Chemistry of Heterocyclic Compounds, Vol. 45, No. 5, 2009

4-HYDROXY-2-QUINOLONES. 154*. PYRIMIDIN-2-YLAMIDES OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACIDS. SYNTHESIS, STRUCTURE, AND PROPERTIES

I. V. Ukrainets[1], A. A. Tkach[1], L. A. Grinevich[1], A. V. Turov[2], and O. V. Bevz[1]**

The synthesis of a series of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids pyrimidin-2-ylamides has been carried out with the aim of subsequent microbiological investigation. In acetic acid it was found that these compounds are brominated by 1 equivalent of bromine at position 5 of the pyrimidine ring. The only exception is the 1-allyl derivative which undergoes heterocyclization under these conditions to give 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic acid pyrimidin-2-ylamide. The results of a study of the antitubercular activity of the synthesized compounds are presented.

Keywords: 2-aminopyrimidine, 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, bromination, antitubercular activity, X-ray structural analysis.

Pyrimidine bases occur in a number of the most widespread heterocyclic systems in nature. Occurring in nucleic acids and coenzymes these compounds play a direct role in encoding and transmitting hereditary information, in the metabolism of carbohydrates and lecithin, and also in many biochemical processes important for animals and plants [2]. As a result, natural pyrimidines have an extremely broad spectrum of biological activities: from vitamins and regulators of biosynthesis amongst specific living organism proteins to antibiotics and alkaloids and to tetrodotoxin [3] which is one of the most powerful non-protein neurotoxins. Of course, pharmaceutical chemistry has not stood aside from the facts listed. As a result, to this day around 100 synthetic preparations [4] based on pyrimidine have been created and indeed used in medicinal practice. The majority of them fit into four broad categories of well known substances: barbiturates, sulfanilamides, antimicrobial pyrimidine-2,4-diamines, and antitumor agents [3]. Less impressive but none the less valuable for public health are such pharmacological groups as diuretics, antihypertensive and antihistamine agents, anticonvulsants, vitamins etc. [3, 4].

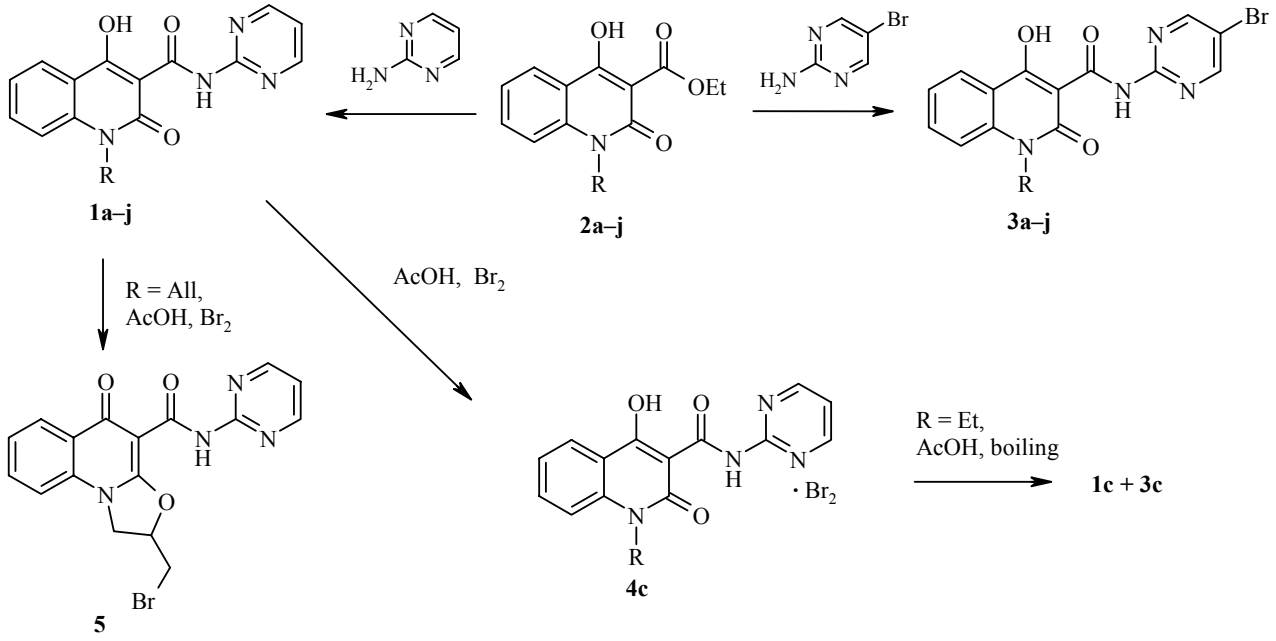
* For Communication 153 see [1].

** To whom correspondence should be addressed, e-mail: uiv@kharkov.ua.

[1]National University of Pharmacy, Kharkiv 61002, Ukraine.
[2]Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: nmrlab@univ.kiev.ua.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 719-734, May, 2009. Original article submitted December 10, 2007.

Of course, study of pyrimidines in not so restricted and preparations have recently appeared for treatment of cancer [5], fungal infections in children [6], Alzheimers disease [7], hepatitis B [8], AIDS [9], and other viral infections [10]. In particular, many publications relate to the search for novel and efficient antimycobacterial agents [11-16] and this is explained by an exceptionally high surge in tubercular morbidity, approaching an epidemic scale in many countries of the world. In many examples of this kind it is necessary to include also the tendency of stimulation of the tubercular mycobacterium to active mutation contributing to rapid formation of resistance (often multiple) to known antitubercular medicines.



1–4 a R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = Pr, **f** R = Bu, **g** R = *i*-Bu, **h** R = C_5H_{11}, **i** R = *i*- C_5H_{11}, **j** R = Hex

We have repeatedly noted the high antimycobacterial activity of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids amides and, primarily, hetarylamides [17, 18]. This report is a logical continuation of previously carried out work based on the above arguments relating to the pyrimidin-2-ylamides **1a-j**. Their synthesis was carried out by a traditional method, i.e. *via* reaction of ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **2a-j** with 2-aminopyrimidine under thermolysis conditions. As in the case of 2-aminopyridine [17] the amidation occurs in quite good yields (Table 1, the ^{1}H NMR spectra are given in Table 2) despite the marked lowering of the reactivity of the amine component. It should be stressed that the 2-aminopyrimidine readily sublimes on heating hence to prevent unwarranted loss before melting it was necessary to add a small amount of a high boiling solvent (e.g. DMF) to the reaction mixture, its presence being helpful but not essential.

The 5-bromopyrimidin-2-ylamides **3a-j** were prepared similarly (Tables 1 and 2) but their synthesis (at least theoretically) is possible by another method *via* bromination of the unsubstituted analog compounds **1a-j**. Considered advantageous economically only on the grounds of avoiding use of the expensive 2-amino-5-bromopyrimidine the method can, in fact, most readily lead to bromination in the amide side chain of N-aryl- and N-hetaryl-substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-caboxamides with certain structural features [19, 20]. However, exclusions from this rule are really not so rare and an unexpected result is sometimes achieved [20]. In other words, the answer to the real behavior of any particular 4-hydroxy-2-quinolone under

TABLE 1. Characteristics of the 1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamides **1** and **3**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (DMF)	Yield, %	Antitubercular activity. Inhibition of the growth of *M. tuberculosis*, %
		C	H	N			
1a	$C_{14}H_{10}N_4O_3$	59.66 / 59.57	3.68 / 3.57	19.76 / 19.85	332 (dec.)	85	0
1b	$C_{15}H_{12}N_4O_3$	60.94 / 60.81	4.20 / 4.08	19.02 / 18.91	237-238	83	0
1c	$C_{16}H_{14}N_4O_3$	62.07 / 61.93	4.65 / 4.55	18.13 / 18.05	216-218	90	0
1d	$C_{17}H_{14}N_4O_3$	63.24 / 63.35	4.31 / 4.38	17.44 / 17.38	199-201	86	0
1e	$C_{17}H_{16}N_4O_3$	62.82 / 62.95	5.08 / 4.97	17.32 / 17.27	205-207	82	0
1f	$C_{18}H_{18}N_4O_3$	63.97 / 63.89	5.45 / 5.36	16.67 / 16.56	184-186	85	13
1g	$C_{18}H_{18}N_4O_3$	63.95 / 63.89	5.30 / 5.36	16.65 / 16.56	175-177	89	28
1h	$C_{19}H_{20}N_4O_3$	64.64 / 64.76	5.66 / 5.72	15.81 / 15.90	162-164	81	91
1i	$C_{19}H_{20}N_4O_3$	64.82 / 64.76	5.79 / 5.72	15.83 / 15.90	171-173	83	93
1j	$C_{20}H_{22}N_4O_3$	65.64 / 65.56	6.12 / 6.05	15.21 / 15.29	159-161	80	99
3a	$C_{14}H_9BrN_4O_3$	46.45 / 46.56	2.58 / 2.51	15.63 / 15.51	311 (dec.)	90	0
3b	$C_{15}H_{11}BrN_4O_3$	47.91 / 48.02	2.88 / 2.96	15.04 / 14.93	264-266	84	0
3c	$C_{16}H_{13}BrN_4O_3$	49.30 / 49.38	3.45 / 3.37	14.28 / 14.39	243-245	86	0
3d	$C_{17}H_{13}BrN_4O_3$	50.97 / 50.89	3.32 / 3.27	14.04 / 13.96	231-233	80	0
3e	$C_{17}H_{15}BrN_4O_3$	50.56 / 50.64	3.67 / 3.75	13.80 / 13.89	240-242	85	0
3f	$C_{18}H_{17}BrN_4O_3$	51.93 / 51.81	4.03 / 4.11	13.32 / 13.43	232-234	82	0
3g	$C_{18}H_{17}BrN_4O_3$	51.89 / 51.81	4.14 / 4.11	13.48 / 13.43	244-246	84	0
3h	$C_{19}H_{19}BrN_4O_3$	53.03 / 52.91	4.53 / 4.44	13.10 / 12.99	229-231	80	0
3i	$C_{19}H_{19}BrN_4O_3$	52.88 / 52.91	4.49 / 4.44	13.06 / 12.99	235-237	81	0
3j	$C_{20}H_{21}BrN_4O_3$	53.87 / 53.94	4.66 / 4.75	12.69 / 12.58	224-226	79	0

bromination conditions can only be obtained by experiment and we have carried out this in the case of the 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**1c**). Its behavior compared with other quinoline-3-carboxamides was different immediately upon addition of bromine to a solution of amide **1c** in glacial acetic acid. In place of the usually instantaneous decolorization observed a light-orange crystalline precipitate was obtained. The reaction mixture was diluted with water and the precipitate was filtered off, and recrystallized from a mixture of DMF and acetone. For an unambiguous solution as to which bromination route had occurred X-ray structural analysis was carried out and it was unexpectedly found that the product is just the starting pyrimidin-2-ylamide **1c** (see Figure 1, Tables 3 and 4).

The bicyclic fragment, hydroxyl, carbamide, and carbonyl groups as well as atom C(15) in this compound lie in a single plane to within 0.03 Å which is allowed by the formation of strong intramolecular hydrogen bonds O(2)–H(2O)···O(3) (H···O 1.32 Å, O–H···O 158º) and N(2)–H(2N)···O(1) (H···O 1.80 Å, N–H···O 143º).

TABLE 2. ^{1}H NMR Spectra of the Pyrimidin-2-ylamides **1** and **3**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)								
	OH (1H, s)	NH (1H, s)	Quinolone ring				Pyrimidine ring		R
			H-5 (1H, d)	H-7 (1H, t)	H-8 (1H, d)	H-6 (1H, t)	H-4',6' (2H)	H-5' (1H, t)	
1	2	3	4	5	6	7	8	9	10
1a	16.32	13.16	8.03 (*J* = 8.0)	7.74 (*J* = 7.6)	7.58 (*J* = 8.4)	7.49 (*J* = 7.5)	8.73 (d, *J* = 4.9)	7.24 (*J* = 4.6)	12.00 (1H, s, NH)
1b	16.35	13.14	8.08 (*J* = 8.0)	7.80 (*J* = 7.5)	7.60 (*J* = 8.5)	7.42 (*J* = 7.5)	8.72 (d, *J* = 5.0)	7.27 (*J* = 4.8)	3.66 (3H, s, NCH_3)
1c	16.36	13.21	8.10 (*J* = 8.0)	7.81 (*J* = 7.7)	7.67 (*J* = 8.4)	7.36 (*J* = 7.4)	8.73 (d, *J* = 5.0)	7.26 (*J* = 4.7)	4.31 (2H, q, *J* = 7.0, NCH_2); 1.23 (3H, t, *J* = 7.0, CH_3)
1d	16.44	13.15	8.14 (*J* = 8.0)	7.80 (*J* = 7.8)	7.56 (*J* = 8.5)	7.39 (*J* = 7.5)	8.74 (d, *J* = 5.0)	7.30 (*J* = 4.8)	5.96 (1H, m, C<u>H</u>=CH_2); 5.15 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); 5.02 (1H, d, *J* = 17.8, NCH_2CH=C<u>H</u>-*trans*); 4.94 (2H, s, NCH_2)
1e	16.25	13.23	8.15 (*J* = 8.1)	7.85 (*J* = 7.7)	7.68 (*J* = 8.6)	7.43 (*J* = 7.5)	8.76 (d, *J* = 5.0)	7.29 (*J* = 4.8)	4.27 (2H, t, *J* = 7.3, NCH_2); 1.69 (2H, m, $NCH_2C\underline{H}_2$); 1.00 (3H, t, *J* = 7.2, CH_3)
1f	16.33	13.18	8.13 (*J* = 8.0)	7.81 (*J* = 7.6)	7.64 (*J* = 8.5)	7.42 (*J* = 7.5)	8.75 (d, *J* = 4.9)	7.28 (*J* = 4.7)	4.27 (2H, t, *J* = 7.5, NCH_2); 1.55 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$); 0.91 (3H, t, *J* = 7.3, CH_3)
1g	16.31	13.22	8.15 (*J* = 8.0)	7.84 (*J* = 7.7)	7.67 (*J* = 8.4)	7.40 (*J* = 7.5)	8.73 (d, *J* = 5.0)	7.30 (*J* = 4.7)	4.29 (2H, d, *J* = 7.4, NCH_2); 2.24 (1H, m, CH); 0.96 (6H, d, *J* = 6.7, $2CH_3$)
1h	16.26	13.16	8.14 (*J* = 8.0)	7.83 (*J* = 7.5)	7.66 (*J* = 8.4)	7.40 (*J* = 7.4)	8.74 (d, *J* = 5.0)	7.27 (*J* = 4.7)	4.28 (2H, t, *J* = 7.4, NCH_2); 1.70 (2H, q, *J* = 7.0, $NCH_2C\underline{H}_2$); 1.43 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.90 (3H, t, *J* = 6.9, CH_3)
1i	16.37	13.25	8.14 (*J* = 8.0)	7.83 (*J* = 7.6)	7.62 (*J* = 8.5)	7.39 (*J* = 7.6)	8.74 (d, *J* = 4.9)	7.28 (*J* = 4.8)	4.28 (2H, t, *J* = 7.7, NCH_2); 1.74 (1H, m, CH); 1.50 (2H, q, *J* = 7.6, $NCH_2C\underline{H}_2$); 0.97 (6H, d, *J* = 6.6, $2CH_3$)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
1j	16.30	13.28	8.15 (*J* = 8.0)	7.84 (*J* = 7.6)	7.65 (*J* = 8.5)	7.38 (*J* = 7.5)	8.76 (d, *J* = 4.9)	7.29 (*J* = 4.8)	4.26 (2H, t, *J* = 7.1, NCH_2); 1.68 (2H, q, *J* = 7.0, $NCH_2C\underline{H_2}$); 1.49-1.27 (6H, m, $(C\underline{H_2})_3CH_3$); 0.91 (3H, t, *J* = 6.8, CH_3)
3a	16.04	13.26	8.03 (*J* = 8.1)	7.72 (*J* = 7.8)	7.44 (*J* = 8.3)	7.26 (*J* = 7.6)	8.85 s	—	11.92 (1H, s, NH)
3b	16.23	13.30	8.09 (*J* = 8.0)	7.81 (*J* = 7.6)	7.69 (*J* = 8.4)	7.37 (*J* = 7.5)	8.90 s	—	3.64 (3H, s, NCH_3)
3c	16.15	13.34	8.12 (*J* = 8.0)	7.83 (*J* = 7.7)	7.70 (*J* = 8.6)	7.39 (*J* = 7.5)	8.89 s	—	4.32 (2H, q, *J* = 7.0, NCH_2); 1.23 (3H, t, *J* = 6.9, CH_3)
3d	16.18	13.29	8.10 (*J* = 8.0)	7.81 (*J* = 7.7)	7.68 (*J* = 8.3)	7.36 (*J* = 7.5)	8.82 s	—	5.98 (1H, m, $C\underline{H}=CH_2$); 5.14 (1H, d, *J* = 10.1, $NCH_2CH=C\underline{H}$-*cis*); 5.05 (1H, d, *J* = 17.2, $NCH_2CH=C\underline{H}$-*trans*); 4.97 (2H, s, NCH_2)
3e	16.29	13.35	8.07 (*J* = 7.9)	7.80 (*J* = 7.6)	7.66 (*J* = 8.2)	7.38 (*J* = 7.6)	8.88 s	—	4.25 (2H, t, *J* = 7.1, NCH_2); 1.66 (2H, m, $NCH_2C\underline{H_2}$); 0.97 (3H, t, *J* = 7.0, CH_3)
3f	16.32	13.31	8.13 (*J* = 8.0)	7.83 (*J* = 7.7)	7.67 (*J* = 8.3)	7.35 (*J* = 7.6)	8.86 s	—	4.24 (2H, t, *J* = 7.3, NCH_2); 1.58 (4H, m, $C\underline{H_2}C\underline{H_2}CH_3$); 0.98 (3H, t, *J* = 7.1, CH_3)
3g	16.28	13.24	8.11 (*J* = 8.0)	7.78 (*J* = 7.6)	7.71 (*J* = 8.4)	7.39 (*J* = 7.5)	8.88 s	—	4.26 (2H, d, *J* = 7.3, NCH_2); 2.20 (1H, m, CH); 0.98 (6H, d, *J* = 6.7, $2CH_3$)
3h	16.26	13.27	8.10 (*J* = 8.0)	7.82 (*J* = 7.6)	7.70 (*J* = 8.3)	7.40 (*J* = 7.4)	8.85 s	—	4.25 (2H, t, *J* = 7.4, NCH_2); 1.68 (2H, q, *J* = 6.9, $NCH_2C\underline{H_2}$); 1.47 (4H, m, $(C\underline{H_2})_2CH_3$); 0.95 (3H, t, *J* = 6.9, CH_3)
3i	16.30	13.30	8.12 (*J* = 8.1)	7.79 (*J* = 7.6)	7.68 (*J* = 8.2)	7.38 (*J* = 7.6)	8.87 s	—	4.30 (2H, t, *J* = 7.5, NCH_2); 1.72 (1H, m, CH); 1.53 (2H, q, *J* = 7.4, $NCH_2C\underline{H_2}$); 0.99 (6H, d, *J* = 6.8, $2CH_3$)
3j	16.33	13.32	8.11 (*J* = 8.0)	7.80 (*J* = 7.7)	7.65 (*J* = 8.3)	7.34 (*J* = 7.5)	8.84 s	—	4.28 (2H, t, *J* = 7.2, NCH_2); 1.71 (2H, q, *J* = 7.1, $NCH_2C\underline{H_2}$); 1.47–1.28 (6H, m, $(C\underline{H_2})_3CH_3$); 0.98 (3H, t, *J* = 6.9, CH_3)

Formation of these strong hydrogen bonds also leads to redistribution of the electron density in the quinolone fragment as indicated by lengthening of the bonds O(1)–C(9) 1.244(2) and O(3)–C(10) 1.251(2) Å (when compared with their mean value [21] 1.210 Å) and C(7)–C(8) 1.376(2) Å (mean value 1.326 Å) and also shortening of the bonds O(2)–C(7) 1.326(2) (1.362) and C(8)–C(9) 1.449(2) Å (1.455 Å). The pyrimidine substituent has an *ap*-type conformation relative to the C(8)–C(10) bond and is somewhat twisted relative to the C(10)–N(2) bond (torsional angles C(11)–N(2)–C(10)–(C8) 173.9(1)º and C(10)–N(2)–C(11)–N(3) -13.2(2)º) which is likely explained by repulsion between the carbamide group oxygen atom and the aromatic ring (shortened intramolecular contact N(3)···O(3) 2.76 Å, sum of van der Waal radii [22] 2.79 Å). This repulsion evidently causes lengthening of the N(2)–C(11) bond 1.399(3) Å when compared with its mean value of 1.380 Å.

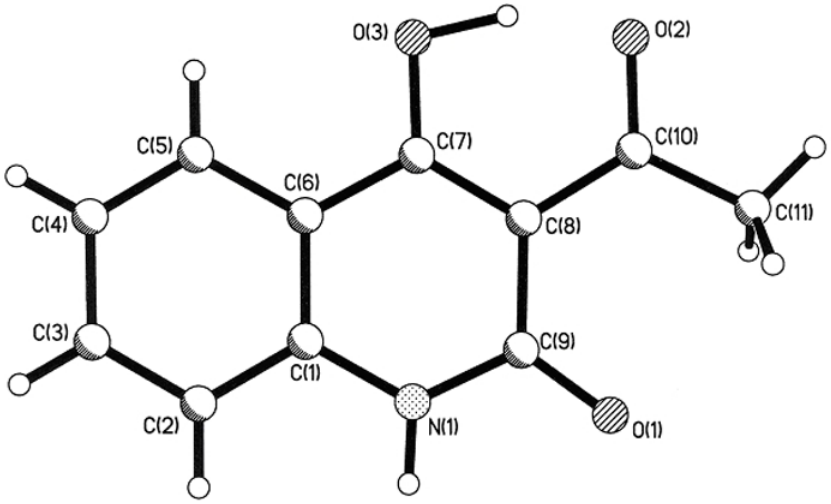


Fig. 1. Structure of the pyrimidin-2-ylamide **1c** molecule with atomic numbering.

Rather powerful repulsion between the ethyl substituent on the N(1) atom and the quinolone fragment [shortened intramolecular contacts H(2)···C(15) 2.53 (2.87), H(2)···H(15a) 2.05 (2.34), H(15a)···C(2) 2.58 (2.87), H(15b)···O(1) 2.28 (2.46), and H(16c)···C(2) 2.85 Å (2.87 Å] lead to lengthening of the bonds N(1)–C(9) 1.386(2) and N(1)–C(1) 1.390(2) Å when compared with their mean values of 1.353 and 1.371 Å respectively and this has been observed in previously studied quinolone series compounds. An alkyl substituent is placed such that the C(15)–C(16) bond is virtually perpendicular to the plane of the bicyclic fragment (torsional angle C(9)–N(1)–C(15)–C(16) 95.5(2)º).

In the crystal the pyrimidin-2-ylamide **1c** molecules forms two types of layer. The first layer is parallel to the crystallographic plane (1 1 0) and the second to the plane (-1 1 1). Molecules within the layer are bound by weak intermolecular hydrogen bonding C(12)–H(12)···O(3)' (1-*x*, -*y*, -*z*) H···O 2.43 Å, C–H···O 159º.

It is most likely that the reason for the failure of bromination of the pyrimidin-2-ylamide **1c** is that it undergoes a pyridine type reaction [23] with bromine to form a rather unreactive perbromide **4c** which readily decomposes upon further separation and purification. Experimental confirmation for such a conclusion was achieved by changing the synthesis conditions where the reaction mass formed by the bromine addition was initially refluxed to decolorization before addition of water (about 3 h). A comparative analysis of the ^{1}H NMR spectra obtained for this compound and for the amides **1c** and **3c** (i.e. substances with a well established structure) showed that the situation changes sharply and the bromination does occur and the content of the bromo-substituted derivative in the mixture reaches about 40%. Electrophilic attack is seen exclusively at position 5 in the pyrimidine ring. The occurrence of bromination was confirmed by mass spectrometry and its

TABLE 3. Bond lengths (*l*) in the Pyrimidin-2-ylamide **1c** Structure

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(9)	1.386(2)	N(1)–C(1)	1.390(2)
N(1)–C(15)	1.470(2)	N(2)–C(10)	1.348(2)
N(2)–C(11)	1.399(2)	N(3)–C(11)	1.327(2)
N(3)–C(12)	1.332(2)	N(4)–C(11)	1.329(2)
N(4)–C(14)	1.336(2)	O(1)–C(9)	1.244(2)
O(2)–C(7)	1.326(2)	O(3)–C(10)	1.251(2)
C(1)–C(6)	1.399(2)	C(1)–C(2)	1.401(2)
C(2)–C(3)	1.365(2)	C(3)–C(4)	1.383(2)
C(4)–C(5)	1.373(2)	C(5)–C(6)	1.397(2)
C(6)–C(7)	1.443(2)	C(7)–C(8)	1.376(2)
C(8)–C(9)	1.449(2)	C(8)–C(10)	1.470(2)
C(12)–C(13)	1.359(2)	C(13)–C(14)	1.360(2)
C(15)–C(16)	1.505(2)		

TABLE 4. Valence angles (ω) in the Pyrimidin-2-ylamide **1c** Structure

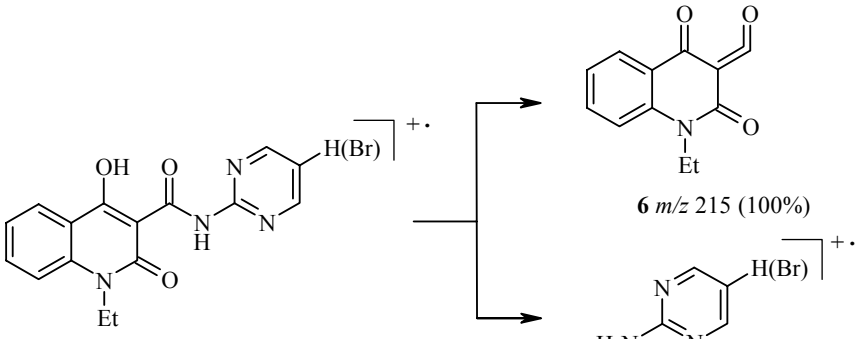
Valence angle	ω, deg.	Valence angle	ω, deg.
C(9)–N(1)–C(1)	122.9(1)	C(9)–N(1)–C(15)	117.0(1)
C(1)–N(1)–C(15)	120.0(1)	C(10)–N(2)–C(11)	129.0(1)
C(11)–N(3)–C(12)	115.2(1)	C(11)–N(4)–C(14)	114.6(1)
N(1)–C(1)–C(6)	119.8(1)	N(1)–C(1)–C(2)	121.9(1)
C(6)–C(1)–C(2)	118.3(1)	C(3)–C(2)–C(1)	120.2(2)
C(2)–C(3)–C(4)	121.6(2)	C(5)–C(4)–C(3)	119.2(2)
C(4)–C(5)–C(6)	120.3(2)	C(5)–C(6)–C(1)	120.3(1)
C(5)–C(6)–C(7)	121.1(1)	C(1)–C(6)–C(7)	118.6(1)
O(2)–C(7)–C(8)	122.0(1)	O(2)–C(7)–C(6)	117.1(1)
C(8)–C(7)–C(6)	120.9(1)	C(7)–C(8)–C(9)	120.0(1)
C(7)–C(8)–C(10)	118.0(1)	C(9)–C(8)–C(10)	122.1(1)
O(1)–C(9)–N(1)	118.9(1)	O(1)–C(9)–C(8)	123.4(1)
N(1)–C(9)–C(8)	117.7(1)	O(3)–C(10)–N(2)	122.5(1)
O(3)–C(10)–C(8)	119.9(1)	N(2)–C(10)–C(8)	117.6(1)
N(3)–C(11)–N(4)	127.5(1)	N(3)–C(11)–N(2)	119.3(1)
N(4)–C(11)–N(2)	113.2(1)	N(3)–C(12)–C(13)	122.6(2)
C(12)–C(13)–C(14)	117.2(2)	N(4)–C(14)–C(13)	122.9(2)
N(1)–C(15)–C(16)	112.0(1)		

course by chromato mass spectrometry. Although in the latter case not one of the components in the analyzed mixture could survive column gas chromatography without degradation it was, none the less, found that only one contained a bromine fragment and this proved to be 2-amino-5-bromopyrimidine. It was identified by comparison of the experimental spectrum with that taken from an internal mass spectrometry library of standard samples.

From this discussion it follows that the synthesis of the 5-bromopyridin-2-ylamides **3a-j** by bromination of the unsubstituted analogs **1a-j** with bromine is actually possible but demands a significant modification. However, for one of the pyrimidin-2-ylamides (in fact the 1-allyl derivative **1d**) a similar scheme cannot be realized in principle. In contrast to the examples discussed before this compound is brominated very readily, the reaction occurring virtually instantaneously (even at room temperature).

A characteristic features of the mass spectra of the pyrimidin- and 5-bromopyrimidin-2-ylamides of the 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids (**1c** and **3c**) is the initial cleavage of the

hetarylamide bond under electron impact conditions. The ability of the 4-hydroxyquinolin-2-ones to undergo ready conversion to the tautomeric 2,4-dioxo form infers that the decomposition of the molecular ions of amides **1c** and **3c** occurs principally as a ketene type to form two kinds of fragment ions: i.e. ketene **6** with *m/z* 215 and the radical cations of the 2-aminopyrimidines **7a** and **7b** with *m/z* 95 and 173/175 respectively.



1c *m/z* 310 (35.8%),
3c *m/z* 388/390 (18.1/17.0%)

7a *m/z* 95 (21.8),
7b *m/z* 173/175 (25.0/23.1%)

Degradation of the molecular ion of the product of bromination of the 1-allyl derivative under the same conditions clearly follows three routes. Judged by the peak intensities the major route also begins with cleavage of the amide bond, not *via* a ketene type since this is unlikely on structural grounds. A further distinguishing feature is that the bromine atom remains not in the amine fragment but rather in the acylium cation **8** with *m/z* 306/308 which can form the methyleneoxazoloquinolone **10** after initial loss of CO and elimination of HBr. However, according to the ^{1}H NMR spectra, the chemical transformation discussed involves neither the pyrimidine ring nor the benzene part of the quinolone molecule. Only the 1-allyl substituent undergoes a significant change. Collation of all these factors is the basis for our proposal that, according to the properties reported, the structure can only be the 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid pyrimidin-2-ylamide (**5**).

The probability of the second fragmentation route for the molecular ion of the amide **5** is approximately four times less than the first. While leading to the above mentioned radical cation of the methyleneoxazoloquinolone **10** it initially loses HBr (typical of bromine-containing organic compounds) and then in stages eliminates 2-aminopyrimidine from amide **11** and CO from the acyl fragment **12**.

Also occurring, but least likely, is a third degradation route for the molecular ion of amide **5** and this deserves individual attention because of the primary elimination of CO (unusual for 4-hydroxy-2-quinolones), the source of which is the 4-carbonyl group of the pyridone ring. This feature again indicates that the basis for the studied compound lies not in a 4-hydroxy-1,2-dihydroquinoline ring for the starting amide **1d** but a 4-oxo-1,4-dihydroquinoline. Hence a decision regarding the structure of amide **5** was made right. Further degradation of the primary fragmentation ion formed from the 2-bromomethyl-2,3-dihydrooxazolo[3,2-*a*]indole-9-carboxylic acid pyrimidin-2-ylamide (**13**) occurs by the usual scheme of loss of HBr, cleavage of the amide bond in the methyleneoxazoloindole **14**, and decarbonylation of cation **15**.

By analogy with previous investigations [24, 25] the ^{1}H NMR spectrum (in particular the "aliphatic" region) suggests that bromination of the allyl derivative **1d** is accompanied by heterocyclization to form the amide **5**. The weightiest argument supporting the proposed structure comes from analysis of the 2D NOESY spectrum and through HMBC heteronuclear correlation spectroscopy. In particular, the NOESY spectrum showed that the proton signals for one of the methylene groups at 4.75 and 4.35 ppm has a strong NOE with the aromatic signal at 7.55 ppm. This points to the steric proximity of the indicated protons and this is only possible if the oxazolidine ring is joined at the "*a*" edge of the 4-quinolinone.

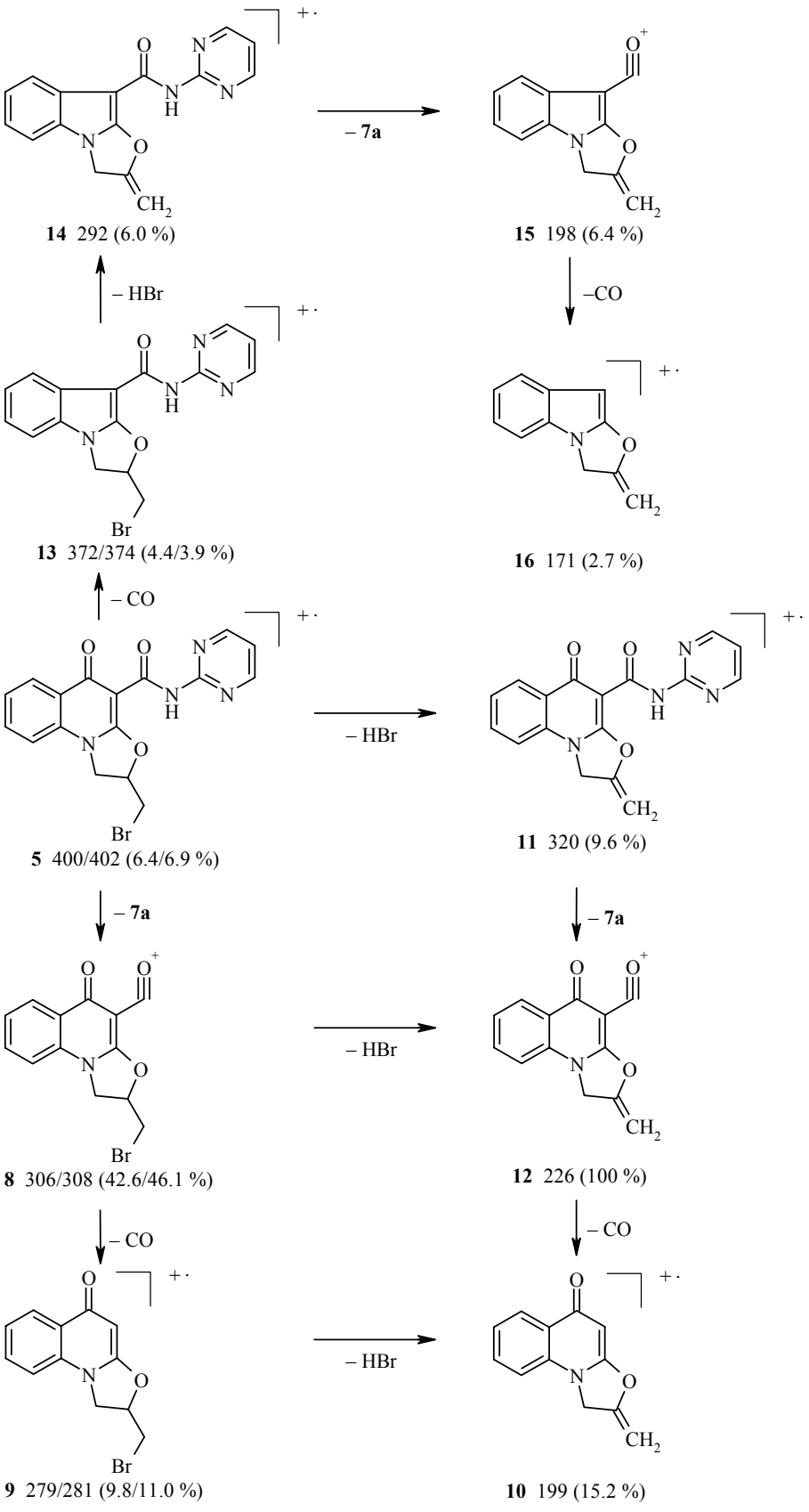
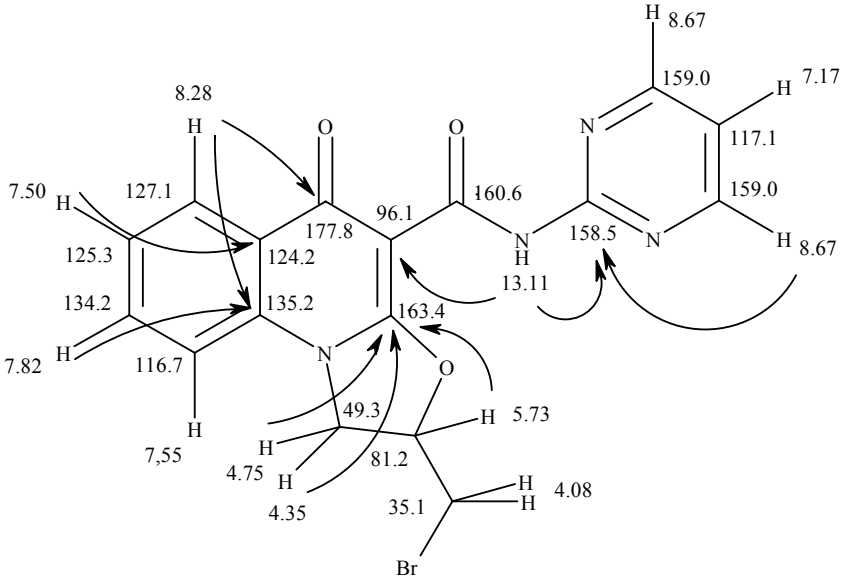

– 7a
14 292 (6.0 %)
15 198 (6.4 %)
– HBr
–CO
13 372/374 (4.4/3.9 %)
16 171 (2.7 %)
– CO
– HBr
5 400/402 (6.4/6.9 %)
11 320 (9.6 %)
– 7a
– 7a
– HBr
8 306/308 (42.6/46.1 %)
12 226 (100 %)
– CO
– CO
– HBr
9 279/281 (9.8/11.0 %)
10 199 (15.2 %)

TABLE 5. Full Listing of Heteronuclear $^{1}H–^{13}C$ Correlations found for the Oxazoloquinoline **5**

^{1}H signal, δ, ppm	^{13}C Cross peaks observed, δ, ppm	
	HMQC	HMBC
13.11	—	158.5; 96.1
8.67	159.0	158.5; 117.1
8.28	127.1	135.2; 134.2; 177.8
7.82	134.2	135.2; 127.1; 116.7
7.55	116.7	125.3; 124.2; 177.8
7.50	125.3	135.2; 134.2; 127.1; 124.2; 116.7
7.17	117.1	159.0
5.73	81.2	35.1; 163.4
4.75	49.3	81.2; 35.1; 163.4
4.35	49.3	81.2; 35.1; 163.4
4.08	35.1	81.2; 49.3

Cross peaks were observed for the heteronuclear correlations in the HMBC and HMQC spectra and these are presented in Table 5.

These HMBC and HMQC spectroscopic cross peaks permit a safe interpretation of all of the carbon signals. The diagram in Table 5 shows the $^{1}H–^{13}C$ heteronuclear correlations found for the compound studied and the arrows indicate the important HMBC correlations which serve as the basis for the assignments made.



The presence of the oxazolidine fragment annelated to the 4-quinolinone in the molecule studied is confirmed by the cross peaks seen between the C(3a) atom with a chemical shift of 163.4 ppm and the signals for the N-methylene unit protons and the CH proton placed next to the heterocyclic oxygen atom. Localization of the pyrimidin-2-ylaminocarbonyl substituent follows from the correlation between the NH proton signal and the neighboring carbon atoms. From the point of view of the chemical structure the chemical shift of the C(4) at 96.1 ppm is highly indicative as it occurs within the pyrid-4-one ring and is between two carbonyl groups. Almost the same chemical shifts were also found earlier in other oxazoloquinolines closely related in structure [24, 25].

Hence the bromination with molecular bromine of 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**1d**) is accompanied by heterocyclization to give the pyrimidin-2-ylamide **5**. Meanwhile, the high rate of this reaction does not make possible a full confirmation that it has to occur *via* intermediate formation of the corresponding perbromide **4**. Nevertheless, an alternative mechanism in which bromine directly attacks the double bond of the 1-allyl substituent in amide **1d** also remains in question.

The ability of the synthesized compounds to inhibit the growth of *Mycobacterium tuberculosis* H37Rv ATCC 27294 *in vitro* has been studied radiometrically [26, 27] within the framework of the International TAACF program (Tuberculosis Antimicrobial Acquisition and Coordinating Facility). The microbiological screening data at a concentration of 12.5 μg/ml for the pyrimidin-2-ylamide unsubstituted at position 1 (**1a**) and its close homologs **1b-e** presented in Table 1 shows that they have no antitubercular properties at all. Weak activity appears beginning with the butyl derivative **1f** and further lengthening of the hydrocarbon chain in the 1-alkyl substituent gives a rapid increase reaching a virtual maximum in the 1-hexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**1j**) where the growth of the tubercular mycobacterium is inhibited by 99%. There is an extremely significant effect for 1-alkylsubstituents upon the antitubercular properties of the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides as a whole, the same course again being followed (although not decisive). Undoubtedly much high activity in such compounds depends of the structure of the amide part of the molecule. Hence, against expectations, it turned out that a bromine atom in position 5 of the pyrimidine ring (compounds **3a-j**) completely deactivated the molecule.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra for the oxazoloquinoline **5**, 2D COSY ^{1}H NMR experiments, the homonuclear NOESY-2D Overhauser effect, and the heteronuclear HMQC and HMBC spectra were taken on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively for ^{1}H and ^{13}C). All 2D experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequences were $^1J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz respectively. The numbers of increments in the COSY and HMQC experiments were 128 and in the HMBC spectra 400. The mixing time in the NOESY-2D experiment was 500 msec. The ^{1}H NMR spectra of the remaining compounds were recorded on a Varian Mercury-VX-200 instrument (200 MHz). In all cases the solvent was DMSO-d_6 and the internal standard TMS. Mass and chromato-mass spectroscopic investigations were made on a Varian 1200L instrument in full scanning mode in the range 35-700 *m/z* with an electron impact ionization of 70 eV introducing the sample either directly or *via* the gas chromatograph. The parameters for the CP-SIL 8CB chromatographic column were: length 50 m, internal diameter 0.25 mm, stationary phase polysiloxane film (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm, gas carrier helium, injector temperature 300ºC, and ion source temperature 250ºC.

The amidation of the ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **2a-j** by 2-aminopyrimidine or 2-amino-5-bromopyrimidine was carried out as described in a previous method [18].

1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 5-Bromopyrimidin-2-ylamide (3c). A solution of bromine (0.52 ml, 0.01 mol) in glacial acetic acid (5 ml) was added to a solution of 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**1c)** (3.10 g, 0.01 mol) in the same solvent (50 ml). A light-orange precipitate was formed immediately but dissolved upon subsequent heating. The reaction mixture was refluxed to decolorization (about 3 h) after which it was cooled, diluted with cold water, and Na_2CO_3 was added to pH ~ 5.5. The precipitate was filtered off, washed with water, dried, and crystallized from a mixture of DMF and acetone. According to ^{1}H NMR data the product contains 40% of the 5-bromopyrimidin-2-ylamide **3c**, the other 60% being the starting unsubstituted pyrimidin-2-ylamide **1c**.

Water treatment of the reaction mixture formed immediately after mixing the starting reagents and recrystallization of the obtained material from the DMF acetone mixture gave only the starting pyridimin-2-ylamide **1c**.

X-ray Structural Study. Crystals of the pyrimidin-2-ylamide **1c** are monoclinic (mixture of DMF and acetone); at 20ºC: a = 7.765(1), b = 10.589(1), c = 17.902(2) Å, β = 99.77(1)º, V = 1460.6(2) Å^3, M_r = 310.31, Z = 4, space group $P2_1/n$, d_{calc} = 1.421 g/cm^3, μ(MoKα) = 0.102 mm^{-1}, F(000) = 648. Unit cell parameters and intensities of 12 071 reflections (4193 independent with R_{int} = 0.032) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 60º).

The structure was solved by a direct method using the SHELXTL program package [28]. The positions of the hydrogen atoms were revealed through electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ (n = 1.5 for a methyl group and n = 1.2 for remaining hydrogen atoms). The positions of the hydrogen atoms taking part in hydrogen bonding were refined in the isotropic approximation for non-hydrogen atoms to wR_2 = 0.093 for 4123 reflections (R_1 = 0.039 for 1582 reflections with $F > 4\sigma$ (F), S = 0.735). The full crystallographic information has been placed in the Cambridge structural database, reference CCDC 672207. Interatomic distances and valence angles are given in Tables 3 and 4.

2-Bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic acid pyrimidin-2-ylamide (5). A solution of bromine (0.52 ml, 0.01 mol) in glacial acetic acid (5 ml) was added to a solution of the 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**1d)** (3.22 g, 0.01 mol) in the same solvent (40 ml). Decolorization of the bromine occurred virtually instantly. The reaction mixture was diluted with water, Na_2CO_3 was added in small portions to pH ~ 5.5, and the solution was allowed to stand at room temperature for 12-14 h. The precipitated pyrimidin-2-ylamide **5** was filtered off, washed with water, and dried. Yield 2.76 g (69%); mp 170-172ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 13.11 (1H, s, NH); 8.67 (2H, d, J = 4.5, H-4',6' pyrimidine); 8.28 (1H, d, J = 7.8, H-6); 7.82 (1H, t, J = 7.6, H-8); 7.55 (1H, d, J = 8.2, H-9); 7.50 (1H, t, J = 7.4, H-7); 7.17 (1H, t, J = 4.6, H-5' pyrimidine); 5.73 (1H, m, $NCH_2C\underline{H}O$); 4.75 (1H, dd, J = 9.8 and J = 9.8, NCH); 4.35 (1H, dd, J = 9.8 and J = 6.7, NCH); 4.08 (2H, m, CH_2Br). ^{13}C NMR spectrum, δ, ppm: 177.8 (5-C=O), 163.4 (C-3a), 160.6 (CONH), 159.0 (C-4',6' pyrimidine), 158.5 (C-2' pyrimidine), 135.2 (C-9a), 134.2 (C-8), 127.1 (C-6), 125.3 (C-7), 124.2 (C-5a), 117.1 (C-5' pyrimidine), 116.7 (C-9), 96.1 (C-4), 81.2 ($NCH_2\underline{C}HO$), 49.3 (NCH_2), 35.1 (CH_2Br). Mass spectrum, m/z (I_{rel}, %): 400 $[M]^+$ (6.4), 372 $[M\text{-}CO]^+$ (4.4), 320 $[M\text{-}HBr]^+$ (9.6), 306 [M-2-aminopyrimidine]$^+$ (42.6), 292 $[M\text{-}CO\text{-}HBr]^+$ (6.0), 279 [M-2-aminopyrimidine-CO]$^+$ (9.8), 226 [M-HBr-2-aminopyrimidine]$^+$ (100), 199 [M-HBr-2-aminopyrimidine-CO]$^+$ (15.2), 198 [M-CO-HBr-2-aminopyrimidine]$^+$ (6.4), 171 [M-CO-HBr-2-aminopyrimidine-CO]$^+$ (2.7). Values for m/z are given only for the ^{79}Br isotope. Found, %: C 50.73; H 3.13; N 13.85. $C_{17}H_{13}BrN_4O_3$. Calculated, %: C 50.89; H 3.27; N 13.96.

The authors express their thanks to the National Institute for Allergy and Infective Diseases (USA) for studying the antitubercular properties of the compounds we have prepared (contract No. 01-AI-45246).

REFERENCES

1. I. V. Ukrainets, N. L. Bereznyakova, and V. A. Parshikov, *Khim. Geterotsikl. Soedin.*, 426 (2009). [*Chem. Heterocycl. Comp.*, **45**, 345 (2009)].
2. A. F. Pozharskii and A. T. Soldatenkov, *Ring Molecules* [in Russian], Khimiya (1993).
3. D. J. Brown, in: A. R. Katritzky and C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry on CD-ROM: 7- Volume Set*, Volume 3, Elsevier, Oxford (1997), p. 142.
4. A. Kleemann and J. Engel, *Pharmaceutical Substances. Synthesis, Patents, Applications, Multimedia Viewer, Version 2.00*, Georg Thieme Verlag, Stuttgart (2001).
5. A. M. Youssef and E. Noaman, *Arzneimittelforschung*, **57**, 547 (2007).
6. B. Almirante and D. Rodriguez, *Paediatr. Drugs*, **9**, 311 (2007).

7. K. Sugaya, Y. D. Kwak, O. Ohmitsu, A. Marutle, N. H. Greig, and E. Choumrina, *Curr. Alzheimer Res.*, **4**, 370 (2007).
8. A. M. Dougherty, H. Guo, G. Westby, Y. Liu, E. Simsek, J. T. Guo, A. Mehta, P. Norton, B. Gu, T. Block, and A. Cuconati, *Antimicrob. Agents Chemother.*, **51**, 4427 (2007).
9. A. Mai, M. Artico, D. Rotili, D. Tarantino, I. Clotet-Codina, M. Armand-Ugón, R. Ragno, S. Simeoni, G. Sbardella, M. B. Nawrozkij, A. Samuele, G. Maga, and J. A. Este, *J. Med. Chem.*, **50**, 5412 (2007).
10. S. Benzaria, D. Bardiot, T. Bouisset, C. Counor, C. Rabeson, C. Pierra, R. Storer, A. G. Loi, A. Cadeddu, M. Mura, C. Musiu, M. Liuzzi, R. Loddo, S. Bergelson, V. Bichko, E. Bridges, E. Cretton-Scott, J. Mao, J. P. Sommadossi, M. Seifer, D. Standring, M. Tausek, G. Gosselin, and P. La Colla, *Antivir. Chem. Chemother.*, **18**, 225 (2007).
11. M. Johar, T. Manning, D. Y. Kunimoto, and R. Kumar, *Bioorg. Med. Chem.*, **13**, 6663 (2005).
12. D. Sriram, T. R. Bal, and P. Yogeeswari, *Med. Chem.*, **1**, 277 (2005).
13. N. C. Srivastav, T. Manning, D. Y. Kunimoto, and R. Kumar, *Med. Chem.*, **2**, 287 (2006).
14. D. Rai, M. Johar, N. C. Srivastav, T. Manning, B. Agrawal, D. Y. Kunimoto, and R. Kumar, *J. Med. Chem.*, **50**, 4766 (2007).
15. M. H. R. I. El-Hamamsy, A. W. Smith, A. S. Thompson, and M. D. Threadgill, *Bioorg. Med. Chem.*, **15**, 4552 (2007).
16. A. Talukdar, B. Illarionov, A. Bacher, M. Fischer, and M. Cushman, *J. Org. Chem.*, **72**, 7167 (2007).
17. I. V. Ukrainets, S. A. El' Kayal', O. V. Gorokhova, L. V. Sidorenko, and T. V. Alekseeva, *Visnik Farmatsii*, No. 1 (37), 12 (2004).
18. I. V. Ukrainets, E. V. Mospanova, and L. V. Sidorenko, *Khim. Geterotsikl. Soedin.*, 1023 (2007). [*Chem. Heterocycl. Comp.*, **43**, 863 (2007)].
19. I. V. Ukrainets, A. A. Tkach, L. V. Sidorenko, and O. V. Gorokhova, *Khim. Geterotsikl. Soedin.*, 1508 (2006). [*Chem. Heterocycl. Comp.*, **42**, 1301 (2006)].
20. Amzhad Abu Sharkh, Diss. Cand. Pharm. Sci, Kharkiv (2003).
21. H.-B. Burgi and J. D. Dunitz, *Structure Correlation*, Vol. 2, VCH, Weinheim (1994), p. 741.
22. Yu. V. Zefirov, *Kristallografiya*, **42**, 936 (1997).
23. L. Fieser and M. Fieser, *Reagents for Organic Synthesis* [Russian translation], Vol. 3, Mir, Moscow (1970), p. 115.
24. I. V. Ukrainets, N. L. Bereznyakova, A. V. Turov, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 1034 (2007). [*Chem. Heterocycl. Comp.*, **43**, 871 (2007)].
25. I. V. Ukrainets, N. L. Bereznyakova, O. V. Gorokhova, A. V. Turov, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 1180 (2007). [*Chem. Heterocycl. Comp.*, **43**, 1001 (2007)].
26. L. B. Heifets, in: L. B. Heifets (editor), *Drug Susceptibility in the Chemotherapy of Mycobacterial Infections*, CRC Press, Boca Raton (1991), p. 89.
27. C. B. Inderleid and K. A. Nash, in: V. Lorian (editor), *Antibiotics in Laboratory Medicine*, Williams and Wilkins, Baltimore (1996), p. 127.
28. G. M. Sheldrick, *SHELXTL PLUS. PC Version. A System of Computer Programs for the Determination of Crystal Structure from X-ray Diffraction Data*, Rev. 5.1 (1998).