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4-HYDROXY-2-QUINOLONES. 168*. SYNTHESIS, CHEMICAL AND ANTITUBERCULAR PROPERTIES OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID PYRAZIN-2-YLAMIDES

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1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrazin-2-ylamides have been synthesized as potential antitubercular agents. In contrast to pyrimidin-2-ylamides the compounds prepared are brominated by molecular bromine in glacial acetic acid at position 6 of the quinolone ring rather than in the amide part of the molecule. The 1-N-allyl derivative behaves similarly but undergoes halocyclization to give 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic acid pyrazin-2-ylamide. A comparative analysis of the antimycobacterial properties of the synthesized compounds and their isomeric pyrimidin-2-ylamides has been carried out.

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

In searching for novel chemotherapeutic agents suitable for treatment of many human infectious illnesses special interest has been paid to pyrazine derivatives. Based on this heterocycle efficient preparations have been created relating to different types of both aerobic and anaerobic bacteria [2-4] and to viruses (influenza [5], yellow fever [6], arenoviruses [7], HIV [8] etc). The reported high antitubercular activity of the unsubstituted amide and the 4-morpholylmethylamide of pyrazine-2-carboxylic acids (known under the names pyrazinamide and morinamide respectively [9]) has strongly stimulated a generally successful search for novel antimycobacterial medicinal agents amongst their structural analogs [10-15]. It is also interesting that many preparations containing a pyrazine ring have long been used medicinally for totally different indications, e.g. the diuretic amiloride and the antihypertensive benzamil where testing also showed them to be very good antitubercular agents [16].

Based on this, it was totally logical and seemed promising also to involve 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrazin-2-ylamides **1a-m** within the scope of studies of potential antitubercular agents which we carried out several years ago, in particular because high activity had already been repeatedly confirmed before in closely structurally related compounds.

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* For Communication 167 see [1].

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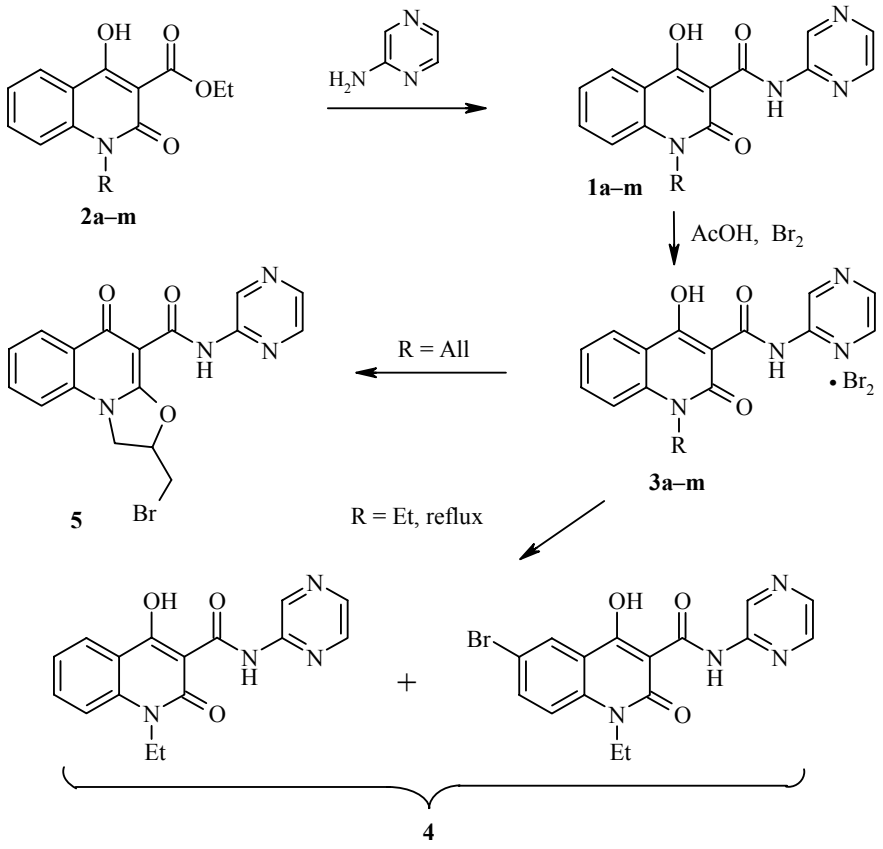
The target pyrazin-2-ylamides **1a-m** (Table 1) were prepared by amidation of the corresponding ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **2a-m** with 2-aminopyrazine using a known method [17]. Their structure was confirmed from their ^{1}H NMR spectra (Table 2), the distinguishing feature of which being the aromatic region. The assignment of signals in this part of the spectrum does not generally present a problem despite the fact that several of them have an unusual appearance. Hence, for example, the quinoline ring gives a set of doublets and triplets of intensity of 1H each typical of an ABCD system. However, the pyrazine fragment unexpectedly shows only two singlets of one proton (H-3) and two protons (H-5 and H-6) where in the latter case the signals at least for H-5 and H-6 should be observed as two separate doublets with a characteristically small α-pyridine type vicinal spin-spin coupling.



1–3 a R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = C_3H_7, **f** R = C_4H_9, **g** R = *i*-C_4H_9, **h** R = C_5H_{11}, **i** R = *i*-C_5H_{11}, **j** R = C_6H_{13}, **k** R = C_7H_{15}, **l** R = C_8H_{17}, **m** R = C_9H_{19}

Similarly to the 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamides we have previously reported [18], treatment of pyrazin-2-ylamides **1** with saturated 1-N-alkyl substituents in glacial acetic acid medium with molecular bromine gives light-orange crystalline precipitates which are evidently the perbromides **3a-m**. 2-Aminopyrazines can be halogenated in the *para* position to the amino group [19] so subsequent refluxing of the reaction mixture (as in the case of the pyrimidin-2-ylamides [18]) would logically be expected to brominate the amide part of the molecule, i.e. to convert the perbromides **3a-m** to the 5-bromopyrazin-2-ylamides of the corresponding quinoline-3-carboxylic acids.

In the experiments carried out on the 1-N-ethyl-substituted amide **1c** it was found that the separated colorless compound **4** actually contains halogen as indicated by a positive Beilstein test. At the same time the ^{1}H NMR spectra of this compound and its synthetic precursor **1c** appeared to be completely identical.

TABLE 1. Characteristics of the 1-R-4-Hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic Acids Pyrazin-2-ylamides **1a-m**

Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	Yield, %	Antitubercular activity. Inhibition of the growth of *M. tuberculosis*, %
		C	H	N			
1a	$C_{14}H_{10}N_4O_3$	59.48 / 59.57	3.49 / 3.57	19.72 / 19.85	296 (decomp.)	93	96
1b	$C_{15}H_{12}N_4O_3$	60.70 / 60.81	3.96 / 4.08	18.83 / 18.91	215-217	95	100
1c	$C_{16}H_{14}N_4O_3$	61.82 / 61.93	4.47 / 4.55	17.94 / 18.05	187-189	91	0
1d	$C_{17}H_{14}N_4O_3$	63.46 / 63.35	4.45 / 4.38	17.50 / 17.38	210-212	93	0
1e	$C_{17}H_{16}N_4O_3$	63.07 / 62.95	5.10 / 4.97	17.19 / 17.27	191-193	89	2
1f	$C_{18}H_{18}N_4O_3$	63.98 / 63.89	5.49 / 5.36	16.68 / 16.56	148-150	90	74
1g	$C_{18}H_{18}N_4O_3$	63.77 / 63.89	5.26 / 5.36	16.43 / 16.56	176-178	91	7
1h	$C_{19}H_{20}N_4O_3$	64.85 / 64.76	5.86 / 5.72	15.98 / 15.90	129-131	85	100
1i	$C_{19}H_{20}N_4O_3$	64.88 / 64.76	5.85 / 5.72	16.04 / 15.90	134-136	87	91
1j	$C_{20}H_{22}N_4O_3$	65.44 / 65.56	5.93 / 6.05	15.36 / 15.29	113-115	89	100
1k	$C_{21}H_{24}N_4O_3$	66.45 / 66.30	6.48 / 6.36	14.60 / 14.73	92-94	84	100
1l	$C_{22}H_{26}N_4O_3$	67.11 / 66.99	6.78 / 6.64	14.33 / 14.20	95-97	82	5
1m	$C_{23}H_{28}N_4O_3$	67.76 / 67.63	7.05 / 6.91	13.62 / 13.72	88-90	85	100

* Crystallization solvent: DMF (compounds **1a-c**) and ethanol (compounds **1d-m**).

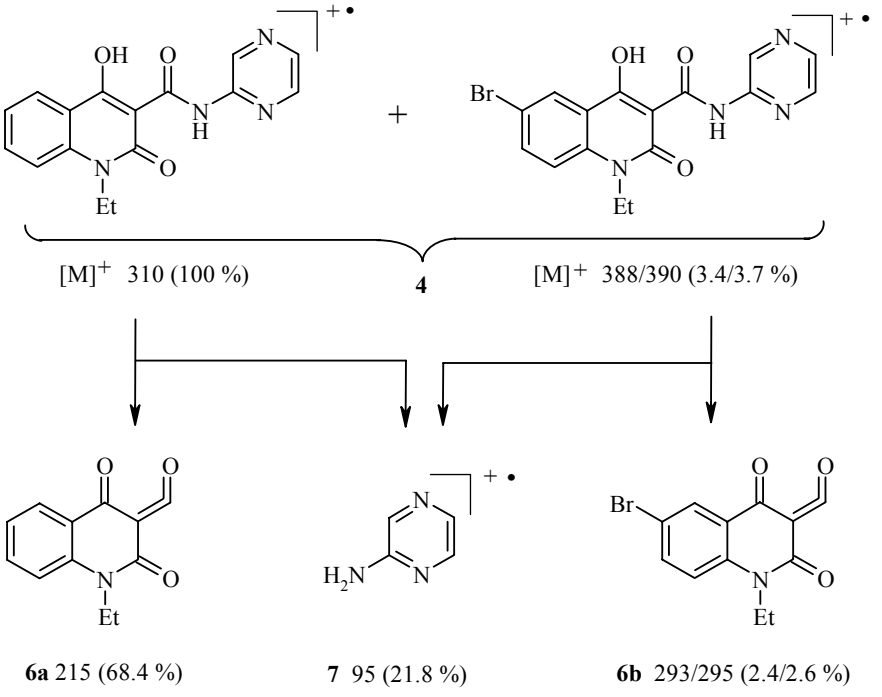


TABLE 2. ^{1}H NMR Spectra of the 1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids Pyrazin-2-ylamides **1a-m**

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	OH (1H, s)	OH (1H, s)	Quinolone ring				Pyrazine ring		R
			H-5 (1H, d)	H-7 (1H, t)	H-8 (1H, d)	H-6 (1H, t)	H-3' (1H, s)	H-5',6' (2H, s)	
1a	15.78	13.11	8.01 (*J* = 8.0)	7.65 (*J* = 7.8)	7.44 (*J* = 8.5)	7.25 (*J* = 7.5)	9.50	8.41	12.00 (1H, s, NH)
1b	15.92	13.06	8.19 (*J* = 7.9)	7.81 (*J* = 7.8)	7.60 (*J* = 8.4)	7.39 (*J* = 7.4)	9.49	8.40	3.74 (3H, s, NCH_3)
1c	15.73	13.23	8.17 (*J* = 8.0)	7.85 (*J* = 7.8)	7.71 (*J* = 8.5)	7.40 (*J* = 7.5)	9.48	8.47	4.34 (2H, q, *J* = 7.0, NCH_2); 1.24 (3H, t, *J* = 7.0, CH_3)
1d	15.79	13.08	8.14 (*J* = 7.9)	7.80 (*J* = 7.8)	7.56 (*J* = 8.4)	7.40 (*J* = 7.4)	9.40	8.46	5.96 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.7, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.7, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2)
1e	15.91	13.10	8.18 (*J* = 8.0)	7.82 (*J* = 7.8)	7.59 (*J* = 8.5)	7.45 (*J* = 7.5)	9.49	8.41	4.30 (2H, t, *J* = 7.4, NCH_2); 1.78 (2H, m, $NCH_2C\underline{H}_2$); 1.09 (3H, t, *J* = 7.1, CH_3)
1f	15.93	13.11	8.20 (*J* = 8.0)	7.79 (*J* = 7.7)	7.57 (*J* = 8.4)	7.33 (*J* = 7.5)	9.50	8.41	4.34 (2H, t, *J* = 7.5, NCH_2); 1.75 (2H, q, *J* = 7.2, $C\underline{H}_2CH_2CH_3$); 1.50 (2H, q, *J* = 7.1, $CH_2\underline{CH}_2CH_3$); 1.03 (3H, t, *J* = 7.2, CH_3)
1g	15.77	13.12	8.07 (*J* = 7.9)	7.78 (*J* = 7.6)	7.64 (*J* = 8.6)	7.33 (*J* = 7.5)	9.43	8.43	4.14 (2H, d, *J* = 7.5, NCH_2); 2.12 (1H, m, CH); 0.91 (6H, d, *J* = 6.9, $2CH_3$)
1h	15.75	13.19	8.13 (*J* = 8.0)	7.84 (*J* = 7.8)	7.67 (*J* = 8.6)	7.38 (*J* = 7.5)	9.49	8.46	4.27 (2H, t, *J* = 7.5, NCH_2); 1.64 (2H, q, *J* = 7.1, $NCH_2C\underline{H}_2$); 1.36 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.88 (3H, t, *J* = 6.9, CH_3)
1i	15.90	13.15	8.15 (*J* = 8.0)	7.81 (*J* = 7.7)	7.65 (*J* = 8.4)	7.36 (*J* = 7.5)	9.48	8.40	4.30 (2H, t, *J* = 7.6, NCH_2); 1.77 (1H, m, CH); 1.53 (2H, q, *J* = 7.5, $NCH_2C\underline{H}_2$); 0.99 (6H, d, *J* = 6.8, $2CH_3$)
1j	15.94	13.14	8.18 (*J* = 8.0)	7.80 (*J* = 7.8)	7.57 (*J* = 8.5)	7.36 (*J* = 7.5)	9.50	8.41	4.32 (2H, t, *J* = 7.3, NCH_2); 1.73 (2H, q, *J* = 7.1, $NCH_2C\underline{H}_2$); 1.51-1.32 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.96 (3H, t, *J* = 6.9, CH_3)
1k	15.95	13.11	8.20 (*J* = 8.0)	7.79 (*J* = 7.7)	7.55 (*J* = 8.5)	7.36 (*J* = 7.5)	9.49	8.40	4.30 (2H, t, *J* = 7.4, NCH_2); 1.72 (2H, q, *J* = 7.2, $NCH_2C\underline{H}_2$); 1.48-1.30 (8H, m, $(C\underline{H}_2)_4CH_3$); 0.93 (3H, t, *J* = 6.8, CH_3)
1l	15.92	13.10	8.21 (*J* = 8.0)	7.80 (*J* = 7.8)	7.58 (*J* = 8.4)	7.34 (*J* = 7.6)	9.50	8.42	4.33 (2H, t, *J* = 7.5, NCH_2); 1.75 (2H, q, *J* = 7.2, $NCH_2C\underline{H}_2$); 1.50-1.29 (10H, m, $(C\underline{H}_2)_5CH_3$); 0.92 (3H, t, *J* = 6.8, CH_3)
1m	15.93	13.09	8.22 (*J* = 8.0)	7.79 (*J* = 7.8)	7.54 (*J* = 8.4)	7.37 (*J* = 7.5)	9.50	8.40	4.35 (2H, t, *J* = 7.4, NCH_2); 1.74 (2H, q, *J* = 7.1, $NCH_2C\underline{H}_2$); 1.50-1.27 (12H, m, $(C\underline{H}_2)_6CH_3$); 0.90 (3H, t, *J* = 6.9, CH_3)

Perhaps the most reliable explanation of these opposing factors is that the sample of **4** prepared is not a pure compound but a mixture of the starting pyrazin-2-ylamide **1c** and its brominated derivative. The content of the latter does not exceed 5% or it could not remain "unnoticed" in the ^{1}H NMR spectrum.

Having a greater sensitivity, mass spectrometry confirms the presence of the monobrominated compound in the studied sample of **4**. The sample introduced directly clearly shows low intensity peaks douplet for its molecular ion with *m/z* 388/390. It should be noted here that the 1-R-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid hetarylamides do not survive gas column chromatography without destruction hence we could not carry out the corresponding chromato-mass spectrometric analysis. As is known, under electron impact ionization the primary degradation of the molecular ions for this type of compounds occurs *via* a ketene [18]. In the example we are discussing, this behavior is retained but the bromine is found exclusively in the ketene fragment **6b** with *m/z* 293/295. This gave good reason for confirming that electrophilic attack upon bromination of the pyrazin-2-ylamides **1a-m** occurs in the quinolone and not the pyrazine ring (most likely at position 6).

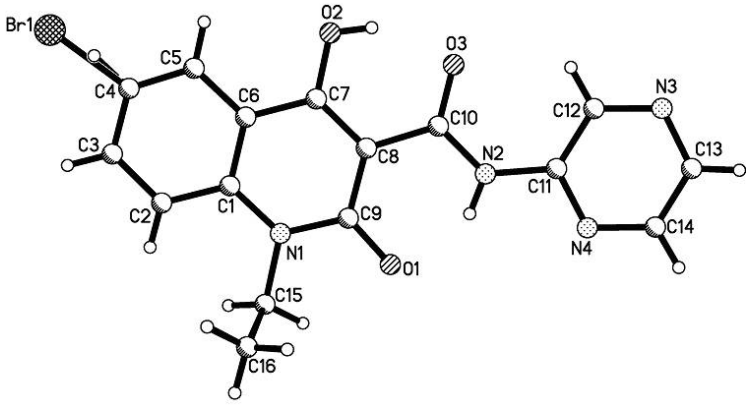


Fig. 1. Structure of the mixed pyrazin-2-ylamide **4** molecule with atomic numbering.

The X-ray analysis carried out (see Fig.1 and Tables 3 and 4) fully confirmed this conclusion and also finally identified that the sample of **4** studied is indeed a mixture of the pyrazin-2-ylamide **1c** (95%) and its 6-bromo derivative (5%). None the less it should be kept in mind that this composition actually relates to a mixed monocrystal while, in the mixture **4** obtained, the real ratio of components may be totally different. The presence of a bromine atom in the benzene part of the quinolone ring does not affect the structure of the basic molecule. It may happen, however, that the presence of the brominated compound in the mixed crystal will, none the less, bring about some systematic increase in the error when determining the geometric parameters.

With the exclusion of atom C(16) all of the non-hydrogen atoms in the molecule of the mixed pyrazin-2-ylamide **4** lie in a single plane to an accuracy of 0.03 Å enabling the formation of the intramolecular hydrogen bonds: O(2)–H(2O)···O(3) (H···O 1.76, O–H···O 147º), N(2)–H(2N)···O(1) (H···O 1.87, N–H···O 143º), and C(12)–H(12)···O(3) (H···O 2.30 Å, C–H···O 121º). This also leads to a redistribution of electron density in the quinolone fragment as evidenced by the increase in the O(1)–C(9) 1.248(3) and O(3)–C(10) 1.244(3) Å bonds when compared with the mean value [20] of 1.210 Å, the C(8)–C(10) bond 1.480(4) (mean value 1.455), and C(7)–C(8) bond 1.384(4) (mean value 1.326) and also shortening of the O(2)–C(7) 1.322(3) (1.362) and C(8)–C(9) 1.444(4) Å (1.455 Å) bonds. It should be noted that in the previously studied isomeric compound 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide the pyrimidine ring was somewhat twisted relative to the carbamide fragment and the O(2)–H(2O)···O(3) hydrogen bond markedly stronger [18]. Evidently in the pyrazin-2-ylamide **4** mixed molecule the C–H···O hydrogen bond stabilizes the coplanarity of the carbamide group and the pyrazine substituent and somewhat weakens the O(2)–H(2O)···O(3) intramolecular hydrogen bond. The steric hindrance arising in this way is compensated by lengthening of the N(2)–C(11) bond to 1.404(4) Å (1.353 Å).

TABLE 3. Bond Lengths (*l*) in the Mixed Pyrazin-2-ylamide **4** Structure

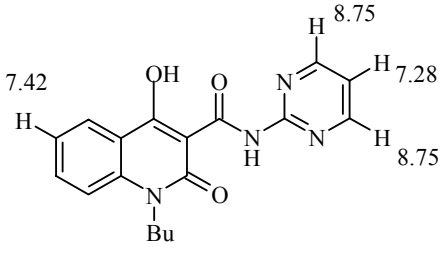
Bond	*l*, Å	Bond	*l*, Å
Br(1)–C(4)	1.896(1)	N(1)–C(1)	1.381(4)
N(1)–C(9)	1.391(4)	N(1)–C(15)	1.485(4)
N(2)–C(10)	1.335(3)	N(2)–C(11)	1.404(4)
N(3)–C(13)	1.325(4)	N(3)–C(12)	1.327(4)
N(4)–C(14)	1.331(4)	N(4)–C(11)	1.332(4)
O(1)–C(9)	1.248(3)	O(2)–C(7)	1.322(3)
O(3)–C(10)	1.244(3)	C(1)–C(2)	1.406(4)
C(1)–C(6)	1.410(4)	C(2)–C(3)	1.374(5)
C(3)–C(4)	1.352(5)	C(4)–C(5)	1.353(4)
C(5)–C(6)	1.392(4)	C(6)–C(7)	1.435(4)
C(7)–C(8)	1.384(4)	C(8)–C(9)	1.444(4)
C(8)–C(10)	1.480(4)	C(11)–C(12)	1.389(4)
C(13)–C(14)	1.354(4)	C(15)–C(16)	1.509(5)

The rather strong repulsion between the atoms of the ethyl substituent and the quinolone ring (shortened intramolecular contacts H(2)···C(15) 2.56 (sum of van der Waal radii [21] 2.87), H(2)···H(15a) 2.04 (2.34), H(15a)···C(2) 2.57 (2.87), and H(15b)···O(1) 2.29 Å (2.46 Å)) leads to lengthening of the N(1)–C(9) 1.391(4), N(1)–C(1) 1.381(4), and N(1)–C(15) 1.485(4) Å bonds when compared with their mean values of 1.353, 1.371, and 1.469 Å respectively, as observed previously in quinolone series compounds studied. The alkyl substituent is placed such that the C(15)–C16) bond is situated almost perpendicularly to the plane of the bicyclic fragment (torsional angle C(9)–N(1)–C(15)–C(16) 91.9(3)º). In the crystal the molecules of the mixed pyrazin-2-ylamide **4** form stacks along the crystallographic [1 0 0] axis. The molecules occur "head to tail" in the stacks, their separation being 3.35 Å and this allows us to infer a marked stacking interaction between the π-systems of the neighboring molecules.

TABLE 4. Valence Angles (ω) in the Mixed Pyrazin-2-ylamide **4** Structure

Angle	ω, deg	Angle	ω, deg
C(1)–N(1)–C(9)	122.7(2)	C(1)–N(1)–C(15)	121.3(3)
C(9)–N(1)–C(15)	116.0(3)	C(10)–N(2)–C(11)	129.9(3)
C(13)–N(3)–C(12)	116.4(3)	C(14)–N(4)–C(11)	116.7(3)
N(1)–C(1)–C(2)	121.6(3)	N(1)–C(1)–C(6)	120.2(3)
C(2)–C(1)–C(6)	118.2(3)	C(3)–C(2)–C(1)	120.1(3)
C(4)–C(3)–C(2)	119.9(3)	C(3)–C(4)–C(5)	122.8(3)
C(3)–C(4)–Br(1)	111.6(4)	C(5)–C(4)–Br(1)	125.5(4)
C(4)–C(5)–C(6)	119.0(3)	C(5)–C(6)–C(1)	120.0(3)
C(5)–C(6)–C(7)	121.6(3)	C(1)–C(6)–C(7)	118.4(3)
O(2)–C(7)–C(8)	122.5(3)	O(2)–C(7)–C(6)	116.8(3)
C(8)–C(7)–C(6)	120.7(3)	C(7)–C(8)–C(9)	120.2(3)
C(7)–C(8)–C(10)	118.0(2)	C(9)–C(8)–C(10)	121.8(3)
O(1)–C(9)–N(1)	118.6(3)	O(1)–C(9)–C(8)	123.7(3)
N(1)–C(9)–C(8)	117.7(3)	O(3)–C(10)–N(2)	121.9(3)
O(3)–C(10)–C(8)	120.9(3)	N(2)–C(10)–C(8)	117.2(3)
N(4)–C(11)–C(12)	121.1(3)	N(4)–C(11)–N(2)	113.3(3)
C(12)–C(11)–N(2)	125.6(3)	N(3)–C(12)–C(11)	121.5(3)
N(3)–C(13)–C(14)	122.7(3)	N(4)–C(14)–C(13)	121.7(3)
N(1)–C(15)–C(16)	112.0(3)		

Hence our work has shown that, by contrast to the isomeric 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamides, the pyrazin-2-ylamides **1a-m** are brominated in glacial acetic acid in the quinolone rather than the amide part of the molecule. The reason for such a significant difference in reactivities of closely related structures evidently lies in the marked lowering of the nucleophilicity providing potential targets for electrophilic attack of the C-3 and C-5 atoms of the pyrazine ring when compared with pyrimidines and quinolones. Indirectly these indicators can correlate with the chemical shifts of the protons in the ^{1}H NMR spectra. The lower the shift of the proton signal the greater the electron density on the carbon atom bonded to it. From the information in the scheme below it is seen that the least shift (7.28 ppm) seen in the 1-butyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrimidin-2-ylamide (**8**) is for the pyrimidine H-5 proton and it is known, in fact, that bromination occurs at this position [18]. In the case of the isomeric pyrazin-2-ylamide **1f** the picture is very different. All of the carbon atoms of the pyrazine ring are next to electronegative nitrogen atoms which lower their electron density *via* a *-I* effect. Correspondingly the chemical shifts of the protons associated with them increase thus being much greater than the proton at position 6 of the quinolone. While not being distinguished by high reactivity the carbon atom in this position does, none the less, become a more energetically favored center for bromination.



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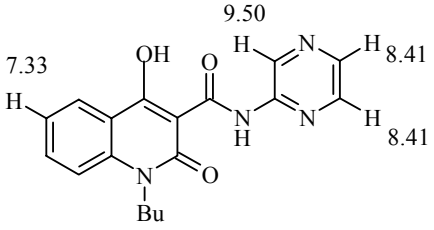
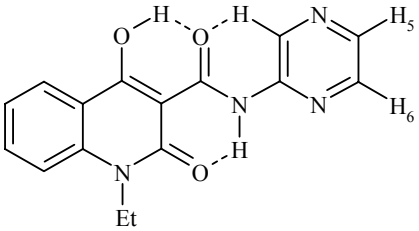
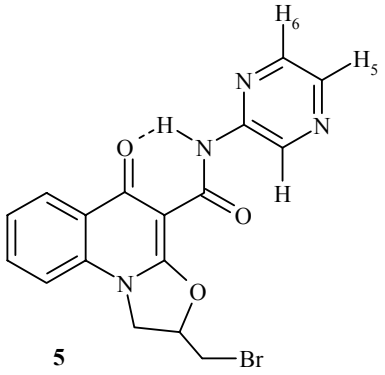


1f

As has been proposed, the 1-N-allyl derivative **1d** behaves distinctively in the conditions studied and heterocyclizes almost immediately upon addition of bromine to give the 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid pyrazin-2-ylamide (**5**). It is interesting that, in contrast to amides **1a-m**, the ^{1}H NMR spectrum of the pyrazine ring in this compound has the expected appearance for this heterocycle. Most likely, the observed effect is due to differences in the systems forming the intramolecular hydrogen bonds. Hence, according to the X-ray analytical data given above, the amides **1a-m** show two strong intramolecular hydrogen bonds (4-OH···O=C–3 and 2-C=O···HNOC-3 [18, 22-24] typical of this class of compound) together with one involving the acyclic carbonyl group and the pyrazine H-3 proton such that the molecule overall is changed in form to a symmetrical quasi polycyclic structure:



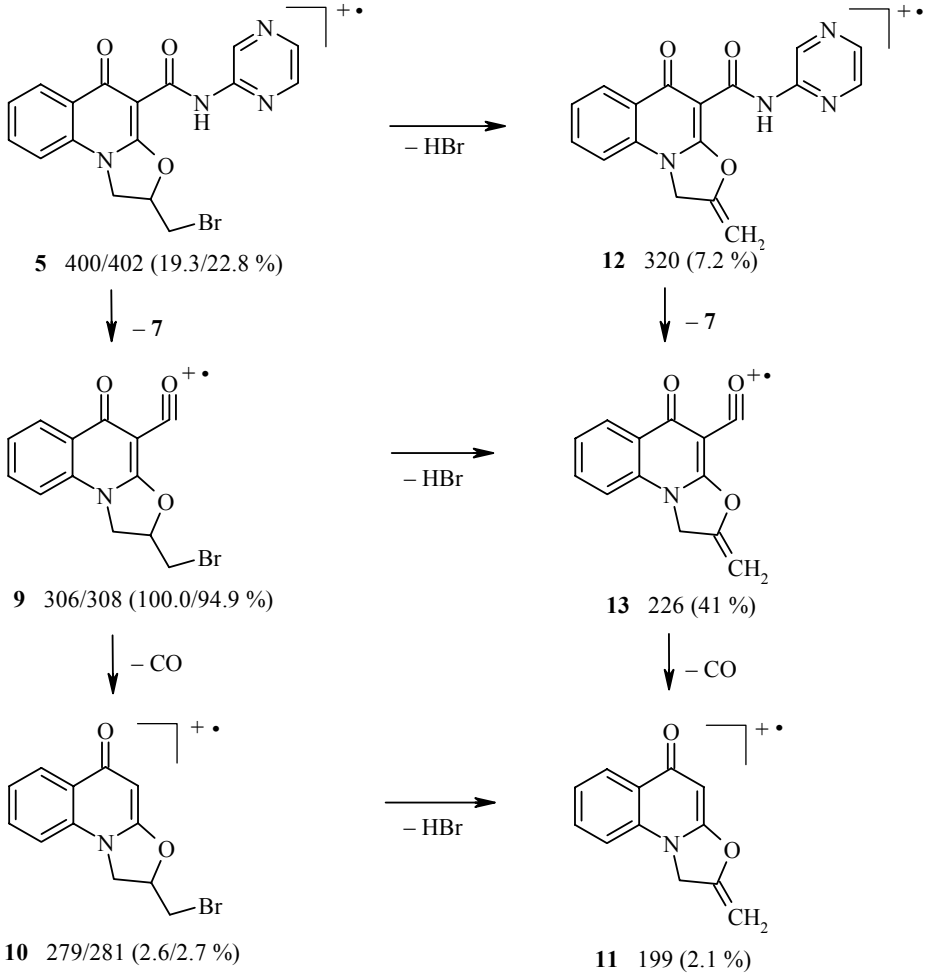
1c



5

It is possible that in such way carbonylaminopyrazine fragment acquires a structural similarity to a quinoxaline ring as a result of which the pyrazine H-5 and H-6 protons in the ^{1}H NMR spectra of amides **1a-m** appear just the same as the corresponding H-2 and H-3 protons in a quinoxaline [19] as one overall signal of intensity 2H to low field. And on the contrary, the 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo-[3,2-*a*]quinoline-4-carboxylic acid N-R-amides show just the one characteristic 5-C=O···HNOC-4 intramolecular hydrogen bond [25]. Even if one proposes (experimentally this has not been confirmed) that in amide **5** the pyrazine H-3 proton also forms a nonclassical intramolecular hydrogen bond with 4-C=O the appearance of symmetry is impossible all the same. Hence the magnetic properties of the H-5 and H-6 protons of the pyrazine ring cannot be similar.

The mass-spectrometric behavior of the pyrazin-2-ylamide **5** and its pyrimidine analog [18] show an overall pattern but also show specific features. In particular, electron impact ionization of amide **5** also shows a molecular ion which is more stable and the intensity of the 400/402 peak increases by three times. The basic route of the subsequent fragmentation of the molecular ion is still cleavage of the terminal amide bond leading to the formation of the acylium cation **9** which then loses CO and HBr (or initially HBr and only then CO, which is preferred) to form the methyleneoxazoloquinolone **11**.



5 400/402 (19.3/22.8 %) **12** 320 (7.2 %)

9 306/308 (100.0/94.9 %) **13** 226 (41 %)

10 279/281 (2.6/2.7 %) **11** 199 (2.1 %)

By comparison with the pyrimidine derivative the likelihood is reduced of a second route for cleavage of the molecular ion for amide **5** beginning with elimination of an HBr molecule and also leading to the methyleneoxazoloquinolone **11** in the final step. But here a third route of cleavage of the molecular ion of

2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid pyrimidin-2-ylamide initially involving elimination of CO from the pyridone fragment proved totally uncharacteristic of the pyrazine analog **5**.

The antitubercular activity of all of the synthesized pyrazin-2ylamides **1a-m** was studied *in vitro* by a radiometric method [26, 27] with respect to *Mycobacterium tuberculosis* H37Rv ATCC 237294 at a concentration of 6.25 μg/ml. Comparative analysis of the antimycobacterial activity of the test materials (Table 1) and the previously reported isomeric pyrimidin-2-ylamides [18] shows that exchange of the pyrimidine ring for the pyrazine is accompanied by a marked increase in activity. The majority of the amides **1a-m** can more efficiently inhibit the growth of the tuberculosis mycobacterium despite a twofold decrease in concentration. The minimum inhibitory concentrations for the most active of these compounds, *viz.* the 1-N-nonyl (**1m**), heptyl (**1k**), and hexyl (**1j**) derivatives were 0.39-0.78 μg/ml. It was particularly interesting to note the clear antitubercular activity of the pyrazin-2-ylamide unsubstituted at position 1 (**1a**) and its close 1-N-methyl analog **1b**. For amidated 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids the appearance of highly active compounds worthy of attention only usually begins with the 1-N-butyl derivative.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were taken on a Varian Mercury VX-200 (200 MHz) instrument using DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Varian 1200L instrument with full scanning in the range 35 to 700 *m/z*, 70 eV EI ionization, and direct sample introduction. The amidation of ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **2a-m** by 2-aminopyrazine was carried out as reported in the method [17].

Mixed pyrazin-2-ylamide 4 was prepared by bromination of the 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrazin-2-ylamide (**1c**) by molecular bromine in glacial acetic acid using the method [18].

X-ray Structural Investigation. Crystals of the mixed pyrazin-2-ylamide **4** are monoclinic (DMF), at 20ºC: a = 7.876(1), b = 9.746(1), c = 19.008(1) Å, β = 97.36(1)º, V = 1447.0(1) Å^3, M_r = 314.26, Z = 4, space group $P2_1/n$, d_{calc} = 1.443 g/cm^3, μ(MoKα) = 0.240 mm^{-1}, F(000) 655. The unit cell parameters and intensities of 7561 reflections (2505 independent, R_{int} = 0.039) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, scanning to ω $2\theta_{max}$ = 50º).

The structure was solved by a direct method using the SHELXTL program package [28]. The positions of the hydrogen atoms were revealed from 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 structure was refined by F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.146 for 2469 reflections (R_1 = 0.050 for 1173 reflections with $F > 4\sigma$ (F), S = 0.852). The full crystallographic information has been placed in the Cambridge structural data base (deposit CCDC 717534). 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 Pyrazin-2-ylamide (5) was prepared by bromination of 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid pyrazin-2-ylamide (**1d**) with an equimolar amount of molecular bromine in glacial acetic acid using the method in [18]. Yield 74%, mp 233ºC (decomp., ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 13.17 (1H, s, NH); 9.49 (1H, d, J = 1.6, H-3' pyrazine); 8.38 (1H, dd, J = 2.6 and J = 1.6, H-5' pyrazine); 8.33 (1H, d, J = 2.6, H-6' pyrazine); 8.27 (1H, dd, J = 8.1 and J = 1.2, H-6); 7.83 (1H, td, J = 7.8 and J = 1.4, H-8); 7.57 (1H, d, J = 8.3, H-9); 7.49 (1H, t, J = 7.8, H-7); 5.70 (1H, m, $NCH_2C\underline{H}O$); 4.71 (1H, t, J = 9.9, NCH); 4.34 (1H, dd, J = 9.7 and J = 6.7, NCH); 4.07 (2H, m, CH_2Br). Mass spectrum, *m/z* (I_{rel}, %): 400 $[M]^+$ (19.3), 320 $[M\text{-}HBr]^+$ (7.2), 306 [M-2-aminopyrazine]$^+$ (100), 279 (M-2-aminopyrazine-CO)$^+$ (2.6), 226 (M-HBr-2-aminopyrazine)$^+$ (41.0), 199 [M-HBr-2-aminopyrazine-CO]$^+$ (2.1). The *m/z* values are reported only for the ^{79}Br isotope. Found, %: C 50.71; H 3.12; N 14.09. $C_{17}H_{13}BrN_4O_3$. Calculated, %: C 50.89; H 3.27; N 13.96.

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