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4-HYDROXY-2-QUINOLONES. 122*. 1-HYDROXY-3-OXO-5,6-DIHYDRO-3H-PYRROLO[3,2,1-*ij*]-QUINOLINE-2-CARBOXYLIC ACID HETARYLAMIDES AS POTENTIAL ANTITUBERCULAR AGENTS

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An improved method is reported for the synthesis of a series of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-ij]quinoline-2-carboxylic acid hetarylamides. The antitubercular activity of all of the compounds prepared has been studied. The structure – biological activity dependence revealed is discussed.

Keywords: hetarylamides, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, amidation, antitubercular activity.

The tuberculosis epidemic touches the entire world and is becoming a more threatening problem for contemporary human society. According to World Health Organization data this infection now infects every third inhabitant of the planet. Every year tuberculosis takes away the lives of more than 3 million human beings, running ahead of the unfortunate figure for malaria and other infection illnesses [2, 3]. This developing situation cuts across not just its occurrence in many countries thus worsening their socio-economic conditions but it is also seen in the appearance and global spread of multiresistant strains of the tubercular micobacterium for which known agents fail [4, 5]. In this connection the search and development of novel, more active and less toxic antimicrobacterial preparations has taken on an extreme urgency at this time. For resolution of such problems the international TAACF program (*Tuberculosis Antimicrobial Acquisition and Coordinating Facility*) was set up and under whose terms our current investigation was carried out, the aim being to synthesize and study the antitubercular properties of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-quinoline-2-carboxylic acid hetarylamides **1, 2**.

It is clear that amidation of the ethyl ester **3** in ethanol (used by us successfully in the synthesis of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid alkylamides [1]) did not give the desired result in the preparation of the heteroanalogs **1** or **2**. In addition, the previously [6] proposed length of refluxing ester **3** with 40% excess hetarylamine in bromobenzene (up to 20 h) is effectively also a complication. In our view, the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid hetarylamides **1, 2** can be most conveniently prepared by simple heating of the mixture of ester **3** and the corresponding primary

* For Communication 121 see [1].

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TABLE 1. Characteristics of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid hetarylamides **1a-y**, **2a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Antitubercular activity	
		C	H	N			Inhibition of the growth of *M. tuberculosis*, % *	MIC, μg/ml
1	2	3	4	5	6	7	8	9
1a	$C_{17}H_{13}N_3O_3$	66.57 / 66.44	4.35 / 4.26	13.79 / 13.67	222-224	95	100	3.13
1b	$C_{17}H_{13}N_3O_3$	66.55 / 66.44	4.21 / 4.26	13.58 / 13.67	192-194	92	100	6.25
1c	$C_{17}H_{13}N_3O_3$	66.36 / 66.44	4.15 / 4.26	13.60 / 13.67	217-219	90	49	—
1d	$C_{17}H_{13}N_3O_4$	63.25 / 63.16	4.17 / 4.05	13.08 / 13.00	238-240	81	0	—
1e	$C_{18}H_{15}N_3O_3$	67.32 / 67.28	4.66 / 4.71	13.01 / 13.08	180-182	83	8	—
1f	$C_{18}H_{15}N_3O_3$	67.24 / 67.28	4.79 / 4.71	13.18 / 13.08	229-231	91	0	—
1g	$C_{18}H_{15}N_3O_3$	67.19 / 67.28	4.62 / 4.71	13.21 / 13.08	253-255	94	25	—
1h	$C_{18}H_{15}N_3O_3$	67.37 / 67.28	4.80 / 4.71	13.15 / 13.08	224-226	95	71	—
1i	$C_{16}H_{12}N_4O_3$	62.47 / 62.34	3.98 / 3.92	18.31 / 18.17	252-254	80	25	—
1j	$C_{16}H_{12}N_4O_3$	62.40 / 62.34	3.88 / 3.92	18.24 / 18.17	230-232	91	100	1.56
1k	$C_{15}H_{11}N_3O_3S$	50.63 / 57.50	3.62 / 3.54	13.33 / 13.41	271-273	87	61	—
1l	$C_{16}H_{13}N_3O_3S$	58.61 / 58.70	3.92 / 4.00	12.78 / 12.84	266-268	85	100	3.13

TABLE 1. (continued)

1	2	3	4	5	6	7	8	9
1m	$C_{16}H_{13}N_3O_3S$	58.63 58.70	3.95 4.00	12.80 12.84	237-239	88	100	1.56
1n	$C_{19}H_{17}N_3O_5S$	57.22 57.13	4.35 4.29	10.63 10.52	196-198	90	100	6.25
1o	$C_{25}H_{25}N_3O_3S$	67.24 67.09	5.71 5.63	9.30 9.39	263-265	93	98	6.25
1p	$C_{14}H_{10}N_4O_3S$	53.43 53.50	3.17 3.21	17.92 17.82	270-272	88	100	1.56
1q	$C_{15}H_{12}N_4O_3S$	54.95 54.87	3.60 3.68	17.00 17.06	265-267	86	100	1.56
1r	$C_{16}H_{14}N_4O_3S$	56.22 56.13	4.17 4.12	16.45 16.36	234-236	82	100	0.78
1s	$C_{17}H_{16}N_4O_3S$	57.20 57.29	4.42 4.53	15.63 15.72	182-184	83	99	0.78
1t	$C_{17}H_{16}N_4O_3S$	57.18 57.29	4.44 4.53	15.67 15.72	193-195	87	99	0.78
1u	$C_{19}H_{14}N_4O_3$	65.97 65.89	4.16 4.04	16.07 16.18	304-306	90	100	0.39
1v	$C_{19}H_{13}N_3O_3S$	62.73 62.80	3.69 3.61	11.44 11.56	291-293	94	100	0.78
1w	$C_{19}H_{12}BrN_3O_3S$	51.55 51.60	2.67 2.73	9.58 9.50	338-340	92	100	3.13
1x	$C_{20}H_{15}N_3O_3S$	63.70 63.65	4.14 4.01	11.01 11.13	282-284	95	100	6.25
1y	$C_{26}H_{19}N_3O_3S$	68.78 68.86	4.15 4.22	9.19 9.27	295-297	93	0	—
2a	$C_{19}H_{21}N_3O_5$	61.37 61.45	5.61 5.70	11.43 11.31	143-145	82	0	—
2b	$C_{17}H_{19}N_3O_3 \cdot HCl$	58.48 58.37	5.67 5.76	12.12 12.01	201-203	75	0	—
2c	$C_{23}H_{23}N_3O_3 \cdot HCl$	64.74 64.86	5.60 5.68	9.74 9.87	209-211	71	0	—

* Concentration of the compounds studied 6.25 μg/ml.

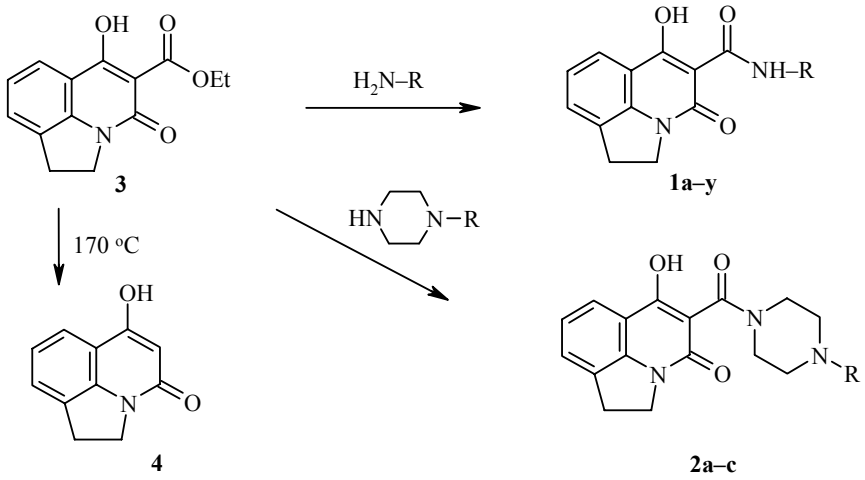
TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	Chemical s,hifts,, δ, ppm. (*J*, Hz)							
	1-OH (1H, s)	NH (1H, s)	Pyrrolloquinoline ring					R
			H-9 (1H, d)	H-7 (1H, d)	H-8 (1H, t)	5-CH_2 (2H, t)	6-CH_2 (2H, t)	
1	2	3	4	5	6	7	8	9
1a	16.20	12.82	7.78 (*J* = 8.1)	7.43 (*J* = 7.2)	7.20 (*J* = 7.5)	4.32 (*J* = 7.9)	3.41 (*J* = 8.0)	8.48 (2H, d, *J* = 6.2, H-2',6'); 7.55 (2H, d, *J* = 6.2, H-3',4')
1b	16.16	12.69	7.73 (*J* = 8.1)	7.45 (*J* = 6.9)	7.17 (*J* = 7.5)	4.39 (*J* = 8.0)	3.44 (*J* = 8.0)	8.70 (1H, s, H-2'); 8.29 (1H, d, *J* = 4.3, H-6'); 8.17 (1H, d, *J* = 8.1, H-4'); 7.27 (1H, t, *J* = 6.3, H-5')
1c	16.23	12.81	7.72 (*J* = 8.0)	7.46 (*J* = 7.0)	7.17 (*J* = 7.6)	4.42 (*J* = 7.8)	3.45 (*J* = 8.0)	8.34 (1H, d, *J* = 4.8, H-6'); 8.23 (1H, d, *J* = 8.8, H-3'); 7.82 (1H, t, *J* = 7.8, H-4'); 7.07 (1H, t, *J* = 6.2, H-5')
1d	16.32	12.70	7.73 (*J* = 7.9)	7.53 (*J* = 7.2)	7.22 (*J* = 7.5)	4.40 (*J* = 7.9)	3.46 (*J* = 7.9)	9.98 (1H, s, OH); 7.89 (1H, dd, *J* = 4.3 и *J* = 1.7, H-6'); 7.27 (1H, dd, *J* = 8.4 and *J* = 1.7, H-4'); 7.06 (1H, t, *J* = 6.2, H-5')
1e	16.50	12.42	7.72 (*J* = 7.9)	7.57 (*J* = 7.2)	7.25 (*J* = 7.7)	4.39 (*J* = 7.9)	3.45 (*J* = 7.9)	8.29 (1H, d, *J* = 4.7, H-6'); 7.69 (1H, d, *J* = 6.5, H-4'); 7.21 (1H, t, *J* = 5.8, H-5'); 2.33 (3H, s, CH_3)
1f	16.28	12.74	7.73 (*J* = 8.1)	7.46 (*J* = 7.4)	7.17 (*J* = 7.6)	4.41 (*J* = 8.0)	3.45 (*J* = 7.9)	8.18 (1H, d, *J* = 5.2, H-6'); 8.06 (1H, s, H-3'); 6.90 (1H, d, *J* = 5.3, H-5'); 2.41 (3H, s, CH_3)
1g	16.21	12.82	7.73 (*J* = 8.0)	7.58 (*J* = 7.0)	7.26 (*J* = 7.5)	4.38 (*J* = 8.1)	3.43 (*J* = 7.8)	8.22 (1H, s, H-6'); 8.05 (1H, d, *J* = 8.6, H-3'); 7.66 (1H, d, *J* = 8.6, H-4'); 2.32 (3H, s, CH_3)
1h	16.23	12.79	7.71 (*J* = 8.0)	7.54 (*J* = 7.1)	7.22 (*J* = 7.5)	4.37 (*J* = 7.9)	3.43 (*J* = 7.8)	7.96 (1H, d, *J* = 8.0, H-3'); 7.66 (1H, t, *J* = 8.0, H-4'); 7.00 (1H, d, *J* = 8.0, H-5'); 2.46 (3H, s, CH_3)
1i	16.35	13.18	7.74 (*J* = 8.0)	7.61 (*J* = 7.3)	7.25 (*J* = 7.4)	4.37 (*J* = 7.8)	3.43 (*J* = 8.0)	8.74 (2H, d, *J* = 5.4, H-4',6'); 7.29 (1H, t, *J* = 4.6, H-5')
1j	15.78	13.03	7.73 (*J* = 8.0)	7.52 (*J* = 7.4)	7.22 (*J* = 7.5)	4.39 (*J* = 8.0)	3.45 (*J* = 7.8)	9.43 (1H, s, H-3'); 8.39 (2H, d, *J* = 2.5, H-5',6')
1k	15.11	13.73	7.77 (*J* = 8.2)	7.61 (*J* = 7.2)	Cm. R	4.42 (*J* = 8.1)	3.46 (*J* = 8.0)	7.54 (1H, d, *J* = 3.7, H-5'); 7.32–7.27 (2H, m, H-8,4')
1l	15.24	13.58	7.76 (*J* = 7.8)	7.57 (*J* = 7.3)	7.26 (*J* = 7.7)	4.42 (*J* = 7.9)	3.47 (*J* = 7.8)	6.74 (1H, s, H-5'); 2.34 (3H, s, CH_3)
1m	15.22	13.49	7.73 (*J* = 8.0)	7.54 (*J* = 6.9)	7.23 (*J* = 7.7)	4.40 (*J* = 8.0)	3.45 (*J* = 8.0)	7.14 (1H, s, H-4'); 2.43 (3H, s, CH_3)
1n	15.16	13.62	7.76 (*J* = 8.1)	7.56 (*J* = 7.1)	7.25 (*J* = 7.8)	4.42 (*J* = 8.0)	3.47 (*J* = 7.9)	7.01 (1H, s, H-5'); 4.14 (2H, q, *J* = 6.8, OCH_2); 3.68 (2H, s, CH_2); 1.28 (3H, t, *J* = 7.1, CH_3)

TABLE 2. (continued)

1	2	3	4	5	6	7	8	9
1o	15.38	13.42	7.77 (J = 8.1)	7.43 (J = 7.0)	7.17 (J = 7.8)	4.44 (J = 8.1)	3.46 (J = 8.0)	6.52 (1H, s, H-5'); 2.09 (3H, s, γ-H-bridghead adamantane); 1.97 (6H, m, δ-H-bridging adamantane); 1.80 (6H, s, β-H-bridging adamantane)
1p	14.79	14.11	7.78 (J = 8.2)	7.63 (J = 6.9)	7.29 (J = 7.6)	4.44 (J = 8.0)	3.48 (J = 7.9)	9.20 (1H, s, H-5')
1q	14.75	13.94	7.74 (J = 8.0)	7.62 (J = 6.8)	7.28 (J = 7.6)	4.40 (J = 7.9)	3.44 (J = 7.8)	2.67 (3H, s, CH_3)
1r	14.85	13.89	7.74 (J = 8.0)	7.57 (J = 7.2)	7.25 (J = 7.6)	4.43 (J = 8.0)	3.47 (J = 7.9)	3.05 (2H, q, J = 7.5, CH_2); 1.41 (3H, t, J = 7.7, CH_3)
1s,	14.89	13.81	7.73 (J = 8.1)	7.49 (J = 7.1)	7.19 (J = 7.6)	4.44 (J = 8.0)	3.47 (J = 7.9)	2.99 (2H, t, J = 7.5, $C\underline{H}_2CH_2CH_3$); 1.85 (2H, m, $C\underline{H}_2CH_3$); 1.07 (3H, t, J = 7.6, CH_3)
1t	14.92	13.81	7.75 (J = 8.2)	7.50 (J = 7.0)	7.20 (J = 7.6)	4.45 (J = 7.9)	3.48 (J = 7.9)	3.38 (1H, m, CH); 1.46 (6H, d, J = 6.5, $2CH_3$)
1u	15.61	13.46	7.77 (J = 7.9)	7.63 (J = 7.2)	7.31 (J = 7.6)	4.39 (J = 7.9)	3.42 (J = 7.9)	12.29 (1H, s, NH); 7.50 (2H, m, H-4',7'); 7.14 (2H, m, H-5',6')
1v	14.84	13.96	7.80 (J = 8.0)	7.62 (J = 6.9)	7.29 (J = 7.6)	4.39 (J = 8.2)	3.44 (J = 8.0)	7.99 (1H, d, J = 8.6, H-7'); 7.76 (1H, d, J = 8.6, H-4'); 7.46 (1H, t, J = 7.7, H-6'); 7.36 (1H, t, J = 7.7, H-5')
1w	15.20	13.99	7.80 (J = 8.1)	7.65 (J = 7.1)	7.33 (J = 7.7)	4.43 (J = 7.9)	3.47 (J = 8.0)	8.23 (1H, s, H-7'); 7.74 (1H, d, J = 8.6, H-4'); 7.60 (1H, d, J = 8.5, H-5')
1x	14.90	13.94	7.74 (J = 8.0)	7.65 (J = 6.9)	7.33 (J = 7.8)	4.42 (J = 7.9)	3.45 (J = 8.0)	7.82 (1H, s, H-7'); 7.71 (1H, d, J = 8.4, H-4'); 7.28 (1H, d, J = 8.4, H-5'); 2.44 (3H, s, CH_3)
1y	16.11	12.85	7.76 (J = 8.0)	7.59 (J = 7.2)	7.28 (J = 7.7)	4.40 (J = 7.8)	3.44 (J = 7.8)	8.08 (2H, d, J = 8.7, H-2,6 C_6H_5); 7.82 (2H, d, J = 8.7, H-3,5 C_6H_5); 7.90 (1H, d, J = 8.4, H-4"); 7.86 (1H, s, H-7"); 7.34 (1H, d, J = 8.4, H-5"); 2.46 (3H, s, CH_3)
2a	11.15	—	7.66 (J = 7.9)	7.34 (J = 7.1)	7.08 (J = 7.5)	4.29 (J = 7.9)	3.40 (J = 8.1)	4.08 (2H, q, J = 7.1, OCH_2); 3.49 (4H, br. s, $N(CH_2)_2$); 2.95 (4H, br. s, $N(CH_2)_2$); 1.25 (3H, t, J = 7.1, CH_3)
2b	Cm. R	—	7.70 (J = 7.8)	7.39 (J = 6.9)	7.11 (J = 7.6)	4.28 (J = 8.0)	3.40 (J = 8.0)	11.88 (2H, br. s, OH + HN^+); 3.04 (8H, br. s, $4CH_2$ piperazine); 2.79 (3H, s, CH_3)
2c	Cm. R	—	7.72 (J = 7.9)	Cm. R	7.13 (J = 7.5)	4.29 (J = 7.9)	3.41 (J = 7.9)	11.26 (2H, br. s, OH + HN^+); 7.60 (2H, m, H-7 + H-4 C_6H_5); 7.43 (4H, m, H-2,3,5,6 C_6H_5); 4.38 (2H, s, CH_2); 3.13 (8H, br. s, $4CH_2$ piperazine)

or secondary hetarylamine at 160ºC for 3-5 min with an equimolar ratio of reagents. In principle, such reactions occur quite readily in most cases with high yields without a solvent. However, on a comparatively large scale or when using amines with high melting points it is advisable to add a small amount of high boiling solvent and this leads to preparation of the final compounds with higher purity. It should be specially pointed out that the volume of the added solvent should not be too large: an optimum amount being 1 ml per 0.01 mol otherwise the reaction rate is significantly lower and the amidation needs several hours.



1 a R = pyridin-4-yl, **b** R = pyridin-3-yl, **c** R = pyridin-2-yl, **d** R = 3-hydroxypyridin-2-yl, **e** R = 3-methylpyridin-2-yl, **f** R = 4-methylpyridin-2-yl, **g** R = 5-methylpyridin-2-yl, **h** R = 6-methylpyridin-2-yl, **i** R = pyrimidin-2-yl, **j** R = pyrazin-2-yl, **k** R = thiazol-2-yl, **l** R = 4-methylthiazol-2-yl, **m** R = 5-methylthiazol-2-yl, **n** R = 4-carbethoxymethylthiazol-2-yl, **o** R = 4-(adamant-1-yl)thiazol-2-yl, **p** R = 1,3,4-thiadiazol-2-yl, **q** R = 5-methyl-1,3,4-thiadiazol-2-yl, **r** R = 5-ethyl-1,3,4-thiadiazol-2-yl, **s** R = 5-propyl-1,3,4-thiadiazol-2-yl, **t** R = 5-isopropyl-1,3,4-thiadiazol-2-yl, **u** R = benzimidazol-2-yl, **v** R = benzothiazol-2-yl, **w** R = 6-bromobenzothiazol-2-yl, **x** R = 6-methylbenzothiazol-2-yl, **y** R = 4-(6-methylbenzothiazol-2-yl)phenyl;
2 a R = COOEt, **b** R = Me·HCl, **c** R = CH_2Ph·HCl

The tricyclic ester **3** is quite stable to heating and can be held at 215ºC without marked change [7]. However, under amidation conditions, it shows a tendency to partial fission of the ester group to give the 1-hydroxy-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinolin-3-one (**4**) which can contaminate the target amides **1** and **2**. A series of experiments carried out by us at various temperatures and using the ^{1}H NMR spectra of the unpurified material showed that, starting at 170ºC, the 2H-derivative **4** was actually formed in quite appreciable amounts and increased at higher temperature. The 2H-quinolin-3-one **4** can be identified by the characteristic signal for the H-2 proton at 5.72 ppm. Its good solubility allows a ready removal of this unwanted admixture after only a single crystallization. None the less, to avoid forming this side product the temperature conditions should be carefully observed and the reaction mixture not heated above 160ºC.

The 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid hetarylamides **1** and **2** (Table 1) are practically insoluble in water (with the exception of the hydrochlorides **2b,c**) as colorless or light yellow crystalline materials. Their structure was confirmed by ^{1}H NMR spectroscopy, superposition of signals in which was very rare and this allowed identification of all of the proton containing functional groups (Table 2).

The antitubercular activities of the synthesized hetarylamides **1** and **2** were studied by a radiometric method [8, 9] using the BACTEC 12B culture medium [10]. The results of a primary microbiological screening (the first level of the investigation) showed that many of the tested substances at initial concentration 6.25 μg/ml *in vitro* showed clear antitubercular activity and inhibited the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294 by 98-100% (Table 1). Compounds showing activity not less than 90% at this stage were carried on to the next screening level to determine the actual minimum inhibitory concentration (MIC). Based on this value (Table 1) the group of samples of interest for further study was reduced to five **1r-v** since samples with an MIC ≤ 1 μg/ml are generally considered as promising.

Comparison of the results for the microbiological investigation with the nature of the amide fragment present on the heterocycle revealed that the series of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-quinoline-2-carboxylic acid hetarylamides **1**, **2** shows about the same structure – biological activity relationship as seen in the 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid amides with the smallest ($C_{(1)}$ to $C_{(3)}$) alkyl substituents on the quinolone ring nitrogen atom. Hence in the series of isomeric pyridylamides **1a-c** the dependence of the antitubercular activity on the position of the nitrogen atom in the pyridine ring (in the order 4 > 3 >>2) can be clearly traced whereas a hydroxyl or methyl group in a pyrid-2-ylamide residue (amides **1d-h**) deactivates the molecule. An analogous effect has also been seen in the corresponding 1R-4-hydroxy-2-oxo-1,2-dihydroxyquinoline-3-carboxamides [11, 12]. In the case of the diazahetarylamide pyrazine derivatives (amide **1j**) the activity is always more than the isomeric pyrimidines (amide **1i**) while the strength of the antimicrobial activity of the thiadiazol-2-ylamides **1r-t** is governed by the $C_{(5)}$ alkyl-substituent. Amongst the thiazole derivatives (amides **1k-o**) the antitubercular effect is also markedly strengthened by the presence of an alkyl substituent at position 5. However, the reliability of this conclusion only refers to a methyl group since it is known [13] that a long chain tetradecyl radical leads to total loss of the effect on the microbacterial cell. All of the benzothiazol-2-ylamides, as do their analogous 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid derivatives, actively inhibit the growth of the tuberculosis microbacterium. But if in the former, as judged by their MIC values, the activity falls in the series of introduced substituents H > 6-Br > 6-CH_3, then a completely different pattern is seen in the latter [14]. At the same time, the role of the phenyl ring situated between the quinoline-3-carbamide and the 6-methylbenzothiazole fragment (in amide **1y**) is identical in all cases and it totally eliminates any kind of antimicrobial properties [14]. The aza biostere of the benzothiazol-2-ylamide **1v** (benzimidazol-2-ylamide **1u**) is of special interest. It was found experimentally that exchanging the sulfur atom for a nitrogen atom led to a two fold lowering of the MIC and can therefore be considered as very favourable. In the 4-substituted piperazin-1-ylamides **2a-c** the tuberculosis bacterium proves completely immune although, e.g. in fluoroquinolone antibiotics the presence of this heterocycle is considered as a structurally helpful fragment [15].

EXPERIMENTAL

^{1}H NMR Spectra for the compounds synthesized were recorded on a Bruker WM-360 instrument (360 MHz) for DMSO-d_6 solvent and TMS internal standard. Ethyl 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-quinoline-2-carboxylate (**3**) was prepared as described in [7].

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Hetarylamides (1a-y, 2a) (General Method). A mixture of ester **3** (2.59 g, 0.01 mol), the corresponding hetarylamine (0.01 mole), in DMF (1 ml) was stirred and held for 3-5 min at 160ºC. The reagents initially dissolved and then a vigorous evolution of ethanol was observed. After this the amide product began to crystallize from the reaction mixture. After cooling, ethanol 10-15 ml) was added and the product was triturated thoroughly. The precipitated amides **1a-y** or **2a** were filtered off, washed with alcohol, dried, and crystallized from DMF.

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Piperazin-1-ylamide hydrochlorides (2b,c). The piperazin-1-ylamides **2b,c** obtained by the previous method were suspended in ethanol (15 ml), gaseous HCl in ethanol was added to pH 3 (the precipitate dissolved) and the product was then left for several hours in an ice bath. The crystals of the piperazin-1-ylamide hydrochlorides **2b,c** were filtered off, washed with ether, and dried.

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