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THE SYNTHESIS AND THE ANTITUBERCULAR ACTIVITY OF 1-BENZYL-4-HYDROXY-2-OXO-1,2,5,6,7,8-HEXAHYDROQUINOLINE-3-CARBOXAMIDES

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Key words: amides; 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids; synthesis; thermolysis; antitubercular activity

Unfortunately, tuberculosis still remains a cause of high mortality in humans and in modern conditions it has become a global health problem. Continuing the search for new antimycobacterial agents among the amidated derivatives of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids the corresponding group of 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides has been synthesized by the reaction of ethyl 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate and anilines or hetarylamines in DMF at 130°C. The chemical structure of the compounds obtained has been confirmed by the data of elemental analysis, NMR ^{1}H spectroscopy and mass spectrometry. It has been noted that the 1H NMR spectra can reliably confirm the presence of the basic functional groups by their corresponding chemical shift, the integrated intensity and multiplicity of signals. It has been shown that under the influence of the electron impact the molecular ions of all the compounds studied undergo the primary fragmentation in two directions: with breaking the amide bond or the quinolone nucleus – the carbamide moiety bond. According to the data of microbiological tests among 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides synthesized the substances that are capable of inhibiting actively the growth of Mycobacterium tuberculosis H37Rv in low concentration have been identified, and therefore, they are of interest for further research.

СИНТЕЗ ТА ПРОТИТУБЕРКУЛЬОЗНА АКТИВНІСТЬ 1-БЕНЗИЛ-4-ГІДРОКСИ-2-ОКСО-1,2,5,6,7,8-ГЕКСАГІДРОХІНОЛІН-3-КАРБОКСАМІДІВ

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Ключові слова: *аміди; 4-гідрокси-2-оксо-1,2-дигідрохінолін-3-карбонові кислоти; синтез; термоліз; протитуберкульозна активність*

На жаль, туберкульоз до сьогодні залишається причиною високої смертності людей і в сучасних умовах перетворився на глобальну проблему системи охорони здоров'я. Продовжуючи пошук нових антимікобактеріальних засобів серед амідованих похідних 4-гідрокси-2-оксо-1,2-дигідрохінолін-3-карбонових кислот, реакцією етил 1-бензил-4-гідрокси-2-оксо-1,2,5,6,7,8-гексагідрохінолін-3-карбоксилату з анілінами чи гетариламінами в ДМФА при 130°С було синтезовано групу відповідних 1-бензил-4-гідрокси-2-оксо-1,2,5,6,7,8-гексагідрохінолін-3-карбоксамідів. Хімічна будова одержаних сполук була підтверджена даними елементного аналізу, спектроскопії ЯМР ^{1}H та мас-спектрометрії. Відмічено, що ЯМР ^{1}H спектри дозволяють надійно підтвердити присутність усіх основних функціональних груп за відповідними їм за хімічним зсувом, інтегральною інтенсивністю та мультиплетністю сигналами. Показано, що під впливом електронного удару молекулярні іони всіх досліджуваних сполук піддаються первинній фрагментації за двома напрямками: з розривом амідного зв'язку чи зв'язку хінолонове ядро – карбамідний фрагмент. За даними мікробіологічних випробовувань серед синтезованих 1-бензил-4-гідрокси-2-оксо-1,2,5,6,7,8-гексагідрохінолін-3-карбоксамідів виявлені речовини, здатні в низькій концентрації активно затримувати ріст Mycobacterium tuberculosis H37Rv і тому представляють інтерес для подальших досліджень.

СИНТЕЗ И ПРОТИВОТУБЕРКУЛЕЗНАЯ АКТИВНОСТЬ 1-БЕНЗИЛ-4-ГИДРОКСИ-2-ОКСО-1,2,5,6,7,8-ГЕКСАГИДРОХИНОЛИН-3-КАРБОКСАМИДОВ

А.А.Давиденко

Ключевые слова: *амиды; 4-гидрокси-2-оксо-1,2-дигидрохинолин-3-карбоновые кислоты; синтез; термолиз; противотуберкулезная активность*

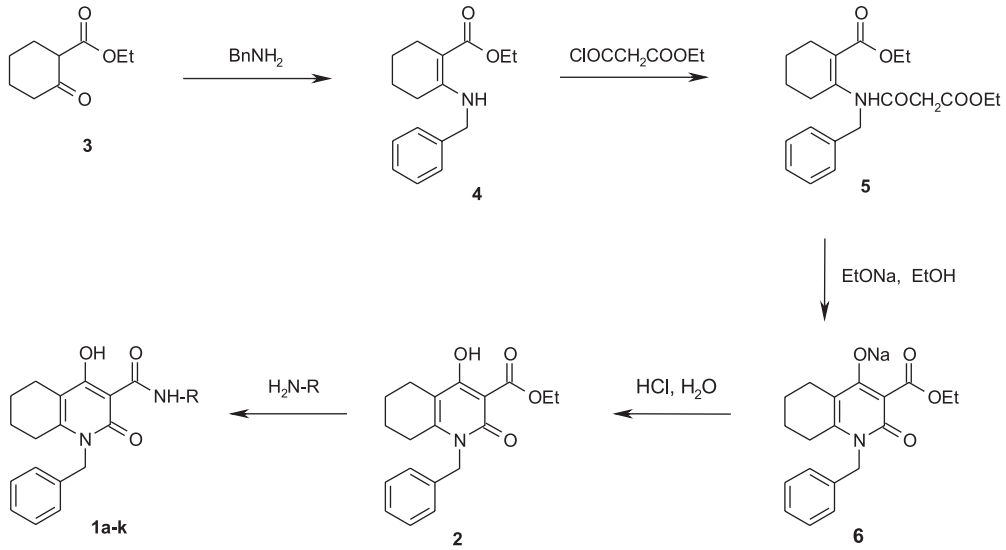
К сожалению, туберкулез до настоящего времени остается причиной высокой смертности людей и в современных условиях превратился в глобальную проблему здравоохранения. Продолжая поиск новых антимикобактериальных средств среди амидированных производных 4-гидрокси-2-оксо-1,2-дигидрохинолин-3-карбоновых кислот, реакцией этил 1-бензил-4-гидрокси-2-оксо-1,2,5,6,7,8-гексагидрохинолин-3-карбоксилата с анилинами или гетарил-аминами в ДМФА при 130°С была синтезирована группа соответствующих 1-бензил-4-гидрокси-2-оксо-1,2,5,6,7,8-гексагидрохинолин-3-карбоксамидов. Химическое строение полученных соединений было подтверждено данными элементного анализа, спектроскопии ЯМР ^{1}H и масс-спектрометрии. Отмечено, что ЯМР ^{1}H спектры позволяют надежно подтвердить присутствие всех основных функциональных групп по соответствующим им по химическому сдвигу, интегральной интенсивности и мультиплетности сигналам. Показано, что под воздействием электронного удара молекулярные ионы всех изучаемых соединений претерпевают первичную фрагментацию по двум направлениям: с разрывом амидной связи или связи хинолоновое ядро – карбамидный фрагмент. По данным микробиологических испытаний среди синтезированных 1-бензил-4-гидрокси-2-оксо-1,2,5,6,7,8-гексагидрохинолин-3-карбоксамидов обнаружены вещества, способные в низкой концентрации активно ингибировать рост Mycobacterium tuberculosis H37Rv и поэтому представляющие интерес для дальнейших исследований.

Despite the considerable progress and success of modern medicine in the fight against many infectious diseases tuberculosis remains one of the main causes of the high mortality. Unfortunately, in recent years this dangerous disease has not only returned, but is also extremely widespread throughout the world, becoming a global public health problem. One of the main causes for this situation was the unique ability of the causative agent – *Mycobacterium tuberculosis* – to very rapid mutations and, as a result, there is immediate distribution of strains that are resistant to the existing medicines [1-2]. Treatment of such patients is very difficult, time consuming, with substantial financial costs and, moreover, is not always successful. Therefore, in the present circumstances the fight against tuberculosis is carried out in several directions simultaneously. Thus, reliable methods of diagnosis, which allow determining the true pathogen rapidly and accurately, and its sensitivity to drugs are being developed, and it gives the possibility to start treatment promptly and optimally [3-6]. Decoding of the genome of *Mycobacterium tuberculosis* and searching for the genes responsible for production of drug resistance are very interesting [7]. The search of completely new biologically active substances of various chemical classes that can effectively inhibit the growth of *Mycobacterium tuberculosis* at all stages of development do not lose its relevance [8-11].

In this regard 1-R-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides are of undoubted interest. Among them the highly active anti-tuberculosis agents were previously found. At the same time it is repeatedly indicated that the biological activity of these compounds is largely determined by the nature of the substituent at the cyclic nitrogen atom of the quinoline nucleus [12-14]. Anilides and hetarylamides of 1-furfuryl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acids were indicated as promising objects [15]. Continuing research in this area the replacement of the furan cycle in the structure of the 1-N-substituent with the phenyl nucleus close to it by its structure and properties is interesting. The methodology of bioisosteric replacements widely and successfully used in modern medicinal chemistry has become the theoretical underpinning for this modification, i.e. replacing one of the fragments of the molecule with another one having similar physical and chemical characteristics and inducing a similar biological effect [16-18].

The synthesis of the target objects of research – 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides (**1a-k**) was carried out by the reaction of ethyl ester (**2**) and the corresponding primary amines in thermolysis conditions (Scheme 1). Only those anilines and hetarylamines that had already proven themselves as an excellent base for highly active anti-tuberculosis agents were involved in the synthesis. In turn, ester (**2**) was prepared from commercially available 2-oxocyclohexanecarboxylic acid ethyl ester (**3**) easily forming enamine with benzylamine (**4**). The subsequent acylation by ethyl malonyl chloride gives diester (**5**), which intramolecular condensation leads first to sodium salt (**6**) and further to the initial ester (**2**).

The 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides (1a-k) obtained are colourless crystalline substances with the narrow range of melting points, when heating they are readily soluble in DMF and DMSO, sparingly soluble in alcohol, and practically insoluble in water (Table 1). Their structure was confirmed by elemental analysis, ^{1}H NMR spectra and mass spectra.



1 a R = 3-F-C_6H_4; **b** R = 4-F-C_6H_4; **c** R = 3-Cl-C_6H_4; **d** R = 2,4-$(Cl)_2$-C_6H_3; **e** R = 3-Br-C_6H_4; **f** R = 3-Py; **g** R = 1,3-thiazole-2-yl; **h** R = 4-(adamantane-1-yl)-1,3-thiazole-2-yl; **i** R = bebnzothiazole-2-yl; **j** R = 6-bromobebnzothiazole-2-yl; **k** R = 5-methyl-1,3,4-thiadiazole-2-yl

Scheme 1

Table 1

Characteristics of amides (1a-k)

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %	Antitubercular activity*
		C	H	N			
1a	$C_{23}H_{21}FN_2O_3$	70.33 / 70.40	5.48 / 5.39	7.20 / 7.14	131-133	88	13
1b	$C_{23}H_{21}FN_2O_3$	70.31 / 70.40	5.45 / 5.39	7.06 / 7.14	147-149	94	63
1c	$C_{23}H_{21}ClN_2O_3$	67.68 / 67.56	5.11 / 5.18	6.93 / 6.85	126-128	90	28
1d	$C_{23}H_{20}Cl_2N_2O_3$	62.22 / 62.31	4.64 / 4.55	6.42 / 6.32	135-137	85	7
1e	$C_{23}H_{21}BrN_2O_3$	61.02 / 60.94	4.58 / 4.67	6.25 / 6.18	150-152	92	8
1f	$C_{22}H_{21}N_3O_3$	70.47 / 70.38	5.56 / 5.64	11.24 / 11.19	144-146	91	90
1g	$C_{20}H_{19}N_3O_3S$	63.07 / 62.98	4.96 / 5.02	10.95 / 11.02	141-143	87	94
1h	$C_{30}H_{33}N_3O_3S$	69.79 / 69.88	6.53 / 6.45	8.08 / 8.15	165-167	95	10
1i	$C_{24}H_{21}N_3O_3S$	66.88 / 66.80	4.85 / 4.91	9.81 / 9.74	159-161	90	66
1j	$C_{24}H_{20}BrN_3O_3S$	56.56 / 56.48	4.02 / 3.95	8.14 / 8.23	168-170	93	39
1k	$C_{20}H_{20}N_4O_3S$	60.64 / 60.59	5.16 / 5.08	14.05 / 14.13	143-145	86	97

* – The growth inhibition (%) of *Mycobacterium tuberculosis* H37Rv ATCC 27294 in the concentration of 6.25 μg/ml.

All main functional groups of amides (**1a-k**) containing protons in ^{1}H NMR spectra are identified without complications (Table 2). For example, the protons of 4-OH groups are evident as singlets with integrated intensity of 1H in the typically weak field range (15.63-14.11 ppm) as should be expected for enolic hydroxyls. Singlets of protons of amide groups are regularly slightly shifted upfield: 13.94-12.54 ppm. Further there is the "aromatic" area, in which protons of the phenyl nucleus of the 1-N-benzyl substituent resonate, and aromatic protons of anilide and hetarylamide fragments. The methylene bridge separating the cyclic nitrogen atom and the phenyl nucleus is evident as a singlet with the intensity of 2H in a relatively strong field: 5.42-5.38 ppm. Methylene units of the hexahydroquinoline bicycle have the form of narrow multiplets in the strongest field of the spectrum, wherein if the chemical shifts 8-CH_2 and 5-CH_2-groups are significantly different, the resonant frequency of 6-CH_2 and 7-CH_2-groups are so close that they are almost impossible to be distinguished (Table 2).

An important and useful information on the structure of 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides (**1a-k**) is provided by their mass spectra (Table 2). So, all the compounds synthesized under the influence of electron impact form peaks of molecular ions of low intensity and multiplicity corresponding to the isotopic composition [19]. The primary fragmentation of molecular ion occurs in two directions with approximately equal probability. The first of them is C(3)–CONHHet(Ar) bond breaking or the pathway A (Scheme 2), the result is formation of fragment ions of isocyanate **7** and benzylquinoline **8**. The second direction is destruction of the molecular radical cation by the carbamide bond (pathway B), it is the cause of appearance of highly intense peaks of the released amines (2-aminobenzothiazole 9 in case of amide **1i**) in the spectra and, although it is less intense, but it is common for all compounds of the fragment ion of ketene **10** with m/z 281. It is interesting that the loss of the 1-N-benzyl substituent occurs only during the secondary fragmentation, and it is not observed in any of the examples studied in the primary decomposition of the molecular ion.

The anti-tuberculosis activity of 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides (**1a-k**) was studied by the radiometric method [20, 21]. A comparative analysis of the experimental data (Table 1) obtained with the results of

Table 2

^{1}H NMR and mass spectra of amides (1a-k)

Compound	^{1}H NMR spectra, Chemical shifts, δ, ppm (*J*, Hz)							Mass spectra, $[M]^+$ (I_{rel}, %)
	4-OH (1H, s)	NH (1H, s)	1N-CH_2 (2H, s)	Hexahydroquinoline nucleus			Proton signals of other functional groups	
				8-CH_2 (2H, m)	5-CH_2 (2H, m)	6,7-$(CH_2)_2$ (4H, m)		
1a	15.58	12.61	5.40	2.66	2.41	1.65	7.63-6.96 (9H, m, Ph + H arom.)	392 (14)
1b	15.63	12.65	5.38	2.67	2.42	1.64	7.69-7.11 (9H, m, Ph + H arom.)	392 (17)
1c	15.57	12.54	5.41	2.66	2.40	1.67	7.82-7.10 (9H, m, Ph + H arom.)	408/410 (12/3)
1d	15.22	12.98	5.39	2.71	2.41	1.69	8.33-7.32 (8H, m, Ph + H arom.)	442/444/446 (9/6/1)
1e	15.34	12.79	5.40	2.68	2.40	1.68	7.52-7.12 (9H, m, Ph + H arom.)	452/454 (13/12)
1f	15.41	12.77	5.39	2.69	2.40	1.70	8.80 (1H, s, 2-H Py); 8.35 (1H, d, *J* = 4.4, 6-H Py); 8.10 (1H, d, *J* = 8.0, 4-H Py); 7.43-7.12 (6H, m, 5-H Py + Ph)	375 (18)
1g	14.52	13.63	5.38	2.70	2.41	1.69	7.41-7.05 (7H, m, Ph + 4,5-H Th)	381 (15)
1h	14.46	13.68	5.40	2.70	2.40	1.64	7.33-7,12 (5H, m, Ph); 6.88 (1H, s, 5-H Th); 2.00 (3H, s, γ-H Ad); 1.84 (6H, s, δ-H Ad); 1.76 (8H, s, β-H Ad)	515 (4)
1i	14.17	13.92	5.42	2.66	2.39	1.65	7.91-7.10 (9H, m, Ph + H arom.)	431 (10)
1j	14.00	13.89	5.41	2.67	2.40	1.66	8.20 (1H, s, 7′-H); 7.70-7.11 (7H, m, Ph + H arom.)	509/511 (11/12)
1k	14.11	13.94	5.40	2.66	2.41	1.67	7.40-7.12 (5H, m, Ph); 2.72 (3H, s, Me)	396 (19)

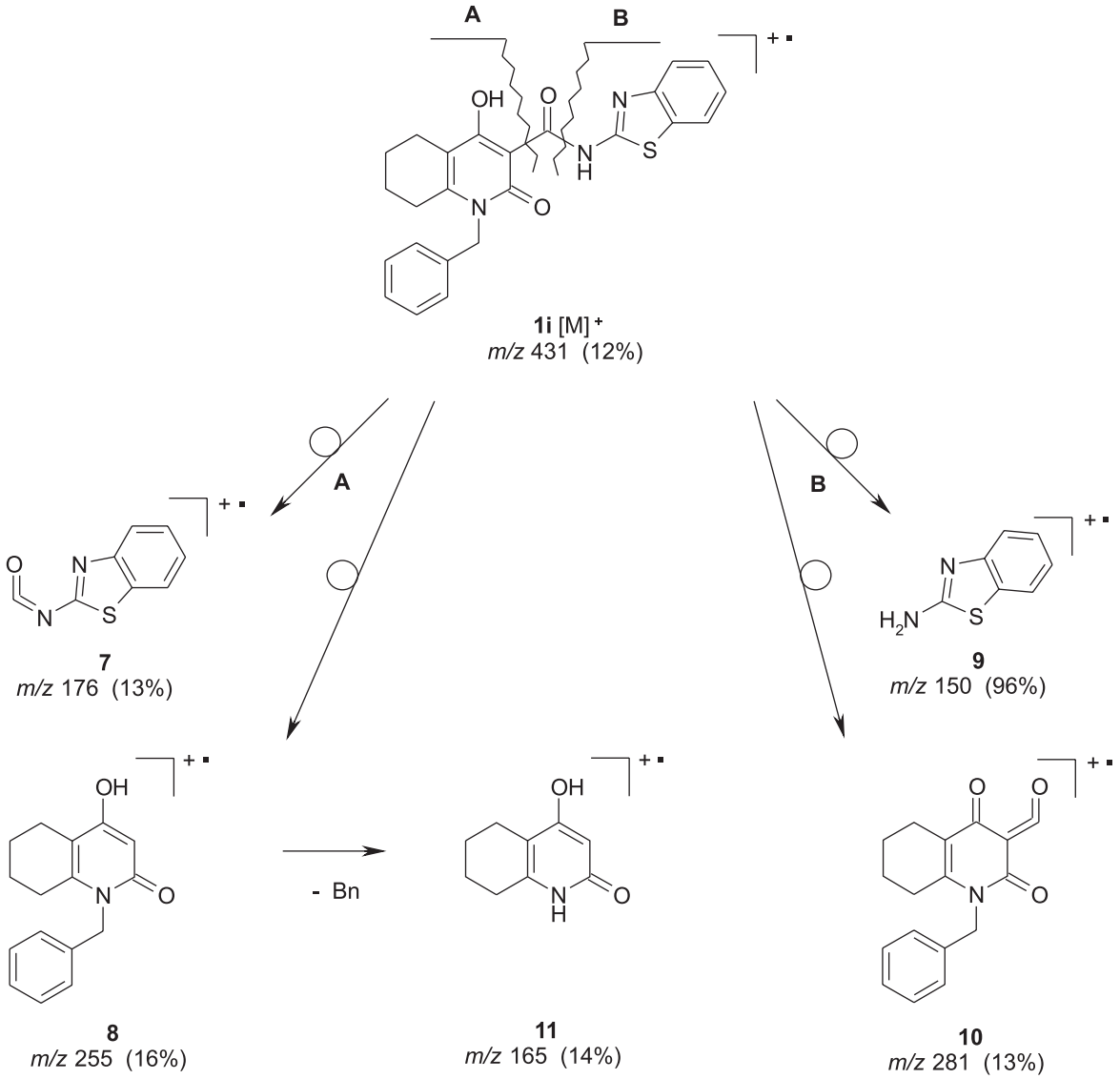
1-N-furfuryl-substituted derivatives with the similar structure shown in similar conditions was performed [15]. It has been found that in the vast majority of cases the replacement of the furan ring with the benzene ring is accompanied by a significant increase in antimycobacterial properties and, therefore, is a good variant of a chemical modification.

The most active compounds of this series – pyridine-3-ylamide 1f, 1,3-thiazole-2-ylamide **1g** and 5-methyl-1,3,4-thiadiazole-2-ylamide **3k** – in the concentration of 6.25 μg/mL can inhibit the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294 by more than 90%, and thus, they are transferred to the next stage of the microbiological testing as promising antimycobacterial agents.

Experimental Part

The ^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer (400 MHz) in DMSO-d_6 solution, the internal standard was TMS. Mass spectra were recorded of a Varian 1200L instrument in full scan mode in the range of 35-700 *m/z*, with EI ionization (70 eV) and direct sample introduction. Elemental analysis was carried out on a EuroVector EA-3000 microanalyzer. Melting points were determined in capillaries on a SMP10 Stuart digital melting point analyzer. The commercial 2-oxocyclohexanecarboxylic acid ethyl ester, benzylamine and ethoxymalonyl chloride of Fluka company were used in the synthesis.

Ethyl 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (2). Stir vigorously the mixture of 17.02 g (0.1 Mol) 2-oxocyclohexanecarboxylic acid ethyl ester (**3**) and 12.00 mL (0.11 Mol) of benzylamine at room temperature for 1 h. Heat the reaction mixture to 50°C, and continue to stir for 5 h, then remove the excess of benzylamine in vacuum. Dissolve the residue 200 mL of CH_2Cl_2. Distill off about 50 ml of the solvent, while removing azeotropically the water formed during the reaction of cyclohexanone **3** with benzylamine. To the solution of the enamine **4** obtained in CH_2C_{l2} add at first 14 mL (0.1 Mol) of triethylamine and then while stirring and cooling 15.05 g (0.1 Mol) of ethoxymalonyl chloride. In 5-6 h add 300 mL of cold water to the reaction mixture and mix thoroughly. Separate the organic layer, dry over anhydrous $CaCl_2$. At the end distill the solvent under reduced pressure. To the residue (amido ester **5**) add the solution of sodium ethoxide [4.6 g (0.2 Mol) of sodium metal and 150 mL of absolute ethanol], heat to boiling and allow to stand for 3 h at room temperature. Add 500 mL of cold water, acidify with HCl to pH4. Filter the precipitate of ester **2** formed, wash with cold water and dry. Yield – 26.5 g (81%). M.p. – 87-89°C (EtOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 13.32 (1H, s, OH); 7.33 (2H, t, *J* = 7.8, 3,5-H Ph); 7.24 (1H, t, *J* = 7.6, 4-H Ph); 7.10 (2H, d, *J* = 8.1, 2,6-H Ph); 5.26 (2H, s, N-CH_2); 4.32 (2H, q, *J* = 7.0, O$\underline{C}H_2CH_3$); 2.62 (2H, m, 8-CH_2); 2.43 (2H, m, 5-CH_2); 1.62 (4H, m, 6,7-CH_2); 1.30 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$). Found, %:



Scheme 2

C 69.80; H 6.53; N 4.21. $C_{19}H_{21}NO_4$. Calculated, %: C 69.71; H 6.47; N 4.28.

1-Benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides (1a-k). The general procedure. Stir the mixture of 3.27 g (0.01 Mol) of ethyl ester **2**, the corresponding aniline or hetarylamine (0.01 Mol) and 2 ml of DMF and allow to stand on a metal bath at 130°C for 5 min. Cool the reaction mixture, add 10 ml of ethanol and triturate thoroughly. Filter the amide **1a-k** precipitated, wash with alcohol, dry, and recrystallize from the mixture DMF and EtOH.

Conclusions

1. The preparative method for obtaining the substances has been proposed, and the synthesis of a new series of 1-benzyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamides has been carried out. Their structure has been confirmed by elemental analysis, ^{1}H NMR spectra and mass spectra.

2. According to the data of the microbiological testing some substances exhibiting a high anti-tuberculosis activity in low concentrations have been identified and recommended for *in vivo* studies in the range of the compounds studied.

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