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4-HYDROXY-2-QUINOLONES. 38.* SYNTHESIS, STRUCTURE, AND ANTICONVULSANT ACTIVITY OF OPTICALLY ACTIVE 1-PHENYLETHYLAMIDES OF 1-R-4-HYDROXY-2-OXO-3-QUINOLINECARBOXYLIC ACIDS

I. V. Ukrainets[1], S. G. Taran[1], N. V. Likhanova[1], V. B. Rybakov[2], O. V. Gorokhova[1], and Nidal Amin Jaradat[1]

A synthesis is reported for optically pure antipodes of 1-phenylethylamides of 1-R-4-hydroxy-2-oxo-3-quinolinecarboxylic acids. An attempt was made to establish the absolute configuration of these products by X-ray diffraction crystallographic analysis. The anticonvulsant activity of the S-enantiomers was studied.

Keywords: 4-hydroxyquinolone, carbostyril, 1-phenylethylamides, optical activity, X-ray diffraction structural analysis, anticonvulsants.

Diseases, which directly or indirectly affect the central nervous system, are often accompanied by convulsions such as in various forms of epilepsy and Parkinson's disease. The drug therapy for such diseases is pathogenetic, i.e., the agents do not eliminate the cause of the disease and, thus, are used for prolonged periods, sometimes during the entire lifetime of patients. Furthermore, even after elimination of the pathological source causing the convulsive disorder, prolonged and continual anticonvulsant therapy is generally required [2, 3]. The search for new efficient anticonvulsants with low toxicity and no pronounced side effects remains important in pharmaceutical chemistry.

In a study of the chemical structure of biologically active compounds found in *Haplophyllum* plants of the *Rutaceae* family and long since used in folk medicine as anticonvulsants, many new 4-hydroxy-2-oxoquinolines were isolated. We have also repeatedly noted the favorable effect of arylalkylamide residues for the manifestation of anticonvulsant properties [4-6]. The *S*(-) enantiomers proved more active in the case of 1-phenylethylamides.

Hence, we undertook a study of the anticonvulsant activity of 1-phenylethylamides of 1-R-4-hydroxy-2-oxo-3-quinolinecarboxylic acids with *S*-configuration (**1**), which were synthesized by the amidation of 1-R-3-carbethoxy-4-hydroxy-2-oxo-quinolines **2** using *S*(-)-1-phenylethylamine. In light of the structural features of these products, namely, presence of alkyl groups, 1-phenylethylamide residues, quinolone fragment, and optical activity, PMR spectroscopy and polarimetry were used to confirm the structure. The purity of the products was monitored by thin-layer chromatography (Tables 1 and 2) but, when working with optically active compounds, complete chemical individuality does not guarantee stereochemical purity. In such cases, the optical purity must also be known. Optically pure *S*(-)-1-phenylethylamine ($[\alpha]_D^{24} = -39°$) was used possessing rather high optical stability and not racemizing upon acylation [7]. Nevertheless, the wide variety of factors causing the racemization of optically active compounds predetermined the necessity to check the optical purity of amides **1**. Various

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[1] Ukrainian Pharmaceutical Academy, 310002 Kharkov, Ukraine; e-mail: igor@uiv.kharkov.ua. [2] M. V. Lomonosov Moscow State University, 119899 Moscow, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 55-63, January, 2000. Original article submitted February 10, 1999.

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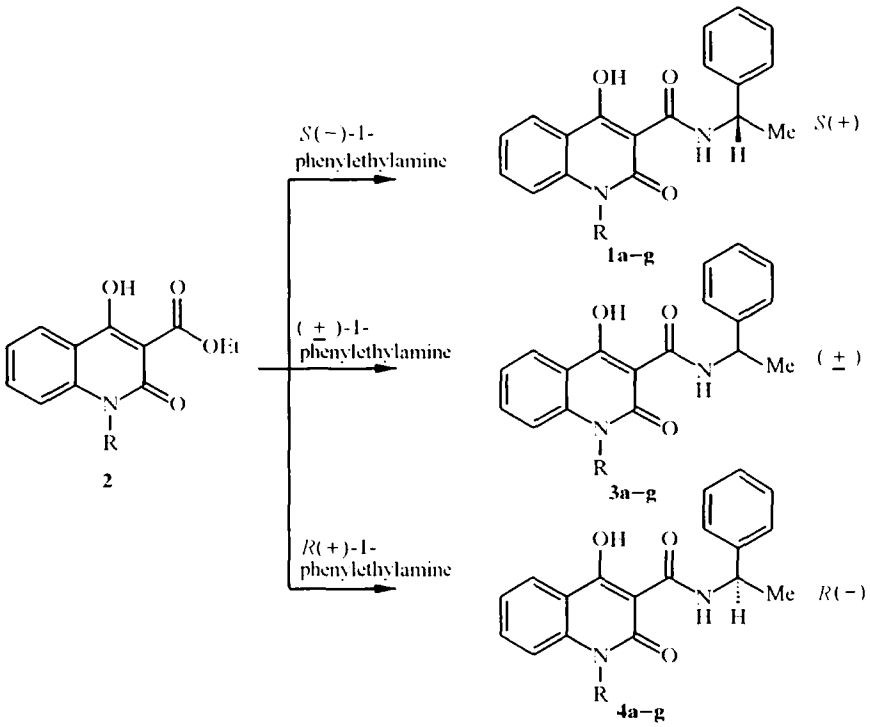
methods were used for this purpose such as the introduction of additional chirality into the compound studied. The formation of one or two diastereomers readily determined by PMR spectroscopy is possible depending on the purity of the starting sample. In practice, the differences in the chemical shifts of the diastereotopic protons are usually slight and may be amplified using lanthanide shift reagents (LSR). The use of chiral LSR permits us to determine the enantiomeric purity directly without conversion to diastereomers [8]. Such a reagent is europium *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. However, our experiments showed that PMR spectroscopy does not permit us to monitor the optical purity of amides **1** since the addition of this LSR even to optically inactive 1-phenylmethylamides of 1-R-4-hydroxy-2-oxo-3-quinolinecarboxylic acids (**3**) does not lead to doubling of any signals, probably as a result of the acidic properties of the compounds analyzed.



1–4 a R = H; b Me; c Et; d $CH_2CH{=}CH_2$; e C_3H_7; f C_4H_9; g C_5H_{11}

The preparation of both antipodes with identical absolute value of optical rotation is a rather good indication of complete optical purity [7], especially if both antipodes are obtained independently using different asymmetric reagents. Therefore, we synthesized antipodes of amides **1**, i.e., 1-phenylethylamides **4**. We also used optically pure 1-phenylethylamine but with *R*-configuration: $[\alpha]^{24}_D = +39°$. Comparison of the properties of the products obtained (see Tables 1 and 2) indicated that they had identical melting points, PMR spectra, and specific rotation values, differing only in sign. Thus, amides **1** and **4** are optically pure enantiomers.

We should note that rotation of the polarization plane for amides **1** and **4** is opposite to rotation for the starting amines although such an effect has not been found for N,N′-di-1-phenylethylamides of alkylmalonic acids or, even more so, for 1-phenylmethylamides of 1H-4-hydroxy-2-oxo-3-quinolineacetic acid [9]. In principle, the configuration of compounds and the direction of rotation of the polarization plane are unrelated [7, 9]. Nevertheless, we attempted to determine the true spatial configuration of amides **1** by carrying out an X-ray diffraction analysis of amide **1g**.

The Cambridge Structural Data Base (October, 1998) [11] features only one compound with a similar structure, namely, 3-benzoyl-1-ethyl-4-hydroxy-2-oxoquinoline [12]. An intramolecular hydrogen bond $O_{(1)}\cdots H_{(8)}$ (d = 1.395 Å) was found to exist in compound under study as in the compound described in the literature. The basic distances in the comparable molecular fragments are within standard deviations and do not require commentary.

TABLE 1. Characteristics of 1-Phenylethylamides of 1-R-4-Hydroxy-2-oxo-3-quinolinecarboxylic Acids

Compound	Empirical formula	Found, % / Calculated, %			R_f*		mp, °C (ethanol)	$[\alpha]_{546}^{20}$, deg. (c, g/100 ml)	Yield, %
		C	H	N	1	2			
1a	$C_{18}H_{16}N_2O_3$	70.20 / 70.12	5.15 / 5.23	9.13 / 9.09	0.49	0.25	269-270	+31.5 (2)	89
3a	$C_{18}H_{16}N_2O_3$	70.17 / 70.12	5.28 / 5.23	9.16 / 9.09	0.49	0.25	247-249		93
4a	$C_{18}H_{16}N_2O_3$	70.22 / 70.12	5.17 / 5.23	9.04 / 9.09	0.49	0.25	269-270	-31.5 (2)	90
1b	$C_{19}H_{18}N_2O_3$	70.86 / 70.79	5.58 / 5.63	8.60 / 8.69	0.58	0.40	99-101	+12.4 (5)	86
4b	$C_{19}H_{18}N_2O_3$	70.77 / 70.79	5.69 / 5.63	8.61 / 8.69	0.58	0.40	99-101	-12.4 (5)	84
1c	$C_{20}H_{20}N_2O_3$	71.50 / 71.41	5.90 / 5.99	8.38 / 8.33	0.63	0.47	116-118	+2.6 (10)	85
4c	$C_{20}H_{20}N_2O_3$	71.48 / 71.41	5.89 / 5.99	8.40 / 8.33	0.63	0.47	116-118	-2.6 (10)	81
1d	$C_{21}H_{20}N_2O_3$	72.32 / 72.40	5.85 / 5.79	8.00 / 8.04	0.65	0.51	107-109	+8.2 (4)	92
4d	$C_{21}H_{20}N_2O_3$	72.47 / 72.40	5.81 / 5.79	8.09 / 8.04	0.65	0.51	107-109	-8.2 (4)	87
1e	$C_{21}H_{22}N_2O_3$	71.90 / 71.98	6.38 / 6.33	7.91 / 7.99	0.67	0.52	123-125	+42.8 (2)	82
4e	$C_{21}H_{22}N_2O_3$	72.06 / 71.98	6.27 / 6.33	7.90 / 7.99	0.67	0.52	123-125	-42.8 (2)	86
1f	$C_{22}H_{24}N_2O_3$	72.44 / 72.51	6.71 / 6.64	7.66 / 7.69	0.68	0.53	112-114	+22.7 (3)	79
3f	$C_{22}H_{24}N_2O_3$	72.47 / 72.51	6.58 / 6.64	7.73 / 7.69	0.68	0.53	95-97		80
4f	$C_{22}H_{24}N_2O_3$	72.59 / 72.51	6.67 / 6.64	7.60 / 7.69	0.68	0.53	112-114	-22.7 (3)	80
1g	$C_{23}H_{26}N_2O_3$	72.90 / 72.99	6.98 / 6.92	7.45 / 7.40	0.70	0.57	88-90	+30.2 (2)	83
3g	$C_{23}H_{26}N_2O_3$	73.05 / 72.99	6.87 / 6.92	7.37 / 7.40	0.70	0.57	72-74		88
4g	$C_{23}H_{26}N_2O_3$	72.91 / 72.99	6.96 / 6.92	7.46 / 7.40	0.70	0.57	88-90	-30.2 (2)	78

* R_f values determined in: 1) 6:1 propan-2-ol–hexane or 2) 6:1 methylene chloride–hexane.

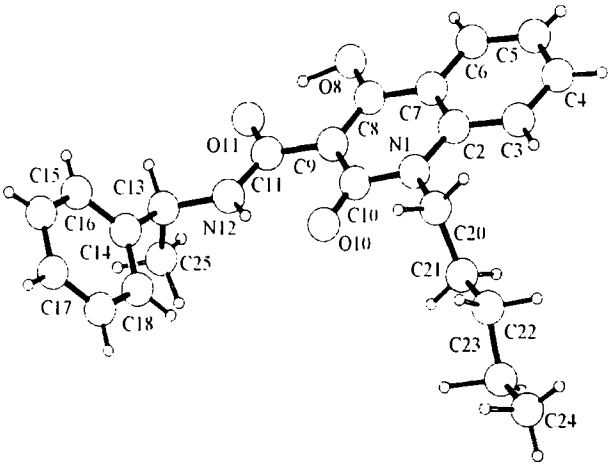


Fig. 1. General view of amide **1g** molecule.

TABLE 2. PMR Spectral Characteristics of 1-Phenylethylamides of 1-R-4-Hydroxy-2-oxo-3-quinolinecarboxylic Acids, δ, ppm*

Compound	5-H (1H, d)	7-H (1H, t)	8-H (1H, d)	6-H + Ph (6H, m)	CH CH$_3$ (1H, q)	CH-CH$_3$ (3H, d)	R
1a, 3a, 4a	7.97	7.66	7.47	7.36-7.14	5.19	1.53	11.87 (1H, s, NH)
1b, 4b	8.03	7.76	7.55	7.44-7.20	5.16	1.52	3.57 (3H, s, Me)
1c, 4c	8.05	7.78	7.60	7.45-7.21	5.16	1.53	4.27 (2H, q, NCH$_2$); 1.20 (3H, t, Me)
1d, 4d	8.06	7.76	7.49	7.43-7.17	5.17 (3H, m, CH + NCH$_2$)	1.51	5.99 (1H, m, CH=); 4.87 (2H, s, CH$_2$=)
1e, 4e	8.03	7.77	7.61	7.46-7.20	5.16	1.52	4.16 (2H, t, NCH$_2$); 1.69 (2H, m, CH$_2$Me); 0.94 (3H, t, Me)
1f, 3f, 4f	8.05	7.76	7.58	7.44-7.22	5.16	1.55	4.19 (2H, t, NCH$_2$); 1.30 (4H, m, (CH$_2$)$_2$Me); 0.92 (3H, t, Me)
1g, 3g, 4g	8.04	7.77	7.59	7.45-7.19	5.16	1.53	4.20 (2H, t, NCH$_2$); 1.721 (2H, q, NCH$_2$CH$_2$); 1.36 (4H, m, (CH$_2$)$_2$Me); 0.93 (3H, t, Me)

* The signals for the 4-OH group protons appear as a singlet at 17.01-17.18 ppm, while the protons of the NH groups appear as a doublet at 10.75-10.82 ppm.

Since the space group of crystals of amide **1g** is noncentrosymmetrical, we attempted to determine the absolute configuration by taking two regions of inverse space: $0 \rightarrow h$; $0 \rightarrow k$, $0 \rightarrow l$ and $-h \rightarrow 0$, $-k \rightarrow 0$; $-l \rightarrow 0$. In the least squares refinement of the structure, the Flack parameter X (when $X = 0$, the structure should be true in the sense of the absolute configuration and when $X = -1$, the structure should be inverted to obtain the "correct" configuration [13, 14]) proved equal to zero, but with standard deviation of 2, which indicated that our attempt to establish the absolute configuration with high precision was unsuccessful. This failure may be partially attributed to the lack of atoms heavier than oxygen in the molecule. Since amide **1g** was synthesized from 1-phenylethylamine with known, namely, *S*-configuration and the asymmetric site was not affected in the course of the chemical reaction, the final product presumably has the same configuration.

The effect of amides **1a-1g** on antispasmodic activity was studied with white rats using pharmacological and physiological epilepsy models [15-17]. Only amides **1d-1f** displayed pronounced antiepileptic effect on background of experimental epilepsy and a sedative effect was noted in some cases. The preventive administration of these compounds led to an increase of the latent period, hastened the termination of epistatus in the animals, and had a sedative effect, which indicates promise for finding anticonvulsant agents among this class of compounds.

EXPERIMENTAL

The PMR spectra of the compounds synthesized were taken on a Bruker WP-100SY spectrometer for solutions in DMSO-d_6 using TMS as the internal standard. The specific rotation was determined on a Polamat A spectropolarimeter. Thin-layer chromatography was carried out on Silufol UV-254 plates with indication of the compounds in UV light at 254 nm.

TABLE 3. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors ($Å^2 \times 10^3$) in the Structure of Amide **1g**

Atom	x	y	z	U_{eq}
$N_{(1)}$	3174(1)	2771(1)	4224(1)	48(1)
$C_{(2)}$	3015(2)	3343(1)	4704(1)	47(1)
$C_{(3)}$	2938(2)	4542(1)	4730(1)	58(1)
$C_{(4)}$	2820(2)	5092(1)	5207(1)	67(1)
$C_{(5)}$	2778(2)	4468(1)	5672(1)	70(1)
$C_{(6)}$	2830(2)	3306(1)	5629(1)	60(1)
$C_{(7)}$	2919(1)	2715(1)	5175(1)	47(1)
$C_{(8)}$	2900(1)	1488(1)	5146(1)	48(1)
$O_{(8)}$	2780(1)	912(1)	5599(1)	62(1)
$C_{(9)}$	2951(1)	932(1)	4667(1)	46(1)
$C_{(10)}$	3105(2)	1587(1)	4183(1)	48(1)
$O_{(10)}$	3201(1)	1138(1)	3739(1)	62(1)
$C_{(11)}$	2887(2)	-330(1)	4661(1)	52(1)
$O_{(11)}$	2750(1)	-878(1)	5090(1)	65(1)
$N_{(12)}$	3012(1)	-878(1)	4204(1)	58(1)
$C_{(13)}$	2959(2)	-2133(1)	4157(1)	60(1)
$C_{(14)}$	4052(2)	-2500(1)	3674(1)	56(1)
$C_{(15)}$	5637(2)	-3179(1)	3718(1)	81(1)
$C_{(16)}$	6604(2)	-3559(2)	3279(1)	115(1)
$C_{(17)}$	5974(2)	-3260(1)	2787(1)	112(1)
$C_{(18)}$	4439(3)	-2584(1)	2739(1)	105(1)
$C_{(19)}$	3453(2)	-2192(1)	3177(1)	83(1)
$C_{(20)}$	3458(2)	3408(1)	3729(1)	56(1)
$C_{(21)}$	1627(2)	3687(1)	3450(1)	67(1)
$C_{(22)}$	2004(2)	4434(1)	2967(1)	83(1)
$C_{(23)}$	441(2)	4521(2)	2585(1)	109(1)
$C_{(24)}$	837(3)	5260(2)	2119(1)	150(1)
$C_{(25)}$	898(2)	-2555(1)	4157(1)	88(1)
$H_{(3)}$	3004(15)	4950(7)	4428(4)	60(3)
$H_{(4)}$	2777(16)	5936(8)	5199(4)	78(3)
$H_{(5)}$	2627(19)	4914(9)	5999(4)	85(4)
$H_{(6)}$	2782(15)	2842(8)	5951(3)	67(3)
$H_{(8)}$	2707(14)	24(7)	5452(3)	59(3)
$H_{(12)}$	3199(14)	-429(7)	3927(3)	51(3)
$H_{(13)}$	3620(14)	-2412(8)	4472(4)	71(3)
$H_{(13)}$	5978(14)	-3438(7)	4035(3)	58(3)
$H_{(16)}$	7521(17)	-4031(9)	3296(4)	88(4)
$H_{(17)}$	6675(14)	-3508(7)	2491(3)	63(3)
$H_{(18)}$	3966(16)	-2383(9)	2403(4)	86(3)
$H_{(19)}$	2362(17)	-1727(8)	3135(4)	81(3)
$H_{(20A)}$	4234(17)	4076(9)	3804(4)	83(3)
$H_{(20B)}$	4353(15)	2916(9)	3513(3)	70(3)
$H_{(21A)}$	860(13)	2982(8)	3376(3)	61(3)
$H_{(21B)}$	647(17)	4073(9)	3690(4)	82(4)
$H_{(22A)}$	3124(16)	4158(9)	2785(4)	90(3)
$H_{(22B)}$	1926(15)	5318(8)	3036(4)	84(3)
$H_{(23A)}$	575(17)	3491(9)	2531(4)	103(4)
$H_{(23B)}$	-850(16)	4579(9)	2788(4)	85(3)
$H_{(24A)}$	-240(15)	5340(9)	1893(4)	86(3)
$H_{(24B)}$	1403(15)	5943(8)	2196(4)	92(3)
$H_{(24C)}$	1703(16)	4685(9)	1944(4)	90(3)
$H_{(25A)}$	880(16)	-3398(9)	4126(4)	80(3)
$H_{(25B)}$	342(15)	-2397(9)	4501(4)	85(3)
$H_{(25C)}$	228(16)	-2217(10)	3831(4)	90(4)

TABLE 4. Bond Lengths d (Å) in the Structure of Compound **1g**

Bond	d	Bond	d
$N_{(1)}$–$C_{(10)}$	1.3839(12)	$C_{(14)}$–$C_{(19)}$	1.374(2)
$N_{(1)}$–$C_{(2)}$	1.3919(12)	$C_{(15)}$–$C_{(16)}$	1.373(2)
$N_{(1)}$–$C_{(20)}$	1.4706(12)	$C_{(15)}$–$H_{(15)}$	0.891(8)
$C_{(2)}$–$C_{(3)}$	1.3993(14)	$C_{(16)}$–$C_{(17)}$	1.366(2)
$C_{(2)}$–$C_{(7)}$	1.4024(13)	$C_{(16)}$–$H_{(16)}$	0.845(11)
$C_{(3)}$–$C_{(4)}$	1.371(2)	$C_{(17)}$–$C_{(18)}$	1.335(2)
$C_{(3)}$–$H_{(3)}$	0.904(9)	$C_{(17)}$–$H_{(17)}$	0.941(9)
$C_{(4)}$–$C_{(5)}$	1.384(2)	$C_{(18)}$–$C_{(19)}$	1.383(2)
$C_{(4)}$–$H_{(4)}$	0.984(10)	$C_{(18)}$–$H_{(18)}$	0.941(10)
$C_{(5)}$–$C_{(6)}$	1.355(2)	$C_{(19)}$–$H_{(19)}$	0.940(11)
$C_{(5)}$–$H_{(5)}$	0.984(10)	$C_{(20)}$–$C_{(21)}$	1.495(2)
$C_{(6)}$–$C_{(7)}$	1.4063(13)	$C_{(20)}$–$H_{(20A)}$	0.967(11)
$C_{(6)}$–$H_{(6)}$	0.918(9)	$C_{(20)}$–$H_{(20B)}$	1.008(10)
$C_{(7)}$–$C_{(8)}$	1.4319(14)	$C_{(21)}$–$C_{(22)}$	1.525(2)
$C_{(8)}$–$O_{(8)}$	1.3307(11)	$C_{(21)}$–$H_{(21A)}$	0.997(9)
$C_{(8)}$–$C_{(9)}$	1.3769(13)	$C_{(21)}$–$H_{(21B)}$	1.021(11)
$O_{(8)}$–$H_{(8)}$	1.101(8)	$C_{(22)}$–$C_{(23)}$	1.460(2)
$C_{(9)}$–$C_{(10)}$	1.4485(13)	$C_{(22)}$–$H_{(22A)}$	0.962(11)
$C_{(9)}$–$C_{(11)}$	1.4717(13)	$C_{(22)}$–$H_{(22B)}$	1.046(10)
$C_{(10)}$–$O_{(10)}$	1.2415(11)	$C_{(23)}$–$C_{(24)}$	1.488(2)
$C_{(11)}$–$O_{(11)}$	1.2632(11)	$C_{(23)}$–$H_{(23A)}$	1.211(11)
$C_{(11)}$–$N_{(12)}$	1.3253(12)	$C_{(23)}$–$H_{(23B)}$	1.038(11)
$O_{(11)}$–$H_{(8)}$	1.395(8)	$C_{(24)}$–$H_{(24A)}$	0.949(10)
$N_{(12)}$–$C_{(13)}$	1.4681(13)	$C_{(24)}$–$H_{(24B)}$	0.909(10)
$N_{(12)}$–$H_{(12)}$	0.886(8)	$C_{(24)}$–$H_{(24C)}$	1.005(10)
$C_{(13)}$–$C_{(14)}$	1.504(2)	$C_{(25)}$–$H_{(25A)}$	0.986(10)
$C_{(13)}$–$C_{(25)}$	1.519(2)	$C_{(25)}$–$H_{(25B)}$	0.970(10)
$C_{(13)}$–$H_{(13)}$	0.977(9)	$C_{(25)}$–$H_{(25C)}$	1.027(10)
$C_{(14)}$–$C_{(15)}$	1.364(2)		

TABLE 5. Bond Angles ω (deg) in the Structure of Compound **1g**

Angle	ω	Angle	ω
1	2	3	4
$C_{(10)}$–$N_{(1)}$–$C_{(2)}$	122.71(7)	$C_{(16)}$–$C_{(15)}$–$H_{(15)}$	119.4(6)
$C_{(10)}$–$N_{(1)}$–$C_{(20)}$	116.35(7)	$C_{(17)}$–$C_{(16)}$–$C_{(15)}$	119.9(2)
$C_{(2)}$–$N_{(1)}$–$C_{(20)}$	120.93(8)	$C_{(17)}$–$C_{(16)}$–$H_{(16)}$	117.1(7)
$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	121.53(8)	$C_{(15)}$–$C_{(16)}$–$H_{(16)}$	122.7(7)
$N_{(1)}$–$C_{(2)}$–$C_{(7)}$	119.87(8)	$C_{(18)}$–$C_{(17)}$–$C_{(16)}$	119.53(14)
$C_{(3)}$–$C_{(2)}$–$C_{(7)}$	118.59(9)	$C_{(18)}$–$C_{(17)}$–$H_{(17)}$	121.6(6)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	120.76(9)	$C_{(16)}$–$C_{(17)}$–$H_{(17)}$	118.8(6)
$C_{(4)}$–$C_{(3)}$–$H_{(3)}$	120.3(6)	$C_{(17)}$–$C_{(18)}$–$C_{(19)}$	121.24(13)
$C_{(2)}$–$C_{(3)}$–$H_{(3)}$	118.9(6)	$C_{(17)}$–$C_{(18)}$–$H_{(18)}$	120.7(7)
$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	120.32(10)	$C_{(19)}$–$C_{(18)}$–$H_{(18)}$	118.0(7)
$C_{(3)}$–$C_{(4)}$–$H_{(4)}$	116.7(6)	$C_{(14)}$–$C_{(19)}$–$C_{(18)}$	119.91(13)
$C_{(5)}$–$C_{(4)}$–$H_{(4)}$	122.9(6)	$C_{(14)}$–$C_{(19)}$–$H_{(19)}$	120.0(6)
$C_{(6)}$–$C_{(5)}$–$C_{(4)}$	120.29(10)	$C_{(18)}$–$C_{(19)}$–$H_{(19)}$	120.1(6)
$C_{(6)}$–$C_{(5)}$–$H_{(5)}$	123.5(6)	$N_{(1)}$–$C_{(20)}$–$C_{(21)}$	113.43(9)
$C_{(4)}$–$C_{(5)}$–$H_{(5)}$	116.1(6)	$N_{(1)}$–$C_{(20)}$–$H_{(20A)}$	108.3(6)
$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	120.75(9)	$C_{(21)}$–$C_{(20)}$–$H_{(20A)}$	113.3(7)
$C_{(5)}$–$C_{(6)}$–$H_{(6)}$	124.6(6)	$N_{(1)}$–$C_{(20)}$–$H_{(20B)}$	105.0(5)
$C_{(7)}$–$C_{(6)}$–$H_{(6)}$	114.6(6)	$C_{(21)}$–$C_{(20)}$–$H_{(20B)}$	113.3(5)
$C_{(2)}$–$C_{(7)}$–$C_{(6)}$	119.24(9)	$H_{(20A)}$–$C_{(20)}$–$H_{(20B)}$	102.6(9)

TABLE 5 (continued)

1	2	3	4
$C_{(2)}$–$C_{(7)}$–$C_{(8)}$	118.53(8)	$C_{(20)}$–$C_{(21)}$–$C_{(22)}$	110.86(10)
$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	122.23(8)	$C_{(20)}$–$C_{(21)}$–$H_{(21A)}$	111.6(5)
$O_{(8)}$–$C_{(8)}$–$C_{(9)}$	121.61(9)	$C_{(22)}$–$C_{(21)}$–$H_{(21A)}$	114.4(5)
$O_{(8)}$–$C_{(8)}$–$C_{(7)}$	117.35(8)	$C_{(20)}$–$C_{(21)}$–$H_{(21B)}$	112.7(6)
$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	121.01(8)	$C_{(22)}$–$C_{(21)}$–$H_{(21B)}$	110.0(6)
$C_{(8)}$–$O_{(8)}$–$H_{(8)}$	100.7(4)	$H_{(21A)}$–$C_{(21)}$–$H_{(21B)}$	96.7(8)
$C_{(8)}$–$C_{(9)}$–$C_{(10)}$	120.05(8)	$C_{(23)}$–$C_{(22)}$–$C_{(21)}$	116.21(13)
$C_{(8)}$–$C_{(9)}$–$C_{(11)}$	118.53(8)	$C_{(23)}$–$C_{(22)}$–$H_{(22A)}$	108.2(6)
$C_{(10)}$–$C_{(9)}$–$C_{(11)}$	121.41(8)	$C_{(21)}$–$C_{(22)}$–$H_{(22A)}$	109.5(6)
$O_{(10)}$–$C_{(10)}$–$N_{(1)}$	119.06(8)	$C_{(23)}$–$C_{(22)}$–$H_{(22B)}$	90.2(6)
$O_{(10)}$–$C_{(10)}$–$C_{(9)}$	123.27(9)	$C_{(21)}$–$C_{(22)}$–$H_{(22B)}$	114.7(5)
$N_{(1)}$–$C_{(10)}$–$C_{(9)}$	117.66(8)	$H_{(22A)}$–$C_{(22)}$–$H_{(22B)}$	116.9(9)
$O_{(11)}$–$C_{(11)}$–$N_{(12)}$	120.88(9)	$C_{(22)}$–$C_{(23)}$–$C_{(24)}$	115.3(2)
$O_{(11)}$–$C_{(11)}$–$C_{(9)}$	119.95(8)	$C_{(22)}$–$C_{(23)}$–$H_{(23A)}$	87.1(6)
$N_{(12)}$–$C_{(11)}$–$C_{(9)}$	119.15(8)	$C_{(24)}$–$C_{(23)}$–$H_{(23A)}$	118.0(5)
$C_{(11)}$–$O_{(11)}$–$H_{(8)}$	100.7(3)	$C_{(22)}$–$C_{(23)}$–$H_{(23B)}$	109.0(6)
$C_{(11)}$–$N_{(12)}$–$C_{(13)}$	123.28(8)	$C_{(24)}$–$C_{(23)}$–$H_{(23B)}$	121.0(6)
$C_{(11)}$–$N_{(12)}$–$H_{(12)}$	114.8(6)	$H_{(23A)}$–$C_{(23)}$–$H_{(23B)}$	100.8(8)
$C_{(13)}$–$N_{(12)}$–$H_{(12)}$	121.8(6)	$C_{(23)}$–$C_{(24)}$–$H_{(24A)}$	112.9(7)
$N_{(12)}$–$C_{(13)}$–$C_{(14)}$	109.69(8)	$C_{(23)}$–$C_{(24)}$–$H_{(24B)}$	114.7(6)
$N_{(12)}$–$C_{(13)}$–$C_{(25)}$	110.28(9)	$H_{(24A)}$–$C_{(24)}$–$H_{(24B)}$	112.8(9)
$C_{(14)}$–$C_{(13)}$–$C_{(25)}$	112.78(9)	$C_{(23)}$–$C_{(24)}$–$H_{(24C)}$	94.3(6)
$N_{(12)}$–$C_{(13)}$–$H_{(13)}$	104.7(6)	$H_{(24A)}$–$C_{(24)}$–$H_{(24C)}$	105.9(9)
$C_{(14)}$–$C_{(13)}$–$H_{(13)}$	109.3(6)	$H_{(24B)}$–$C_{(24)}$–$H_{(24C)}$	114.7(9)
$C_{(25)}$–$C_{(13)}$–$H_{(13)}$	109.8(6)	$C_{(13)}$–$C_{(25)}$–$H_{(25A)}$	109.6(7)
$C_{(15)}$–$C_{(14)}$–$C_{(19)}$	118.14(11)	$C_{(13)}$–$C_{(25)}$–$H_{(25B)}$	108.5(6)
$C_{(15)}$–$C_{(14)}$–$C_{(13)}$	120.68(10)	$H_{(25A)}$–$C_{(25)}$–$H_{(25B)}$	104.9(9)
$C_{(19)}$–$C_{(14)}$–$C_{(13)}$	121.14(10)	$C_{(13)}$–$C_{(25)}$–$H_{(25C)}$	107.9(6)
$C_{(14)}$–$C_{(15)}$–$C_{(16)}$	121.29(13)	$H_{(25A)}$–$C_{(25)}$–$H_{(25C)}$	108.1(9)
$C_{(14)}$–$C_{(15)}$–$H_{(15)}$	119.0(6)	$H_{(25B)}$–$C_{(25)}$–$H_{(25C)}$	117.8(9)

General Method for the Preparation of 1-Phenylethylamides of 1-R-4-Hydroxy-2-oxo-3-quinolinecarboxylic acids. Sample of 1-phenylethylamine (1.42 ml, 0.011 mol) was added to solution of the corresponding ethyl ester of 1-R-4-hydroxy-2-oxo-3-quinolinecarboxylic acid (**2**) (0.01 mol) in ethanol (20 ml) and heated at reflux for 6-7 h. After cooling, the mixture was diluted with water and brought to pH 4 by adding hydrochloric acid. The residue was filtered off, washed with water, and dried.

X-ray Diffraction Study. A CAD-4 automatic single-crystal diffractometer was used with λMoK_{α} radiation and graphite monochromator. The unit cell parameters were determined and refined at • from 14° to 16° using 25 reflections. Orthorhombic crystals of amide **1g** were assigned to the $P2_12_12_1$ space group. The unit cell parameters at 20°C: $a = 6.973(1)$, $b = 11.653(2)$, $c = 25.334(4)$ Å; $V = 2058.5(6)$ Å^3; $Z = 4$. The structure was solved by direct methods using the SHELXS-97 program [18] and refined anisotropically by the full-matrix method of least squares using the SHELXL-97 program [19] for the nonhydrogen atoms. The positions of all the hydrogen atoms were localized from the Fourier difference map. The final R-factor was 0.0646 using 5898 reflections with $I > 2\sigma(I)$. The positional parameters of the atoms in the compound studied and the isotropic temperature parameters equivalent to the corresponding anisotropic parameters are given in Table 3. The interatomic distances and bond angles are given in Tables 4 and 5. The arrangement of the atoms in the molecule and numbering of the atoms are shown in Fig. 1 obtained using the PLUTON program [20].

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