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4-HYDROXY-2-QUINOLONES.
39.* STRUCTURE OF 6-BROMO-4-HYDROXY-1-ISOAMYL-2-OXO-3-QUINOLINECARBOXYLIC ACID

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S-(-)-1-phenylethylamide of 6-bromo-4-hydroxy-1-isoamyl-2-oxo-3-quinolinecarboxylic acid was synthesized. X-ray diffraction investigation of this product was carried out to determine its absolute configuration.

Keywords: 4-hydroxy-2-quinolone, carbostyril, *S*-(-)-phenylethylamide of 6-bromo-4-hydroxy-1-isoamyl-2-oxo-3-quinolinecarboxylic acid, absolute configuration, X-ray diffraction structural analysis.

Our previous attempt to determine the absolute configuration of *S*-(+)-phenylethylamides of 1-R-4-hydroxy-2-oxo-3-quinolinecarboxylic acids by X-ray diffraction analysis was unsuccessful [1]. One reason for this failure was the lack of atoms heavier than oxygen in the molecule studied since the determination of absolute configuration on the basis of X-ray diffraction data is based on anomalous X-ray scattering [2]. This effect is pronounced only for atoms of elements of the third and subsequent periods and, thus, the presence of such atoms in the molecule permits a precise solution of most structural problems.

With the purpose to determine the absolute configuration a bromine-substituted analog, namely, 1-phenylethylamide of 6-bromo-4-hydroxy-1-isoamyl-2-oxo-3-quinolinecarboxylic acid (**1**) was synthesized using optically pure *S*-(-)-1-phenylethylamine. Polarimetric data indicate that amide **1** is an optically active compound (see Experimental), i.e., racemization is not observed upon amidation. In contrast to analogs lacking a bromine atom at $C_{(6)}$ in the quinoline system [1], amide **1** rotates the polarization plane in the same direction as the starting amine.

The performed X-ray diffraction investigation has shown that the quinolone fragment in amide **1** is planar to ±0.05 Å and slightly deformed such that the maximum extrusions from the plane are -0.09 Å for $N_{(1)}$, -0.07 Å for $C_{(5)}$, and +0.07 Å for $C_{(7)}$ atoms. Such a deformation may result from the steric hindrance of the isoamyl group attached to $N_{(1)}$ since the deflection of $C_{(10)}$ from this plane is -0.29 Å and distortion of the planarity in the vicinity of $N_{(1)}$ was not observed. The steric hindrance of $C_{(10)}$ is characterized by short intramolecular contacts $H_{(8)} \cdots H_{(10a)}$ (2.74 Å) and $O_{(1)} \cdots H_{(10b)}$ (2.30 Å). The amide fragment attached to $C_{(2)}$ is coplanar with the hydroxyquinolone fragment. The extrusions of $N_{(2)}$, $O_{(3)}$, and $C_{(15)}$ atoms from the quinolone plane do not exceed 0.05 Å. The chiral center at $C_{(16)}$ has S-configuration and lies virtually in the same plane. The attachment of the ethylbenzene fragment is such that the torsion angles $C_{(15)}-N_{(2)}-C_{(16)}-C_{(17)}$, $C_{(15)}-N_{(2)}-C_{(16)}-C_{(23)}$, $N_{(2)}-C_{(16)}-C_{(17)}-C_{(22)}$, and $C_{(23)}-C_{(16)}-C_{(17)}-C_{(22)}$ are -150, 85, 126, and -108°, respectively.

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* For communication 38, see ref. [1].

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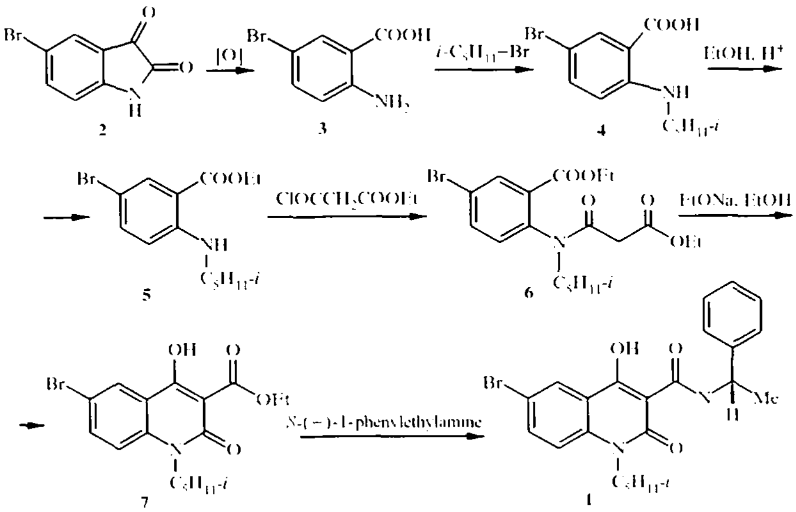

TABLE 1. Atomic Coordinates (Å×10^4) and Equivalent Temperature Factors (Å^2×10^4) in the Structure of Amide **1**

Atom	x	y	z	U_{eq}
Br	7029(1)	1977(3)	2278(1)	89(1)
$O_{(1)}$	11647(5)	1699(16)	7523(5)	66(3)
$O_{(2)}$	11328(4)	1997(18)	3684(4)	59(2)
$O_{(3)}$	13176(4)	2021(19)	4679(4)	62(2)
$N_{(1)}$	9948(6)	1594(10)	6559(6)	37(2)
$N_{(2)}$	13424(6)	1820(2)	6449(6)	60(3)
$C_{(1)}$	11140(8)	1790(2)	6687(7)	57(4)
$C_{(2)}$	11548(7)	1890(3)	5584(7)	52(2)
$C_{(3)}$	10905(6)	1920(2)	4611(6)	34(2)
$C_{(4)}$	9744(6)	1850(2)	4586(6)	43(2)
$C_{(5)}$	9065(7)	1840(3)	3602(7)	51(3)
$C_{(6)}$	7968(7)	1910(3)	3616(6)	48(2)
$C_{(7)}$	7498(7)	1900(3)	4550(8)	68(3)
$C_{(8)}$	8093(7)	1780(2)	5523(9)	65(4)
$C_{(9)}$	9302(6)	1726(17)	5600(7)	33(3)
$C_{(10)}$	9510(9)	1217(13)	7606(8)	52(3)
$C_{(11)}$	9097(11)	2991(17)	8083(10)	87(5)
$C_{(12)}$	8484(10)	2640(2)	9068(9)	97(6)
$C_{(13)}$	9049(15)	1510(4)	9945(12)	162(11)
$C_{(14)}$	7993(15)	4310(2)	9457(13)	158(8)
$C_{(15)}$	12786(6)	1910(3)	5555(7)	43(2)
$C_{(16)}$	14644(7)	1810(3)	6494(8)	61(3)
$C_{(17)}$	15155(8)	726(15)	7467(8)	49(3)
$C_{(18)}$	14974(9)	1161(15)	8503(8)	71(4)
$C_{(19)}$	15514(12)	110(2)	9365(10)	103(5)
$C_{(20)}$	16215(13)	-1270(3)	9142(19)	124(6)
$C_{(21)}$	16329(13)	-1750(2)	8144(17)	120(6)
$C_{(22)}$	15870(11)	-673(19)	7347(10)	78(4)
$C_{(23)}$	15099(10)	3740(2)	6477(11)	99(5)

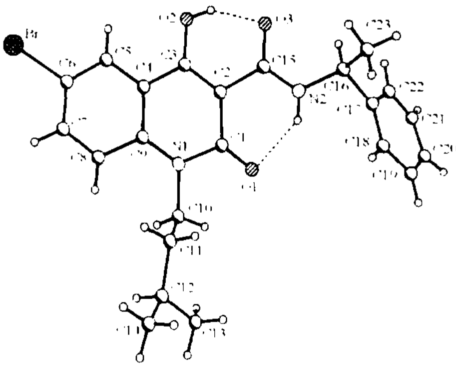

Fig. 1. Structure of amide **1**.

The molecule features a strong redistribution of electron density leading to a change in the bond lengths in the amide-quinoline fragment. Thus, the $N_{(1)}$–$C_{(1)}$, $C_{(1)}$–$C_{(2)}$, and $C_{(2)}$–$C_{(15)}$ bonds are single bonds, while the $C_{(3)}$–$C_{(4)}$ and $C_{(4)}$–$C_{(9)}$ bonds are considerably longer than aromatic bonds, the $C_{(3)}$–$O_{(2)}$ and $N_{(2)}$–$C_{(15)}$ bonds are shorter than ordinary single bonds, and the $C_{(15)}$–$O_{(3)}$ bond is longer than a double bond (Table 2). The reason for this rearrangement lies in the formation of intramolecular O–H···O ($H_{(2)}$···$O_{(3)}$, 1.77 Å; $O_{(2)}$···$O_{(3)}$, 2.51 Å) and N–H···O hydrogen bonds ($H_{(2N)}$···$O_{(1)}$, 2.03 Å; $N_{(2)}$···$O_{(1)}$, 2.73 Å).

EXPERIMENTAL

The PMR spectrum of amide **1** was taken on a Bruker WP-100 SY spectrometer for solutions in DMSO-d_6 using TMS as the internal standard. Oxidation of bromoisatin (**2**) [3] and alkylation and esterification of the resultant 5-bromoanthranilic acid were carried out according to known procedures.

***S*-(-)-1-Phenylethylamide of 6-Bromo-4-hydroxy-1-isoamyl-2-oxo-3-quinolinecarboxylic Acid (1).** Sample of triethylamine (1.54 ml, 0.011 mol) was added to solution of ethyl anthranilate **5** (3.14 g, 0.01 mol) in methylene chloride (30 ml) and then, ethoxymalonyl chloride (1.65 g, 0.011 mol) was added with stirring. The

TABLE 2. Bond Lengths (*l*) in the Structure of Amide **1**

Bond	*l*, Å	Bond	*l*, Å
Br–$C_{(6)}$	1.950(8)	$C_{(5)}$–$C_{(6)}$	1.38(1)
$O_{(1)}$–$C_{(1)}$	1.17(1)	$C_{(6)}$–$C_{(7)}$	1.38(1)
$O_{(2)}$–$C_{(3)}$	1.340(8)	$C_{(7)}$–$C_{(8)}$	1.37(1)
$O_{(2)}$–$H_{(2)}$	0.9200	$C_{(8)}$–$C_{(9)}$	1.51(1)
$O_{(3)}$–$C_{(15)}$	1.262(9)	$C_{(10)}$–$C_{(11)}$	1.54(1)
$N_{(1)}$–$C_{(9)}$	1.38(1)	$C_{(11)}$–$C_{(12)}$	1.56(2)
$N_{(1)}$–$C_{(1)}$	1.49(1)	$C_{(12)}$–$C_{(14)}$	1.47(2)
$N_{(1)}$–$C_{(10)}$	1.51(1)	$C_{(12)}$–$C_{(13)}$	1.50(2)
$N_{(2)}$–$C_{(15)}$	1.31(1)	$C_{(16)}$–$C_{(23)}$	1.52(2)
$N_{(2)}$–$C_{(16)}$	1.52(1)	$C_{(16)}$–$C_{(17)}$	1.54(2)
$C_{(1)}$–$C_{(2)}$	1.54(1)	$C_{(17)}$–$C_{(22)}$	1.38(2)
$C_{(2)}$–$C_{(3)}$	1.39(1)	$C_{(17)}$–$C_{(18)}$	1.39(1)
$C_{(2)}$–$C_{(15)}$	1.55(1)	$C_{(18)}$–$C_{(19)}$	1.44(2)
$C_{(3)}$–$C_{(4)}$	1.45(1)	$C_{(19)}$–$C_{(20)}$	1.39(2)
$C_{(4)}$–$C_{(5)}$	1.43(1)	$C_{(20)}$–$C_{(21)}$	1.33(2)
$C_{(4)}$–$C_{(9)}$	1.45(1)	$C_{(21)}$–$C_{(22)}$	1.36(2)

TABLE 3. Bond Angles (ω) in the Structure of Amide **1**

Angle	ω, deg	Angle	ω, deg
$C_{(3)}\ O_{(2)}\ H_{(2)}$	109.5	$C_{(7)}\ C_{(8)}\ C_{(9)}$	120.1(9)
$C_{(9)}\ N_{(1)}\ C_{(1)}$	124.6(7)	$N_{(1)}\ C_{(9)}\ C_{(4)}$	122.3(7)
$C_{(9)}\ N_{(1)}\ C_{(10)}$	123.1(8)	$N_{(1)}\ C_{(9)}\ C_{(8)}$	122.9(8)
$C_{(1)}\ N_{(1)}\ C_{(10)}$	112.3(8)	$C_{(4)}\ C_{(9)}\ C_{(8)}$	114.8(8)
$C_{(15)}\ N_{(2)}\ C_{(16)}$	123.0(7)	$N_{(1)}\ C_{(10)}\ C_{(11)}$	111.0(8)
$C_{(15)}\ N_{(2)}\ H_{(2N)}$	118.5	$C_{(10)}\ C_{(11)}\ C_{(12)}$	113.1(10)
$C_{(16)}\ N_{(2)}\ H_{(2N)}$	118.5	$C_{(11)}\ C_{(12)}\ C_{(13)}$	112.9(12)
$O_{(1)}\ C_{(1)}\ N_{(1)}$	121.8(8)	$C_{(14)}\ C_{(12)}\ C_{(11)}$	113.2(12)
$O_{(1)}\ C_{(1)}\ C_{(2)}$	128.2(9)	$C_{(13)}\ C_{(12)}\ C_{(14)}$	116.7(11)
$N_{(1)}\ C_{(1)}\ C_{(2)}$	109.6(8)	$O_{(3)}\ C_{(15)}\ N_{(2)}$	120.2(7)
$C_{(3)}\ C_{(2)}\ C_{(1)}$	125.7(8)	$O_{(3)}\ C_{(15)}\ C_{(2)}$	120.4(8)
$C_{(3)}\ C_{(2)}\ C_{(15)}$	117.3(7)	$N_{(2)}\ C_{(15)}\ C_{(2)}$	119.5(7)
$C_{(1)}\ C_{(2)}\ C_{(15)}$	117.0(8)	$C_{(23)}\ C_{(16)}\ N_{(2)}$	112.0(13)
$O_{(2)}\ C_{(3)}\ C_{(2)}$	121.8(7)	$C_{(23)}\ C_{(16)}\ C_{(17)}$	111.5(10)
$O_{(2)}\ C_{(3)}\ C_{(4)}$	118.3(7)	$N_{(2)}\ C_{(16)}\ C_{(17)}$	110.8(9)
$C_{(2)}\ C_{(3)}\ C_{(4)}$	119.8(7)	$C_{(22)}\ C_{(17)}\ C_{(18)}$	116.7(11)
$C_{(5)}\ C_{(4)}\ C_{(3)}$	121.1(7)	$C_{(22)}\ C_{(17)}\ C_{(16)}$	120.8(10)
$C_{(5)}\ C_{(4)}\ C_{(9)}$	121.4(8)	$C_{(18)}\ C_{(17)}\ C_{(16)}$	122.5(11)
$C_{(3)}\ C_{(4)}\ C_{(9)}$	117.4(7)	$C_{(17)}\ C_{(18)}\ C_{(19)}$	118.6(11)
$C_{(6)}\ C_{(5)}\ C_{(4)}$	119.1(8)	$C_{(20)}\ C_{(19)}\ C_{(18)}$	119.2(13)
$C_{(5)}\ C_{(6)}\ C_{(7)}$	122.2(8)	$C_{(21)}\ C_{(20)}\ C_{(19)}$	121.5(16)
$C_{(5)}\ C_{(6)}\ Br$	119.7(7)	$C_{(20)}\ C_{(21)}\ C_{(22)}$	117.9(15)
$C_{(7)}\ C_{(6)}\ Br$	118.1(7)	$C_{(21)}\ C_{(22)}\ C_{(17)}$	125.2(13)
$C_{(8)}\ C_{(7)}\ C_{(6)}$	122.0(8)		

mixture was left at room temperature for 4-5 h. Then, water (100 ml) was added to the reaction mixture, which was brought to pH 4 by the addition of hydrochloric acid. The mixture was stirred and the organic layer was separated. The residue was treated with methylene chloride (20 ml). The organic extracts were combined and dried over anhydrous $CaCl_2$. The solvent was removed by heating on a water bath (under reduced pressure toward the end). Solution of sodium ethylate obtained from metallic sodium (0.69 g, 0.03 mol) and absolute ethanol (20 ml) was added to anilide **6** and left at room temperature for 5 h. Upon completion of the cyclization, the reaction mixture was diluted with cold water (100 ml) and brought to pH 4 by adding hydrochloric acid. The oily precipitate of ester **7** was extracted with methylene chloride (3 × 20 ml) and the solvent was distilled off. Then, ethanol (30 ml) and *S*-(-)-1-phenylethylamine (1.42 ml, 0.011 mol) were added to the residue and heated at reflux for 6-7 h. Upon cooling, water was added and the mixture was brought to pH 4 by adding hydrochloric acid. The precipitate was filtered off, washed with water, and dried to give 2.78 g of compound **1** (61% relative to ester **5**); mp 59-60°C (ethanol), $[\alpha]_D^{20} = -8.2°$ ($c = 3$, DMF). PMR spectrum: 17.00 (1H, s, OH); 10.74 (1H, d, NH); 8.11 (1H, d, $^4J = 2.1$ Hz, 5-H); 7.90 (1H, dd, $J = 9.0$ and 2.1 Hz, 7-H); 7.52 (1H, d, $J = 9.0$ Hz, 8-H); 7.35 (5H, m, Ph); 5.17 (1H, q, $NC\underline{H}$); 4.12 (2H, t, NCH_2); 1.80-1.32 (6H, m, $NCH_2\underline{CH_2}\underline{CH}$ + $\underline{CH_3}CH{-}Ph$); 0.96 ppm (6H, d, $CH(\underline{CH_3})_2$). Found, %: C 60.44; H 5.49; Br 17.42; N 6.15. $C_{23}H_{25}BrN_2O_3$. Calculated, %: C 60.40; H 5.51; Br 17.47; N 6.12.

X-ray Diffraction Analysis of Amide 1. The unit cell parameters of monoclinic crystals of amide **1** at 20°C: $a = 12.511(8)$, $b = 7.312(5)$, $c = 12.640(7)$ Å; $\beta = 96.39(5)°$; $V = 1149(1)$ Å^3; $M_r = 457.4$; $F(000) = 472$; $Z = 2$; $d_{calc} = 1.32$ g/cm^3; space group $P2_1$, $\mu(MoK_\alpha) = 1.81$ mm^{-1}. The intensities were measured on a Siemens P3/PC automatic four-circle diffractometer using molybdenum radiation with a graphite monochromator (2θ/θ scanning at $5° \leq 2\theta \leq 55°$, two control reflections for each 98 reflections). A total of 2051 intensities were measured, of which 1268 were independent ($R_{int} = 0.067$) and 817 were observed ($I > 2\sigma(I)$). Lorentz and polarization factors were taken into account in converting the intensities to structural factors; profile analysis according to Lehmann-Larsen was carried out and an absorption correction was employed. The structure was solved by the direct method and refined anisotropically by the full-matrix least-squares method relative to F^2 for the non-hydrogen atoms. The hydrogen atoms were introduced geometrically and refined attached to the corresponding nonhydrogen atoms with a total isotropic temperature factor. The final confidence factors: $R = 0.0475$ and $wR_2 = 0.0856$ over the observed reflections and $R = 0.1016$ and $wR_2 = 0.0978$ for all the independent reflections. The absolute configuration of the molecule is characterized by Flack parameter -0.02±0.03. The calculations were carried out using the SHELXTL-PLUS program package. The atomic coordinates in the structure of amide **1** are given in Table 1, while the bond lengths and angles are given in Tables 2 and 3. The three-dimensional arrangement of the atoms and their numbering are shown in Fig. 1.

REFERENCES

1. I. V. Ukrainets, S. G. Taran, N. V. Likhanova, V. B. Rybakov, O. V. Gorokhova, and Nidal Amin Dzharadat, *Khim. Geterotsikl. Soedin.*, No. 1, 55 (2000).
2. A. Domenicano and I. Hargittai (editors), *Molecular Structures* [Russian translation], Mir, Moscow (1997), p. 299.
3. G. I. Zhungietu and M. A. Rekhter, *Isatin and Its Derivatives* [in Russian], Shtinitsa, Kishinev (1977), p. 228.
4. S. G. Taran, Nidal Amin Dzharadat, N. V. Likhanova, I. V. Ukrainets, and O. V. Gorokhova, in: *Scientific Basis for Drug Development, Proceedings of the Chemical Division of the National Academy of Sciences of Ukraine* [in Russian], Osnova, Kharkov (1998), p. 255.
5. A. E. Agronomov and Yu. S. Shabarov, *Laboratory Procedures in Organic Chemistry* [in Russian], Khimiya, Moscow (1974), p. 75.