH 4.5-5. The solid ester **5a** was filtered off, washed with water, and dried. Yield 18.52 g (83%). After recrystallization from ethanol mp (capillary) 214-216°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.30 (1H, s, OH); 11.16 (1H, s, NH); 3.78 (3H, s, OCH_3); 2.46 (2H, m, 8-CH_2); 2.31 (2H, m, 5-CH_2); 1.64 (4H, m, 6,7-CH_2). Found, %: C 59.31; H 5.96; N 6.20. $C_{11}H_{13}NO_4$. Calculated, %: C 59.19; H 5.87; N 6.27.

4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid Ethyl Ester (5b) was obtained analogously. In the cyclization of diester **4** sodium ethylate in absolute ethanol was used as basic catalyst. Yield 80%. After recrystallization from ethanol mp (capillary) 222-224°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.50 (1H, s, OH); 11.20 (1H, s, NH); 4.29 (2H, q, J = 8.0, OCH_2); 2.45 (2H, m, 8-CH_2); 2.30 (2H, m, 5-CH_2); 1.65 (4H, m, 6,7-CH_2); 1.28 (3H, t, J = 8.0, CH_3). Found, %: C 60.80; H 6.48; N 5.81. $C_{12}H_{15}NO_4$. Calculated, %: C 60.75; H 6.37; N 5.90.

4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline (6). Compound **5a** (2.23 g, 0.01 mol) was maintained at 230°C for 10 min, then cooled. The 3-H derivative **6** (1.97 g, 96%) was obtained; mp 355-357°C (DMF). Mass spectrum, *m/z* (I_{rel}, %): 165 (100) $[M]^+$, 137 (16) $[M\text{-}CO]^+$, 109 (42) $[M\text{-}CO\text{-}CO]^+$, 95 (44), 81 (94), 67 (76), 54 (52). ^{1}H NMR spectrum, d, ppm (*J*, Hz); 10.70 (1H, s, OH); 10.46 (1H, s, NH); 5.40 (1H, s, H-3); 2.36 (2H, m, 8-CH_2); 2.21 (2H, m, 5-CH_2); 1.60 (4H, m, 6,7-CH_2). Found, %: C 65.35; H 6.60; N 8.53. $C_9H_{11}NO_2$. Calculated, %: C 65.44; H 6.71; N 8.48.

Hetarylamides of 4-Hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid 1a-u (General Procedure). A mixture of compound **5a** (2.23 g, mol), the appropriate hetarylamine (0.01 mol), and DMF (1-2 ml) was stirred and maintained at 160-170°C for 3 min. The reactants dissolved and practically straight away amide **1** began to crystallize from the reaction mixture. The mixture was cooled, alcohol (30 ml) was added, the mixture was thoroughly stirred, and filtered. The amide **1** obtained was washed with alcohol, and dried. The product was crystallized from DMF.

X-ray Structural Investigation. Crystals of amide **1m** were triclinic, at 20°C a = 6.498(1), b = 15.476(4), c = 22.411(6) Å; α = 71.92(2), β = 89.58(2), γ = 88.24(2)°; V = 2141.4(9) Å^3; M_r = 430.58; Z = 4; space group $P1$; d_{calc} = 1.336 g/cm^3; μ(Mo$K\alpha$) = 0.182 mm^{-1}; F(000) = 924. The parameters of the unit cell and the intensities of 6821 reflections (6195 independent, R_{int} = 0.04) were measured on a Siemens P3/PC automatic four-circle diffractometer (λMo$K\alpha$, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the SHELX97 set of programs [15]. The position of the hydrogen atoms was calculated geometrically and refined by the rider model with $U_{iso} = 1.2 \times U_{eq}$ for the nonhydrogen atom linked to a given hydrogen. The disordered fragments were refined with the imposition of limitations on the C–C bond length of 1.54(1) Å. The structure was refined on F^2 with the full matrix least squares method in anisotropic approximation for the nonhydrogen atoms to wR_2 = 0.282 for 6195 reflections (R_1 = 0.086 for 3122 reflections with $F > 4\sigma$ (F), S = 0.998). All the crystallographic information has been deposited in the Cambridge Structural Data Bank (deposit No. CCDC 257524). Interatomic distances and valence angles are given in Tables 3 and 4.

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REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, and O. V. Shishkin, *Khim. Geterotsikl. Soedin.*, 718 (2006).
2. A. G. Khomenko, *Probl. Tuberkuleza*, No. 2, 2 (1994).
3. A. G. Khomenko, *Probl. Tuberkuleza*, No. 1, 4 (1995).
4. I. V. Ukrainets, Abdel Naser Kh. N. Dakkakh, P. A. Bezuglyi, O. V. Gorokhova, L. V. Sidorenko, and T. V. Alekseeva, *Vestn. Farm.*, No. 1(25), 9 (2001).
5. I. V. Ukrainets, M. Amer, P. A. Bezugly, O. V. Gorokhova, L. V. Sidorenko, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 654 (2002).
6. I. V. Ukrainets, Amzhad Abu Sharekh, P. A. Bezuglyi, L. V. Sidorenko, and O. V. Gorokhova, *Farm. Zh.*, No. 5, 52 (2002).
7. I. V. Ukrainets, S. A. El Kayal, O. V. Gorokhova, L. V. Sidorenko, and T. V. Alekseeva, *Vestn. Farm.*, No. 1(37), 12 (2004).
8. I. V. Ukrainets, O. S. Prokopenko, L. V. Sidorenko, and O. V. Gorokhova, *Vestn. Farm.*, No. 3(39), 3 (2004).
9. I. V. Ukrainets, E. A. Taran, O. V. Shishkin, O. V. Gorokhova, S. G. Taran, Jaradat Nidal Amin, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 516 (2000).
10. H. Gunther, *NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry*, John Wiley & Sons, Chichester (1995).
11. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, V. B. Rybakov, V. V. Chernishev, and E. V. Kolesnik, *Vestn. Farm.*, No. 2(38), 7 (2004).
12. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim*., **58**, 713 (1989).
13. H.-B. Burgi and J. D. Dunitz, *Structure Correlation*, Vol. 2, VCH, Weinheim (1994), p. 741.
14. S. H. Siddiqui in H. D. Isenberg (editor), *Clinical Microbiology Procedures Handbook*, Vol. 1, American Society for Microbiology, Washington D. C. (1992), p. 5.14.2.
15. G. M. Sheldrick, *SHELX97. PC Version. A System of Computer Programs for Crystal Structure Solution and Refinement*, Rev. 2, (1998).