Chemistry of Heterocyclic Compounds, Vol. 43, No. 8, 2007

4-HYDROXY-2-QUINOLONES 126*. 1-HYDROXY-3-OXO-5,6-DIHYDRO-3H-PYRROLO[3,2,1-*ij*]QUINOLINE-2-CARBOXYLIC ACID HYDRAZIDE AND ITS DERIVATIVES

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A preparative method has been developed for the synthesis of 1-hydroxy-3-oxo-5,6-dihydro-3H pyrrolo[3,2,1-ij]quinoline-2-carboxylic acid hydrazide and its derivatives. The results of a study of the antitubercular activity of the synthesized compounds are presented.

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

Hydrazine derivatives occupy a special place in the chemotherapy of tuberculosis which is one of the most dangerous contemporary infectious illnesses. Thus isonicotinic acid hydrazide has been used in medical practice for more than half a century under the name of *isoniazid* and it has not lost its value to the present day [2]. Further, on its basis it has given rise to *phthivazid*, *saluzid*, *metazid* [3] and there continue to be discovered modified analogs with improved pharmacological properties (e.g. *flurenizid* [4]). *Rifampicin* and *rifapentin* are amongst the most effective semi-synthetic antitubercular agents and they also contain a hydrazine fragment in their structure [2].

In continuing our systematic search for potential agents amongst amidated 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids we repeatedly noted the high activity of the corresponding hydrazides [5], in particular the benzylidenehydrazides [6-8], in relation to the stimulation of tubercular and non-tubercular micobacteria. Following on in this area and with the aim of revealing a structure biological activity relationship in the studied series this report concerns tricyclic analogs of 4-hydroxy-2-quinolones and particularly the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid derivative.

Ethyl 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylate (**1**) reacts with hydrazine hydrate in alcohol solution at room temperature to give the hydrazine **2** in virtually quantitative yield. An attempt to purify this material by crystallization from DMF led to a very unexpected result. Immediately

* For Communication 125 see [1].

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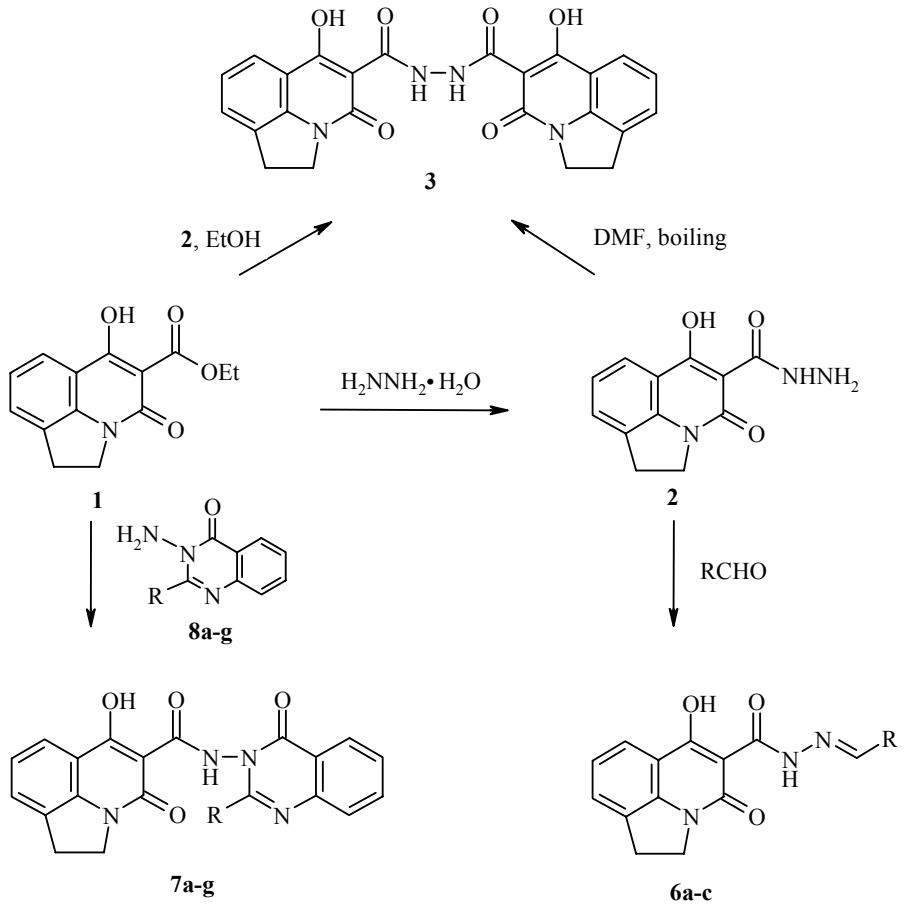
 0009-3122/07/4308-1014

after reaching the boiling point a copious precipitate began to form from the solution. The solubility of this material was so low that it was not possible to record the ^{1}H NMR spectrum. Hence to establish its structure we have used mass spectrometry and this has shown that hydrazide **2** is converted in boiling DMF to the symmetrical N,N'-di(1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-2-quinolinoyl)hydrazine (**3**). Additional confirmation came from a counter synthesis via reaction of hydrazine **2** with ethyl ester **1**.



6 a R = 2-Py, **b** R = 3-Py, **c** R = 4-Py; **7**, **8 a** R = Me, **b** R = Et, **c** R = Pr, **d** R = Bu, **e** R = C_5H_{11}, **f** R = C_6H_{13}, **g** R = CH_2Ph

It was interesting to note that none of the previously studied 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazides was characterized by similar properties and crystallization from DMF occurred without complication and that a similar conversion to N,N'-diacylhydrazines was only possible under much more forcing pyrolysis conditions [9].

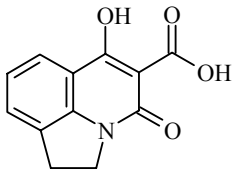
The reason for this phenomenon is likely due to a specific effect of the pyrrole ring which leads to some increase in the electrophilic properties of the carbonyl carbon atom in the hydrazide fragment when compared with normal hydrazides, i.e. of 1-N-alkyl-substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids. As a result it appears reasonable for the reaction to occur by a reamidation transformation mechanism of hydrazide **2** to diacylhydrazine **3** under relatively mild conditions. This proposal is supported by the dissociation

TABLE 1. Characteristics of Compounds **2,6** and **7**

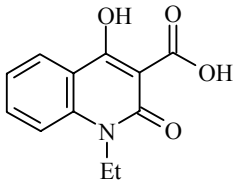
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Antitubercular activity	
		C	H	N			Inhibition of growth of *M. Tuberculosis*, %*	MIC*[2], μg/ml
2	$C_{12}H_{11}N_3O_3$	58.63 / 58.77	4.40 / 4.52	17.22 / 17.13	236-238	97	16	—
6a	$C_{18}H_{14}N_4O_3$	64.54 / 64.67	4.28 / 4.22	16.85 / 16.76	252-254	86	80	—
6b	$C_{18}H_{14}N_4O_3$	64.76 / 64.67	4.14 / 4.22	16.64 / 16.76	257-259	89	100	6.25
6c	$C_{18}H_{14}N_4O_3$	64.77 / 64.67	4.16 / 4.22	16.80 / 16.76	281-283	93	100	6.25
7a	$C_{21}H_{16}N_4O_4$	64.81 / 64.94	4.22 / 4.15	14.51 / 14.43	315-317	85	17	—
7b	$C_{22}H_{18}N_4O_4$	65.56 / 65.67	4.49 / 4.51	13.88 / 13.92	255-257	84	14	—
7c	$C_{23}H_{20}N_4O_4$	66.25 / 66.34	4.72 / 4.84	13.52 / 13.45	218-220	81	8	—
7d	$C_{24}H_{22}N_4O_4$	66.89 / 66.97	5.21 / 5.15	13.10 / 13.02	174-176	87	5	—
7e	$C_{25}H_{24}N_4O_4$	67.64 / 67.56	5.50 / 5.44	12.53 / 12.60	170-172	84	0	–
7f	$C_{26}H_{26}N_4O_4$	68.02 / 68.11	5.81 / 5.73	12.17 / 12.22	199-201	80	0	3.13
7g	$C_{27}H_{20}N_4O_4$	69.90 / 69.82	4.44 / 4.34	12.13 / 12.06	180-182	89	99	0.78

* Concentration of material studied 6.25 μg/ml.
*[2] MIC – minimum inhibitory concentration.

constants (p*K*a) for the carboxyl group of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid (**4**) and its acyclic analog 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**5**). A comparison of these values shows that closing the pyrrole ring for the same length N-alkyl substituent actually leads to an increase in the reactivity of the carboxyl group.



4
p*K*a = 7.20 ± 0.03



5
p*K*a = 7.53 ± 0.05

Bearing in mind the instability of hydrazide **2** in refluxing DMF the synthesis of the derived pyridylmethylidenehydrazides **6** was carried out in ethanol. This places limits on the method of preparing the 2-alkyl-4-oxoquinazolin-3-ylamides **7** (Table 1). In particular it is clear that the reaction of hydrazide **2** with 2-R-4H-3,1-benzoxazin-4-ones is known in this case to be unacceptable since, to avoid the formation of acyclic compounds, the syntheses are carried out in strictly anhydrous and high boiling solvents [10]. From several other theoretically possible variants of the synthesis of this class of compound we have used a method avoiding an ambiguous reaction route, i.e. the amidation of ester **1** by the previously synthesized 3-amino-2-R-quinazolin-4(3H)-ones **8a-g**.

TABLE 2. ^{1}H NMR Spectra of Synthesized Compounds **6** and **7**

Com-pound	Chemical shiftsи, δ, ppm. (*J*, Hz)
6a	16.10 (1H, s, OH); 13.43 (1H, s, NH); 8.68 (1H, d, *J* = 4.8, H-6'); 8.39 (1H, s, CH=N); 7.99 (1H, d, *J* = 7.7, H-3'); 7.87 (1H, t, *J* = 7.5, H-4'); 7.71 (1H, d, *J* = 8.0, H-9); 7.60 (1H, d, *J* = 7.2, H-7); 7.42 (1H, t, *J* = 5.8, H-5'); 7.26 (1H, t, *J* = 7.4, H-8); 4.40 (2H, t, *J* = 8.1, 5-CH_2); 3.43 (2H, t, *J* = 8.0, 6-CH_2)
6b	16.23 (1H, s, OH); 13.45(1H, s, NH); 8.91 (1H, s, H-2'); 8.64 (1H, d, *J* = 4.9, H-6'); 8.50 (1H, s, CH=N); 8.15 (1H, d, *J* = 7.9, 4'-H); 7.74 (1H, d, *J* = 8.1, H-9); 7.60 (1H, d, *J* = 7.1, H-7); 7.46 (1H, t, *J* = 7.7, H-5'); 7.27 (1H, t, *J* = 7.5, H-8); 4.37 (2H, t, *J* = 8.0, 5-CH_2); 3.44 (2H, t, *J* = 8.0, 6-CH_2)
6c	16.25 (1H, s, OH); 13.50 (1H, s, NH); 8.71 (2H, d, *J* = 5.3, H-2',6'); 8.43 (1H, s, CH=N); 7.78 (1H, d, *J* = 8.1, H-9); 7.69 (2H, d, *J* = 5.3, H-3',5'); 7.58 (1H, d, *J* = 7.3, H-7); 7.26 (1H, t, *J* = 7.6, H-8); 4.40 (2H, t, *J* = 8.1, 5-CH_2); 3.43 (2H, t, *J* = 8.1, 6-CH_2)
7a	15.35 (1H, s, OH); 12.30 (1H, s, NH); 8.13 (1H, d, *J* = 7.6, H-8'); 7.81 (1H, t, *J* = 8.0, H-7'); 7.74 (1H, d, *J* = 8.0, H-9); 7.61 (2H, m, H-5' + H-7); 7.49 (1H, t, *J* = 7.6, H-6'); 7.26 (1H, t, *J* = 7.7, H-8); 4.43 (2H, t, *J* = 8.2, 5-CH_2); 3.47 (2H, t, *J* = 8.1, 6-CH_2); 2.47 (3H, s, CH_3)
7b	15.28 (1H, s, OH); 12.36 (1H, s, NH); 8.12 (1H, d, *J* = 7.7, H-8'); 7.80 (1H, t, *J* = 8.0, H-7'); 7.75 (1H, d, *J* = 7.9, H-9); 7.63 (2H, m, H-5' + H-7); 7.47 (1H, t, *J* = 7.6, H-6'); 7.20 (1H, t, *J* = 7.7, H-8); 4.42 (2H, t, *J* = 8.0, 5-CH_2); 3.44 (2H, t, *J* = 8.0, 6-CH_2); 2.77 (2H, q, *J* = 7.2, C$\underline{H_2}$$CH_3$); 1.10 (3H, t, *J* = 7.1, CH_3)
7c	15.30 (1H, s, OH); 12.33 (1H, s, NH); 8.17 (1H, d, *J* = 7.8, H-8'); 7.82 (1H, t, *J* = 7.9, H-7'); 7.74 (1H, d, *J* = 8.0, H-9); 7.65 (2H, m, H-5' + H-7); 7.48 (1H, t, *J* = 7.5, H-6'); 7.22 (1H, t, *J* = 7.8, H-8); 4.44 (2H, t, *J* = 8.1, 5-CH_2); 3.45 (2H, t, *J* = 8.0, 6-CH_2); 2.80 (2H, m, CH_2-Et); 1.88 (2H, m, C$\underline{H_2}$$CH_3$); 1.07 (3H, t, *J* = 7.3, CH_3)
7d	15.33 (1H, s, OH); 12.27 (1H, s, NH); 8.14 (1H, d, *J* = 7.7, H-8'); 7.84 (1H, t, *J* = 7.9, H-7'); 7.76 (1H, d, *J* = 8.1, H-9); 7.63 (2H, m, H-5' + H-7); 7.45 (1H, t, *J* = 7.4, H-6'); 7.23 (1H, t, *J* = 7.9, H-8); 4.45 (2H, t, *J* = 8.0, 5-CH_2); 3.48 (2H, t, *J* = 7.9, 6-CH_2); 2.79 (2H, m, CH_2-Pr); 1.80 (2H, q, *J* = 7.7, CH_2-Et); 1.46 (2H, m, C$\underline{H_2}$$CH_3$); 0.97 (3H, t, *J* = 7.1, CH_3)
7e	15.26 (1H, s, OH); 12.21 (1H, s, NH); 8.13 (1H, d, *J* = 7.9, H-8'); 7.80 (1H, t, *J* = 8.0, H-7'); 7.77 (1H, d, *J* = 8.0, H-9); 7.62 (2H, m, H-5' + H-7); 7.46 (1H, t, *J* = 7.6, H-6'); 7.20 (1H, t, *J* = 7.7, H-8); 4.42 (2H, t, *J* = 8.0, 5-CH_2); 3.46 (2H, t, *J* = 8.0, 6-CH_2); 2.81 (2H, m, C$\underline{H_2}$-Bu); 1.84 (2H, q, *J* = 7.3, CH_2-Pr); 1.42 (4H, m, (C$\underline{H_2}$)$_2$$CH_3$); 0.93 (3H, t, *J* = 7.0, CH_3)
7f	15.30 (1H, s, OH); 12.25 (1H, s, NH); 8.16 (1H, d, *J* = 8.1, H-8'); 7.82 (1H, t, *J* = 8.0, H-7'); 7.74 (1H, d, *J* = 8.1, H-9); 7.60 (2H, m, H-5' + H-7); 7.43 (1H, t, *J* = 7.5, H-6'); 7.21 (1H, t, *J* = 7.8, H-8); 4.44 (2H, t, *J* = 8.1, 5-CH_2); 3.49 (2H, t, *J* = 8.1, 6-CH_2); 2.73 (2H, m, C$\underline{H_2}$-C_5H_{11}); 1.82 (2H, q, *J* = 7.8, CH_2-Bu); 1.44 (2H, q, *J* = 7.0, CH_2-Pr); 1.35 (4H, m, (C$\underline{H_2}$)$_2$$CH_3$); 0.88 (3H, t, *J* = 7.0, CH_3)
7g	15.09 (1H, s, OH); 12.20 (1H, s, NH); 8.17-7.16 (12H, m, H arom.); 4.45 (2H, t, *J* = 8.0, 5-CH_2); 4.13 (2H, s, CH_2-Ph); 3.48 (2H, t, *J* = 8.0, 6-CH_2)

Amongst the specific features of the ^{1}H NMR spectra of the hydrazide **2** we noted a broad two proton singlet for the free amino group at 4.59 ppm (Table 2). Distinctive features of the pyridylmethylidene derivatives **6a-c** are the azomethine proton singlets at 8.39-8.50 ppm. At lower field there are only observed the OH and CONH group protons and the aromatic protons in the pyridine rings next to the nitrogen atom. Characteristic signals for the protons in the amides **7a-g** are found in the aliphatic part of the spectrum and these correspond to the alkyl substituents in position 2 of the quinazolone fragments.

The ability of the synthesized compound to inhibit the growth of tuberculosis bacteria was studied radiometrically [11, 12]. Experimental data for primary microbiological screening has shown high activity towards *Mycobacterium tuberculosis* H37Rv ATCC 27294 only for the 3- and 4-pyridylmethylidenehydrazides **6b,c** (Table 1). At the same time, a comparative analysis of the biological properties of these compounds and their structural analogs with open 1-N-alkyl chains shows that annelation of a quinolone ring with a pyrrole overall causes some lowering of the antimicrobial activity; the MIC increasing with this modification from 3.13 to 6.25 μg/ml.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker WM-360 (360 MHz) instrument using DMSO-d_6 solvent and TMS internal standard. The mass spectrum of the diacylhydrazine **3** was recorded on a Finnigan MAT Incos 50 quadrupole spectrometer with full scanning in the range 33-700 *m/z*, EI ionization of 70 eV, direct sample introduction, and heating rate of about 5ºC/s. The acid-base equilibria were measured using method [13] with 80% aqueous dioxane solvent. For preparation of the mixed solvent it was freshly doubly distilled and freed from CO_2 and the dioxane for UV spectroscopy was supplied by the company Labscan. The 0.01 mol·l^{-1} aqueous KOH titrant was freed from CO_2. The concentration of the titrated solutions was 0.0005 mol·l^{-1} at the half neutralization point. The potentiometric titration was performed on a steady state SevenEasy S-20-K Mettler Toledo pH meter with an InLab 413 combination electrode at 25ºC. The accuracy of the results obtained was calculated by mathematical statistics [14]. Ethyl 1-hydroxy-3-oxo-4,5-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylate (**1**) was prepared by the method in [15] and 2-R-3-aminoquinazolin-4(3H)-ones **8a-b** by that in [9].

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Hydrazide (2). Hydrazine hydrate (0.011 mol, calculated from the actual content) was added to a solution of ester **1** (2.59 g, 0.01 mol) in ethanol (15 ml). After 2 h the reaction mixture was diluted with cold water. The precipitated hydrazide **2** was filtered off, washed with water, and dried. Yield 2.38 g (97%); mp 236-238ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.68 (1H, s, OH); 10.90 (1H, s, CONH); 7.68 (1H, d, *J* = 8.1, H-9); 7.46 (1H, d, *J* = 7.0, H-7); 7.16 (1H, t, *J* = 7.9, H-8); 4.59 (2H, br. s, NNH_2); 4.34 (2H, t, *J* = 8.0, 5-CH_2); 3.42 (2H, t, *J* = 8.0, 6-CH_2).

N,N'-Di(1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-2-quinolinoyl)hydrazine (3). A mixture of the hydrazide **2** (2.45 g, 0.01 mol) and DMF (15 ml) was heated. The material initially dissolved and then began to form a precipitate on reaching reflux temperature. It was then refluxed for 20 min and cooled. The precipitated diacylhydrazine **3** was filtered off, washed with alcohol, and dried. Yield 2.06 g (90%); mp 395-397ºC. Mass spectrum, *m/z* (I_{rel}, %): 458 $[M]^+$ (2), 245 (68), 214 (100), 187 (12), 145 (7). Found, %: C 62.96; H 4.05; N 12.12. $C_{24}H_{18}N_4O_6$. Calculated, %: C 62.88; H 3.96; N 12.22.

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid (4). Ester (2.59 g, 0.01 mol) was added to a solution of HCl in acetic acid (20 ml) with a low water content prepared as in the method [16] and the product was held at 60ºC for 5 h. It was then cooled and the precipitated crystals of acid **4** were filtered off, washed with alcohol and then water, and dried. Yield 1.92 g (83%); mp 260-262ºC (decomp., sealed capillary). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.90 (1H, s, OH); 14.37 (1H, s, COOH); 7.78 (1H, d, *J* = 8.3, H-9); 7.70 (1H, d, *J* = 7.4, H-7); 7.36 (1H, t, *J* = 7.7, H-8); 4.40 (2H, t, *J* = 7.8, 5-CH_2); 3.44 (2H, t, *J* = 7.8, 6-CH_2). Found, %: C 62.41; H 3.88; N 6.11. $C_{12}H_9NO_4$. Calculated, %: C 62.34; H 3.92; N 6.06.

4-Hydroxy-2-oxo-1-ethyl-1,2-dihydroquinoline-3-carboxylic Acid (5) was prepared from the corresponding ethyl ester [17] using the method reported above. Yield 1.75 g (75%); mp 133-135ºC (decomp., sealed capillary). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.97 (1H, s, 4-OH); 14.36 (1H, s, COOH); 8.12 (1H, dd, *J* = 8.1 and 1.5, H-5); 7.81 (1H, td, *J* = 7.8 and 1.5, H-7); 7.45 (1H, d, *J* = 8.3, H-8); 7.18 (1H, t, *J* = 7.5, H-6); 4.22 (2H, q, *J* = 7.2, NCH_2); 1.21 (3H, t, *J* = 7.2, CH_3). Found, %: C 61.86; H 4.84; N 5.94. $C_{12}H_{11}NO_4$. Calculated, %: C 61.80; H 4.75; N 6.01.

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Pyridylmethylidenehydrazides 6a-c (General Method). The corresponding pyridylaldehyde (0.011 mol) was added to a solution of the hydrazide **2** (2.45 g, 0.01 mol) in hot ethanol (50 ml) and refluxed for 1 h. The product was cooled and the precipitated crystals of the pyridylmethylidenehydrazide **6a-c** were filtered off, washed with alcohol, and dried. They were recrystallized from a mixture of DMF and ethanol.

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid 2-R-4-oxo-4H-quinazolin-3-ylamides 7a-g (General Method). A mixture of ester **1** (2.59 g, 0.01 mol), the corresponding 3-amino-2-R-quinazolin-4(3H)-one **8a-g** (0.01 mol), and DMF (1 ml) was stirred and held for 3-5 min at 160ºC. The product was cooled, ethanol (10-15 ml) added, and thoroughly triturated. The precipitated amide **7a-g** was filtered off, washed with alcohol, dried, and recrystallized from DMF.

The authors than the US National Institute of Allergy and Infectious Diseases for carrying out this study of the antitubercular properties of the synthesized compounds within the TAACF (Tuberculosis Antimicrobial and Coordinating Facility) program (contract No. 01-AI-45246).

REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, and O. S. Golovchenko, *Khim. Geterotsikl. Soedin.*, 1189 (2007). [*Chem. Heterocycl. Comp.*, **43**, 1008 (2007)].
2. http://www.taacf.org/about-TB-current-drugs.htm
3. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 2, Torsing, Kharkiv (1997), p. 334.
4. L. I. Petrukh, M. N. Kovalenko, and O. I. Mikhalik, *Farmakom*, No. 2, 9 (1999).
5. I. V. Ukrainets, Jaradat Nidal Amin, P. O. Bezugly, O. V. Gorokhova, L. V. Sidorenko, and I. V. Porokhnyak, *Fisiologichno Aktyvni Rechovyny*, No. 1 (27), 21 (1999).
6. I. V. Ukrainets, Jaradat Nidal Amin, P. O. Bezuglii, O. V. Gorokhova, and L. V. Sidorenko, *Visnyk Farmatsii*, No. 1 (21), 13 (2000).
7. I. V. Ukrainets, O. S. Prokopenko, L. V. Sidorenko, and O. V. Gorokhova, *Visnyk Farmatsii*, No. 3 (39), 3 (2004).
8. I. V. Ukrainets, L. V. Sidorenko, O. S. Prokopenko, V. B. Rybakov, and V. V Chernyshev, *Zhurn. Org. Farm. Khim.*, **2**, No. 4 (8), 17 (2004).
9. Jaradat Nidal Amin, Dissertation of Candidates in Pharm. Chem., Kharkiv (2000).
10. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezugly, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 229 (1994). [*Chem. Heterocycl. Comp.*, **30**, 208 (1994)].
11. L. B. Heifets, in: L. B. Heifets (editor), *Drug Susceptibility in the Chemistry of Mycobacterial Infections*, CRC Press, Boca Raton (1991), p. 89.
12. C. B. Inderleid and K. A. Nash, in: V. Lorian (editor), *Antibiotics in Laboratory Medicine*, Williams and Wilkins, Baltimore (1996), p. 127.
13. A. Albert and E. P. Sergeant, *Ionization Constants of Acids and Bases* [in Russian] Khimiya, Moscow (1964).
14. E. N. L'vovskii, *Statistical Methods for Deriving Empirical Formulae* [in Russian] Higher School, Moscow (1988), p. 41.
15. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, E. V. Mospanova, and O. V. Shishkin, *Khim. Geterotsikl. Soedin.*, 718 (2006). [*Chem. Heterocycl. Comp.*, **42**, 631 (2006)].
16. S. Jönsson, G. Andersson, T. Fex, T. Fristedt, G. Hedlund, K. Jansson, L. Abramo, I. Fritzson, O. Pekarski, A. Runström, H. Sandin, I. Thuvesson, and A. Björk, *J. Med. Chem.*, **47**, 2075 (2004).
17. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezugly, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, *Khim. Geterotsikl. Soedin.*, 958 (1994). [*Chem. Heterocycl. Comp.*, **30**, 829 (1994)].