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4-HYDROXY-2-QUINOLONES 113*. SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF N-R-AMIDES OF 4-HYDROXY-6-METHYL-2-OXO-1-PROPYL-1,2,5,6,7,8-HEXAHYDROQUINOLINE-3-CARBOXYLIC ACID

I. V. Ukrainets[1], E. V. Kolesnik[1], L. V. Sidorenko[1], O. V. Gorokhova[1], and A. V. Turov[2]

A preparative method has been developed and the synthesis has been effected of anilides and heterylamides of 4-hydroxy-6-methyl-2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid. A comparative analysis has been carried out of the structure and antitubercular properties of the synthesized compounds and their analogs unsubstituted in the quinoline nucleus.

Keywords: amides, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, antitubercular activity, X-ray structural analysis, thermolysis.

The clarification of structure–biological activity regularities in any series of chemical compounds, their summation, and detailed analysis lie at the basis of the purpose-directed synthesis of medicinal agents with given pharmacological properties [2].

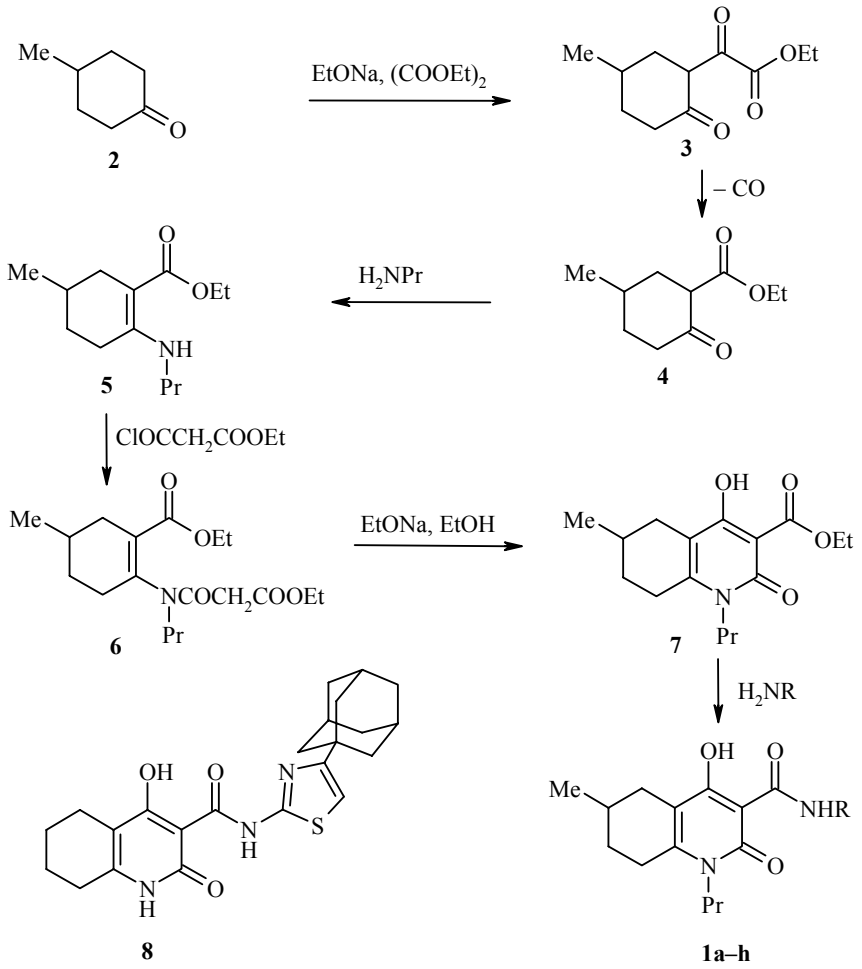
In a continuation of the investigations carried out by us in the search for potentially antitubercular preparations among the amidated derivatives of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, the present communication is devoted to anilides and hetarylamides of 4-hydroxy-6-methyl 2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acids **1a-h** (Table 1).

Synthesis of the desired amides was effected from 4-methylcyclohexanone (**2**). This alicyclic ketone readily undergoes ester condensation with diethyl oxalate forming the β-ketooxalate **3**, which in turn after decarbonylation is converted into the ethyl ester of 5-methyl-2-oxocyclohexanecarboxylic acid (**4**). The further synthetic scheme is analogous to that described previously when obtaining N-R-amides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid [3].

The main difference between the synthesized amides **1a-h** and the unmethylated analogs described previously in [3] from a structural point of view, is the fact that they contain an additional center of chirality, *viz.* the carbon atom at position 6 of the quinoline nucleus. In fact such compounds are mixtures of diastereomers, which usually leads to a doubling of the number of signals in their ^{1}H NMR spectra, or when closely located, to a complication of the shape of multiplets. In reality the observed ^{1}H NMR spectra of amides **1a-h** (more precisely their aliphatic portion) proved to be fairly complex for unambiguous interpretation (Table 2). An attempt to simplify the spectrum undertaken for the example of amide **1b** by heating a solution of the sample being

*For Part 112 see [1].

[1]National Pharmaceutical University, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2]Kiev Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: nmrlab@univ.kiev.ua, Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 405-414, March, 2007. Original article submitted June 27, 2005.



1 a R = 3-fluorophenyl, **b** R = 3-chlorophenyl, **c** R = 3-pyridyl, **d** R = 4-(1-adamantyl)thiazol-2-yl, **e** R = benzothiazol-2-yl, **f** R = 6-bromobenzothiazol-2-yl, **g** R = 1,3,4-thiazol-2-yl, **h** R = 5-methyl-1,3,4-thiazol-2-yl

investigated to 100°C was unsuccessful. However the application of two-dimensional ^{1}H NMR spectroscopy (COSY) enabled reliable assignment to be carried out for the resonance signals of the N-propyl and hexahydroquinolone fragments in the spectrum of this compound. Cross peaks found in this way are shown by arrows.

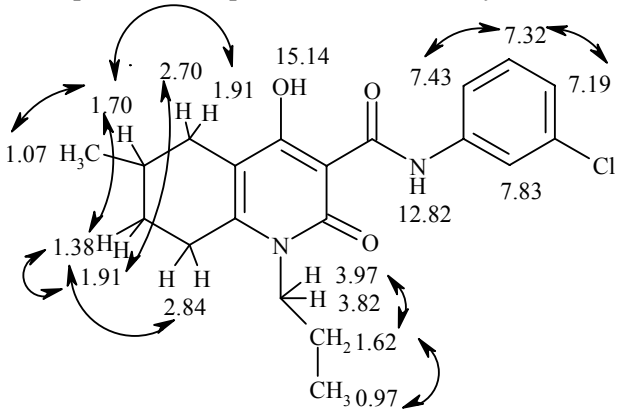


TABLE 1. Characteristics of N-R-Amides of 4-Hydroxy-6-methyl-2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid **1a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (разл.)	Yield, %	Antitubercular activity*
		C	H	N			
1a	$C_{20}H_{23}FN_2O_3$	67.18 / 67.02	6.56 / 6.47	7.67 / 7.82	117-119	82	7
1b	$C_{20}H_{23}ClN_2O_3$	64.20 / 64.08	6.09 / 6.18	7.58 / 7.47	149-151	80	5
1c	$C_{19}H_{23}N_3O_3$	66.71 / 66.84	6.63 / 6.79	12.22 / 12.31	143-145	84	8
1d	$C_{27}H_{35}N_3O_3S$	67.21 / 67.33	7.40 / 7.32	8.84 / 8.72	281-283	77	2
1e	$C_{21}H_{23}N_3O_3S$	63.33 / 63.46	5.72 / 5.83	10.66 / 10.57	223-225	80	10
1f	$C_{21}H_{22}BrN_3O_3S$	52.82 / 52.95	4.76 / 4.65	8.90 / 8.82	241-243	82	10
1g	$C_{16}H_{20}N_4O_3S$	55.03 / 55.16	5.88 / 5.79	16.16 / 16.08	190-192	75	0
1h	$C_{17}H_{22}N_4O_3S$	56.44 / 56.34	6.27 / 6.12	15.34 / 15.46	226-228	76	0

*Depression of growth (%) of *Mycobacterium tuberculosis H37Rv* ATCC 27294 at a concentration of 6.25 μg/ml.

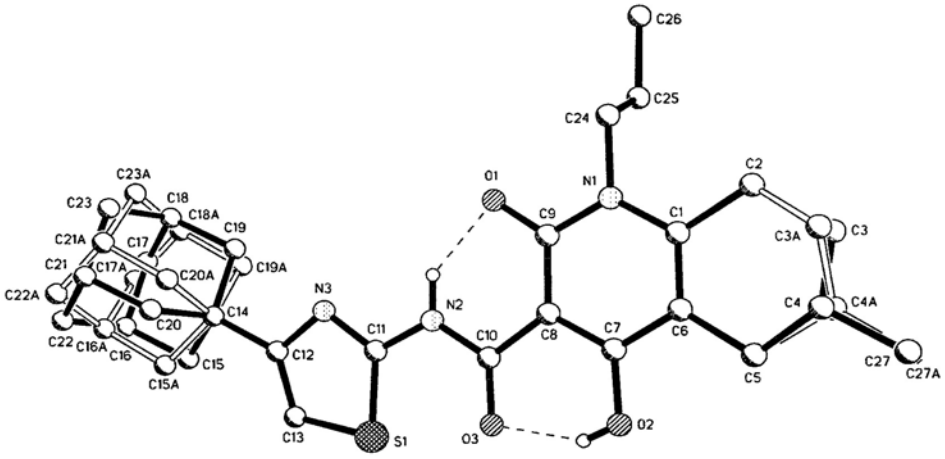


Fig. 1. Structure of the amide **1d** molcule with numbering of the atoms. Intramolcular hydrogen bonds are shown by dotted lines.

As in structure **8** the formation of intramolcular hydrogen bonds was observed in amide **1d** at $N_{(2)}$-H…$O_{(1)}$ (H…O 1.88 Å, N-H…O 139°, $N_{(2)}$…$O_{(1)}$ 2.60 Å) and $O_{(2)}$-H…$O_{(3)}$ (H…O 1.78 Å, O-H…O 147°, $O_{(2)}$…$O_{(3)}$ 2.51 Å), leading to a marked lengthening of the $C_{(9)}$=$O_{(1)}$ and $C_{(10)}$=$O_{(3)}$ bonds and a shortening of the $C_{(7)}$-$O_{(2)}$ bond (Table 3), for which the mean values are 1.210 and 1.362 Å respectively [5]. In difference to compound **8** intermolcular hydrogen bonds were not detected. As in amide **8** a shortened intramolcular contact at $O_{(3)}$…$S_{(1)}$ of 2.787 Å exists in the 6-methylated derivative **1d** (sum of van der Waals radii 3.09 Å [6]), leading to an increase in the $C_{(11)}$-$N_{(2)}$-$C_{(10)}$ valence angle to 124.7°.

Table 2. ^{1}H NMR Spectra (200 MHz) of Amides **1**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)										
	4-OH (1H, s)	CONH (1H, s)	NCH_2 (2H, m)	8-CH_2 (2H, m)	H-5 (1H, dd)	H-7 + H-5 (2H, m)	H-6 + $NCH_2C\underline{H}_2$ (3H, m)	H-7 (1H, m)	6-CH_3 (3H, d)	CH_3 in N–Pr (3H, t)	R
1a	15.20	12.86	3.92	2.78	2.61 (*J* = 16.2, *J* = 4.3)	1.90	1.62	1.36	1.01 (*J* = 6.4)	0.90 (*J* = 7.3)	7.62 (1H, dt, *J* = 11.2 and *J* = 2.2, H-2'); 7.43 (1H, d, *J* = 8.2, H-6'); 7.32 (1H, td, *J* = 8.2 and *J* = 1.7, H-5'); 6.95 (1H, tt, *J* = 8.6 and *J* = 2.1, H-4')
1b	15.18	12.86	3.93	2.80	2.63 (*J* = 16.6, *J* = 4.5)	1.92	1.63	1.37	1.02 (*J* = 6.4)	0.91 (*J* = 7.3)	7.85 (1H, s, H-2'); 7.45 (1H, dt, *J* = 8.2 and *J* = 1.6, H-6'); 7.37 (1H, t, *J* = 7.9, H-5'); 7.18 (1H, dt, *J* = 7.7 and *J* = 1.6, H-4')
1c	15.18	12.80	3.94	2.81	2.63 (*J* = 16.4, *J* = 4.7)	1.92	1.63	1.38	1.02 (*J* = 6.4)	0.91 (*J* = 7.3)	8.78 (1H, d, *J* = 2.6, H-2'); 8.34 (1H, dd, *J* = 4.7 and *J* = 1.4, H-4'); 8.08 (1H, dt, *J* = 8.3 and *J* = 1.7, H-6'); 7.39 (1H, t, *J* = 6.4, H-5')
1d	14.25	13.74	3.94	2.82	2.63 (*J* = 16.3, *J* = 4.1)	1.93	1.63	1.37	1.01 (*J* = 6.2)	0.91 (*J* = 7.3)	6.79 (1H, s, H-5'); 2.01 (3H, s, γ-H adamantane); 1.83 (6H, s, δ-H adamantane); 1.72 (6H, s, β-H adamantane)
1e	14.00	13.96	3.90	2.78	2.58 (*J* = 16.4, *J* = 4.2)	1.83	1.60	1.28	0.97 (*J* = 6.3)	0.91 (*J* = 7.3)	7.95 (1H, d, *J* = 7.6, H-7'); 7.73 (1H, d, *J* = 7.6, H-4'); 7.43 (1H, td, *J* = 7.3 and *J* = 1.4, H-6'); 7.30 (1H, td, *J* = 7.8 and *J* = 1.0, H-5')
1f	14.09	13.88	3.95	2.82	2.61 (*J* = 16.3, *J* = 4.4)	1.90	1.65	1.35	1.02 (*J* = 6.4)	0.93 (*J* = 7.3)	8.23 (1H, d, *J* = 2.0, H-7'); 7.69 (1H, d, *J* = 8.5, H-4'); 7.56 (1H, dd, *J* = 8.6 and *J* = 1.8, H-5')
1g	14.20	13.85	3.96	2.83	2.63 (*J* = 16.4, *J* = 4.2)	1.92	1.64	1.38	1.02 (*J* = 6.3)	0.92 (*J* = 7.4)	9.25 (1H, s, H-5')
1h	14.01	13.87	3.94	2.83	2.58 (*J* = 16.3, *J* = 4.6)	1.89	1.62	1.35	1.00 (*J* = 6.4)	0.92 (*J* = 7.3)	2.66 (3H, s, CH_3)

TABLE 3. Bond Lengths (*l*) in the Amide **1d** Structure

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$S_{(1)}$–$C_{(11)}$	1.706(3)	$C_{(3A)}$–$C_{(4A)}$	1.536(4)	$C_{(17)}$–$C_{(18)}$	1.528(3)
$S_{(1)}$–$C_{(13)}$	1.709(3)	$C_{(4A)}$–$C_{(5)}$	1.490(4)	$C_{(18)}$–$C_{(23)}$	1.529(3)
$O_{(1)}$–$C_{(9)}$	1.256(3)	$C_{(4A)}$–$C_{(27A)}$	1.541(4)	$C_{(18)}$–$C_{(19)}$	1.536(3)
$O_{(2)}$–$C_{(7)}$	1.334(3)	$C_{(5)}$–$C_{(6)}$	1.510(3)	$C_{(20)}$–$C_{(21)}$	1.534(3)
$O_{(3)}$–$C_{(10)}$	1.239(3)	$C_{(6)}$–$C_{(7)}$	1.413(3)	$C_{(21)}$–$C_{(23)}$	1.528(3)
$N_{(1)}$–$C_{(9)}$	1.368(3)	$C_{(7)}$–$C_{(8)}$	1.394(3)	$C_{(21)}$–$C_{(22)}$	1.531(3)
$N_{(1)}$–$C_{(1)}$	1.394(3)	$C_{(8)}$–$C_{(9)}$	1.424(3)	$C_{(15A)}$–$C_{(16A)}$	1.530(2)
$N_{(1)}$–$C_{(24)}$	1.486(3)	$C_{(8)}$–$C_{(10)}$	1.468(3)	$C_{(16A)}$–$C_{(22A)}$	1.531(3)
$N_{(2)}$–$C_{(10)}$	1.363(3)	$C_{(12)}$–$C_{(13)}$	1.343(4)	$C_{(16A)}$–$C_{(17A)}$	1.535(3)
$N_{(2)}$–$C_{(11)}$	1.397(3)	$C_{(12)}$–$C_{(14)}$	1.527(3)	$C_{(17A)}$–$C_{(18A)}$	1.534(3)
$N_{(3)}$–$C_{(11)}$	1.311(3)	$C_{(14)}$–$C_{(19)}$	1.523(2)	$C_{(18A)}$–$C_{(23A)}$	1.532(3)
$N_{(3)}$–$C_{(12)}$	1.400(3)	$C_{(14)}$–$C_{(20)}$	1.527(2)	$C_{(18A)}$–$C_{(19A)}$	1.535(2)
$C_{(1)}$–$C_{(6)}$	1.351(3)	$C_{(14)}$–$C_{(15)}$	1.534(2)	$C_{(20A)}$–$C_{(21A)}$	1.534(2)
$C_{(1)}$–$C_{(2)}$	1.521(3)	$C_{(14)}$–$C_{(19A)}$	1.536(2)	$C_{(21A)}$–$C_{(22A)}$	1.532(3)
$C_{(2)}$–$C_{(3A)}$	1.480(4)	$C_{(14)}$–$C_{(20A)}$	1.538(2)	$C_{(21A)}$–$C_{(23A)}$	1.534(3)
$C_{(2)}$–$C_{(3)}$	1.505(3)	$C_{(14)}$–$C_{(15A)}$	1.538(2)	$C_{(24)}$–$C_{(25)}$	1.533(4)
$C_{(3)}$–$C_{(4)}$	1.532(4)	$C_{(15)}$–$C_{(16)}$	1.533(3)	$C_{(25)}$–$C_{(26)}$	1.527(4)
$C_{(4)}$–$C_{(5)}$	1.487(3)	$C_{(16)}$–$C_{(22)}$	1.529(3)		
$C_{(4)}$–$C_{(27)}$	1.541(3)	$C_{(16)}$–$C_{(17)}$	1.531(3)		

In the 6-methyl-substituted quinolone **1d** disorder was observed not only of the tetrahydro ring of the cyclohexene fragment (as for compound **8**) but also of the adamantane substituent. Of several disordered conformations of the cyclohexene ring, found for the two basic molcules in structure **8**, only one was observed in compound **1d**, an asymmetric *half-chair*. The deviations of the $C_{(3)}$, $C_{(4)}$, $C_{(3A)}$, and $C_{(4A)}$ atoms from the mean plane of the $C_{(1)}$, $C_{(2)}$, $C_{(5)}$, and $C_{(6)}$ atoms were +0.47, -0.27, -0.29, and +0.43 Å respectively. The two conformations of the cyclohexene fragment in amide **1d** have different populations equal to 0.73 for atoms $C_{(3)}$, $C_{(4)}$, and $C_{(27)}$ and 0.27 for atoms $C_{(3A)}$, $C_{(4A)}$, and $C_{(27A)}$.

The adamantane fragment is disordered at two positions differing in the angle of rotation around the $C_{(12)}$-$C_{(14)}$ bond. The population of conformers was 0.56 for atoms $C_{(15A)}$ to $C_{(22A)}$ and 0.44 for atoms $C_{(15)}$ to $C_{(22)}$. The first of the disordered fragments is disposed such that one of the C-C bonds is in the plane of the thiazole ring and the second is turned relative to it [torsion angles $C_{(13)}$-$C_{(12)}$-$C_{(14)}$-$C_{(15A)}$ and $C_{(13)}$-$C_{(12)}$-$C_{(14)}$-$C_{(15)}$ are 2.8(4) and –21.4(4)° respectively].

In both the molcules of **1d** and **8** investigated it is possible to separate two fragments planar to a precision of 0.02 Å. The first of these includes the 1,2-dihydropyridine ring and atoms $O_{(1)}$, $O_{(2)}$, $O_{(3)}$, and $C_{(10)}$, the thiazole ring and atoms $N_{(2)}$, $C_{(14)}$ form the second. In amide **1d** the angle between these fragments is somewhat smaller and is 8.8°.

On studying the antitubercular properties of N-R-amides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid [3] it was noted that reduction of the benzene portion of the quinoline leads as a rule to a significant drop in activity in comparison with the unhydrogenated analogs. In the case of amides **1a-h** (Table 1) it may be confirmed that a methyl group in position 6 of such compounds deactivates the molcule practically completely.

TABLE 4. Valence Angles (ω) in the Amide **1d** Structure

Angle	ω, deg	Angle	ω, deg.
$C_{(11)}$–$S_{(1)}$–$C_{(13)}$	87.6(1)	$C_{(12)}$–$C_{(14)}$–$C_{(15)}$	108.5(2)
$C_{(9)}$–$N_{(1)}$–$C_{(1)}$	122.9(2)	$C_{(20)}$–$C_{(14)}$–$C_{(15)}$	109.5(2)
$C_{(9)}$–$N_{(1)}$–$C_{(24)}$	116.1(2)	$C_{(19)}$–$C_{(14)}$–$C_{(19A)}$	22.3(2)
$C_{(1)}$–$N_{(1)}$–$C_{(24)}$	121.0(2)	$C_{(12)}$–$C_{(14)}$–$C_{(19A)}$	109.8(2)
$C_{(10)}$–$N_{(2)}$–$C_{(11)}$	124.7(2)	$C_{(20)}$–$C_{(14)}$–$C_{(19A)}$	129.4(2)
$C_{(11)}$–$N_{(3)}$–$C_{(12)}$	108.8(2)	$C_{(15)}$–$C_{(14)}$–$C_{(19A)}$	90.1(2)
$C_{(6)}$–$C_{(1)}$–$N_{(1)}$	120.2(2)	$C_{(19)}$–$C_{(14)}$–$C_{(20A)}$	87.7(2)
$C_{(6)}$–$C_{(1)}$–$C_{(2)}$	120.4(2)	$C_{(12)}$–$C_{(14)}$–$C_{(20A)}$	108.1(2)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	119.4(2)	$C_{(20)}$–$C_{(14)}$–$C_{(20A)}$	25.0(2)
$C_{(3A)}$–$C_{(2)}$–$C_{(3)}$	29.6(3)	$C_{(15)}$–$C_{(14)}$–$C_{(20A)}$	129.4(2)
$C_{(3A)}$–$C_{(2)}$–$C_{(1)}$	115.1(2)	$C_{(19A)}$–$C_{(14)}$–$C_{(20A)}$	108.8(2)
$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	112.8(2)	$C_{(19)}$–$C_{(14)}$–$C_{(15A)}$	124.9(2)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	110.7(2)	$C_{(12)}$–$C_{(14)}$–$C_{(15A)}$	111.8(2)
$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	110.2(2)	$C_{(20)}$–$C_{(14)}$–$C_{(15A)}$	87.2(2)
$C_{(5)}$–$C_{(4)}$–$C_{(27)}$	110.2(2)	$C_{(15)}$–$C_{(14)}$–$C_{(15A)}$	23.0(2)
$C_{(3)}$–$C_{(4)}$–$C_{(27)}$	108.4(3)	$C_{(19A)}$–$C_{(14)}$–$C_{(15A)}$	109.1(2)
$C_{(2)}$–$C_{(3A)}$–$C_{(4A)}$	111.1(3)	$C_{(20A)}$–$C_{(14)}$–$C_{(15A)}$	109.2(2)
$C_{(5)}$–$C_{(4A)}$–$C_{(3A)}$	110.8(3)	$C_{(14)}$–$C_{(15)}$–$C_{(16)}$	108.9(2)
$C_{(5)}$–$C_{(4A)}$–$C_{(27A)}$	110.2(4)	$C_{(22)}$–$C_{(16)}$–$C_{(17)}$	109.6(2)
$C_{(3A)}$–$C_{(4A)}$–$C_{(27A)}$	108.0(3)	$C_{(22)}$–$C_{(16)}$–$C_{(15)}$	109.3(2)
$C_{(4)}$–$C_{(5)}$–$C_{(4A)}$	27.3(3)	$C_{(17)}$–$C_{(16)}$–$C_{(15)}$	109.5(2)
$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	114.9(2)	$C_{(18)}$–$C_{(17)}$–$C_{(16)}$	109.8(2)
$C_{(4A)}$–$C_{(5)}$–$C_{(6)}$	112.6(2)	$C_{(17)}$–$C_{(18)}$–$C_{(23)}$	109.7(2)
$C_{(1)}$–$C_{(6)}$–$C_{(7)}$	118.4(2)	$C_{(17)}$–$C_{(18)}$–$C_{(19)}$	109.0(2)
$C_{(1)}$–$C_{(6)}$–$C_{(5)}$	123.0(2)	$C_{(23)}$–$C_{(18)}$–$C_{(19)}$	109.1(2)
$C_{(7)}$–$C_{(6)}$–$C_{(5)}$	118.6(2)	$C_{(14)}$–$C_{(19)}$–$C_{(18)}$	109.3(2)
$O_{(2)}$–$C_{(7)}$–$C_{(8)}$	120.8(2)	$C_{(14)}$–$C_{(20)}$–$C_{(21)}$	109.0(2)
$O_{(2)}$–$C_{(7)}$–$C_{(6)}$	116.8(2)	$C_{(23)}$–$C_{(21)}$–$C_{(22)}$	109.8(2)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	122.4(3)	$C_{(23)}$–$C_{(21)}$–$C_{(20)}$	109.4(2)
$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	117.8(2)	$C_{(22)}$–$C_{(21)}$–$C_{(20)}$	109.0(2)
$C_{(7)}$–$C_{(8)}$–$C_{(10)}$	118.7(2)	$C_{(16)}$–$C_{(22)}$–$C_{(21)}$	109.6(2)
$C_{(9)}$–$C_{(8)}$–$C_{(10)}$	123.4(2)	$C_{(21)}$–$C_{(23)}$–$C_{(18)}$	109.9(2)
$O_{(1)}$–$C_{(9)}$–$N_{(1)}$	118.5(2)	$C_{(16A)}$–$C_{(15A)}$–$C_{(14)}$	109.7(2)
$O_{(1)}$–$C_{(9)}$–$C_{(8)}$	123.2(2)	$C_{(15A)}$–$C_{(16A)}$–$C_{(22A)}$	109.8(2)
$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	118.3(2)	$C_{(15A)}$–$C_{(16A)}$–$C_{(17A)}$	109.7(2)
$O_{(3)}$–$C_{(10)}$–$N_{(2)}$	121.7(2)	$C_{(22A)}$–$C_{(16A)}$–$C_{(17A)}$	109.2(2)
$O_{(3)}$–$C_{(10)}$–$C_{(8)}$	122.5(2)	$C_{(18A)}$–$C_{(17A)}$–$C_{(16A)}$	109.3(2)
$N_{(2)}$–$C_{(10)}$–$C_{(8)}$	115.8(3)	$C_{(23A)}$–$C_{(18A)}$–$C_{(19A)}$	109.5(2)
$N_{(3)}$–$C_{(11)}$–$N_{(2)}$	118.7(2)	$C_{(23A)}$–$C_{(18A)}$–$C_{(17A)}$	109.7(2)
$N_{(3)}$–$C_{(11)}$–$S_{(1)}$	117.1(2)	$C_{(19A)}$–$C_{(18A)}$–$C_{(17A)}$	109.3(2)
$N_{(2)}$–$C_{(11)}$–$S_{(1)}$	124.2(2)	$C_{(18A)}$–$C_{(19A)}$–$C_{(14)}$	110.0(2)
$C_{(13)}$–$C_{(12)}$–$N_{(3)}$	113.8(2)	$C_{(21A)}$–$C_{(20A)}$–$C_{(14)}$	109.9(2)
$C_{(13)}$–$C_{(12)}$–$C_{(14)}$	129.2(2)	$C_{(22A)}$–$C_{(21A)}$–$C_{(23A)}$	109.6(2)
$N_{(3)}$–$C_{(12)}$–$C_{(14)}$	116.9(2)	$C_{(22A)}$–$C_{(21A)}$–$C_{(20A)}$	109.6(2)
$C_{(12)}$–$C_{(13)}$–$S_{(1)}$	112.6(2)	$C_{(23A)}$–$C_{(21A)}$–$C_{(20A)}$	109.3(2)
$C_{(19)}$–$C_{(14)}$–$C_{(12)}$	111.4(2)	$C_{(16A)}$–$C_{(22A)}$–$C_{(21A)}$	109.4(2)
$C_{(19)}$–$C_{(14)}$–$C_{(20)}$	110.5(2)	$C_{(18A)}$–$C_{(23A)}$–$C_{(21A)}$	109.3(2)
$C_{(12)}$–$C_{(14)}$–$C_{(20)}$	107.2(2)	$N_{(1)}$–$C_{(24)}$–$C_{(25)}$	109.8(2)
$C_{(19)}$–$C_{(14)}$–$C_{(15)}$	109.6(2)	$C_{(26)}$–$C_{(25)}$–$C_{(24)}$	110.2(2)

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX 200 (200 MHz) instrument. The ^{1}H NMR COSY spectrum of amide **1d** was recorded on a Varian Mercury 400 (400 MHz) spectrometer. The solvent was DMSO-d_6 in all cases, internal standard was TMS. Commercial 4-methylcyclohexanone from Fluka was used in the study.

5-Methyl-2-oxocyclohexanecarboxylic Acid Ethyl Ester (4). Diethyl oxalate (14.6 g, 0.1 mol) was added to a solution of sodium ethylate [from metallic sodium (2.3 g, 0.1 mol) and absolute alcohol (50 ml)] with vigorous stirring and then 4-methylcyclohexanone (11.2 g, 0.1 mol) was added. The stirring was stopped and the reaction mixture was left at room temperature. After 5 h, cold water (200 ml) was added, and the mixture acidified with dilute H_2SO_4 to pH 3. The precipitated β-ketooxalate **3** was extracted with CH_2Cl_2 (3×50 ml). The organic extracts were combined, and the solvent distilled off. The residue was heated in a flask with a still head in a metal bath at a pressure of ~15 mm Hg, gradually increasing the bath temperature to 170°C, and maintaining this temperature until evolution of CO had finished. At the end of the reaction (after 2 to 2½ h) the reaction mixture was distilled in vacuum, collecting the fraction with bp 78-80°C (8 mm Hg). Ester **4** (14.9 g, 81%) was obtained.

5-Methyl-2-propylaminocyclohex-1-enecarboxylic Acid Ethyl Ester (5). A mixture of compound **4** (18.4 g, 0.1 mol) and propylamine (12.4 ml, 0.15 mol) was stirred at 45°C for 5 h, after which it was left at room temperature for 8-10 h. The separated water and the excess of propylamine were removed in vacuum. The residue (crude enamine **5**) was used in further synthesis without additional purification.

4-Hydroxy-6-methyl-2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid Ethyl Ester (7). Unpurified enamine **5**, obtained from ester **4** (0.1 mol) by the method described above, was dissolved in CH_2Cl_2 (100 ml), triethylamine (15.4 ml, 0.11 mol) was added, and then ethoxymalonyl chloride (16.56 g, 0.11 mol) was added dropwise with stirring and cooling. The mixture was left at room temperature for 4-5 h. The reaction mixture was diluted with water, the organic layer separated, and dried with anhydrous $CaCl_2$. The solvent was distilled (finally in vacuum). A solution of sodium ethylate [from metallic sodium (3.45 g, 0.15 mol) and absolute alcohol (150 ml)] was added to the residue (diester **6**), the mixture boiled for 30 min, after which heating was stopped, and the mixture left for 7-8 h at room temperature. The reaction mixture was diluted with water and acidified with dilute (1 : 1) HCl to pH 4.5-5.0. The separated ester **7** was extracted with CH_2Cl_2 (3×100 ml). The solvent was distilled off (finally in vacuum). Ester **7** (25.2 g, 86%) was obtained as a bright yellow oily mass, used in the synthesis of amides **1a-h** without additional purification.

N-R-Amides of 4-Hydroxy-6-methyl-2-oxo-1-propyl-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic Acid 1a-h (General Procedure). A mixture of ethyl ester **7** (2.93 g, 0.01 mol), the appropriate aniline or hetarylamine (0.01 mol), and DMF (1 ml) was stirred and maintained at 160-170°C for 3 min. The mixture was cooled, diluted with alcohol (20 ml), thoroughly mixed, and filtered. The amide **1** obtained was washed on the filter with alcohol, dried, and crystallized from DMF.

X-Ray Structural Investigation. Crystals of amide **1d**, grown from DMF, were monoclinic, at 20°C a = 12.306(2), b = 14.516(3), c = 14.516(3) Å, β = 112.767(14)°, V = 2455.2(8) Å^3, M_r = 481.64, Z = 4, space group $P2_1/c$, d_{calc} = 1.303 g/cm^3, μ(MoKα) = 0.166 mm^{-1}, F(000) = 1032. The parameters of the unit cell and the intensities of 4515 reflections (4340 independent, R_{int} = 0.086) were measured on a Siemens P3/PC automatic four-circle diffractometer (MoKα, graphite mono-chromator, θ/2θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the SHELX97 set of programs [7]. The positions of the hydrogen atoms were calculated geometrically and refined with the rider model with $U_{iso} = 1.2 \times U_{eq}$ of the non-hydrogen atom linked with the given hydrogen. The disordered fragments were refined by superimposing limitations on C-C bond length and valence angles. The total number of geometric limitations was 618. The structure was refined on F_2 by the full-matrix least squares method in an anisotropic approximation for the

nonhydrogen atoms to $wR_2 = 0.0892$ for 4340 reflections ($R_1 = 0.064$ for 1704 reflections with $F > 4\sigma(F)$, $S = 0.905$). The full crystallographic information has been deposited with the Cambridge Structural Data Bank (deposition No. CCDC 283260). Interatomic distances and valence angles are given in Tables 3 and 4.

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